Radical Framework Reconstruction as a Novel Paradigm in Steroid Chemistry — Synthesis of Swinhoeisterol A, Dankasterone A and B, Periconiastone A and Herbarulide

Inaugural-Dissertation
to obtain the academic degree
Doctor rerum naturalium (Dr. rer. nat.)

Submitted to the Department of Biology, Chemistry and Pharmacy
of Freie Universität Berlin

by

Fenja Leena Dücker

from Felde

June 2020

The doctoral studies presented herein were conducted at the Department of Chemistry, Biology and Pharmacy of Freie Universität Berlin under supervision of Prof. Dr. Philipp Heretsch from April 2016 to February 2020.

1st Reviewer: Prof. Dr. Philipp Heretsch, Freie Universität Berlin

2nd Reviewer: Prof. Dr. Mathias Christmann, Freie Universität Berlin

Date of defense: 5th August 2020

I hereby affirm in lieu of oath that I have prepared the dissertation entitled 'Radical Framework Reconstruction as a Novel Paradigm in Steroid Chemistry — Synthesis of Swinhoeisterol A, Dankasterone A and B, Periconiastone A and Herbarulide' independently and without the help of any impermissible resources. All citations are marked as such. This thesis has not been accepted in any previous doctorate degree procedure nor at any other department or university.

Berlin, 2nd June 2020

Fenja Leena Dücker

Acknowledgements

I would like to express my sincere gratitude to Prof. Dr. Philipp Heretsch for the opportunity to conduct my doctoral studies on this fascinating topic in his research group, for helpful discussions and for constant motivation and support during the last four years. I highly appreciated the possibility to participate in numerous international conferences.

I want to thank Prof. Dr. Mathias Christmann for agreeing to be the second reviewer and for constructive advice during my doctoral studies.

I am grateful to Gregor Drendel, Anja Peuker, Bettina Zeisig, Xuan Pham and Dr. Andreas Schäfer for smooth NMR measurements and to Gregor Drendel, Xuan Pham, Fabian Klautzsch and Dr. Andreas Springer for support with MS measurements. I want to thank Christiane Groneberg for measuring my IR spectra. I am also thankful to Christiane Groneberg and Dr. Carlo Fasting for the provided assistance concerning HPLC purifications and to Prof. Dr. Dieter Lentz and Dr. Simon Steinhauer for performing X-ray diffraction analyses.

Special thanks go to all former and present members of the Heretsch group. I want to extend deep appreciation to Dr. Robert Heinze for productive discussions, great support and for being an endless source of ideas. I want to thank Franziska Reuß for lively debates on amongst other things 2D NMR mysteries that appeared to be unsolvable and for always having a partly cracked flask set aside for bad times. I am thankful to both of them for the great atmosphere in our lab, including Harmony FM Fridays and Stadt-Land-Flux sessions with Winson.

I want to thank all students that contributed to this work for their reliability and effort: Mira Müller, Alexander Ozimkovski and Michael Jakob.

I want to thank Franziska Reuß, Dr. Robert Heinze, Carolin Hoyer, Dr. Lisa Schneider and Daniel Wighton for proofreading this thesis.

I am grateful to the Deutsche Forschungsgemeinschaft for financial support.

Special thanks go to my friends and colleagues Carolin Hoyer, Alexandra Gruber, Jessica Stubbe, Anna Herrmann, Doğuş Işik, Felix Reisbeck, Jakob Leppkes, Tuğrul Kaynak, Dr. Frenio Redeker, Tony Stüker and Julian Heinrich. Most of them have accompanied me since our first Bachelor semester at FU Berlin in October 2010 and our incredible BCP internal network and Thursday Mensa dates tackled many challenges.

I want to thank all my friends from the far North, Berlin and many other places. Spending time with you at Volleyball, hiking trips or enjoying Berlin weekends kept my spirits up and provided the best distraction after long days in the lab. Thank you so much for your support Caro, Nele, Lynn, Alex, Ina, Esther, Lisa, Alexa, Clara, Saskia, Nico, Karoly, Dan and everyone else.

Most importantly, I want to thank my family for keeping me grounded and for providing endless support throughout all these years in Berlin even though never understanding a word of what I was doing. I am eternally grateful to my mum for being the best mum one could wish for and my brother Daniel for sharing the tough journey toward graduation.

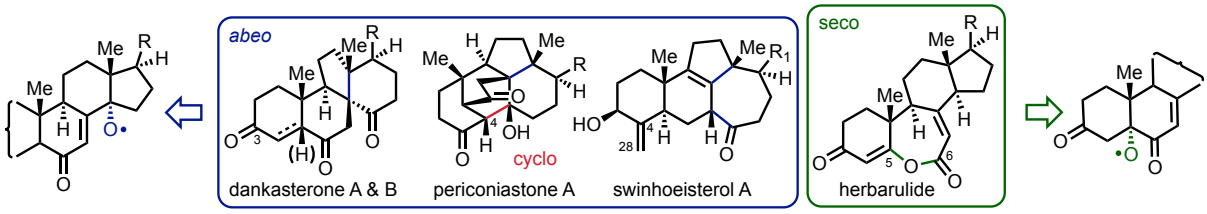
Abstract

Many recently isolated steroidal secondary metabolites consist of rearranged carbon skeletons and often exhibit remarkable biological activities. The project of examining the synthesis of such natural products was ignited by the development of an alkoxy radical-mediated framework reconstruction, which enabled access to not only 13(14→8)*abeo*- but also 13(14→8),14(8→7)di*abeo*-steroids starting from a common γ-hydroxy enone precursor.

Dankasterone A and B are 13(14→8)*abeo*-steroids that both share the same rearranged carbon backbone. Structurally related periconiastone A, a recently isolated anti-MRSA agent, includes an additional 4,14-cyclo-motif. Due to their remarkable biological activities, intriguing structural features and because none of them had been synthetically accessed, these natural products were chosen as synthetic targets. The radical cascade mentioned above enabled selective access to the 13(14→8)*abeo*-skeleton when employing (diacetoxyiodo)benzene and iodine to generate the alkoxy radical. Additional steps yielded dankasterone B, which could either be converted to dankasterone A *via* further oxidation or undergo an aldol reaction to provide pentacyclic periconiastone A.

To date, the swinhoeisterol class of natural products consists of nine members, whereof all display a 6/6/5/7 carbon skeleton and several exhibit interesting biological properties. When employing mercury(II) oxide and iodine to initiate the radical cascade, the di*abeo*-backbone was obtained in a highly selective manner. Initial synthetic attempts focused on the accessibility of the C_{29} skeleton, including the crucial C4 *exo*-methylene group. After setting the oxidation state of the tetracyclic ring system, the introduction of C28 proved difficult but was successfully accomplished when applying the Nishiyama–Stork protocol, and final elimination of a primary alcohol gave the desired exocyclic double bond. After establishing this route to derivatives of swinhoeisterol A, adjustments were made to supply the actual natural product. Oxidative cleavage of the ergostane side chain and subsequent olefination installed the side chain fragment with the correct configuration at C24. However, hydrogenation of this double bond was unsuccessful, and the application of a hydroboration/oxidation/deoxygenation sequence became necessary to obtain the desired, saturated campestane side chain, which enabled the first synthesis of swinhoeisterol A.

Another alkoxy radical-mediated reaction provided access to 5,6-epoxy-5,6-secosteroid herbarulide. The synthesis of this secondary metabolite and its C24-epimer, applying the afore-established strategy, enabled the unambiguous structural assignment of the natural product.



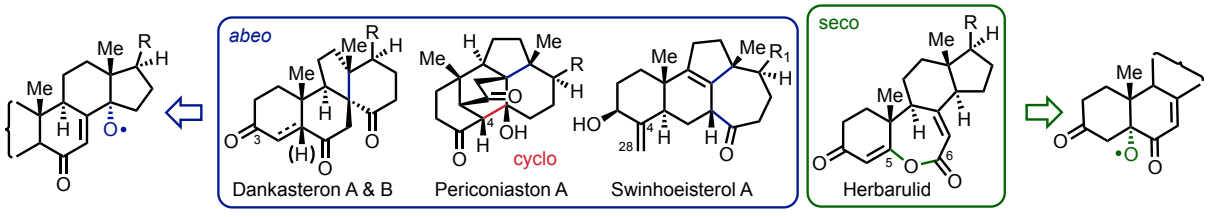
Kurzfassung

Viele kürzlich isolierte, steroidale Sekundärmetabolite enthalten ein umgelagertes Kohlenstoffgerüst und weisen oftmals bemerkenswerte biologische Aktivitäten auf. Die Idee zur Synthese derartiger Naturstoffe wurde mit der Entwicklung einer gerüstverändernden Radikalkaskade zum Ziel dieser Arbeit. Ausgehend von einem gemeinsamen Vorläufer, war es möglich, selektive Zugänge zu sowohl 13(14→8)*abeo*- als auch 13(14→8),14(8→7)di*abeo*-Steroiden zu etablieren.

Die Dankasterone A und B sind 13(14→8)*abeo*-Steroide und teilen das gleiche umgelagerte Kohlenstoffrückgrat. Bei dem strukturell verwandten Periconiaston A handelt es sich um einen vielversprechenden Wirkstoff gegen MRSA, dessen Gerüst ein zusätzliches 4,14-Cycloelement enthält. Aufgrund der einzigartigen strukturellen Eigenschaften und biologischen Aktivitäten dieser Naturstoffe wurde die Erarbeitung eines ersten synthetischen Zugangs zu diesen Verbindungen anvisiert. Eine selektive Bildung des 13(14→8)*abeo*-Gerüsts gelang, wenn die erwähnte radikalische Umlagerung durch die Reagenzien (Bisacetoxyiod)benzol und Iod eingeleitet wurde. Weitere Transformationen vollendeten die erste Synthese von Dankasteron B, welches entweder durch weitere Oxidation zu Dankasteron A oder durch eine Aldolreaktion zu Periconiaston A umgesetzt werden konnte.

Die Klasse der Swinhoeisterole umfasst aktuell neun Verbindungen, die alle das gleiche einzigartige 6/6/5/7 Kohlenstoffgerüst enthalten, welches die Erarbeitung einer Syntheseroute zu dieser Stoffklasse motivierte. Die Verwendung von Quecksilber(II)oxid und Iod zur Generierung des Alkoxyradikals führte im weiteren Verlauf der Reaktion zur selektiven Bildung des gewünschten 13(14→8),14(8→7)di*abeo*-Rückgrats. Die Einführung von C28 gelang nach verschiedenen Redoxmanipulationen durch die Anwendung des Nishiyama–Stork-Protokolls, und eine finale Eliminierung des primären Alkohols führte daraufhin zur Bildung der exozyklischen Doppelbindung. Nachdem ein Zugang zum Kohlenstoffgerüst von Swinhoeisterol A geschaffen wurde, galt es, den eigentlichen Naturstoff zu synthetisieren. Die Einführung des korrekten Seitenkettenfragments gelang durch oxidative Spaltung des Ergostanrests und darauffolgende Olefinierung. Die gesättigte Campestanseitenkette wurde mithilfe einer Hydroborierungs-/Oxidations-/Deoxygenierungssequenz erhalten, was die erste Synthese von Swinhoeisterol A vervollständigte.

Der Zugang zu dem 5,6-Epoxy-5,6-secosteroid Herbarulid wurde durch einen weiteren Alkoxyradikal-vermittelten Prozess erschlossen. Die Synthese dieses Sekundärmetaboliten und seines C24-Epimers ermöglichte eine eindeutige Aufklärung der Struktur des Naturstoffs.



List of Abbreviations & Acronyms

AIBN	2,2'-azobis(isobutyronitrile)
Bn	benzyl
Bz	benzoyl
CBS-cat.	Corey–Bakshi–Shibata catalyst
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAl-H	diisobutylaluminumhydride
DMAPP	dimethylallyl pyrophosphate
DMP	Dess–Martin periodinane
ECD	electronic circular dichroism
ED_{50}	median effective dose
FAD	flavin adenine dinucleotide
FPP	farnesyl pyrophosphate
HMDS	hexamethyldisilazane
IPP	isopentenyl pyrophosphate
IC_{50}	median inhibitory concentration
LUMO	lowest unoccupied molecular orbital
*m*CPBA	*meta*-chloroperoxybenzoic acid
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
NADP	nicotinamide adenine dinucleotide phosphate
NMR	nuclear magnetic resonance spectroscopy
py	pyridine
RNA	ribonucleic acid
SAM	S-adenosyl methionine
SE	squalene epoxidase
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofurane
TMS	trimethylsilyl
TPP	*meso*-tetraphenylporphyrin

Parts of this dissertation have already been published as follows:

'*Rearranged ergostane-type natural products: chemistry, biology and medicinal aspects*'
Fenja L. Duecker, Franziska Reuß, Philipp Heretsch, *Org. Biomol. Chem.* **2019**, 17, 1624–1633.

'*Synthesis of Swinhoeisterol* A, *Dankasterone* A *and* B, *and Periconiastone* A *by Radical Framework Reconstruction*'
Fenja L. Duecker, Robert C. Heinze, P. Heretsch, *J. Am. Chem. Soc.* **2020**, *142*, 104–108.

'*Synthesis of the Alleged Structures of Fortisterol and Herbarulide and Structural Revision of Herbarulide*'
Fenja L. Duecker, Robert C. Heinze, Mira Mueller, Sudong Zhang, Philipp Heretsch, *Org. Lett.* **2020**, 22, 1585–1588.

'*Discoveries and Challenges en route to Swinhoeisterol* A'
Fenja L. Duecker, Robert C. Heinze, Simon Steinhauer, Philipp Heretsch, *Chem. Eur. J.* **2020**, 10.1002/chem.202001405

Table of Contents

1 Introduction

1.1 Steroids

An almost infinite number of compounds isolated from nature possesses unique inherent bioactivities and thus, natural products have been of medicinal use for the treatment of a vast variety of diseases for many centuries. Nowadays, secondary metabolites may either be marketed in their natural appearance, carry derivatized functional groups or act as a mimic for synthetic targets. To understand their modes of action, an explicit structural elucidation is invaluable to the scientific community since biological activities arise from both specific three-dimensional structures and the molecules' functionalities. Steroids belong to the group of triterpenes and constitute a class of biologically highly significant hydrocarbons.[1] They are present in flora as well as fauna and their main duties are the stabilization of cell membranes and to act as signaling molecules in the organism. In addition, they have been found to account for a myriad of different functions in living systems and their structural diversity entails their physiological and pharmaceutical importance.[2]

In the beginning of the 20th century, organic chemists took on enormous efforts to determine the general carbon skeleton of steroids. At that time, the most common practice was to study the reactivities of a molecule along with its degradation and derivatization products. The melting point, elemental composition and molecular weight of these compounds were then determined and compared to the data of reported structures. This procedure was repeated until known derivatives were obtained. In 1927, Wieland was awarded the Nobel prize in chemistry 'for his investigations of the constitution of the bile acids and related substances'[3,4] and only one year later, Windaus received the same recognition 'for the services rendered through his research into the constitution of the sterols and their connection with the vitamins'.[5,6] Especially Windaus' research focused on the structural and biochemical relationship between steroids and the D vitamins,[7–11] which had been found to have a major impact on the occurrence of rickets in the preceding centuries and were discovered to be produced by irradiation of steroidal compounds. Initially, Wieland and Windaus proposed tetracyclic skeleton **1** as the general steroid backbone (Figure 1),[4,6,12] consisting of two six-membered rings (I and III) as well as of two five-membered rings (II and IV) whereof ring IV was carrying a side chain on C19. However, early X-ray studies conducted by Bernal suggested this alkyl moiety to instead be connected to C17.[13,14] Further investigations revealed the parent sterane skeleton (**2**) to be assembled of three six-membered rings (A, B and C) and only one five-membered ring (D) with the possible connection of an alkyl side chain on C17 and two angular methyl groups on C10 and C13.[15] For reasons of nomenclature, steroids are classified into further subgroups, respecting structural characteristics such as the number of carbon atoms attached to the ring system and the composition of the side chain (if present).[16]

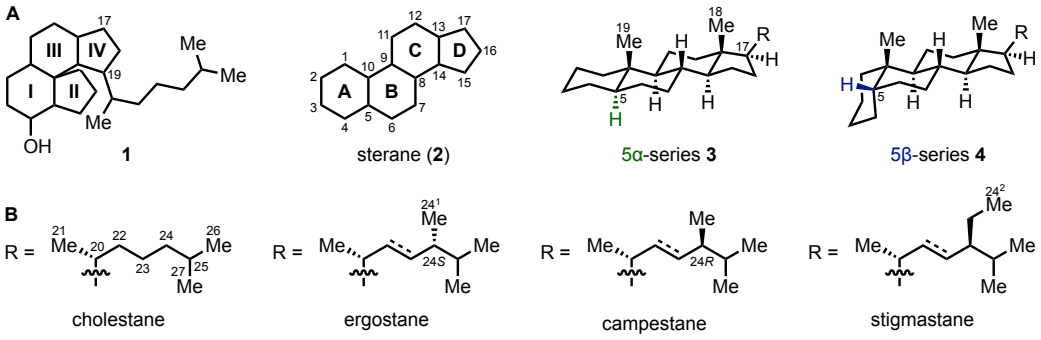
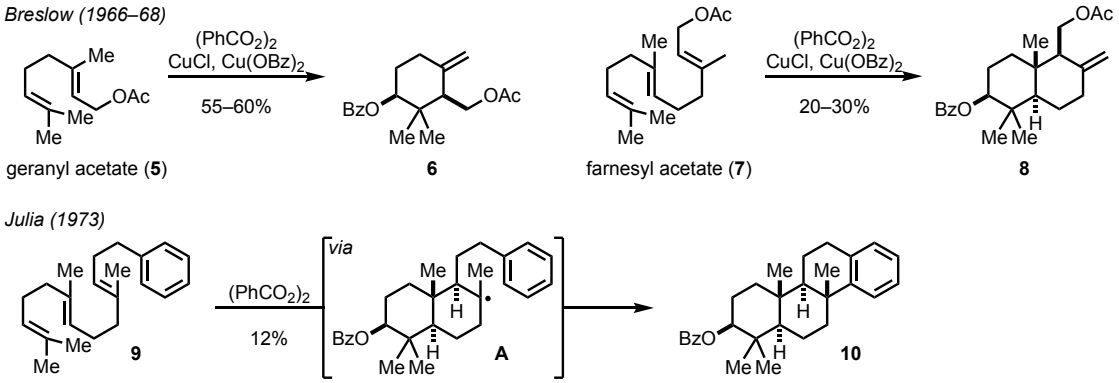


Figure 1 A: Originally proposed and corrected structures of the general steroid skeleton and its three-dimensional representation; B: Constitutional differences of some steroidal side chains.

The C_{19} androstane skeleton (as in **3** and **4** if R = H) for example is parent to the androgens, the male sex hormones, whereas cholesterol (**18**, see Scheme 2), one of the most abundant sterols found in humans and animals and the progenitor of most other mammalian steroids, is a C_{27} cholestane. The structural differences of for example cholestanes, ergostanes, campestanes and stigmastanes originate only from the different substitution pattern on C24; the three latter subclasses may also include an additional C22–23 double bond. Generally, the ring junctions of the tetracyclic carbon backbone are all *trans*, which shapes steroids into relatively flat structures (see **3**) and creates two spaces: below and above the plane of the molecule. These spheres are indicated with α and β, respectively, and serve to describe the orientation of substituents on the skeleton pointing either down or up. The most common divergency to the all *trans* skeleton is a *cis* ring junction in the A–B decalin unit, which leads to a deflection in the skeletal structure as illustrated in the three-dimensional structure of 5β-**4**.

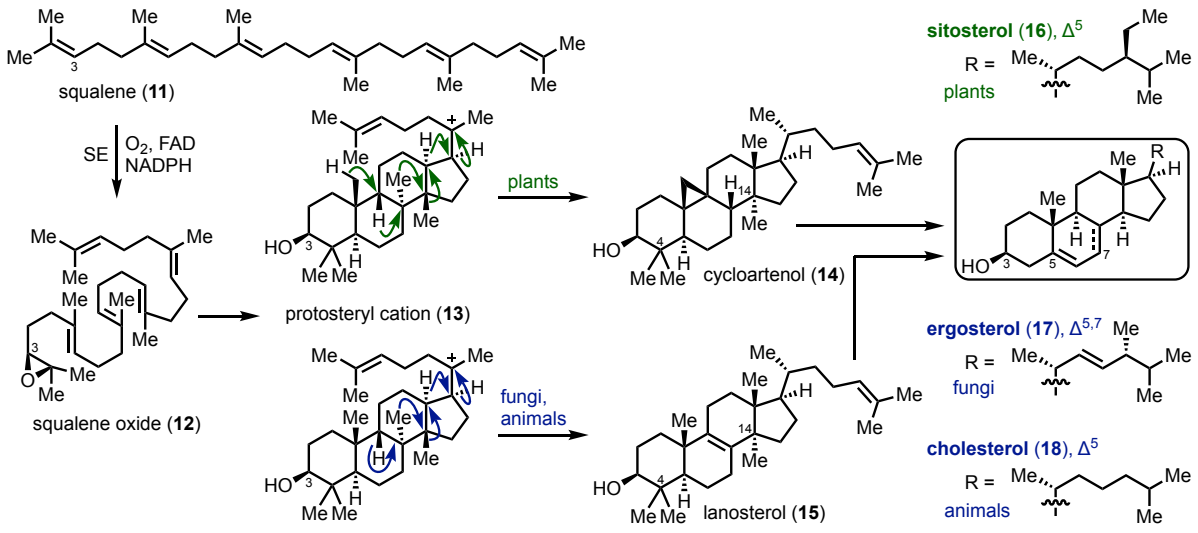
As steroids are terpenoids, they can biosynthetically be traced back to the C_5 isoprene unit, i.e. one of its activated analogs isopentenyl pyrophosphate (IPP) or dimethylallyl pyrophosphate (DMAPP). After loss of the diphosphate leaving group of DMAPP, the resulting resonance-stabilized allylic carbocation can be attacked by the nucleophilic terminal double bond of IPP giving rise to the head-to-tail monoterpene C_{10} building block geranyl pyrophosphate (GPP). The chain prolongation to higher terpenoid precursors follows the same procedure and successive head-to-tail additions of IPP lead to farnesyl pyrophosphate (FPP, C_{15}), geranylgeranyl pyrophosphate (GGPP, C_{20}) and geranylfarnesyl pyrophosphate (GFPP, C_{25}), respectively. However, for the analogous C_{30} unit this logic collapses as squalene (**11**) is established by merging two FPP units in a tail-to-tail fashion to give the prominent steroid precursor (see Scheme 2).[17,18] Although scientists had agreed on the biological significance of squalene (**11**), the mechanism accounting for its transformation to steroidal structures and an incorporation of the characteristic hydroxy group were topics of an ongoing debate in the 1950's and 60's.[19–21] The most popular approach suggested a carbocation-mediated cyclization to establish the tetracyclic ring system, which could be initiated by the addition of an 'HO$^+$' species to C3.[22,23] Breslow, however, stated that many requirements of the envisioned transformation would be better served by a free radical process[24] and his group was able to provide

experimental support for this hypothesis (Scheme 1).[25,26] When treating geranyl and farnesyl acetate (**5** and **7**, respectively) with dibenzoyl peroxide in the presence of copper salts under thermal conditions, a regioselective addition of the initially generated radical to the respective terminal double bond of the polyene occurred and follow up cyclization led to the selective formation of just one cyclic product in each case (**6**[25] and **8**[26]). Julia and co-workers were able to substantiate the possibility of a biological radical cyclization when they obtained only tetracyclic **10** out of 16 possible products applying a similar procedure to polyene **9**.[27] The noticeable low yield of this latter reaction might have arisen from the reluctance of a possible intermediary alkyl radical **A** to add to the aromatic ring in the absence of a copper salt.[28]



Scheme 1 Early examples of biomimetic radical polyene cyclizations reported by Breslow[25,26] and Julia[27].

Nevertheless, the proposal of a radical biosynthetic pathway was dismissed shortly after when Corey and van Tamelen were able to transform squalene oxide (**12**) to lanosterol (**15**) in rat liver homogenate, thereby collecting evidence for an ionic process (Scheme 2).[29,30] Today it is well-established that the polyene cyclization cascade of squalene (**11**) is enzymatically initiated by squalene epoxidase (SE), which, in the presence of oxygen and co-factors (FAD, NADPH), leads to the formation of 2,3-oxidosqualene (**12**) (Scheme 2). This can, if appropriately folded and positioned on



Scheme 2 Biosynthetic transformation of squalene (**11**) to cycloartenol (**14**) and lanosterol (**15**), and their structurally related successors sitosterol (**16**), ergosterol (**17**), and cholesterol (**18**).

the enzyme, first undergo a sequence of carbocation-mediated cyclizations to give the tetracyclic protosteryl cation (**13**), which, after a series of concerted Wagner–Meerwein alkyl and hydride shifts, can then be transformed into two particular steroids. The described process is almost identical for all organisms except that in plants a migration of H-C9 to C8 takes place and the angular methyl group C19 produces the cyclopropane motif of cycloartenol (**14**) whereas in fungi and animals, H-C9 is lost to create the C8–C9 double bond as in lanosterol (**15**). Due to the characteristic 3β-hydroxy group found in many steroids, which arises from the initial 2,3-epoxide, many compounds carry the suffix '-ol', hence calling them sterols, whereas analogs with a 3-oxo functionality commonly end with '-one'. Depending on the producing organism, the basic steroid (**14** or **15**) is successively transformed into either sitosterol (**16**, plants, C_{29}), ergosterol (**17**, fungi, C_{28}) or cholesterol (**18**, animals, C_{27}) by a series of enzyme-catalyzed reactions, namely demethylation at C4 and C14, double bond isomerization and formation, and side chain modification. Common structural features of sterols **16**, **17** and **18** are an all *trans*-fused carbon skeleton, desaturation in the B ring (Δ^5, for **17**: $\Delta^{5,7}$) and the 3β-hydroxy group. These compounds all serve a variety of different biological functions and act as steroidal building blocks in the respective organisms. Cholesterol (**18**) for example is the precursor of a multitude of functionally and structurally diverse compounds that are biologically important such as mammalian sex hormones, bile acids and corticosteroids as well as herbal steroidal saponins and cardioactive glycosides.[31]

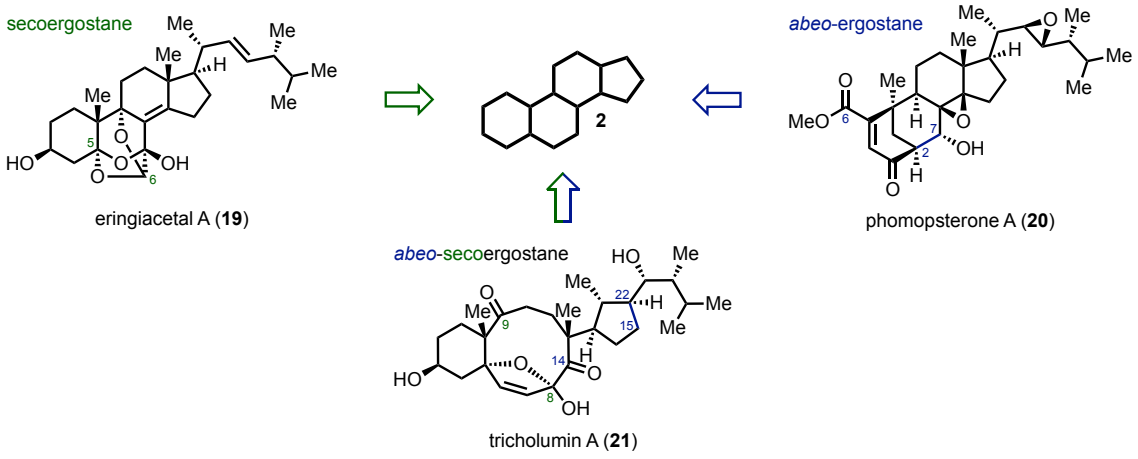
Even though the radical approach suggested by Breslow is not productive in the actual biosynthetic pathway in steroid genesis, it still represents a viable tool in the selective formation of polycyclic structures without enzymatic assistance. To date, radical transformations have found numerous, successful applications in the installation of complex structural features and have also been used to mimic biosynthetic key steps.[32–38] With regard to reactivity, radical processes feature a number of exploitable advantages when compared to their ionic analogs, which is, amongst others, the tolerance toward a multitude of otherwise reactive functional groups, the exclusive formation of *trans* ring junctions in decalins and easy access to exocyclic double bonds along with often observed high selectivities (cf. Scheme 1, Breslow).

1.2 Seco- and *abeo*-Steroids

Even though variations on the classical steroid skeleton by modification of functional groups and substituents are able to provide innumerable different bioactive compounds, nature has provided structurally even more complex derivatives. For instance, the rupture of one or multiple carbon–carbon bonds altering the steroid backbone delivers so-called secosteroids. This structural change is indicated by specifying the bond that has been broken and adding the prefix 'seco' to the generic steroid class.[16] Probably, the most popular examples of this group are the D vitamins, which arise from a UV-light-induced electrocyclic ring opening of either ergosterol (**17**, cf. Scheme 2) or 7-

dehydrocholesterol (7-dehydro-**18**, not shown) leading to vitamin D_2, a 9,10-secoergostane, or D_3, a 9,10-secocholestane, respectively. In the early 20th century, the D vitamins were evaluated to provide a cure for rickets, a disease that had been commonly observed at the time. The characteristic symptoms were deformations and distortions of the skeletal structure induced by insufficient exposure to daylight or an imbalanced diet causing the vitamin deficiency. The chemical correlation between steroids and these vitamins was essentially uncovered by Windhaus and had a profound stake in the research he was awarded the Nobel prize for (*vide supra*).[6] An example for a more recently discovered secosteroid represents eringiacetal A (**19**), which was isolated by the group of Tanaka from the Southeast Asian fungus *Pleurotus eryngii* in 2015.[39] Along with its high level of oxygenation **19** features an unprecedented, basket-like B ring, which arises from a C5–C6 bond scission (Scheme 3).

Further constitutional changes of the tetracyclic steroid backbone may be observed if the scission of a C–C bond is followed by a reconnection to another carbon atom, which implies a bond migration. Compounds resulting from such a transformation are defined as *abeo*-steroids and as to nomenclature, the x(y→z)-*abeo*-notation is used indicating that an initial x–y connectivity is replaced by an x–z bond.[16] Again, the additional information is prefixed to the steroidal subclass of the compound. Phomopsterone A (**20**), thus, represents a 7(6→2)*abeo*-ergostane, which was isolated from the sponge *Phomopsis* sp. TJ507A, originally obtained from the plant *Phyllanthus glaucus*, by the group of Zhang in 2017 and showcases an intriguingly altered carbon skeleton.[40]



Scheme 3 Structures of 5,6-secoergostane eringiacetal A (**19**)[39], 7(6→2)*abeo*-ergostane phomopsterone A (**20**)[40] as well as of 15(14→22)*abeo*-8,9-secoergostane tricholumin A (**21**)[41] and the sterane skeleton (**2**) as their formal structural origin.

It is not surprising that also structures have been elucidated to incorporate both, seco- and *abeo*-motifs, which consequently results in highly rearranged carbon backbones. If both these patterns are present, their terming features are ordered alphabetically[16] so that tricholumin A (**21**) is assigned a 15(14→22)*abeo*-8,9-secoergostane. This natural product was isolated from the marine fungus *Trichoderma asperellum* cf44-2 by the group of Ji in 2018[41] and, in addition to its

unprecedented 10-membered C/B ring, it shares the 15(14→22)*abeo*-motif also found in the strophasterol class of natural products where oxygenation at C23 is present in strophasterol C–F and glaucoposterol A (all not shown).[42–47] Even though the steroidal origin of such rearranged compounds might sometimes not be obvious at first glance, all these structural variations arise from connectivity changes of the original tetracyclic sterane skeleton (**2**) and typically comprise of bond scissions that can be accompanied by the formation of new bonds leading to ring expansions or contractions. Detailed information on the process of structure elucidation, the proposed biosynthetic pathways toward steroids **19**, **20** and **21** as well as an evaluation of their biological activities have been reviewed in the literature by us.[48]

1.3 13(14→8)*abeo*-Steroids

1.3.1 Isolation and Biosynthetic Proposals

Dankasterone A (**22**) was first isolated in 1999 by the group of Numata from the fungal strain *Gymnascella dankaliensis* originally separated from the marine sponge *Halichondria japonica*, and it represents the first secondary metabolite bearing a 13(14→8)*abeo*-motif (Figure 2).[49] The composition of its carbon skeleton was established by various analytical methods. The authors were able to confirm the molecular structure of **22** by X-ray diffraction analysis and even though, this clearly reveals the stereoconfiguration at C24 to be (*R*), it was misassigned as (*S*). Thus, dankasterone A (**22**) was initially classified as an *abeo*-campestane. In 2007, the same group reported on a further 13(14→8)*abeo*-steroid, dankasterone B (**23**), which is structurally alike to **22** but exhibits a ketone instead of an enone functionality and a *cis* ring junction of the A and B ring.[50] Both steroids were now classified as ergostanes (24*R*), thus, correcting the structure of **22**. Dankasterone A (**22**) and B (**23**) both feature a significant cytotoxicity regarding the P388 lymphocytic leukemia test system (ED_{50} 2.2 and 2.8 μg/mL, respectively), whereas against human cancer cell lines only **22** shows noticeable growth inhibition (MG-MID −5.41). In a later study, dankasterone A (**22**) was tested regarding potential anti-inflammatory properties and showed moderate *in vitro* effects on the level of NO production as well as on the inhibition of the iNOS enzyme (IC_{50} 13.04 and 6.58 μM, respectively).[40] In 2007, the group of Baker published five new ecdysteroids isolated from the Antarctic tunicate *Synoicum adareanum*, namely hyousterones A–D (not shown) and abeohyousterone (**24**),

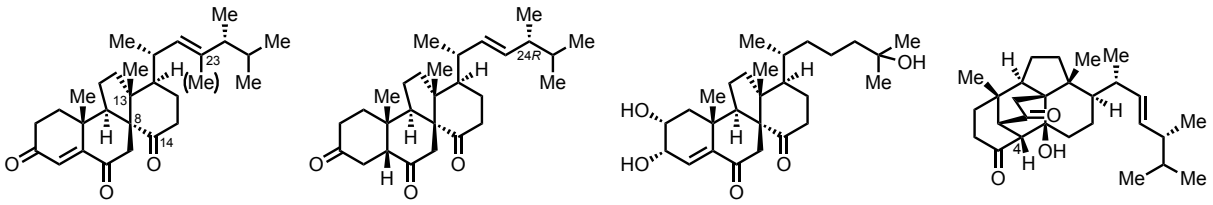
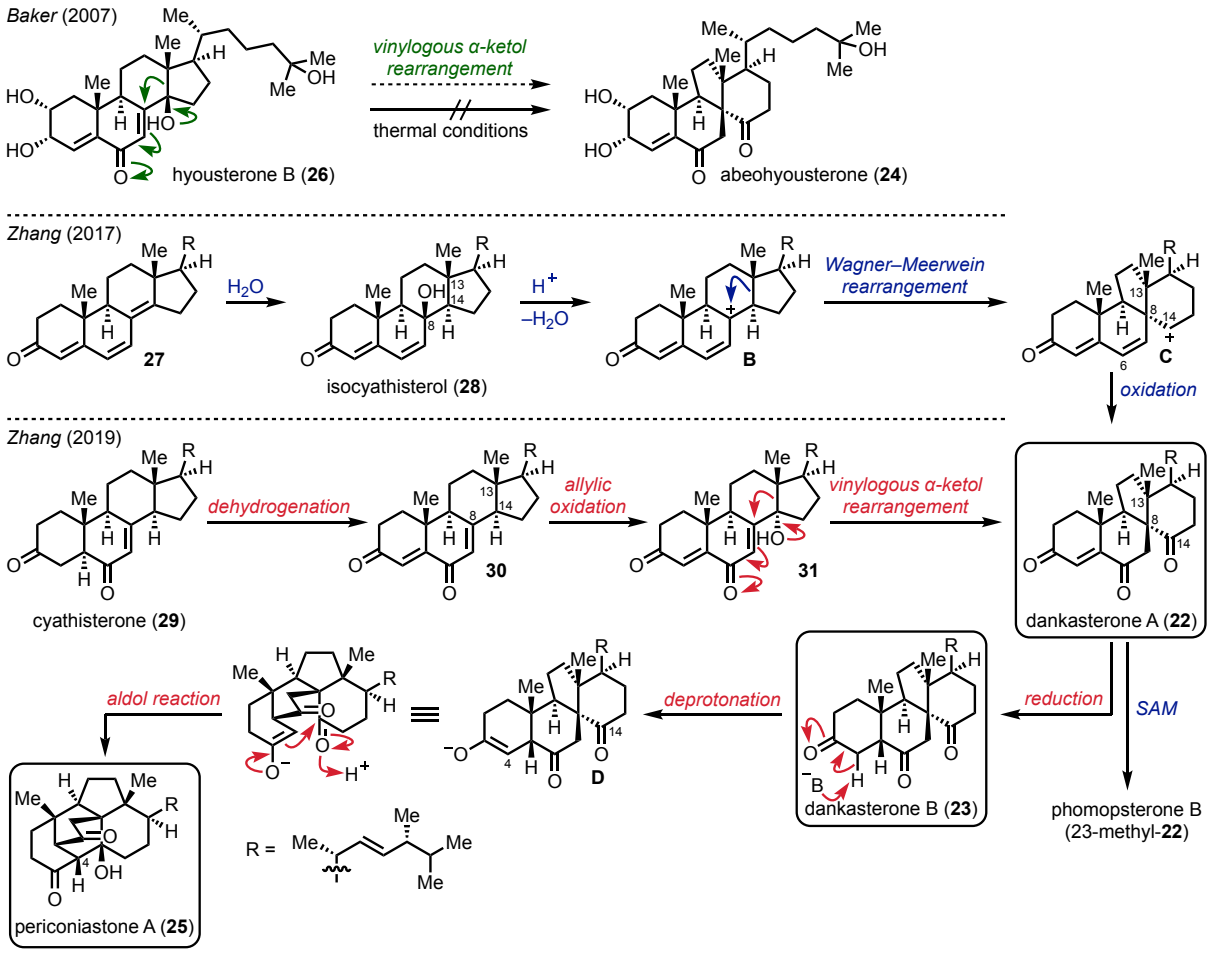


Figure 2 Structures of 13(14→8)*abeo*-steroids isolated between 1999 and 2019.[40,49–52]

whereof the former all possess the classic tetracyclic steroid skeleton while the latter shares the rearranged carbon backbone of **22** and **23**.[51] Ten years later, Zhang and co-workers reported on the isolation of *abeo*-steroids phomopsterone A (**20**, see Scheme 3) and B (23-Me-**22**) from the plant-derived fungus *Phomopsis* sp. TJ507A.[40] The latter represents a C_{29} 13(14→8)*abeo*-steroid, which exhibits a methyl group at C23 and is otherwise structurally identical to dankasterone A (**22**), which was co-isolated from the same source. Phomopsterone B (23-Me-**22**) exhibits promising anti-inflammatory activities when regarding the level of NO production and the inhibitory potency against the iNOS enzyme (IC_{50} 4.65 and 1.49 μM, respectively). Interestingly, the minor structural difference to dankasterone A (**22**) seems to play a significant role in the activity toward these targets (*vide supra*). In 2019, Zhang's group was also able to elucidate the structural composition of periconiastone A (**25**), which they obtained from the fungus *Periconia* sp. TJ403-rc01 isolated from the leaves of *Rosa chinensis* Jacq.[52] This structurally complex steroidal natural product also consists of the 13(14→8)*abeo*-unit but stands out from the formerly discussed metabolites due to an additional 4,14-cyclo-motif and, thus, features an unprecedented 6/6/6/6/5 carbocyclic skeleton. Diverse analytical methods were performed, and interpretation of the data obtained therefrom led to the structural elucidation of **25**, further supported by the comparison of experimental and calculated spectra (NMR and ECD). Periconiastone A (**25**) was assessed for potential antibacterial properties against Gram-negative as well as Gram-positive microbial pathogens and, intriguingly, showed significant activity against the latter, namely *Staphylococcus aureus* and *Enterococcus faecalis*, with MIC values of 4 and 32 μg/mL, respectively.

Concerning imaginable biosynthetic pathways toward the 13(14→8)*abeo*-skeleton the isolators of the dankasterones imagined a 1,2-migration of the C13–C14 bond to C8 to take place.[49] Baker and co-workers put forward a possible vinylogous α-ketol rearrangement of hyousterone B (**26**) to account for the formation of the rearranged skeleton, which they propose to occur under thermal conditions (Scheme 4).[51] Their choice of **26** as a potential biological precursor was motivated by the fact that gymnasterone B (not shown), composed of the classic steroid skeleton and featuring a 14β,15-epoxide, had been isolated from the same producing organism as the dankasterones.[50] This might imply the 14β-oxygenation pattern as a crucial motif in the biosynthesis of 13(14→8)*abeo*-steroids. Nevertheless, no experimental evidence was produced to support this hypothesis as they could not convert hyousterone B (**26**) to abeohyousterone (**24**) under thermal conditions. It is noteworthy that no attempt to rearrange hyousterone A (not shown), the 14-epimer of **26**, was mentioned. Along with phomopsterone B (23-methyl-**22**) and dankasterone A (**22**), the group of Zhang was able to isolate highly conjugated enone **27**[53], which was deemed a possible biosynthetic precursor of the former. Hydration would give rise to known isocyathisterol (**28**)[53], which after loss of water could give tertiary carbocation **B** to undergo a Wagner–Meerwein rearrangement producing secondary cation **C**. Oxidation at C6 and C14 would provide dankasterone A (**22**) and methyltransferase-mediated alkylation with *S*-adenosyl methionine (SAM) would then

lead to phomopsterone B (23-methyl-**22**). However, in 2019, the same group reported an alternative biogenetic pathway to this structural class.[52]

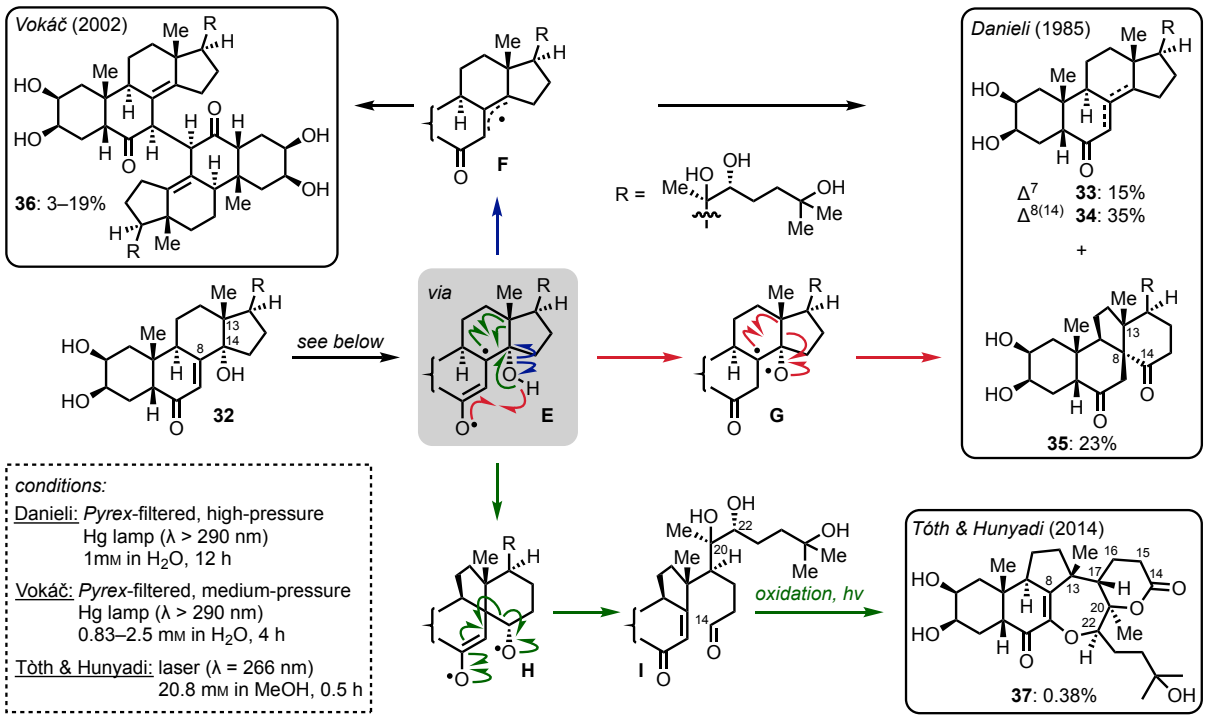


Scheme 4 Proposed biosynthetic pathways toward the 13(14→8)*abeo*-steroids abeohyousterone (**24**)[51], dankasterone A (**22**)[50] and B (**23**)[49], phomopsterone B (23-Me-**22**)[40] and pentacyclic periconiastone A (**25**)[52].

When reporting on the isolation of pentacyclic periconiastone A (**25**), cyathisterone (**29**)[54] was co-isolated from the fungal source and, thus, alleged a possible biological precursor. Two successive oxidations would first lead to dienone **30** and then to γ-hydroxy enone **31**. Revisiting Baker's suggestion,[51] they proposed a vinylogous α-ketol rearrangement to provide dankasterone A (**22**). Subsequent reduction would give dankasterone B (**23**), which after deprotonation would provide enolate **D**, crucial for the envisioned aldol reaction to generate periconiastone A (**25**). Interestingly, the structures of **22** and **23** are depicted in Zhang's publication but not labelled as dankasterone A and B, respectively. Furthermore, no comment on a prior isolation of these metabolites is made nor is any citation of Numata included in the reference section although Zhang's group had referred to those reports in their earlier work on the isolation of the phomopsterones.[40]

1.3.2 Synthetic Access to the 13(14→8)abeo-Skeleton

In 1985, Danieli and co-workers exposed crustecdysone (**32**) to the light of a high-pressure Hg lamp to study an assumed photochemical degradation and they observed the formation of a number of structurally diverse products (Scheme 5).[55] Mechanistically, the enone functionality of **32** is excited and, thus, transformed to 1,4-diradical **E**. Judging from the structures of the isolated products, two different processes may then follow. On the one hand, a homolytic cleavage of the C14–O bond can lead to **F**, which can then generate one of the observed photo-reduced products Δ^7 **33** (15% yield) or $\Delta^{8(14)}$ **34** (35% yield). On the other hand, intramolecular hydrogen atom transfer could provide alkoxy radical **G**. Regioselective β scission of the C13–C14 bond under concomitant transannular recombination would provide 13(14→8)*abeo*-steroid **35**, which was obtained in 23% yield and represents the first ever reported compound comprising of this rearranged steroid skeleton. None of the obtained products showed any biological activity, which supported their initial hypothesis of a photo inactivation of crustecdysone (**32**).

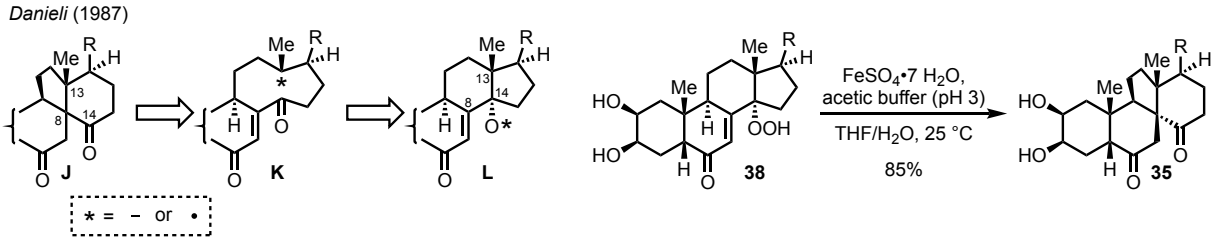


Scheme 5 Conversion of crustecdysone (**32**) under varying photochemical conditions and the suggested radical mechanisms.[55–57]

Intriguingly, the group of Vokáč was not able to reproduce Danieli's results. When equally irradiating **32** with a Hg lamp, dimer **36** was obtained as the main product with up to 19% yield depending on the concentration of the reaction mixture (Scheme 5).[56] As the photolysis of a natural, homo-dimeric steroid, which also features a connection of the B rings, has been reported to yield the monomeric steroid,[58] Vokáč provided this as a possible explanation for the inconsistent results as dimerization of **F** could easily generate **36**. In 2012 and 2014, Tóth and Hunyadi reported on a laser-induced conversion of **32**, which led to the isolation of seven

compounds from a complex mixture of products and unreacted starting material (14%).[57,59] Considering the structural context discussed here, the molecular composition of lactone **37** was of special interest as it also consists of a 13(14→8)*abeo*-unit, which is, however, further modified by a scission of the C8–C14 bond (Scheme 5). Due to the presence of Δ^7, the authors propose the mechanism accounting for the skeletal rearrangement observed to deviate from that of Danieli.[55] According to Tóth and Hunyadi,[57] a scission of the C13–C14 bond in **E** enables the formation of the C8–C13 bond and allows for an intramolecular hydrogen atom transfer to take place, thereby generating secondary alkoxy radical **H**. Homolytic cleavage of the C8–C14 bond would then furnish C14 aldehyde and re-install the enone system in **I**. The lactone formation between C14 and C20-OH could be explained by oxidative conditions and an assumed secondary photoreaction might give rise to the tetrahydrooxepin moiety in **37** which is established by formation of a C7–C22 oxo bridge. Presumably, the modified reaction conditions applied by Tóth and Hunyadi (different wavelength, solvent, and aerobic conditions) account for the different reactivities observed.

In 1987, two years after their initial report on rearranged ecdysteroid **35**,[55] the group of Danieli published a non-photochemical and more selective approach toward the 13(14→8)*abeo*-skeleton.[60] Retrosynthetically, they had envisioned to construct the remodeled steroid skeleton **J** *via* intermediary ketone **K**, which could be generated by fragmentation of a γ-oxygenated enone **L** (Scheme 6). They proposed this sequence to proceed either through ionic or radical intermediates.



Scheme 6 Danieli's selective approach to the 13(14→8)*abeo*-steroid skeleton.[60]

For the polar pathway (* = –), this would require a vinylogous α-ketol rearrangement (cf. Scheme 4) starting once more from crustecdysone (**32**), but various experiments applying basic conditions did not lead to any product formation. Hence, they contemplated the radical-based option (* = •) and chose to generate key C14-oxy radical **K** (* = •) by treating a hydroperoxide with an iron(II) salt.[61,62] When 14α-hydroperoxide **38** was reacted with an acidic solution of ferrous sulphate, they obtained rearranged **35** in a yield of 85% along with 5% of reduced **32** (Scheme 6). The same procedure was applied to two hydroperoxy ergostanes and led to the formation of the corresponding desired 13(14→8)*abeo*-ketones in good yields (79–83%, not shown). The relative and absolute configuration of the products obtained from this tandem fragmentation/reductive alkylation protocol could be unambiguously assigned as the molecular structure of one of the rearranged products was established by X-ray diffraction analysis.

1.4 13(14→8),14(8→7)di*abeo*-Steroids

1.4.1 Isolation and Biosynthetic Proposals

Swinhoeisterol A (**39**) and B (**40**) represent the first two members of an afore unprecedented class of rearranged steroids named after *Theonella swinhoei*, the prolific marine sponge they were isolated from in 2014, which is endemic to the South China Sea.[63] Their characteristic 6/6/5/7 skeleton consists of a contracted five-membered C ring and an expanded seven-membered D ring which can be attributed to two formal bond migrations, making the swinhoeisterols 13(14→8),14(8→7)di*abeo*-steroids (Figure 3). Their structure and absolute configuration were elucidated by evaluation of the data obtained from various analytical methods. The stereoconfiguration of C24 was established as (*R*) by comparison of the ^{13}C NMR chemical shift difference of C26 and C27 to values obtained from epimeric side chains.[64] The molecular structure of swinhoeisterol B (**40**) was confirmed by X-ray diffraction analysis and supported the afore-identified structural features and configurations. The authors carried out an inverse virtual screening for swinhoeisterol A (**39**) to locate promising targets regarding its bioactivity and tested the ten most auspicious candidates in *in vitro* biological assays. The predicted activity against (h)p300, a histone acetyltransferase related to the occurrence of cancer, could, hence, be confirmed with a remarkable inhibition of the selected target (IC_{50} = 2.9 μM). Swinhoeisterol B (**40**) only showed poor inhibitory potency against (h)p300 (IC_{50} = 240 μM). Additionally, both, **39** and **40**, exhibited modest cytotoxicity against A549 (IC_{50} 8.6 and 14.6 μM, respectively) as well as MG-63 cells (IC_{50} 10.3 and 20.0 μM, respectively).

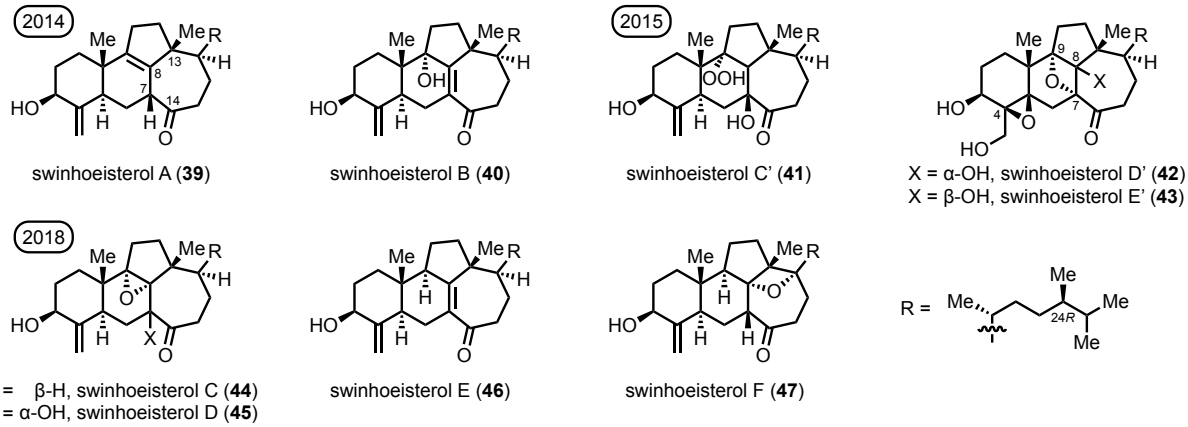
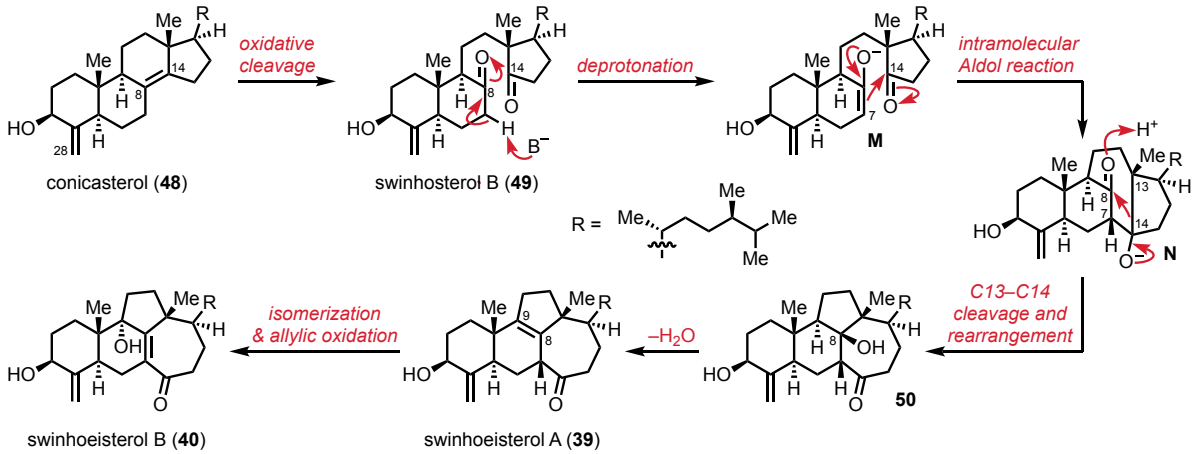


Figure 3 All members of the swinhoeisterol class of natural products known to date.[63,65,66]

In 2015, the same authors filed a patent containing three structurally closely related natural steroids, swinhoeisterols C'–E' (**41**–**43**, originally assigned as C, D and E), which they had isolated from the same sponge.[65] In the publication, the assigned structures are displayed and the three candidates shown possess the same characteristic 13(14→8),14(8→7)di*abeo*-homocampestane skeleton but in higher levels of oxidation. Instead of the *exo*-methylene present in **39**–**41**, swinhoeisterol D' (**42**) and E' (**43**) carry a hydroxymethyl group at C4 and a 4β,5-epoxide. When the same

group reported on the isolation of four new swinhoeisterols in 2018, again obtained from *Theonella swinhoei*, naming them swinhoeisterol C–F (**44**–**47**),[66] no comment was made on the afore described compounds **41**–**43**. A biological assessment of **44**–**47** revealed that only swinhoeisterol C (**44**) exhibits a favorable inhibition of (h)p300 (IC_{50} = 8.8 μM) while **45**–**47** only possess minor activity (IC_{50} > 10 μM). To sum up, all nine swinhoeisterols reported to date share the characteristic C_{29} 6/6/5/7-4α-homocampestane skeleton along with the 3β-hydroxy group and the 14-oxo functionality. The degree of oxidation varies throughout the series with swinhoeisterol A (**39**) and E (**46**) possessing the lowest oxidation level.

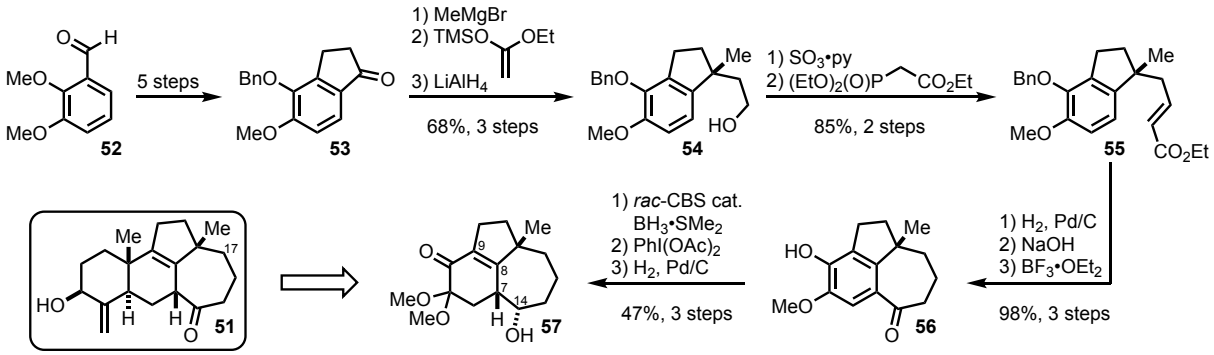
Conicasterol (**48**)[67] and swinhosterol B (**49**)[68,69] have been co-isolated with **39** and **40** from *Theonella swinhoei* in 2014 and were deemed as possible early metabolites in a proposed biogenetic pathway (Scheme 7).[63] Oxidative cleavage of the C8–C14 bond in conicasterol (**48**) could yield swinhosterol B (**49**), which, after deprotonation (as in **M**), would be able to undergo an intramolecular aldol reaction establishing the C7–C14 bond in **N**. Protonation and successive bond migration could produce C8-hydroxy **50**. Loss of water would then provide swinhoeisterol A (**39**), which, after isomerization and allylic oxidation, would give swinhoeisterol B (**40**).



Scheme 7 Biosynthetic proposal for the formation of swinhoeisterol A (**39**) and B (**40**).

1.4.2 Synthetic Studies toward the Swinhoeisterol Skeleton

In 2018, the group of Kigoshi reported its total synthetic efforts toward the BCD ring fragment of the swinhoeisterols starting from a benzene derivative (Scheme 8).[70] They aspired the synthesis of model substrate **51** comprising of the characteristic tetracyclic skeleton but lacking the campestane side chain at C17. Indanone **53** was obtained in five steps from 2,3-dimethoxybenzaldehyde (**52**) following a literature known procedure,[71] which included selective demethylation at the C2-OH group,[72] followed by benzyl protection. The tertiary benzylic alcohol obtained from a Grignard reaction was substituted with a silyl ketene acetal and the resulting ester was reduced to give alcohol **54** in 68% yield over three steps. Parikh–Doering oxidation to the corresponding aldehyde



Scheme 8 Kigoshi's approach to a BCD ring fragment **57** of the swinhoeisterols.[70]

and consecutive Horner–Wadsworth–Emmons reaction yielded α,β-unsaturated ester **55** in 85% yield over two steps. Hydrogenation and concomitant debenzylation followed by saponification provided the precursor for the crucial Friedel–Crafts acylation, which then gave rise to the 6/5/7 skeleton of **56** in almost quantitative yield over three steps. As the product obtained from immediate oxidative dearomatization emerged to be highly unstable, the 14-oxo functionality was reduced to the respective alcohol, which was then treated with (diacetoxyiodo)benzene and subsequently hydrogenated to give 47% of the desired 7β(H)-14α-alcohol **57** and 18% of the 7α-epimer (not shown), each over three steps. The two key steps in the formation of tricyclic **57** are the Friedel–Crafts acylation and the oxidative dearomatization reaction, which gave **57** in an overall yield of 27% over eleven steps starting from commercially available indanone **53**. In their synthetic strategy, the group of Kigoshi proposed to access tetracyclic **51** from this fragment, however, no information was provided on how to develop the A ring and the C19 angular methyl group from **57**.

1.5 Isolation of 5,6-Secosteroids

In 1999, the group of Krohn isolated a secosteroid with an unprecedented carbon backbone from the endophytic fungus *Pleospora herbarum* and accordingly named it herbarulide (**59**, alleged structure).[73] Its characteristic structural feature is a 5,6-epoxy-5,6-seco-motif in the B ring, which could also be described as a ketodivinyllactone functionality connecting the A and B ring (Figure 4). The configurations of C20 and C24 in the side chain were elucidated by comparison of the spectral data obtained with those of co-isolated, known ergostane **58**[74] and established as (20*S*, 24*R*). Nevertheless, the structure depicted in the publication implies the configuration at C24 to be (*S*), which would make it a campestane. Seven years later, Guo and co-workers reported the isolation of fortisterol (**60**, alleged structure), a structurally highly similar secondary metabolite from the marine sponge *Biemna fortis*, which had been collected in the South China Sea.[75] Even though the proposed structure of **60** is epimeric to herbarulide (**59**, alleged structure), Krohn's report was not referenced. The stereoconfiguration of the side chain was this time determined by comparison of the spectral data of dienone **61**[76] and fortisterol (**60**, alleged structure), and was established as (20*S*, 24*R*), which classified **60** as an ergostane. A more detailed discussion about the structural

assignments and repeated isolations of these metabolites has been published in the literature by us.[77]

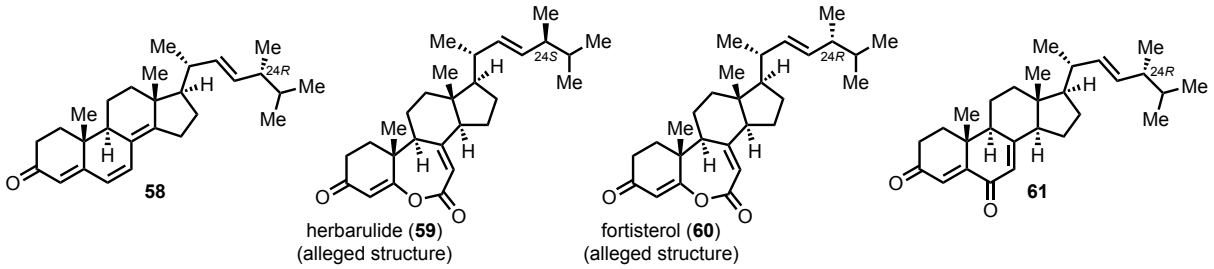
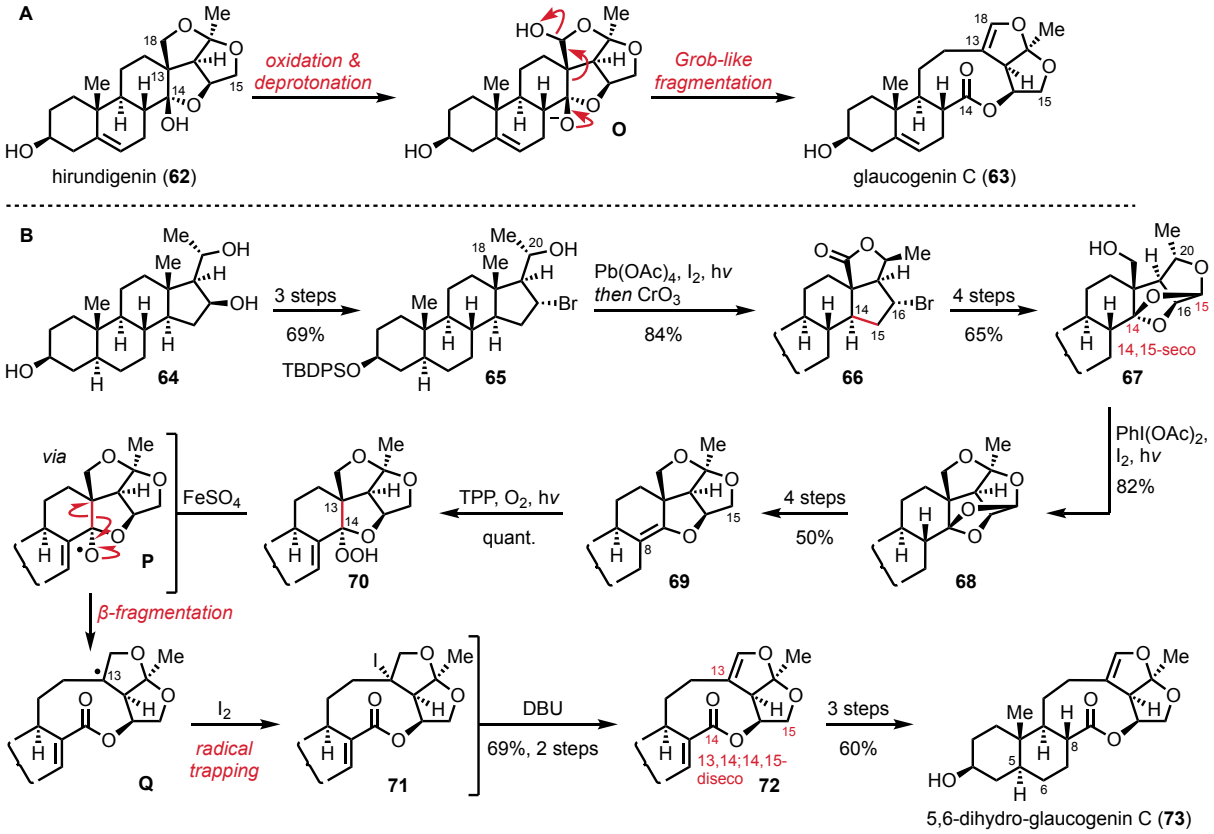


Figure 4 Alleged molecular structures of herbarulide (**59**)[73] and fortisterol (**60**)[75] and molecular structures of ergostanes **58**[74] and **61**[76].

1.6 Radical Key Steps in the Synthesis of Natural Products

Many options are nowadays known to trigger skeletal rearrangements in steroids which can proceed either through ionic intermediates, as suggested in most biosynthetic proposals, or under radical conditions. In the last decades, the synthetic organic community has come to more and more exploit radical approaches as they represent controllable and often highly selective processes. In the 1980's, the group of Mitsuhashi reported on the isolation of structurally intriguing 13,14;14,15-disecopregnanes, the glaucogenins,[78] whereof glaucogenin C (**63**), additional to its altered steroid backbone, exhibits a highly remarkable antiviral activity by selectively inhibiting α-virus-like positive-strand RNA viruses (IC_{50} 17 nM).[79] Due to striking structural similarities, the isolators proposed known hirundigenin (**62**)[80] as a potential biological precursor, which could be transformed to **O** by oxidation at C18 and deprotonation of C14 hydroxyl. This would enable a Grob-like fragmentation to provide glaucogenin C (**63**) with its characteristic nine-membered lactone and $\Delta^{13(18)}$ (Scheme 9, A). Tian and co-workers decided to mimic this suggested biosynthetic transformation using a radical-promoted key step to induce the crucial C13–C14 bond scission in their synthetic endeavor toward these secondary metabolites (Scheme 9, B).[34,81] Starting from C_{21} triol **64**, protection and substitution provided C20-alcohol **65**, which was taken advantage of for a selective radical-mediated C–H oxidation of the angular methyl group C18 applying first Meystre's conditions ($Pb(OAc)_4$, I_2, hν)[82] and then Jones oxidation (CrO_3, H_2SO_4) to give lactone **66**. After adapting the substitution pattern of the D ring, oxidative cleavage of Δ^{14} under ozonolytic conditions established the 14,15-seco-motif of diacetal **67**. Suárez' conditions ($PhI(OAc)_2$, I_2, hν)[83] facilitated further intramolecular, radical-promoted oxidation at C20, which proceeded through the intermediacy of a C18-oxy radical to furnish cage-like furofurane **68**. Further steps enabled selective deoxygenation at C15 and established **69** including $\Delta^{8(14)}$, pivotal for the successive Schenck ene reaction, which provided the crucial alkoxy radical precursor **70** in a highly regio- and stereoselective manner. Thus, the stage for the intended biomimetic key step was set.



Scheme 9 A: Biogenetic proposal of Mitsuhashi;[78] B: Tian's semi synthetic route to 5,6-dihydro-glaucogenin C (**73**) using a biomimetic radical fragmentation key step.[34]

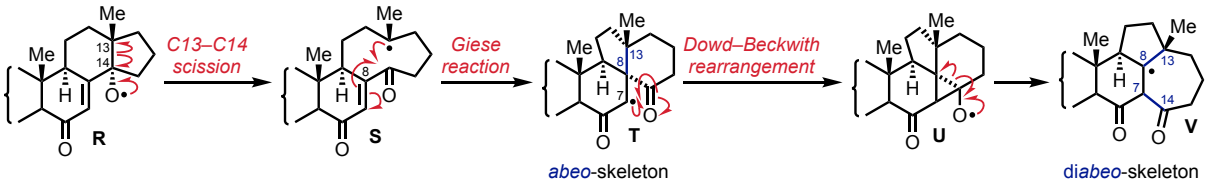
A one-electron transfer from ferrous sulphate to hydroperoxide **70** started the envisioned sequence by generating alkoxy radical **P**,[61] which then possibly underwent fragmentation of the C13–C14 bond to give rise to nine-membered lactone **Q** possessing a carbon-centered radical at C13. Initial attempts to apply a copper(II)-mediated, one-pot oxidation of the radical was planned to trigger further β-H-elimination to give rise to $\Delta^{13(18)}$,[62,84,85] but this method only provided a ~1:1 mixture of the desired product **72** and its dihydro-analog in unsatisfying yields. Trapping of the tertiary alkyl radical of **Q** with iodine proved to be more successful and elimination of intermediary iodide **71** with DBU gave **72** in a satisfying yield of 69% over two steps. 1,4-Reduction of the α,β-unsaturated lactone, deprotection of C3 hydroxyl and final epimerization at C8 provided 5,6-dihydro-glaucogenin C (**73**) in a total of 19 steps and a yield of 6.4%.[34] In 2013, the group of Tian further exploited this synthetic route to gain access to glaucogenin D (7β-hydroxy **63**, not shown) making once more use of the radical fragmentation/trapping key sequence followed by ten more steps to obtain the natural product.[81]

The synthetic access discussed consisted of three highly selective alkoxy radical-mediated reactions that on the one hand were able to perform remote C–H oxidations at C18 and C20 and on the other hand enabled implementing the biomimetic approach by fragmentation of the C13–C14 bond. Tian's strategy of converting a 14α-hydroperoxide to the corresponding alkoxy radical, which then induces scission of the C13–C14 bond equals Danieli's conditions using ferrous sulphate to

obtain 13(14→8)*abeo*-steroids (cf. Scheme 6).[60] However, in case of the glaucogenin synthesis, the C13-centered radical does not undergo further Giese reaction (transannular addition to C8) as in Danieli's work. This might be substantiated by the fact that the energy of the LUMO of the olefin is not increased as hydroperoxide **70** lacks the 6-oxo functionality present in 14α-hydroperoxy crustecdysone (**38**). A further explanation for the distinct reactivities could be the unlike steric and electronic environment in the adjacent ring systems.

2 Comprehensive Interpretation and Evaluation

The idea to access carbon skeletons of rearranged, steroidal natural products starting from the classic tetracyclic backbone was pictured to be realizable with the means of radical cascade reactions. The dankasterone and swinhoeisterol classes of natural products (cf. Figure 2 and Figure 3, respectively) presented themselves as especially intriguing targets since they all share the 13(14→8)*abeo*-structural motif. As a rationale to facilitate not only the initiation of this formal C–C bond reconnection but also of a further migratory event to provide the additional 14(8→7)*abeo*-element of the swinhoeisterols, alkoxy radical **R** was anticipated to be a suitable starting point (Scheme 10). Thus, **R** could undergo a regioselective β scission of the C13–C14 bond, which would lead to the formation of nine-membered ketone **S**. A transannular addition of the tertiary radical to olefinic C8 (Giese reaction) would give rise to 13(14→8)*abeo*-intermediate **T**. The α-keto radical at C7 in **T** could either be quenched or engage in a Dowd–Beckwith rearrangement to provide tertiary alkoxy radical **U**. Opening of the cyclopropane proceeding *via* another β scission would yield the expanded seven-membered D ring of the 13(14→8),14(8→7)di*abeo*-backbone **V** to be quenched and possibly oxidized in follow-up events.

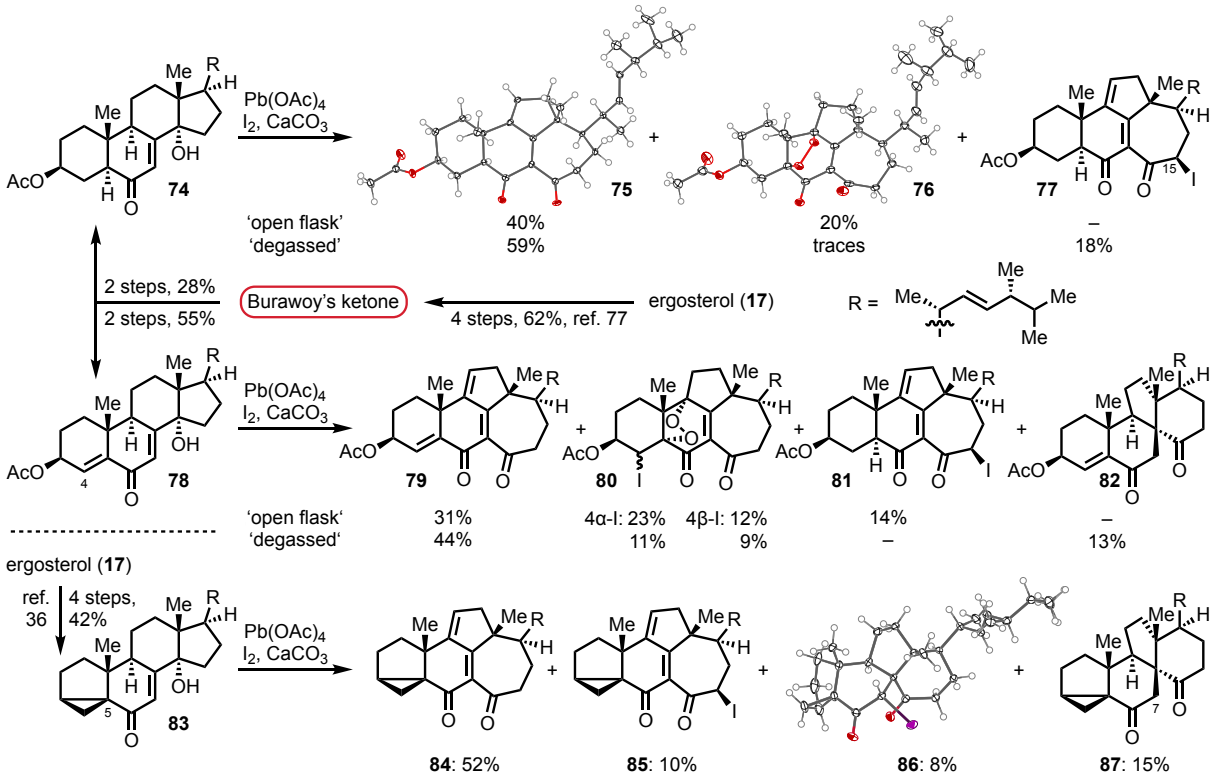


Scheme 10 Mechanistic considerations regarding the formation of a 13(14→8),14(8→7)di*abeo*-skeleton **V** starting from alkoxy radical **R**.[86]

To gain synthetic access to the swinhoeisterols, different substrates sharing the necessary γ-hydroxy enone moiety were evaluated for the radical-promoted cascade reaction using a lead tetraacetate/iodine system[87,88] to induce alkoxy radical formation. Initial studies on 5α-acetate **74**, which was synthesized in six steps starting from ergosterol (**17**) *via* Burawoy's ketone[89] (not shown, optimized synthetic access see ref. 77), indeed provided di*abeo*-diene dione **75** and endoperoxide **76** in 40 and 20% yield, respectively (Scheme 11).[90] When oxygen was rigorously excluded from the reaction mixture, **76** was only isolated in trace amounts, and instead 59% of **75** and 18% of its 15β-iodide **77** were obtained. In addition to extensive NMR studies, the molecular structures of **75** and **76** could be confirmed by X-ray diffraction analysis.

In further studies, Δ^4-acetate **78** was chosen as a suitable synthetic intermediate since the C4–C5 double bond might act as a handle to install the characteristic C4-bound *exo*-methylene group of the swinhoeisterols later on in the synthesis. The products obtained from the skeletal rearrangement of **78** (open flask) resembled the ones isolated before (with Δ^4-diene dione **79** being the

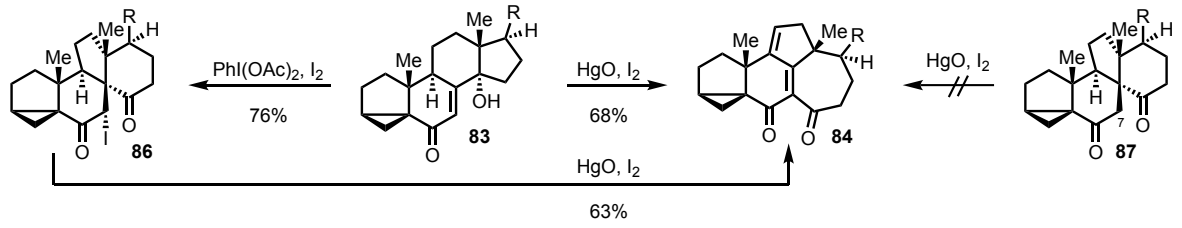
major product) except that an additional iodo-substituent was incorporated at C4 for the endoperoxides 4α-I-**80** and 4β-I-**80** (Scheme 11). Even though the reaction was also carried out under degassed reaction conditions, it was not possible to suppress the formation of the endoperoxides **80**, and instead of iodide **81**, *abeo*-steroid **82** was isolated.[90] The isolation of **82** supported our proposed mechanistic concept (cf. Scheme 10) as the formation of the 13(14→8),14(8→7)di*abeo*-core **V** was assumed to proceed *via* the intermediacy of such a 13(14→8)*abeo*-structure (as in **T**, *vide supra*). Another promising target for the radical cascade reaction was *i*-steroid **83** since its quaternary C5 should circumvent the formation of undesired endoperoxides and, indeed, no such side products were observed. Still, a total of four rearranged products was isolated whereof two were the expected diene dione **84** and iodide **85** along with 13(14→8)*abeo*-steroid **86** and its 7α-iodo analog **87**.[86] The molecular structure of **86** was confirmed by X-ray diffraction analysis.



Scheme 11 Alkoxy radical-mediated rearrangement of γ-hydroxy enones **74**, **78** and **83**. ORTEP plots of **75**, **76** and **86** (thermal ellipsoids are drawn at 50% probability).[86,90]

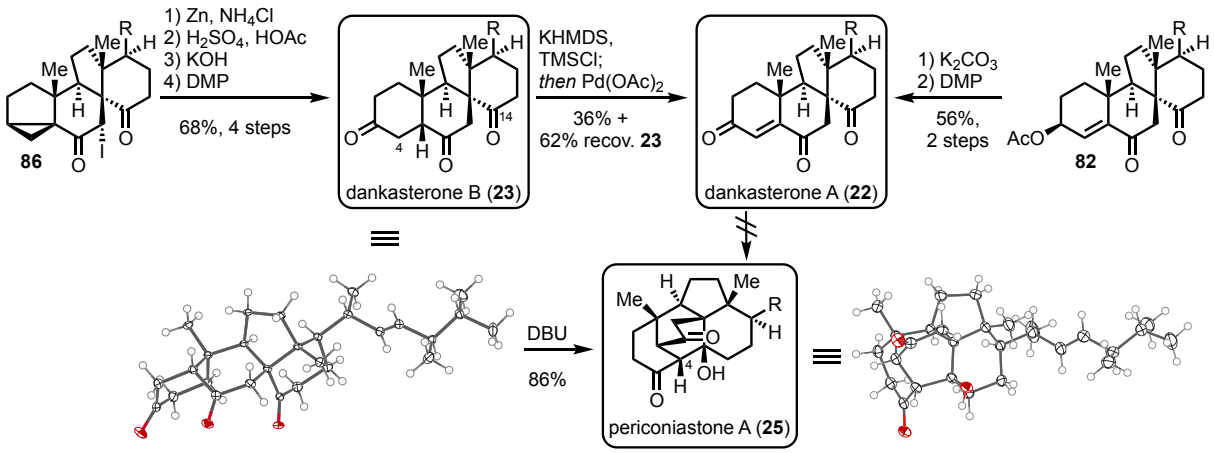
Detailed optimization studies regarding the reagents used to induce alkoxy radical generation enabled selective access to either the 13(14→8)*abeo*- or the 13(14→8),14(8→7)di*abeo*-skeleton. Starting from *i*-steroid **83**, reaction with (diacetoxyiodo)benzene and iodine[83,91,92] delivered iodide **86** in 76% whereas treatment of **83** with mercury(II) oxide and iodine[93] provided diene dione **84** in 68% yield (Scheme 12).[86] Experimental support for our mechanistic proposal was disclosed inasmuch as iodide **86** could be converted to di*abeo* **84** in a yield of 63% when exposing it to HgO/I_2. Experiments to convert dione **87** to the corresponding di*abeo*-compound **84** remained

unsuccessful as the regeneration of the radical at C7 as in **T** (cf. Scheme 10) was not possible, which would have been necessary to enable a progression of the cascade reaction.



Scheme 12 Selective formation of the *abeo*-skeleton in **86** and the di*abeo*-backbone in **84** from a common precursor, and conversion of iodide **86** to **84**.

Exploiting said selective rearrangement to **86** four more steps, namely dehalogenation, *i*-steroid opening, saponification and oxidation, provided access to dankasterone B (**23**, 9 steps, 22% yield) whose molecular structure was confirmed by X-ray diffraction analysis.[86] Further Saegusa–Ito oxidation provided dankasterone A (**22**, 10 steps, 8% yield) along with re-isolated **23** (62%).[86] Additionally, dankasterone B (**23**) could be transformed to recently isolated anti-MRSA agent periconiastone A (**25**, 10 steps, 19% yield) under basic conditions inducing an aldol reaction between C4 and C14 to give rise to its pentacyclic skeleton.[86] Once more, X-ray diffraction analysis could confirm the molecular structure of **25**.[90] As an alternative access, saponification and oxidation of rearranged acetate **82** (cf. Scheme 11) also yielded dankasterone A (**22**). Attempts to produce periconiastone A (**25**) from **22** *via* 1,4-reduction and subsequent aldol reaction remained unsuccessful.[90]

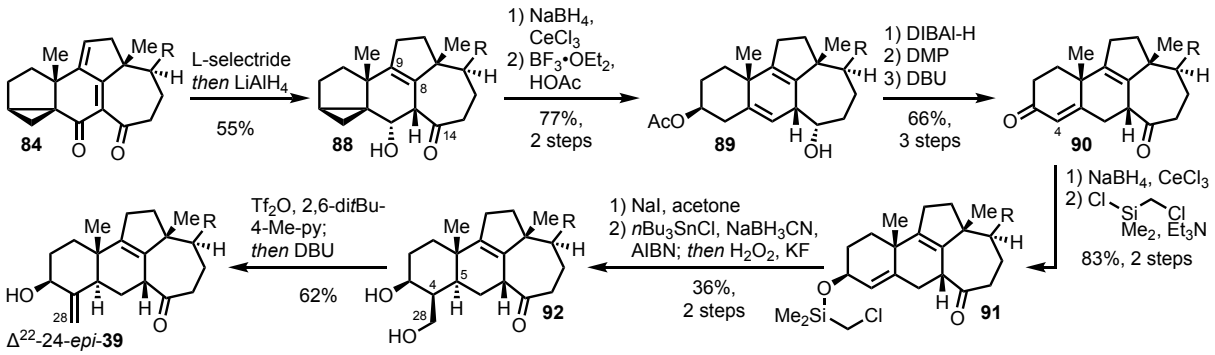


Scheme 13 Synthesis of dankasterone A (**22**) and B (**23**), and periconiastone A (**25**) starting from common intermediate **86**;[86] ORTEP plots of **23** and **25** (thermal ellipsoids are drawn at 50% probability); R as in Scheme 11.

The synthetic access to the swinhoeisterols presented itself considerably more challenging. Even though the construction of the di*abeo*-skeleton had successfully been established employing the mentioned radical cascade (cf. Scheme 10 and Scheme 12), the different substrates available (cf. Scheme 11) had to be evaluated for their utility in the synthesis toward the natural products. Initial experiments employing the rearranged products obtained from Δ^4-acetate **78** (cf. Scheme 11) emerged to demonstrate undesired reactivities causing problems at different stages of the

intended sequence.[90] Even though not of further synthetic use toward the swinhoeisterols, a remarkable skeletal rearrangement was observed during these studies (see appendix D or ref. 90, page 3).

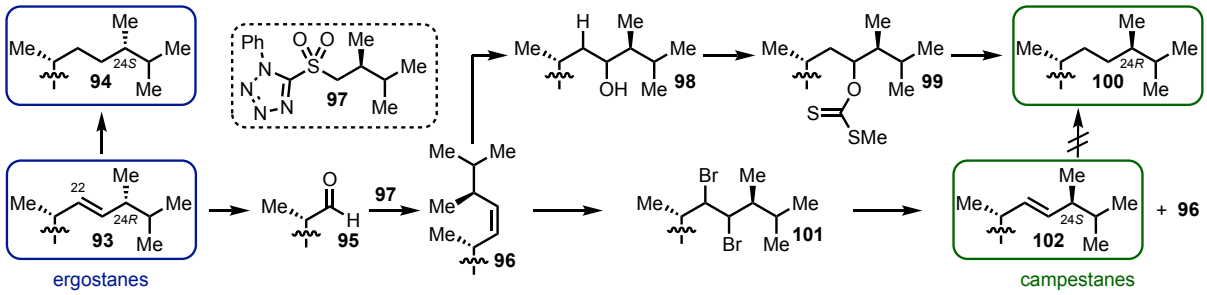
The approach was modified inasmuch as *i*-steroid **84** was chosen as starting point for further synthetic efforts toward the swinhoeisterol skeleton (Scheme 14). A 1,6-reduction was chosen to adjust the oxidation level of the diene dione system and rigorous exclusion of oxygen from the reaction mixture proved crucial to obtain the desired product **88** (see appendix D or ref. 90, page 5 for initial experiments leading to an unexpected anthrasteroid). To avoid isomerization of the C8–C9 double bond, the 14-oxo functionality was reduced prior to *i*-steroid opening, which yielded acetate **89**. In the following, the oxidation state of the A ring was set but further challenges arose from the introduction of the *exo*-methylene group at C4. Initially, a reductive alkylation of enone **90** was envisioned but the hydroxy-methylated product exhibited a strong tendency to undergo a retro-aldol reaction to the corresponding ketone (not shown, see appendix D or ref. 90, page 6). Thus, enone **90** was reduced under Luche conditions and the allylic alcohol was silylated to give chloride **91**. Finkelstein reaction provided the corresponding iodide, which was successfully converted to diol **92** applying a modified Nishiyama–Stork protocol. This facilitated simultaneous introduction of C28 and implementation of the correct configuration at C5. An elimination of the primary alcohol through the intermediacy of a triflate provided access to the core structure of swinhoeisterol A (**39**) concluding the synthesis of Δ^{22}-24-*epi*-**39** in a total of 16 steps and an overall yield of 1.5% starting from ergosterol (**17**).[90]



Scheme 14 Synthetic access to Δ^{22}-24-*epi*-swinhoeisterol A (Δ^{22}-24-*epi*-**39**) starting from **84**; R as in Scheme 11.[90]

As the swinhoeisterols all possess a campestane side chain (24*R*, cf. Figure 1 and Figure 3) and no appropriate campesterol-like starting material was commercially available in sufficient purity, it was then aimed for the synthesis of ergostane 24-*epi*-swinhoeisterol A (24-*epi*-**39**). An attempted early hydrogenation of Δ^{22} in **93** to give **94** (Scheme 15) was successful when using platinum-based hydrogenation catalysts as palladium-mediated reductions resulted in a remarkable epimerization at C24. Executing the afore-established synthetic route accomplished the synthesis of 24-*epi*-**39** in 16 steps and an overall yield of 3% starting from ergosterol (**17**).[86] To access the natural product

39, a late stage replacement of the ergostane side chain **93** *via* a sequence of oxidative cleavage, olefination and hydrogenation was envisioned. Ozonolytic conditions cleaved the C22–C23 double bond to give C22-aldehyde **95**, and subsequent Julia–Kocienski olefination using sulfone **97** facilitated the introduction of the fragment with correctly configured C24 giving **96** (Scheme 15). However, Δ^{22}, which was exclusively obtained in the Z-configuration (as in **96**), still had to be reduced to provide the saturated campestane side chain **100**. Attempts to hydrogenate proved unproductive inasmuch as in case of complete reduction of the double bond major epimerization at C24 occurred. This time, the side reaction could not be suppressed to less than 25%, irrespective of catalyst, pressure, solvent and temperature. As epimerization during hydrogenation of Δ^{22} had been subdued for a 22E substrate in the synthesis of 24-*epi*-**39**, *cis*-*trans* isomerization of the C22–C23 double bond was intended but not successful when applying standard methods.

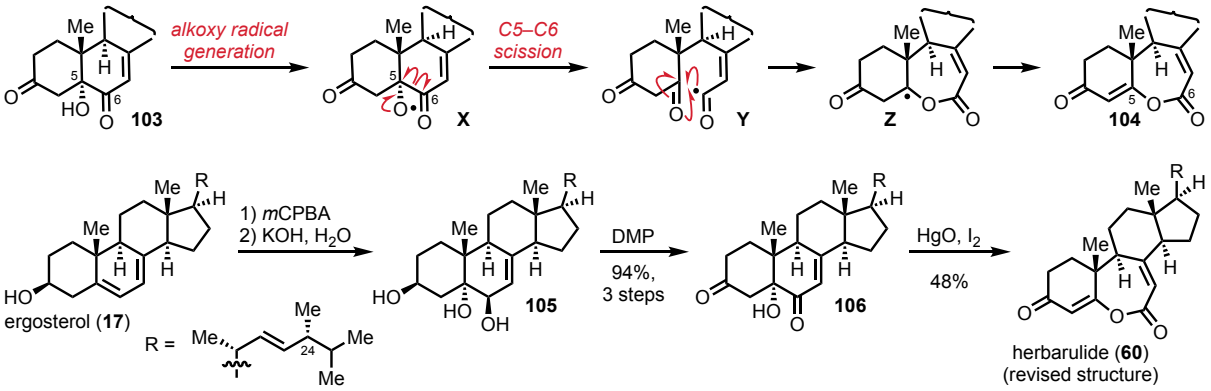


Scheme 15 Transformations of the ergostane side chain **93** facilitating the syntheses of 24-*epi*-swinhoeisterol A (24-*epi*-**39**, incorporating **94**), swinhoeisterol A (**39**, incorporating **100**) and of the alleged structure of herbarulide (**59**, incorporating **102**).[77,86]

To conduct a formal reduction of the double bond, a halogenation/dehalogenation sequence was expected to provide the desired saturated side chain. But treatment of the C22,C23 dibromide **101** with nBu$_3$SnH/AIBN resulted in radical recombination and gave a separable mixture of products containing the respective E- and Z-configured unsaturated campestanes **102** and **96** (Scheme 15). Unfortunately, hydrogenation of the E-isomer **102** was still not productive. Finally, a combination of hydroboration, oxidation and deoxygenation (*via* **98** and **99**) delivered the crucial saturated campestane side chain **100** and, thus, enabled the synthesis of swinhoeisterol A (**39**, see appendix B or ref. 86, page 106) in overall 21 steps and a total yield of 1%[86] following the route elaborated for the synthesis of Δ^{22}-24-*epi*-**39** (cf. Scheme 14).

Another structural element present in a small number of secondary metabolites, which was deemed accessible from the classic tetracyclic skeleton, was the 5,6-epoxy-5,6-seco-motif. This rearranged backbone was expected to be formed by another alkoxy radical-promoted skeletal rearrangement of α-ketol **103** (Scheme 16). Generation of alkoxy radical **X** might induce a β scission of the C5–C6 bond giving rise to acyl radical **Y**, which could recombine with the 5-oxo moiety to provide lactone radical **Z**, a precursor of enol ester **104**. Starting once more from versatile ergosterol (**17**), the respective radical precursor was procurable in only three steps including epoxidation

and subsequent epoxide opening to triol **105**, followed by oxidation to **106**. Just as in case of the radical-mediated rearrangement of γ-hydroxy enone **83** (cf. Scheme 11 and Scheme 12), application of the mercury(II) oxide/iodine system to generate the initial alkoxy radical **X** facilitated the desired framework reconstruction in a selective manner. Hence, the alleged structure of ergostane fortisterol (**60**, cf. Figure 4) was synthesized in overall four steps and a total yield of 45% starting from **17**.[77]



Scheme 16 Envisioned radical cascade to provide the 5,6-epoxy-5,6-seco-motif **104** and synthesis of the revised structure of herbarulide (**60**).[77]

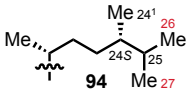
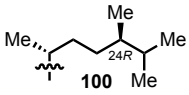
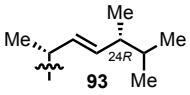
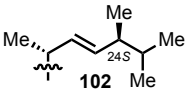
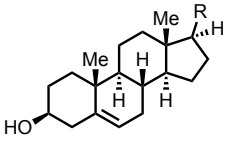
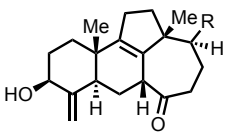
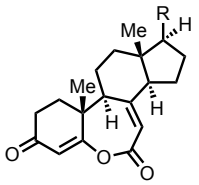
However, close inspection of the NMR data of the synthetic and natural material showed anomalies for some signals assigned to side chain atoms and it became evident that instead of fortisterol, herbarulide was synthesized. As mentioned (cf. section 1.5), Krohn and co-workers classified herbarulide as an ergostane (**60**) but depicted a campestane structure (**59**, cf. Figure 4) in their report on its isolation. These facts in hand, fortisterol was suspected to carry a campestane side chain (**102**, cf. Scheme 15) instead. Thus, the strategy for the installation of the epimeric side chain utilized in the synthesis of swinhoeisterol A (**39**)[86] was applied to possibly provide synthetic support for this hypothesis. As the ozonolysis/Julia–Kocienski sequence was expected to exclusively yield the 22*Z*-isomer **96**, it was intended to make use of the *cis*-*trans* isomerization observed during dehalogenation of a C22,C23-dibromide **101** (cf. Scheme 15). The 5,6-epoxy-5,6-secocampestane **59** was, thus, successfully synthesized following this route (see appendix C or ref. 77, page 1586) but its spectral data were not consistent with those of any of the two natural products.

The structural assignment of side chains in steroidal natural products has proven inaccurate in a number of cases (e.g. dankasterone A and herbarulide) and had frequently been caused by the fact that C24-epimers could not be distinguished by comparison of their spectral data. In 1978, Wright and co-workers outlined a collection of ^{13}C NMR data of a number of 24-methylcholesterol diastereomers with varying alkyl side chains.[64] Based on molecular models and X-ray crystallographic data of steroids carrying a saturated ergostane side chain (cf. **94**, Scheme 15), it was hypothesized that rotation about the C24–C25 bond would be restricted with H–C24 and H–C25 being antiperiplanar in the most stable conformation. If this assumption was correct, C26 (attached

to C25) would be synclinal to C24[1] (attached to C24) and, thus, chemically shielded compared to C27. This would then imply contrary observations in case of a saturated campestane side chain (cf. **100**, Scheme 15). The authors assumed that the configuration at C24 in unknown steroids might be determinable by comparing the ^{13}C NMR chemical shifts of the side chain atoms with the data obtained from epimeric model steroids with the same side chain. Naturally, this would only withstand if differences in the molecular structure of the steroids to be compared were remote from the chiral center considered.

Following this logic, the differences of the C26 and C27 chemical shifts (Δ) of several 24-methylcholesterols (**107**–**110**) were calculated (entry 1, Table 1), including saturated and unsaturated ergostane (**94** and **93**) and campestane side chains (**100** and **102**), respectively. As three out of these four corresponding diastereomers were synthesized for the carbon skeleton of swinhoeisterol A (**39**), the chemical shift differences were calculated and followed the trend observed in case of the classic tetracyclic skeleton (entry 2 vs. entry 1). Interestingly, also herbarulide (**60**, revised structure) and its 24-epimer (**59**) exhibited exactly the same values as obtained from the model substrates (entry 3 vs. entry 1). For dankasterone A (**22**), dankasterone B (**23**) and periconiastone A (**25**), all being Δ^{22} ergostanes **93**, the chemical shift difference Δ of C26 and C27 was 0.3 ppm in all three cases, agreeing with the respective values shown in Table 1.

Table 1 ^{13}C NMR chemical shift differences Δ [ppm] of the side chain atoms C26 and C27 of three steroid backbones with varying C24-alkylated side chains.[64,77,86]

#	carbon skeleton / side chain R	 **94**	 **100**	 **93**	 **102**
1		**107** **Δ = 2.9 ppm**	**108** **Δ = 2.0 ppm**	**109** **Δ = 0.3 ppm**	**110** **Δ = 0.5 ppm**
2		24-*epi*-**39** **Δ = 2.6 ppm**	**39** **Δ = 2.2 ppm**	Δ^{22}-24-*epi*-**39** **Δ = 0.3 ppm**	–
3		–	–	**60** **Δ = 0.3 ppm**	**59** **Δ = 0.5 ppm**

Even though Wright and co-workers outlined ^{13}C NMR data of steroids with the classic tetracyclic skeleton, the chemical shift differences reported were in agreement with the values

calculated for the rearranged natural products and their diastereomers synthesized and discussed in this work. The failure to recognize the limitations of direct NMR chemical shift comparisons has led to numerous assignment errors as the discrepancy of data sets obtained from two epimeric or structurally similar compounds is in most cases marginal. However, the application of Wright's procedure would have provided the correct configuration at C24 in all cases considered herein and, thus, seems to be a viable tool in the assignment of steroidal side chains. As we had now gathered experience in the field of rearranged steroids, outlining a summary of recently isolated such-like natural products presented itself useful in regard of further biosynthetical understanding and in identifying potential synthetic targets (see appendix A or ref. 48). Expanding the scope of this compilation by reporting the ^{13}C NMR data of natural products and their respective synthesized epimers and diastereomers might be of use for the prospective structure elucidation of novel secondary metabolites.

Bibliography

[1] D. H. R. Barton, K. Nakanishi, O. Meth-Cohn, *Comprehensive Natural Products Chemistry: Isoprenoids Including Carotenoids and Steroids*, Volume 2, Elsevier Science Ltd., Oxford, UK, **1999**.

[2] D. Lednicer, *Steroid Chemistry at a Glance*, John Wiley & Sons Ltd., Chichester, UK, **2010**.

[3] "The Nobel Prize in Chemistry 1927," can be found under www.nobelprize.org/prizes/chemistry/1927/summary, **2020**, accessed 2020-04-18.

[4] H. Wieland, *Nobel Lectures, Chemistry 1922-1941*, Elsevier Publishing Company, Amsterdam, NL, **1966**.

[5] "The Nobel Prize in Chemistry 1928," can be found under www.nobelprize.org/prizes/chemistry/1928/summary, **2020**, accessed 2020-04-18.

[6] A. Windaus, *Nobel Lectures, Chemistry 1922-1941*, Elsevier Publishing Company, Amsterdam, NL, **1966**.

[7] A. Windaus, H. H. Inhoffen, S. v. Reichel, *Justus Liebigs Ann. Chem.* **1934**, 510, 248–259.

[8] A. Windaus, *Proc. R. Soc. London, Ser. B* **1931**, 108, 568–575.

[9] A. Windaus, O. Linsert, A. Lüttringhaus, G. Weidlich, *Justus Liebigs Ann. Chem.* **1932**, 492, 226–241.

[10] A. Windaus, W. Thiele, *Justus Liebigs Ann. Chem.* **1935**, 521, 160–175.

[11] A. Windaus, H. Lettré, F. Schenck, *Justus Liebigs Ann. Chem.* **1935**, 520, 98–106.

[12] A. Windaus, *Angew. Chem.* **1923**, 36, 309–310.

[13] J. D. Bernal, *Nature* **1932**, 129, 277–278.

[14] J. D. Bernal, *Nature* **1932**, 129, 721.

[15] I. M. Heilbron, J. C. E. Simpson, F. S. Spring, *J. Chem. Soc.* **1933**, 626–635.

[16] G. P. Moss, *Pure Appl. Chem.* **1989**, 61, 1783–1822.

[17] F. Lynen, B. W. Agranoff, H. Eggerer, U. Henning, E. M. Möslein, *Angew. Chem.* **1959**, 71, 657–684.

[18] D. S. Goodman, G. Popják, *J. Lipid Res.* **1960**, 1, 286–300.

[19] I. M. Heilbron, E. D. Kamm, W. M. Owens, *J. Chem. Soc.* **1926**, 1630–1644.

[20] R. G. Langdon, K. Bloch, *J. Am. Chem. Soc.* **1952**, 74, 1869–1870.

[21] R. B. Woodward, K. Bloch, *J. Am. Chem. Soc.* **1953**, 75, 2023–2024.

[22] L. Ruzicka, *Experientia* **1953**, 9, 357–396.

[23] A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, *Helv. Chim. Acta* **1955**, 38, 1890–1904.

[24] R. Breslow, E. Barrett, E. Mohacsi, *Tetrahedron Lett.* **1962**, 3, 1207–1211.

[25] R. Breslow, J. T. Groves, S. S. Olin, *Tetrahedron Lett.* **1966**, 7, 4717–4719.

[26] R. Breslow, S. S. Olin, J. T. Groves, *Tetrahedron Lett.* **1968**, 9, 1837–1840.

[27] J. Y. Lallemand, M. Julia, D. Mansuy, *Tetrahedron Lett.* **1973**, 14, 4461–4464.

[28] J. Justicia, L. Álvarez De Cienfuegos, A. G. Campaña, D. Miguel, V. Jakoby, A. Gansäuer, J. M. Cuerva, *Chem. Soc. Rev.* **2011**, 40, 3525–3537.

[29] E. J. Corey, W. E. Russey, P. R. O. de Montellano, *J. Am. Chem. Soc.* **1966**, 88, 4750–4751.

[30] E. E. van Tamelen, J. D. Willett, R. B. Clayton, K. E. Lord, *J. Am. Chem. Soc.* **1966**, 88, 4752–4754.

[31] P. M. Dewick, *Medicinal Natural Products - A Biosynthetic Approach*, John Wiley & Sons Ltd., Chichester, UK, **2009**.

[32] D. P. Curran, D. M. Rakiewicz, *J. Am. Chem. Soc.* **1985**, 107, 1448–1449.

[33] R. A. Shenvi, C. A. Guerrero, J. Shi, C. Li, P. S. Baran, *J. Am. Chem. Soc.* **2008**, 130, 7241–7243.

[34] J. Gui, D. Wang, W. Tian, *Angew. Chem. Int. Ed.* **2011**, 50, 7093–7096.

[35] J. Y. Cha, J. T. S. Yeoman, S. E. Reisman, *J. Am. Chem. Soc.* **2011**, 133, 14964–14967.

[36] R. C. Heinze, D. Lentz, P. Heretsch, *Angew. Chem. Int. Ed.* **2016**, 55, 11656–11659.

[37] Z. Lu, X. Zhang, Z. Guo, Y. Chen, T. Mu, A. Li, *J. Am. Chem. Soc.* **2018**, 140, 9211–9218.

[38] R. C. Heinze, P. Heretsch, *J. Am. Chem. Soc.* **2019**, 141, 1222–1226.

[39] T. Kikuchi, Y. Masumoto, Y. In, K. Tomoo, T. Yamada, R. Tanaka, *Eur. J. Org. Chem.* **2015**, 4645–4649.

[40] Z. Hu, Y. Wu, S. Xie, W. Sun, Y. Guo, X.-N. Li, J. Liu, H. Li, J. Wang, Z. Luo, Y. Xue, Y. Zhang, *Org. Lett.* **2017**, 19, 258–261.

[41] Y.-P. Song, Z.-Z. Shi, F.-P. Miao, S.-T. Fang, X.-L. Yin, N.-Y. Ji, *Org. Lett.* **2018**, 20, 6306–6309.

[42] J. Wu, S. Tokuyama, K. Nagai, N. Yasuda, K. Noguchi, T. Matsumoto, H. Hirai, H. Kawagishi, *Angew. Chem. Int. Ed.* **2012**, 51, 10820–10822.

[43] T. Kikuchi, M. Isobe, S. Uno, Y. In, J. Zhang, T. Yamada, *Bioorg. Chem.* **2019**, 89, 103011.

[44] H. T. Aung, A. Porta, M. Clericuzio, Y. Takaya, G. Vidari, *Chem. Biodivers.* **2017**, 14, e1600421.

[45] R. C. Heinze, D. Lentz, P. Heretsch, *Angew. Chem. Int. Ed.* **2016**, 55, 11656–11659.

[46] S. Sato, Y. Fukuda, Y. Ogura, E. Kwon, S. Kuwahara, *Angew. Chem. Int. Ed.* **2017**, 56, 10911–10914.

[47] S. Sato, S. Kuwahara, *Org. Lett.* **2020**, 22, 1311–1315.

[48] F. L. Duecker, F. Reuß, P. Heretsch, *Org. Biomol. Chem.* **2019**, 17, 1624–1633.

[49] T. Amagata, M. Doi, M. Tohgo, K. Minoura, A. Numata, *Chem. Commun.* **1999**, 1321–1322.

[50] T. Amagata, M. Tanaka, T. Yamada, M. Doi, K. Minoura, H. Ohishi, T. Yamori, A. Numata, *J. Nat. Prod.* **2007**, 70, 1731–1740.

[51] Y. Miyata, T. Diyabalanage, C. D. Amsler, J. B. McClintock, F. A. Valeriote, B. J. Baker, *J. Nat. Prod.* **2007**, 70, 1859–1864.

[52] W. Gao, C. Chai, Y. He, F. Li, X. Hao, F. Cao, L. Gu, J. Liu, Z. Hu, Y. Zhang, *Org. Lett.* **2019**, 21,

8469–8472.

[53] X. H. Liu, F. P. Miao, X. R. Liang, N. Y. Ji, *Nat. Prod. Res.* **2014**, *28*, 1182–1186.

[54] N. Kawahara, S. Sekita, M. Satake, *Phytochemistry* **1994**, *37*, 213–215.

[55] L. Canonica, B. Danieli, G. Lesma, G. Palmisano, *J. Chem. Soc., Chem. Commun.* **1985**, 1321–1322.

[56] J. Harmatha, M. Buděšínský, K. Vokáč, *Steroids* **2002**, *67*, 127–135.

[57] W. C. Lai, B. Dankó, J. Csábi, Z. Kele, F. R. Chang, M. L. Pascu, T. Gáti, A. Simon, L. Amaral, G. Tóth, A. Hunyadi, *Steroids* **2014**, *89*, 56–62.

[58] N. Kawahara, S. Sekita, M. Satake, *Chem. Pharm. Bull.* **1993**, *41*, 1318–1320.

[59] A. Hunyadi, B. Danko, M. Boni, A. Militaru, T. Alexandru, V. Nastasa, I. R. Andrei, M. L. Pascu, L. Amaral, *Anticancer Res.* **2012**, *32*, 1291–1297.

[60] L. Canonica, B. Danieli, G. Lesma, G. Palmisano, A. Mugnoli, *Helv. Chim. Acta* **1987**, *70*, 701–716.

[61] B. Acott, A. L. J. Beckwith, *Aust. J. Chem.* **1964**, *17*, 1342–1353.

[62] Ž. Čeković, L. Dimttruević, G. Djokić, T. Srnić, *Tetrahedron* **1979**, *35*, 2021–2026.

[63] J. Gong, P. Sun, N. Jiang, R. Riccio, G. Lauro, G. Bifulco, T. J. Li, W. H. Gerwick, W. Zhang, *Org. Lett.* **2014**, *16*, 2224–2227.

[64] J. L. C. Wright, A. G. McInnes, S. Shimizu, D. G. Smith, J. A. Walter, D. Idler, W. Khalil, *Can. J. Chem.* **1978**, *56*, 1898–1903.

[65] W. Zhang, P. Sun, J. Gong, H. Tang, *PCT Int. Appl.* WO 2015124037 A1, **2015**.

[66] J. Li, H. Tang, T. Kurtán, A. Mándi, C.-L. Zhuang, L. Su, G.-L. Zheng, W. Zhang, *J. Nat. Prod.* **2018**, *81*, 1645–1650.

[67] E. Kho, D. K. Imagawa, M. Rohmer, Y. Kashman, C. Djerassi, *J. Org. Chem.* **1981**, *46*, 1836–1839.

[68] Y. Sugo, Y. Inouye, N. Nakayama, *Steroids* **1995**, *60*, 738–742.

[69] A. Umeyama, N. Shoji, M. Enoki, S. Arihara, *J. Nat. Prod.* **1997**, *60*, 296–298.

[70] A. Takano, Y. Zhao, T. Ohyoshi, H. Kigoshi, *Tetrahedron Lett.* **2019**, *60*, 591–593.

[71] J. P. Day, B. Lindsay, T. Riddell, Z. Jiang, R. W. Allcock, A. Abraham, S. Sookup, F. Christian, J. Bogum, E. K. Martin, R. L. Rae, D. Anthony, G. M. Rosair, D. M. Houslay, E. Huston, G. S. Baillie, E. Klussmann, M. D. Houslay, D. R. Adams, *J. Med. Chem.* **2011**, *54*, 3331–3347.

[72] G. J. Kemperman, T. A. Roeters, P. W. Hilberink, *Eur. J. Org. Chem.* **2003**, 1681–1686.

[73] K. Krohn, C. Biele, H. J. Aust, S. Draeger, B. Schulz, *J. Nat. Prod.* **1999**, *62*, 629–630.

[74] Y. S. Tsantrizos, P. L. Folkins, J. F. Britten, D. N. Harpp, K. K. Ogilvie, *Can. J. Chem.* **1992**, *70*, 158–164.

[75] X. C. Huang, Y. W. Guo, G. Q. Song, *J. Asian Nat. Prod. Res.* **2006**, *8*, 485–489.

[76] N. Kawahara, S. Sekita, M. Satake, *Phytochemistry* **1995**, *38*, 947–950.

[77] F. L. Duecker, R. C. Heinze, M. Mueller, S. Zhang, P. Heretsch, *Org. Lett.* **2020**, *22*, 1585–1588.

[78] T. Nakagawa, K. Hayashi, H. Mitsuhashi, *Tetrahedron Lett.* **1982**, *23*, 757–760.

[79] Y. Li, L. Wang, S. Li, X. Chen, Y. Shen, Z. Zhang, H. He, W. Xu, Y. Shu, G. Liang, R. Fang, X. Hao, *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 8083–8088.

[80] O. Kennard, J. K. Fawcett, D. G. Watson, K. A. Kerr, K. Stöckel, W. Stöcklin, T. Reichstein, *Tetrahedron Lett.* **1968**, *35*, 3799–3804.

[81] J. Gui, H. Tian, W. Tian, *Org. Lett.* **2013**, *15*, 4802–4805.

[82] K. Heusler, P. Wieland, C. Meystre, *Org. Synth.* **1965**, *45*, 57.

[83] J. I. Concepción, C. G. Francisco, R. Hernández, J. A. Salazar, E. Suárez, *Tetrahedron Lett.* **1984**, *25*, 1953–1956.

[84] J. K. Kochi, *J. Am. Chem. Soc.* **1963**, *85*, 1958–1968.

[85] S. L. Schreiber, *J. Am. Chem. Soc.* **1980**, *102*, 6163–6165.

[86] F. L. Duecker, R. C. Heinze, P. Heretsch, *J. Am. Chem. Soc.* **2020**, *142*, 104–108.

[87] C. H. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, A. Wettstein, *Helv. Chim. Acta* **1962**, *45*, 1317–1343.

[88] V. A. Khripach, V. N. Zhabinskii, G. P. Fando, N. B. Khripach, B. Schneider, *ARKIVOC* **2008**, *ix*, 20–28.

[89] A. Burawoy, *J. Chem. Soc.* **1937**, 409–411.

[90] F. L. Duecker, R. C. Heinze, S. Steinhauer, P. Heretsch, *Chem. Eur. J.* **2020**, 10.1002/chem.202001405.

[91] C. W. Ellwood, G. Pattenden, *Tetrahedron Lett.* **1991**, *32*, 1591–1594.

[92] C. E. Mowbray, G. Pattenden, *Tetrahedron Lett.* **1993**, *34*, 127–130.

[93] M. Akhtar, D. H. R. Barton, *J. Am. Chem. Soc.* **1964**, *86*, 1528–1536.

Appendices

Appendix A: Rearranged ergostane-type natural products: chemistry, biology and medicinal aspects

Appendix B: Synthesis of Swinhoeisterol A, Dankasterone A and B, and Periconiastone A by Radical Framework Reconstruction

- Supporting Information

Appendix C: Synthesis of the Alleged Structures of Fortisterol and Herbarulide and Structural Revision of Herbarulide

- Supporting Information

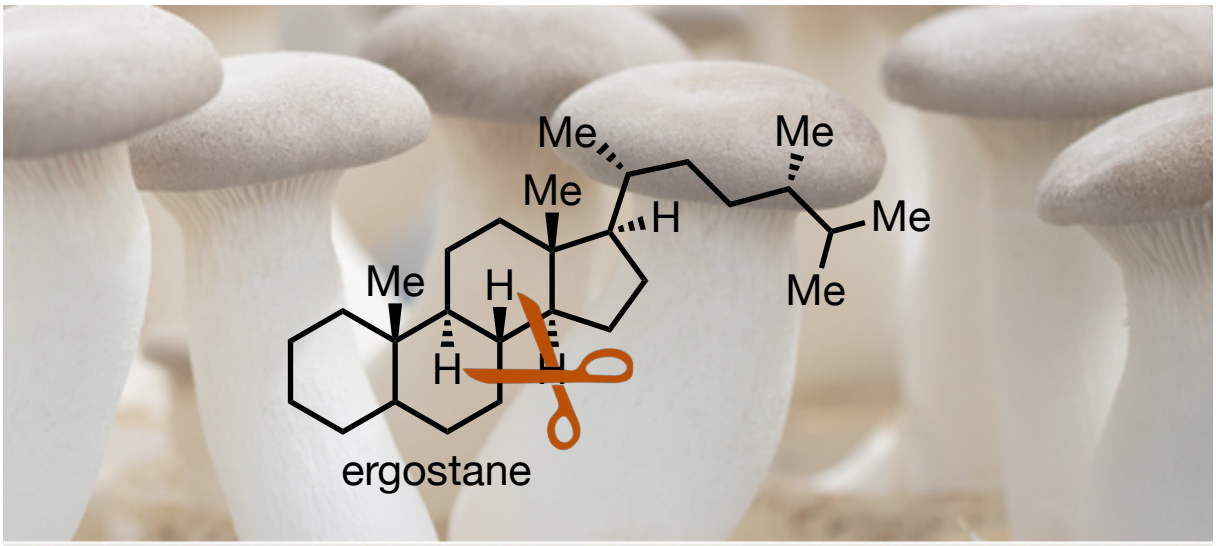
Appendix D: Discoveries and Challenges *en route* to Swinhoeisterol A

- Supporting Information

Appendix A

Rearranged ergostane-type natural products: chemistry, biology and medicinal aspects

Fenja L. Duecker,[‡] Franziska Reuß,[‡] Philipp Heretsch[a]



‡ These authors contributed equally.

a Institut für Chemie und Biochemie
Freie Universität Berlin
Takustraße 3, 14195 Berlin, Germany

This article is reproduced with permission from:
F. L. Duecker, F. Reuß, P. Heretsch, *Org. Biomol. Chem.* **2019**, 17, 1624–1633.
DOI: 10.1039/c8ob02325e

Author contribution: The topic for this review article was designed by Fenja L. Dücker, Franziska Reuß and Philipp Heretsch. The natural products discussed herein were chosen by Fenja L. Dücker and Franziska Reuß. The manuscript was prepared by Fenja L. Dücker, Franziska Reuß and Philipp Heretsch.

Organic & Biomolecular Chemistry

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2019, **17**, 1624

Rearranged ergostane-type natural products: chemistry, biology, and medicinal aspects

Fenja L. Duecker,† Franziska Reuß† and Philipp Heretsch *

Received 19th September 2018,
Accepted 18th October 2018

DOI: 10.1039/c8ob02325e

rsc.li/obc

Classical steroids are long-known privileged leads in drug discovery. Their rearranged counterparts, though, have so far received less attention, although recent isolation and biological testing programmes have revealed a plethora of molecular entities that are both structurally intriguing, as well as biologically relevant. This review will highlight those natural products, and focus on ergostane-derived seco- and *abeo*-steroids. Their isolation, structure elucidation, and biological properties are reported. A special emphasis of this review lies in their respective (and typically proposed) biosyntheses, to help guide future bio-inspired synthetic attempts.

1. Introduction

Ergosterol (**1**) is one of the most abundant steroids in nature and is found primarily in fungal cell membranes where it conducts many of the tasks cholesterol executes in animal cells. A large number of steroidal natural products can be traced back to the ergostane skeleton (Fig. 1) and a fraction of these contain a rearranged steroid skeleton. Many possess biological activities. This review focuses on such ergostanes; their isolation, structure elucidation, proposed biosynthetic routes, as well as biological activities are discussed. The order in which these natural products are discussed follows the respective ring (A, B, C, or D) that is (formally) cut and rearranged, *i.e.* ergostanes with a rearranged A-ring are covered first, followed by those with rearranged B-, C-, and D-rings. To indicate the rearrangement in the steroidal system the IUPAC recommendations for steroid nomenclature are followed. If a bond in the typical tetracyclic steroid system is broken, the compound is referred to as a secosteroid *e.g.*, when the bond between C2 and C3 is cleaved the system should be named as a 2,3-secosteroid. The prefix "*abeo*" is used when a bond migration has occurred *e.g.*, when C10 is not bound to C5 anymore but to C6, the new system is described as 10(5 → 6)*abeo*.[1]

The reader should note that a number of unusual natural product structures that have been proposed, based mainly on spectroscopic evidence, have later been shown to be incorrect.[2] Thus, while we assume that all of the new structures discussed here are correct, the reader should be aware that this is only

Institute of Chemistry and Biochemistry, Freie Universität Berlin, Takustraße 3, 14195 Berlin, Germany. E-mail: philipp.heretsch@fu-berlin.de
†These authors contributed equally.

Fenja L. Duecker

Fenja Leena Duecker grew up in the north of Germany and moved to Berlin in 2010 to study chemistry at Freie Universität Berlin. After finishing her undergraduate studies in 2013, she spent one year at Université de Montréal in Canada and conducted her master thesis on the topic of C–H activation in the group of Prof. Dr P. Heretsch back in Berlin. Since 2016 she is working on the synthesis of rearranged steroidal natural products as part of her doctoral studies.

Franziska Reuß

Franziska Reuß grew up in the south of Germany and studied chemistry at Universität Leipzig where she received her B.Sc. in 2014. During her Master studies, she spent a semester at Monash University in Melbourne, Australia. She completed her M.Sc. in 2016 with a thesis on ortho*-quinone methides in the group of Prof. Dr C. Schneider. She then joined the group of Prof. Dr P. Heretsch for her PhD where she is currently working on the total synthesis of alkaloids.*

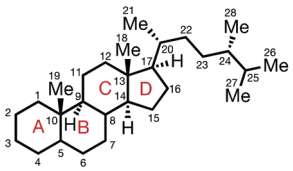


Fig. 1 The ergostane skeleton with ring and carbon numbering.

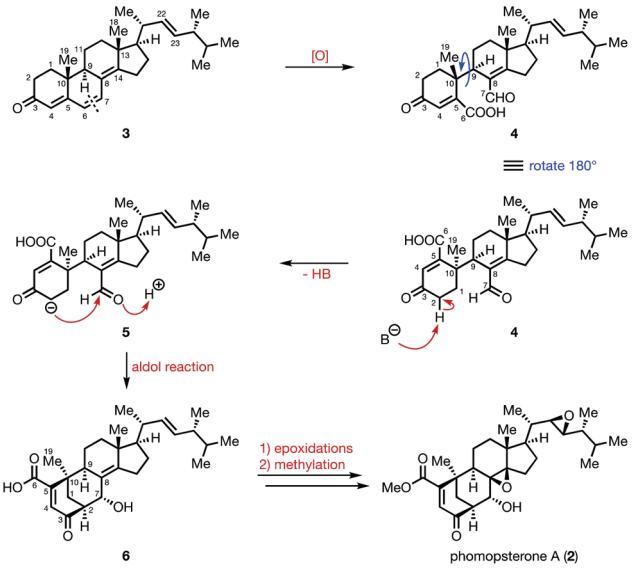
absolutely certain in those cases where a single crystal X-ray diffraction analysis was obtained.

The vast class of withanolides has already been reviewed exhaustively by others and is therefore not part of this article. The interested reader is referred to several highly recommendable reviews.[3,4]

2. Ergostanes with rearranged A-rings

2.1 Phomopsterone A

2.1.1 Isolation and structure elucidation. In 2016, Hu *et al.* isolated phomopsterone A (**2**, Scheme 1) from the fungus *Phomopsis* sp. TJ507A, which in turn had been isolated from the plant *Phyllantus glaucus*.[5] The structure and absolute configuration were elucidated using a combination of various analytical methods. The molecular formula was inferred from its HRESIMS and ^{13}C-NMR data, which suggested a hexacyclic structure. The interpretation of 2D-NMR experiments confirmed an unprecedented bicyclo[3.3.1]nonane motif but still allowed for six possible structures to match the obtained data regarding their oxygenation pattern. Further NOESY experiments and additional computer-generated 3D models as well as ball-and-stick models permitted the selection of only one of these proposed structures for **2** based on its relative configuration. Its absolute stereoconfiguration was determined using three different approaches. Application of the modified Mosher method on the afore-prepared (*S*)- and (*R*)-MTPA esters revealed the absolute configuration which was further confirmed by fitting of experimental and calculated ECD spectra (B3LYP/6-311++G**) and eventually by single crystal X-ray diffraction (Cu Kα radiation). Besides the unique 7(6 → 2)*abeo*-skeleton, an α-oriented C19 methyl group is rarely observed in steroids.



Scheme 1 Proposed biosynthetic formation of phomopsterone A (**2**).

2.1.2 Proposed biosynthetic pathway. Hu *et al.* propose the structural singularity of **2** to result from the depicted biosynthesis (Scheme 1), which includes scission of the B-ring and a subsequent rotation of the A-ring. A similar process was described in 2000 by Mulholland *et al.* delineating the structural relationship between limonoids.[6] The isolators' biosynthetic proposal for **2** starts with the oxidative cleavage of co-isolated compound **3** leading to **4**. A 180° rotation of the A-ring along the C9–C10 bond would enable an aldol reaction between C2 and C7 (*via* deprotonated **5**) which would then generate intermediate **6**. Further epoxidation of the $\Delta^{8(14)}$ and Δ^{22} double bonds and esterification would, thus, provide phomopsterone A (**2**).

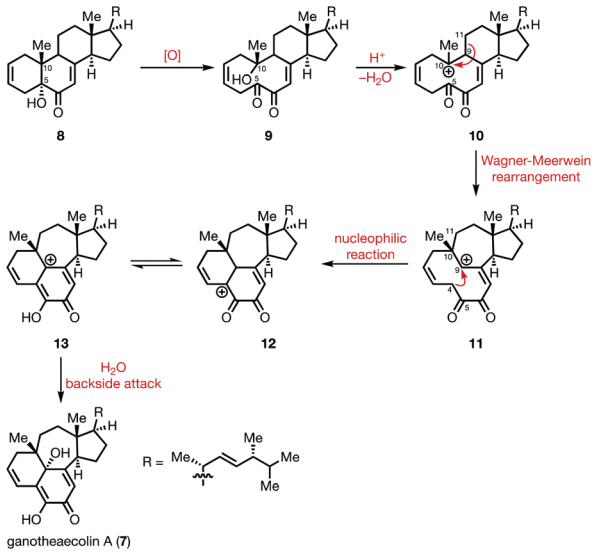
2.1.3 Biological studies. Since steroids are well known for their anti-inflammatory activity, phomopsterone A (**2**) was subjected to a virtual screen against typical inflammation-related targets. Lipopolysaccharide (LPS)-induced nitric oxide (NO)-production in RAW 264.7 mouse macrophages was thus identified as the most promising target but an *in vitro* assay showed that phomopsterone A (**2**) exhibits only minor effects both on the level of NO production and on inhibition of iNOS enzyme (IC_{50} >25 and 16.53 μM, respectively).

2.2 Ganotheaecolin A

2.2.1 Isolation and structure elucidation. In 2017, the group of Cheng reported the isolation of a steroidal natural

Philipp Heretsch

Philipp Heretsch was born in Lippstadt, Germany, in 1982. He obtained his PhD degree from Universität Leipzig (supervisor: Prof. Dr. A. Giannis) in 2009. After a postdoctoral stay with K.C. Nicolaou at The Scripps Research Institute, La Jolla, California, and at Rice University, Houston, Texas, he was appointed assistant professor at Freie Universität Berlin in 2015. Philipp Heretsch has been working in the total synthesis of biologically active natural products since the beginning of his career. His group is now interested in C–C-bond manipulation strategies in the context of the synthesis of complex abeo-*steroids, guided by biosynthetic hypotheses.*



Scheme 2 Biosynthetic proposal for the formation of the 6/6/7/5-fused ring system of ganotheaecolin A (**7**).

product named ganotheaecolin A (**7**, Scheme 2), composed of an unprecedented 6/6/7/5-fused carbon skeleton, from the mushroom *Ganoderma theaecolum*.[7] Combining the results of HREIMS and NMR studies, an initial structure proposal pointed out that rings A and B are fused and share the C4–C9 bond, thus, leading to a naphtho[1,8-*ef*]azulene ring system. The absolute configuration of C20 and C24 was determined with the aid of diagnostic chemical shifts of the signals of adjacent methyl groups (C21 and C28, respectively) and was assigned as 20*R*,24*R*. To further clarify the absolute configuration of the chiral carbon atoms, ECD calculations were executed and compared with obtained spectra. High accordance thereof combined with the fact that ^{13}C chemical shifts obtained from DFT calculations matched measured data as well, further confirmed the suggested structure.

2.2.2 Proposed biosynthetic pathway. Cheng *et al.* proposed the following steps (Scheme 2) to take place starting from known steroid **8** which would lead to ganotheaecolin A (**7**). Oxidative cleavage of the C5–C10 bond and subsequent dehydration would provide cationic 5,10-secosteroid intermediate **10**. Thereafter, a Wagner–Meerwein rearrangement could build up the 11(9 → 10)*abeo*-motif of **11** that could undergo cyclization *via* a nucleophilic reaction and lead to the additional 9(11 → 4)*abeo*-system as in **12**. Keto–enol tautomerism and final backside attack would then give 9(11 → 4), 11(9 → 10) di*abeo*-5,10-secosteroid structure of **7**.

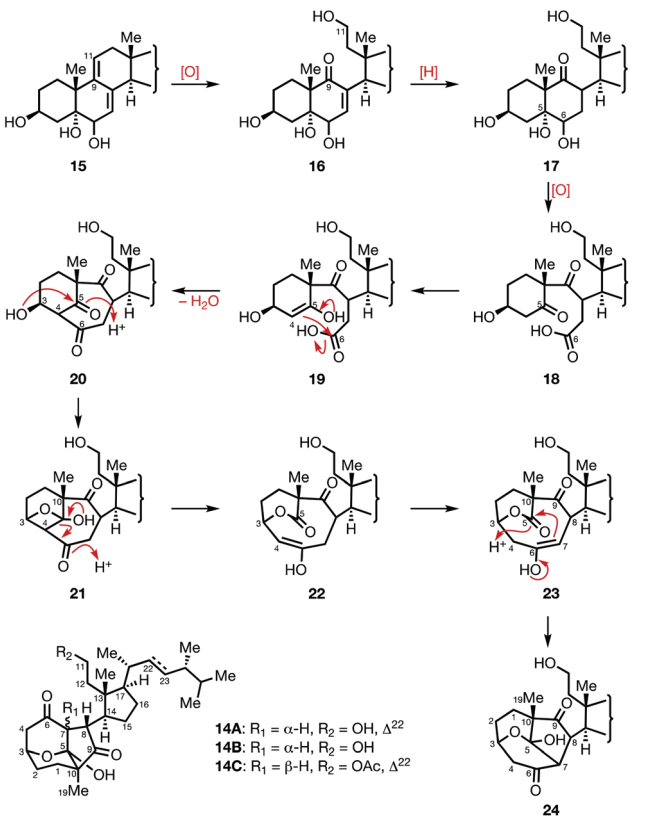
2.2.3 Biological studies. Considering the urgent need for small-molecule neurotrophic factor mimetics and the fact that *Ganoderma* is traditionally employed as treatment for neurological diseases, the potential of the neurite outgrowth-promoting activity (PC12 cells) of ganotheaecolin A (**7**) was evaluated. As a result, **7** stimulated cell differentiation in a dose-dependent manner (max. effect: 10 μM).

3. Ergostanes with rearranged B-rings

3.1. Pinnigorgiols A–C

3.1.1 Isolation and structure elucidation. In 2015, Sung *et al.* reported the isolation of pinnigorgiols A–C (**14A–C**, Scheme 3) from the gorgonian coral *Pinnigorgia* sp.[8] Using a combination of HRESIMS and NMR studies, C5 was identified as hemiacetal, thus, hinting at a tricyclic core structure. NMR data of the skeletal core of pinnigorgiol A (**14A**) were identical with those of only recently published (2015) aplysiasecosterol A (structure not shown) the structure proposal of which was supported by extensive DFT and ECD calculations.[9] The stereoconfiguration of C20 and C24 in **14A** was assigned as (*R*) with the help of the chemical shifts of C21 and C28, respectively. The structure of pinnigorgiol B (**14B**) was elucidated by comparing the analytical data with those of **14A** and as the only difference, **14B** possesses a saturated side chain. In the case of pinnigorgiol C (**14C**), the same procedure led again to a very similar carbon skeleton only carrying an acetoxy group at C11 and having inverted configuration at C7, which was further confirmed by CD spectra.

All three natural products are, thus, composed of a tricyclo [5,2,1,1]decane ring and can also be described as 5(4 → 7), 6(5 → 4)di*abeo*-9,11-secosteroids.



Scheme 3 Proposed biosynthetic pathway *via* a 9,11-secosteroid to the cage-like structure of the pinnigorgiols (**14A–C**).

In 2018, the group of Li published a total synthesis of aplysiasecosterol A and thereby confirmed its proposed structure.[10] Additionally, Kigoshi *et al.* were able to synthesize the cage fragment and obtained a single crystal X-ray diffraction and analytical data in agreement with the respective elements in the natural product.[11]

3.1.2 Biosynthetic proposal. In their proposed biosynthesis of the pinnigorgiols (Scheme 3), Sung *et al.* first postulate the formation of 9,11-secosteroid **17** of which the C5–C6 bond would then be cleaved oxidatively to give **18**. Subsequent dehydration would generate the 6(5 → 4)*abeo* unit in **19**. Nucleophilic attack of the 3-hydroxy group to the C5 carbonyl would form hemiacetal **20**, which, after rupture of the C4–C5 bond, would lead to 4,5-secolactone **22**. Final cyclization may then furnish the 5(4 → 7)*abeo* unit and give rise to the cage-like structure of the pinnigorgiols as in **24**.

The isolation chemists of aplysiasecosterol A propose an alternative biosynthetic pathway to this unprecedented structural motif comprising an α-ketol rearrangement followed by a vinylogous α-ketol rearrangement and subsequent hemiacetal formation.[9] This proposal is corroborated by the isolation of the potential biosynthetic precursors aplysiasecosterol B and C from the same sea hare (*Aplysia kurodai*).[12]

3.1.3 Biological studies. Pinnigorgiols A–C were tested against the HSC-T6 rat hepatic stellate cell line whose cells are the major type involved in liver fibrosis. **14A** and **14B** showed a significant decrease of cell viability at 10 μM with IC_{50} values of 5.77 ± 0.27 and 7.89 ± 0.52 μM, respectively. However, **14C** displayed no effect on the examined cell line, indicating an importance of the configuration of C7 for bioactivity. Regarding anti-inflammatory effects, all compounds (**14A–C**) displayed inhibitory effects both on the formation of superoxide anions (IC_{50} = 4.0, 2.5, and 2.7 μM) as well as on the release of elastase by human neutrophils (IC_{50} = 5.3, 3.1 and 2.7 μM).

3.2 Erinarol J

3.2.1 Isolation and structure elucidation. In 2015, Kim, Lee *et al.* isolated erinarol J (**25**, Fig. 2) from the fruiting bodies of the edible mushroom *Hericium erinaceum*, also known as the Lion's Mane Mushroom.[13] The isolation team identified the molecular formula to be $C_{28}H_{42}O_2$ by HRESIMS. From ^{1}H- and ^{13}C-NMR spectra, one tetrasubsituted as well as two disubstituted double bonds, an acetal moiety and a hydroxy group were deduced. HMBC correlations concluded **25** to be a $\Delta^{6,8(14)}$-ergostane derivative containing an unusual 6,8-dioxabicyclo[3.2.1]oct-2-ene ring in place of the B-ring. Thus, **25** is a 9,10-epoxy-9,10-secosteroid. A NOESY experiment showed that the A-ring is in a boat-like conformation and that the dioxolane ring is *cis*-fused to the A-ring.

3.2.2 Biological studies. Erinarol J (**25**) was tested for its effect on LPS-induced production of the inflammatory mediators NO and tumor necrosis factor (TNF-α) by RAW 267.4 cells. The NO production was measured using the Griess reaction assay. **25** showed an inhibition value of 38.4% at a concentration of 10 μM. TNF-α secretion was also decreased by treatment with **25** (inhibition value 43.3% at 10 μM). These parameters indicate that **25** can potentially be used for the treatment of inflammatory diseases.

3.3 Eringiacetal A

3.3.1 Isolation and structure elucidation. Eringiacetal A (**26**, Scheme 4) was isolated in 2015 by Tanaka *et al.* from the south east Asian fungus *Pleurotus eryngii*, also called King Trumpet Mushroom.[14] The molecular formula of $C_{28}H_{42}O_5$ was determined by HRMS and implied eight degrees of unsaturation. From the IR-spectrum, the isolation team deducted the presence of hydroxy groups. The ^{13}C-NMR spectrum revealed the presence of two C–C double bonds, two annular methyl groups, four secondary methyl groups, as well as three acetal carbon atoms. A cyclohexyl alcohol structure of the steroidal A-ring was confirmed by COSY- and HMBC-spectra. These spectra also showed, that the remaining four oxygen atoms were located in the B-ring. By further analyzing the HMBC spectrum, the acetal carbon atoms were proposed to be located in positions 5, 6, and 7. A single crystal X-ray diffraction of **26** proved the proposed structure of a 5,6-secosteroid and its relative stereoconfiguration could be determined. Eringiacetal A (**26**) with its basket-like B-ring, may, thus, be the first isolated 5,6-secosteroid.

3.3.2 Proposed biosynthetic pathway. Tanaka *et al.* proposed a biosynthesis starting from the known steroid 3β,5α,9α-trihydroxyergosta-7,22-dien-6-one (**27**) that was co-isolated with eringiacetal A (**26**, Scheme 4). The pathway starts with the migration of the Δ^7 double bond to tetrasubstituted $\Delta^{8(14)}$. After oxidation of C7, an intermediate acetal would be formed that after collapsing would cleave the C5–C6 bond. Further acetalization might furnish the characteristic B-ring.

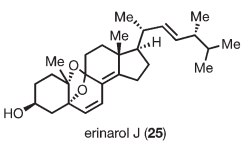
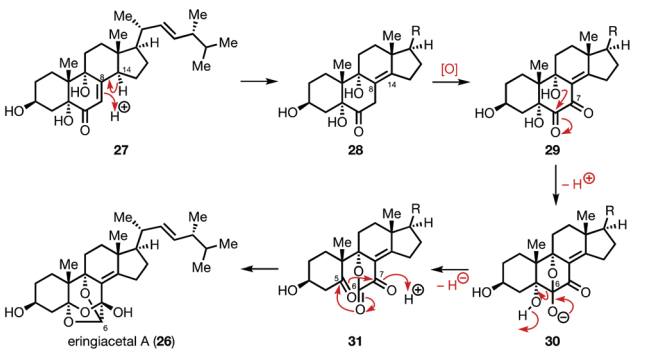


Fig. 2 Structure of erinarol J (**25**).



Scheme 4 Proposed biosynthesis of eringiacetal A (**26**).

3.3.3 Biological studies. Eringiacetal A (**26**) was tested for its inhibitory effect on NO production induced by LPS in macrophages as well as for its cytotoxicity using the 3-(4,5-dimethyl-2-thiazolyl)-2,5-di-phenyl-2*H*-tetrazolium bromide MTT assay. It was shown that **26** exhibits an inhibitory effect on NO production with an IC_{50} of 19.9 μM, likely attributed to its cytotoxicity (IC_{50} = 25.6 μM).

3.4 Solanioic acid

3.4.1 Isolation and structure elucidation. In 2015, de Silva, Andersen *et al.* extracted solanioic acid (**32**, Scheme 5) from laboratory cultures of *Rhizoctonia solani*, a fungus isolated from the tubers of the Sri Lankan weed *Cyperus rotundus*.[15] HRESIMS analysis provided the chemical formula of $C_{28}H_{40}O_5$. A set of 1D- and 2D-NMR spectra led to the conclusion, that two aldehydes (one in conjugation), a carboxylic acid, and three alkenes are present in the natural product. These structural motifs accounted for six of nine sites of unsaturation that were derived from the molecular formula. The remaining three sites of unsaturation were assigned to three rings. By the interpretation of COSY-, HSQC- and HMBC-spectra, five fragments were identified, which could be assembled to the final structure of **32**, an 8(7 → 6)*abeo*-11,12-secosteroid. ROESY correlations and the proposed biogenesis of **32** allowed for a tentative assignment of the absolute configuration. While the relative stereoconfiguration was proven by single crystal X-ray diffraction of a triol obtained by reduction with $NaBH_4$, the absolute configuration could be determined by Mosher ester analysis of a derivative of **32**.

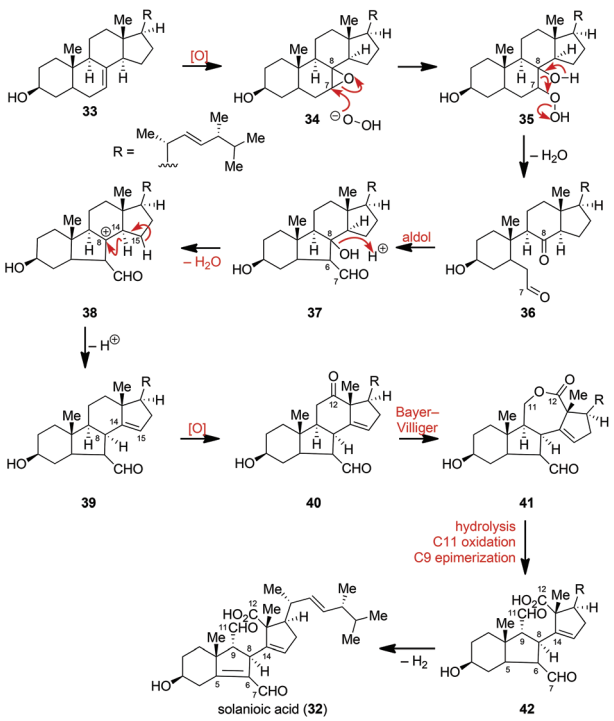
3.4.2 Proposed biosynthetic pathway. The biosynthetic pathway to solanioic acid (**32**) was proposed to start from 22,23-dehydro-fungisterol (**33**, Scheme 5). Oxidation, epoxide opening by a hydroperoxide anion and collapse of the thus-formed hydroperoxide would give keto aldehyde (**36**). This compound would react in an aldol reaction and, thus, contract the steroidal B-ring. The formation of a tertiary cation by dehydration would induce a Wagner–Meerwein migration and elimination sequence to generate the Δ^{14} double bond. After oxidation at C12 and subsequent Bayer–Villiger rearrangement, a δ-lactone would be formed which could be transformed to **32** *via* hydrolysis, oxidation of C11, epimerization at C9 and dehydrogenation. Contrarily, for the related natural product atheronal B (not shown), the Hock reaction has been postulated to account for the formation of the cyclopentene carbaldehyde motif.[16,17]

3.4.3 Biological studies. Solanioic acid (**32**) was tested *in vitro* against a small panel of human pathogens. In these experiments, **32** showed minimal inhibitory concentrations (MIC) of 1 μg mL^{-1} against *Bacillus subtilis*, *Staphylococcus aureus*, and MRSA. Weaker activity was observed against the yeast *Candida albicans* (16 μg mL^{-1}), whereas no activity against the Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* was observed.

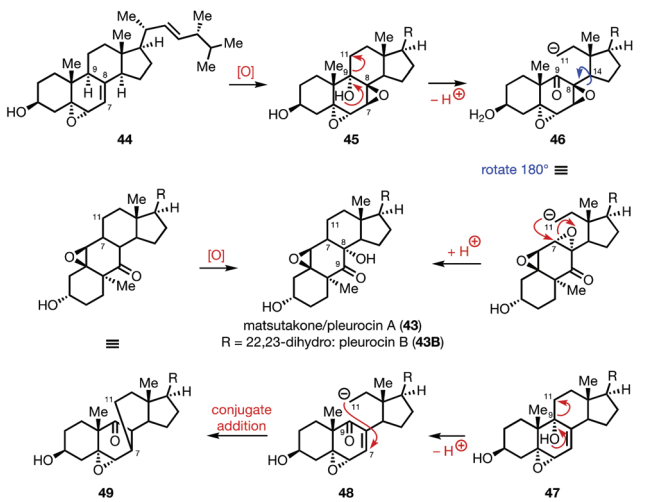
4. Ergostanes with rearranged C-rings

4.1 Matsutakone/pleurocin A and pleurocin B

4.1.1 Isolation and structure elucidation. Matsutakone (**43**, Scheme 6) was isolated by Liu *et al.* in 2017 from the mycorrhizal fungus *Tricholoma matsutake*, an edible mushroom that forms a symbiotic relationship with roots of pine and oak trees.[18] The molecular formula of **43** was determined to be $C_{28}H_{44}O_4$ by HRESIMS indicating seven degrees of unsaturation. Initially, interpretation of ^{1}H- and ^{13}C-NMR spectra led to



Scheme 5 Proposed biosynthesis of solanioic acid (**32**).



Scheme 6 Proposed biosynthetic pathways to matsutakone (**43**).

the conclusion that the new compound is a steroid with a double bond within the steroidal side chain. The COSY-spectrum identified three isolated spin systems. By HMBC the A- and B-ring were determined to be fused at C5–C10 and C- and D-ring at C13–C14. In contrast to the classical steroid nucleus though, the B- and C-ring were fused at C7–C8 instead of C8–C9, thus, **43** exhibits the structure of an 11(9 → 7)*abeo*-ergostane. The double bond in the side chain as well as the fused ring system accounted for six of the seven degrees of unsaturation. The last one was assigned to an epoxide at C5 and C6. The relative stereoconfiguration of **43** was determined by a ROESY experiment, while the absolute stereoconfiguration was determined by comparison of the experimental ECD spectrum with a calculated one [time-dependent density functional theory at B3LYP/6–31G(d,p) level in gas phase with PCM model].

Shortly after the isolation report of matsutakone (**43**), pleurocin A and B (**43** and **43B**), isolated from *Pleurotypus eryngii*, were described by Tanaka *et al.*[19] Spectral data as well as a single crystal X-ray diffraction of the *p*-bromobenzoyl derivative of pleurocin A confirmed the identity of matsutakone (**43**) and pleurocin A. Pleurocin B (**43B**) exhibits a similar structure but possesses a hydrogenated side chain.

4.1.2 Proposed biosynthetic pathway. Liu *et al.* proposed a biosynthesis starting from co-isolated 5,6-epoxy ergosterol (**44**, Scheme 6).[18] After oxidation of C7, C8, and C9, the C9–C11 bond would be cleaved under basic conditions leaving an carbanion on C11. The latter could open the epoxide at C8 after a 180° rotation around the C8–C13 bond to yield matsutakone (**43**). Tanaka *et al.* proposed a slightly different mechanism for the formation of **43**.[19] The oxidation of ergosterol would give **47** in which the C9–C11 bond would be cleaved to also give a carbanion at C11. After rotation around the C8–C13 bond, a conjugate addition should take place. Subsequent hydroxylation on C8 would lead to the formation of **43**.

4.1.3 Biological studies. Matsutakone (**43**) was tested against acetylcholinesterase (AChE) and, as positive control, tacrine was used in the assay. **43** showed an IC_{50} of 20.9 μM. Since decrease of acetylcholine (ACh) content can cause neurodegenerative diseases such as Alzheimer's, **43** may show beneficial effects and slow down their progression.[18] Tanaka *et al.* tested **43** and related congeners for inhibitory activity of NO production in LPS-stimulated macrophages. Both compounds showed similar effects as L-NMMA (IC_{50}: **43**: 25.0 μM, **43B**: 23.6 μM) and negligible cytotoxicity at these concentrations.[19]

4.2 Leptosterol A, ganoderin A, and pinnisterol A, D, and E

4.2.1 Isolation and structure elucidation. In 2011, Duh *et al.* reported the isolation of the ergostane-type steroid leptosterol A (**50**, Fig. 3) from the soft coral *Sinularia leptoclados*.[20] Combining the results of HRESIMS and NMR studies, the compound was found to contain a tricyclic system and by comparison of the obtained data with those of known secosteroids, the 9,11-seco motif was identified. The absolute configuration of C24 was assigned with the diagnostic chemical shift of the C28 methyl group leading to the proposed structure of **50**.

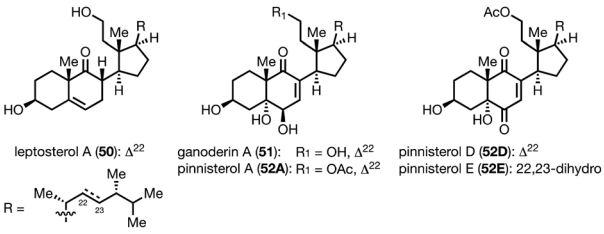


Fig. 3 Proposed structures of leptosterol A (**50**), ganoderin A (**51**) and pinnisterol A, D, and E (**52A**, **52D**, **52E**).

In 2016, the Shi group isolated structurally related ganoderin A (**51**) from the spore oil of *Ganoderma lucidum*.[21] Again, analytical methods (HRESIMS and NMR) and comparison of the obtained data with those of published natural products allowed for the proposal of the structure **51**.

Eventually, Sung *et al.* were able to isolate ergostane-type 9,11-secosteroids pinnisterol A, D and E (**52A**, **52D**, and **52E**) from the gorgonian coral *Pinnigorgia* sp. in 2016[22] and 2017,[23] respectively. Once more, comparison of the obtained analytical data (HRESIMS and NMR) enabled the assignment as 9,11-secosteroids.

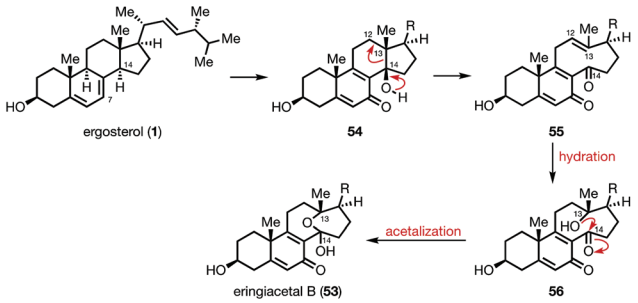
4.2.2 Biosynthetic proposal. 9,11-Secosteroids are typically formed by an oxidative cleavage of the C9–C11 bond (Scheme 3).

4.2.3 Biological studies. Leptosterol A (**50**) has been evaluated for cytotoxicity against several cancer cell lines (P-388, A-459, and HT-29) and potential antiviral activity against HCMV, but did not show any appreciable effects.[20]

Pinnisterol A, D, and E (**52A**, **52D**, **52E**) were tested regarding their cytotoxic effect on hepatic stellate cell lines (HSC-T6), which are known to be the major cell type involved in liver fibrosis. Testing at a concentration of 10 μM, **52A** and **52D** could significantly decrease the cell viability (IC_{50}>10 (ref. 22) and 3.93 μM (ref. 23)) whereas **52E** did not show any effect. In anti-inflammatory testing, **52A** and **52E** displayed an inhibitory effect on the release of elastase (IC_{50} = 3.32 (ref. 22) and 2.33 μM (ref. 23)). However, only **52A** showed a notable effect regarding the generation of superoxide anions by human neutrophils (IC_{50} = 2.33 μM).[22]

4.3 Eringiacetal B

4.3.1 Isolation and structure elucidation. In 2015, Tanaka *et al.* isolated eringiacetal B (**53**, Scheme 7) from *Pleurotypus eryngii*.[19] By HREIMS the molecular formula of the natural product was determined to be $C_{28}H_{42}O_4$ indicating eight degrees of unsaturation. UV- and IR-spectra of the compound suggested the presence of hydroxy groups and a conjugated enone system. By interpretation of 1D- and 2D-NMR spectra, the A/B-ring structure and the side chain was determined as 3β-hydroxy-(22*E*,24*R*)-ergosta-5,8,22-trien-7-one, with deviations in the C- and D-ring. These differences were assigned to the fact that instead of the C13–C14 bond an epoxy bridge was present, making **53** a 13,14-seco-13,14-epoxy steroid. With a NOESY experiment it was possible to determine the relative



Scheme 7 Biosynthetic pathway to eringiacetal B (**53**).

stereoconfiguration of **53** to be (13*R*,14*R*). The only other 13,14-seco-13,14-epoxy-steroid known is gloeophyllin I, isolated in 2015 by Liu *et al.*[24]

4.3.2 Proposed biosynthetic pathway. The proposed biosynthesis starts from abundant ergosterol (**1**), which is oxidized to a C14 alcohol that was co-isolated during the study (Scheme 7). After cleavage of the C13–C14 bond, an alkene in C12–C13 position is formed. Hydration of the Δ^{12} double bond and subsequent acetalization would give eringiacetal B (**53**).

4.3.3 Biological studies. Eringiacetal B (**53**) exhibits a more potent inhibitory activity on production of NO in macrophages stimulated with LPS (IC_{50} = 13.0 μM) than tilarginine acetate (L-NMMA) (IC_{50} = 23.9 μM) and shows almost no cytotoxicity at concentrations lower than 30 μM.

4.4 Dankasterone A and B

4.4.1 Isolation and structure elucidation. In 1999, Numata *et al.* were able to isolate dankasterone A (**57A**, Scheme 8) from a strain of *Gymnascella dankaliensis* that had originally been separated from the sponge *Halichondria japonica*.[25] To elucidate its correct structure, a combination of HREIMS and NMR studies as well as single crystal X-ray diffraction were used. Building on these results, Numata and co-workers were able to report the first 13(14 → 8)*abeo*-ergostane type natural product containing a five-membered C- and a six-membered D-ring. When the same group reported the isolation of dankasterone B (**57B**) in 2007, the absolute configuration of C24 in **57A** was reassigned from (*S*) to (*R*).[26] Similarities of the obtained analytical data of dankasterone A and B suggested that the two compounds only differ in the degree of desaturation of the A-ring (A: Δ^4, B: 4,5-dihydro).

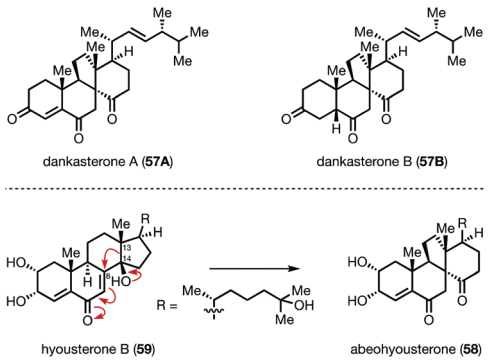
4.4.2 Proposed biosynthetic pathway. The isolation chemists only shortly mention a possible formation of the rearranged steroidal skeleton. Meanwhile, the Baker group proposed the vinylogous α-ketol-rearrangement shown in Scheme 8 as a possible biosynthetic pathway in their publication concerning the isolation of structurally related abeohyousterone (**58**).[27] Their suggestion is supported by the fact that hyousterone B (**59**), the likely precursor, was co-isolated from the same tunicate.

4.4.3 Biological studies. Dankasterone A and B (**57A** and **57B**) both exhibit significant cytotoxicity in the P388 lymphocytic leukemia test system (ED_{50} = 2.2 and 2.8 μg mL^{-1}, respectively). Additionally, the former shows appreciable growth inhibition against human cancer cell lines (MG MID 5.41).

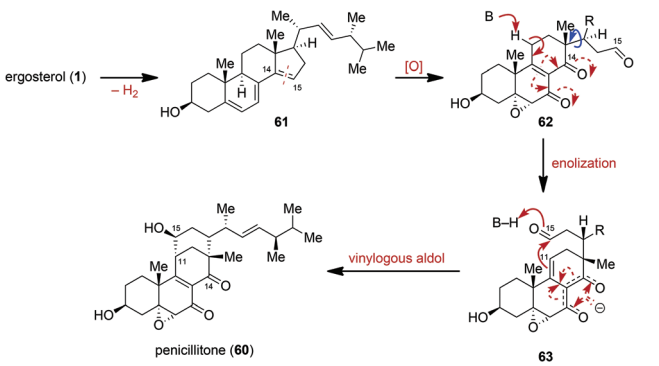
5. Ergostanes with rearranged D-rings

5.1 Penicillitone

5.1.1 Isolation and structure elucidation. Penicillitone (**60**, Scheme 9) was isolated in 2014 by Wei *et al.* from cultures of the fungus *Penicillium purpurogenum* SC0070.[28] The molecular formula was determined by HRESIMS to be $C_{28}H_{40}O_5$. The ^{1}H- and ^{13}C-NMR spectra as well as the HSQC spectrum showed the presence of six methyl groups, three oxymethines, a *trans*-configured double bond, two conjugated carbonyls and two quaternary olefinic carbons. Together with the interpretation of the HMBC spectrum, it was possible to identify the B/C-ring system as a hexahydronaphthalene-1,8-dione resulting in the proposal of an unprecedented 15(14 → 11)*abeo*-steroid structure for **60**. The relative configuration determined by NOESY matched the one of the lowest energy conformer generated by MMFF conformational search followed by DFT calculation at B3LYP/6-31G(d,p) level. The ECD calculation of this lowest energy conformer was consistent with the measured ECD-



Scheme 8 Dankasterone A and B (**57A** and **57B**), hypothesized origin of the 13(14 → 8)*abeo*-skeleton.



Scheme 9 Biosynthetic pathway to penicillitone (**60**).

spectrum and, thus, led to the proposed absolute configuration. Further proof for the structure of **60** was obtained by single crystal X-ray diffraction.

5.1.2 Proposed biosynthetic pathway. Wei *et al.* proposed the biosynthesis of **60** to start from abundant fungal steroid ergosterol (**1**, Scheme 9). After dehydrogenation, an oxidative cleavage of the Δ^{14} double bond would give diketo aldehyde **62**. The isolation team emphasized this transformation as the key step of the sequence, as it would increase the acidity of the proton in γ-position to both carbonyl groups. As a consequence, enolization is facilitated. The conjugate enolate would then react in an intramolecular vinylogous aldol addition with the aldehyde to give penicillitone (**60**).

5.1.3 Biological studies. Penicillitone (**60**) was tested for its growth inhibitory activity against A549 (lung carcinoma), HepG2 (liver cancer) and MCF-7 (breast cancer) cells using the MTT method. The compound showed good potency against these cell lines with IC_{50} values of 5.57, 4.44 and 5.98 μM, respectively. **60** also possessed dose-dependent anti-inflammatory activity on the production of TNF-α and IL-6 in LPS-stimulated RAW 264.7 macrophages.

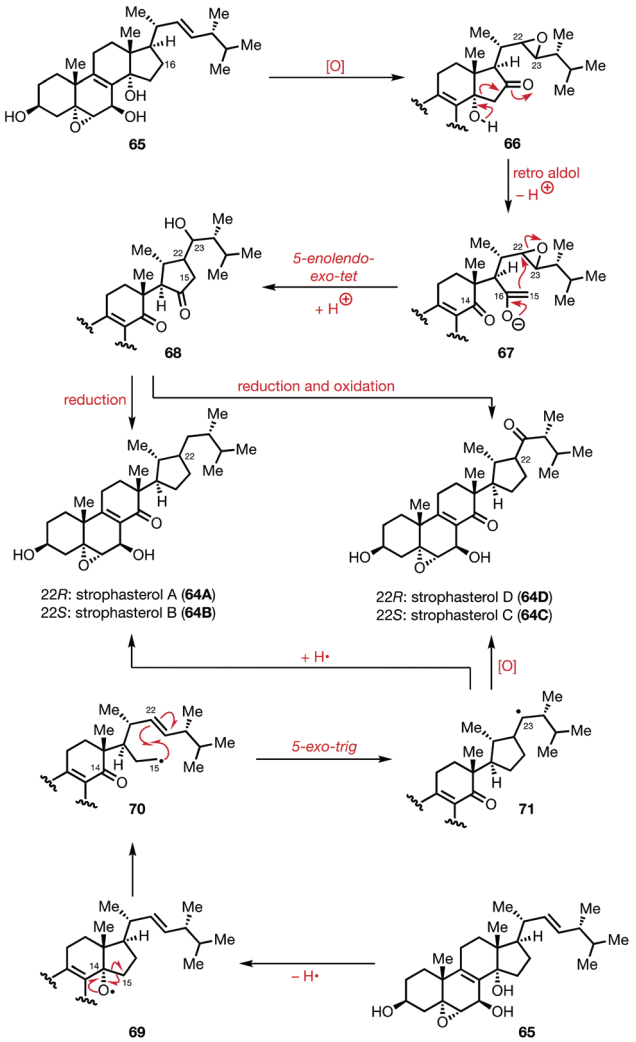
5.2 Strophasterol A–D and glaucoposterol A

5.2.1 Isolation and structure elucidation. The strophasterols A–D (**64A–D**, Scheme 10) were isolated in 2012 by Kawagishi *et al.* from the edible mushroom *Stropharia rugosoannulata*.[29] The molecular formula of **64A** was determined as $C_{28}H_{44}O_4$ by HRESIMS, suggesting seven degrees of unsaturation. Interpretation of a variety of 1D- and 2D-NMR spectra led to the conclusion that **64A** has the structure of a sterol, but exhibits an isolated five-membered ring instead of the typical fused steroidal D ring. This 15(14 → 22)*abeo*-steroid structure was confirmed by single crystal X-ray diffraction of the bis (*p*-bromo)benzoate derivative.

HRESIMS indicated strophasterol B (**64B**) to have the same molecular formula as **64A**. The NMR data led the isolation team to the conclusion that **64B** has the same connectivity as **64A**, but differences in the ^{1}H- and ^{13}C-NMR chemical shifts of C20–C23 indicated **64B** to be a diastereomer. This assumption was proven by single crystal X-ray diffraction one year after the first isolation report.[30]

For strophasterol C and D (**64C** and **64D**) the molecular formula was determined by HRESIMS as $C_{28}H_{44}O_5$, indicating the presence of eight degrees of unsaturation. Comparison of the 1D- and 2D-NMR spectra of **64C** and **64D** with those of **64A** and **64B** suggested the same carbon skeleton, but **64C** and **64D** to possess an additional carbonyl group (C23) instead of the methylene group in **64A** and **64B**. The stereoconfiguration for **64C** and **64D** was not determined by Kawagishi *et al.*, but Aung *et al.* proposed the configuration of (3*S*,5*R*,6*S*,7*R*,10*R*,13*R*,17*R*,20*S*,22*S*,24*R*) for **64C**. This remains to be further corroborated by synthesis or single crystal X-ray diffraction, though.[31]

Glaucoposterol A (not shown), another member of the strophasterol family was isolated in 2017 by Aung *et al.* from *Cortinarius glaucopus* (Schaeff.) Fr.[31] The structure of glaucoposterol A with a hydroxy group at C23 was elucidated by HRFABMS as well as 1D- and 2D-NMR techniques. Its absolute stereoconfiguration remains undetermined.



Scheme 10 Proposed biosynthetic pathways for strophasterol A–D (**65A–65D**) (alleged stereoconfiguration shown for **65C** and **65D**).

5.2.2 Proposed biosynthetic pathway. Kawagishi *et al.* proposed two different pathways for the biosynthesis of the strophasterol class of natural products (Scheme 10).[30] The original proposal starts with the oxidation of **65**, a compound previously isolated from *Stropharia rugosoannulata*. After a retro aldol reaction, a 5-*enolendo-exo-tet* cyclization might lead to the formation of the five-membered ring. Reduction or a reduction/oxidation sequence would then result in the formation of the natural products **64A–D**.

As 5-*enolendo-exo-tet* cyclizations are disfavored according to Baldwin's rules, a radical pathway was also suggested. This hypothesis starts with the formation of tertiary alkoxy radical **69**, which would undergo β-scission to yield a carbonyl group and a primary radical while the C14–C15 bond would be cleaved in the process. Radical 5-*exo-trig* cyclization (favored by Baldwin's rules) and quenching the thus-formed secondary radical **71** with

a hydrogen atom or oxidation would then furnish the strophasterols. This second proposal requires the formation of a (high-energy) primary radical from an alkoxy radical as a key step.

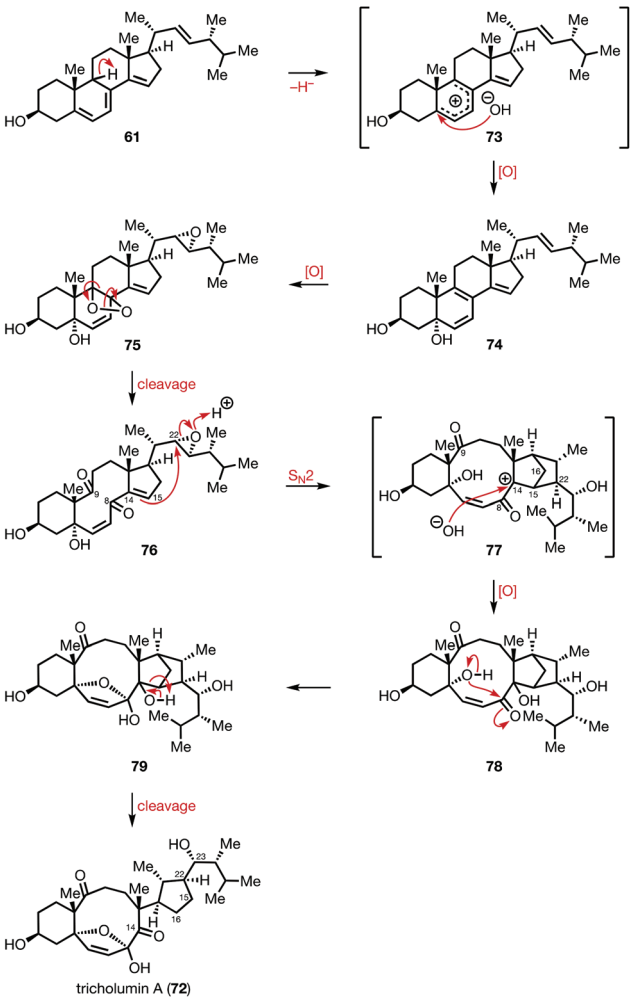
5.2.3 Biological studies. Strophasterol A (**64A**) shows a dose-dependent inhibitory effect on thapsigargin toxicity, which indicates that the compound may be able to reduce endoplasmatic reticulum associated stress and, thus, potentially prevent apoptotic pathways in neural cells.[30] This would make **64A** a possible lead for the treatment of neurodegenerative diseases such as Alzheimer's. Furthermore, **64A** shows weak activity against MRSA.

5.2.4 Semisyntheses. Up to date, two semisyntheses of **64A** and one of **64B** have been reported, both starting from the abundant fungal metabolite ergosterol. Our group used the innate reactivity of a α-chloro-γ-hydroxy-δ-keto enone for the scission of the C14–C15 bond *via* an α-ketol rearrangement to yield a keto acid.[32] The characteristic five-membered ring was constructed by a bio-inspired radical cyclization of the corresponding iodide. Further transformations gave **64A** in 15 steps and an overall yield of 6%. Kuwahara *et al.* cleaved the C14–C15 bond by oxidation of an epoxide.[33] An acyl radical cyclization yielded a cyclopentanone which could be stereoselectively hydrogenated using either one of two different catalysts. One epimer was transformed by several oxidation steps to **64A** (17 steps, 1.8% overall yield), the other one to **64B** (17 steps, 1.1% overall yield).

5.3 Tricholumin A

5.3.1 Isolation and structure elucidation. Tricholumin A (**72**, Scheme 11) was isolated in 2018 by Ji *et al.* from the fungus *Trichoderma asperellum* cf44-2, an endophyte from the marine brown alga *Saragassum* sp.[34] The molecular formula was determined to be $C_{28}H_{44}O_6$ by HRESIMS. The ^{1}H-NMR spectrum together with HSQC data revealed the presence of two oxymethines as well as two olefinic protons. COSY correlations revealed the presence of a cyclopentyl unit. A dihydrofuran moiety and a hemiketal were assigned by comparison of the NMR data with literature. Combining all structural features identified by NMR techniques, tricholumin A (**72**) is proposed to be a 15(14 → 22)*abeo*-8,9-secosteroid which can possibly be traced back to ergosterol. This 15(14 → 22)*abeo*-motif is also found in the strophasterol family of natural products, but the isolators did not comment on a possible biosynthetic connection.[28] The relative stereoconfiguration was determined by NOE correlations for all but the C23 and C24 stereocenters. (The numbering of the carbon atoms in this review was made according to the IUPAC rules and does not reflect the isolators' proposal.) The absolute configuration was assigned by single crystal X-ray diffraction using Cu Kα radiation. Further prove was gained by comparison of the measured ECD spectrum with a simulated one for an energy-minimized conformer (obtained by conformational optimization at the B3LYP/6-31G (d) level in MeOH with the integral equation formalism variant of the polarizable continuum model).

5.3.2 Proposed biosynthetic pathway. Ji *et al.* proposed a biosynthesis for tricholumin A (**72**) starting from ergosterol (**1**) that was also isolated from the same organism (Scheme 11).



Scheme 11 Proposed biosynthetic pathway for tricholumin A (**72**).

Thus, after dehydrogenation, a Δ^{14} double bond would be formed leading to **61**. Hydride abstraction might lead to mesomerically stabilized carbocation **73** so that a hydroxide anion could attack at C5. Oxidation of the Δ^{22} and Δ^{8} double bonds by dioxygenases and monooxygenases might then lead to dioxetane **75**. Cleavage of the C8–C9 bond would give diketone **76**, which could then, according to Ji *et al.*, react in an intramolecular S$_N$2 reaction to open the side chain epoxide. Carbocation **77** might then be trapped by a hydroxide ion. After hemiketal formation, the C14–C15 bond would be cleaved to yield tricholumin A (**72**). Since an electron deficient double bond rarely shows the activity as a nucleophile in a S$_N$2 reaction (**76** to **77**), the construction of the D-ring as proposed for the strophasterols could alternatively be considered.[29]

5.3.3 Biological studies. Tricholumin A (**72**) was tested for its inhibitory activity against microalgae and pathogenic bacteria that threaten marine aquacultures. It has shown to inhibit four phytoplankton species with IC_{50} values between 0.27 and 0.59 μM. Additionally, a weak antibacterial activity against *Vibro harveyi*, *V. splendidus*, and *Pseudoalteromonas citrea* was observed. The antifungal activity against *Glomerella*

cingulate, a phytopathogen in agriculture, was determined to be 12 μg mL^{-1} (MIC).

6. Conclusion

In recent years, several new rearranged ergostane-type natural products have been reported and, in many cases, their respective biological activities were studied to reveal new leads for future drug discovery programs, *e.g.* for the treatment of cancer, neurodegenerative processes, bacterial infections, and inflammatory diseases. While the classical steroidal skeleton is long-known to be a privileged lead structure for molecular entities with diverse and potent biological activities, it becomes ever more obvious that this is also true for the rearranged derivatives. Nature has chosen to synthesize these natural products from the parent steroids such as ergosterol. The organic chemist can profit from this lesson, do likewise, and contribute designed compounds for future drug discovery programs.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

The authors thank Dr R. Heinze for helpful discussions. F.R. thanks the Studienstiftung des Deutschen Volkes for a PhD scholarship.

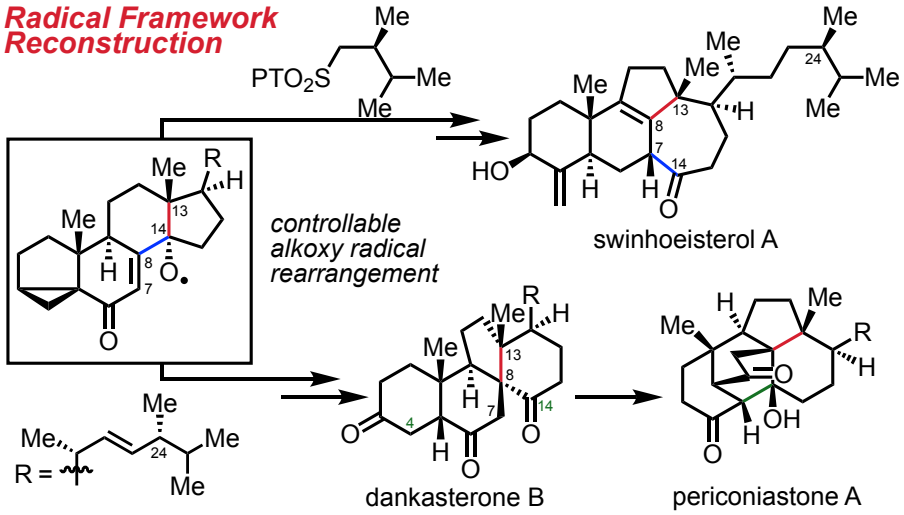
Notes and references

1 G. P. Moss, *Pure Appl. Chem.*, 1989, **61**, 1783–1822.
2 B. K. Chhetri, S. Lavoie, A. M. Sweeney-Jones and J. Kubanek, *Nat. Prod. Rep.*, 2018, **35**, 514–531.
3 L. Chen, H. He and F. Qiu, *Nat. Prod. Rep.*, 2011, **28**, 705–740.
4 N. Dhar, S. Razdan, S. Rana, W. W. Bhat, R. Vishwakarma and S. K. Lattoo, *Front. Plant Sci.*, 2015, **6**, 1031.
5 Z. Hu, Y. Wu, S. Xie, W. Sun, Y. Guo, X.-N. Li, J. Liu, H. Li, J. Wang, Z. Luo, Y. Xue and Y. Zhang, *Org. Lett.*, 2017, **19**, 258–261.
6 D. A. Mulholland, B. Parel and P. H. Coombes, *Curr. Org. Chem.*, 2000, **4**, 1011–1054.
7 Q. Luo, Z.-L. Yang, Y.-M. Yan and Y.-X. Cheng, *Org. Lett.*, 2017, **19**, 718–721.
8 Y.-C. Chang, L.-M. Kuo, J.-H. Su, T.-L. Hwang, Y.-H. Kuo, C.-S. Lin, Y.-C. Wu, J.-H. Sheu and P.-J. Sung, *Tetrahedron*, 2016, **72**, 999–1004.
9 A. Kawamura, M. Kita and H. Kigoshi, *Angew. Chem., Int. Ed.*, 2015, **54**, 7073–7076, (*Angew. Chem.*, 2015, **127**, 7179–7182).
10 Z. Lu, X. Zhang, Z. Guo, Y. Chen, T. Mu and A. Li, *J. Am. Chem. Soc.*, 2018, **140**, 9211–9218.
11 T. Ohyoshi, H. Tano, K. Akemoto and H. Kigoshi, *Tetrahedron Lett.*, 2017, **58**, 3327–3329.
12 M. Kita, A. Kawamura and H. Kigoshi, *Tetrahedron Lett.*, 2016, **57**, 858–860.
13 W. Li, W. Zhou, J. Y. Cha, S. U. Kwon, K. H. Baek, S. H. Shim, Y. M. Lee and Y. H. Kim, *Phytochemistry*, 2015, **115**, 231–238.
14 T. Kikuchi, Y. Masumoto, Y. In, K. Tomoo, T. Yamada and R. Tanaka, *Eur. J. Org. Chem.*, 2015, 4645–4649.
15 P. B. Ratnaweera, D. E. Williams, B. O. Patrick, E. D. de Silva and R. J. Andersen, *Org. Lett.*, 2015, **17**, 2074–2077.
16 J. Brinkhorst, S. J. Nara and D. A. Pratt, *J. Am. Chem. Soc.*, 2008, **130**, 12224.
17 S. Tomono, N. Miyoshi, H. Shiokawa, T. Iwabuchi, Y. Aratani, T. Higashi, H. Nukaya and H. Ohshima, *J. Lipid Res.*, 2011, **52**, 87.
18 Z. Z. Zhao, H. P. Chen, B. Wu, L. Zhang, Z. H. Li, T. Feng and J. K. Liu, *J. Org. Chem.*, 2017, **82**, 7974–7979.
19 T. Kikuchi, Y. Horii, Y. Maekawa, Y. Masumoto, Y. In, K. Tomoo, H. Sato, A. Yamano, T. Yamada and R. Tanaka, *J. Org. Chem.*, 2017, **82**, 10611–10616.
20 S.-Y. Cheng, H.-P. Chen, S.-K. Wang and C.-Y. Duh, *Bull. Chem. Soc. Jpn.*, 2011, **84**, 648–652.
21 F.-H. Ge, M.-H. Duan, J. Li and Q.-L. Shi, *J. Asian Nat. Prod. Res.*, 2017, **19**, 1252–1257.
22 Y.-C. Chang, L.-M. Kuo, T.-L. Hwang, J. Yeh, Z.-H. Wen, L.-S. Fang, Y.-C. Wu, C.-S. Lin, J.-H. Sheu and P.-J. Sung, *Mar. Drugs*, 2016, **14**, 1–9.
23 Y.-C. Chang, T.-L. Hwang, L.-M. Kuo and P.-J. Sung, *Mar. Drugs*, 2017, **15**, 1–11.
24 J.-J. Han, L. Bao, Q.-Q. Tao, Y.-J. Yao, X.-Z. Liu, W.-B. Yin and H.-W. Liu, *Org. Lett.*, 2015, **17**, 2538–2541.
25 T. Amagata, M. Doi, M. Tohgo, K. Minoura and A. Numata, *Chem. Commun.*, 1999, 1321–1322.
26 T. Amagata, M. Tanaka, T. Yameda, M. Doi, K. Minoura, H. Ohishi, T. Yamori and A. Numata, *J. Nat. Prod.*, 2007, **70**, 1731–1740.
27 Y. Miyata, T. Diyabalanage, C. D. Amsler, J. B. McClintock, F. A. Valeriote and B. J. Baker, *J. Nat. Prod.*, 2007, **70**, 1859–1864.
28 J. Xue, P. Wu, L. Xu and X. Wei, *Org. Lett.*, 2014, **16**, 1518–1521.
29 J. Wu, S. Tokuyama, K. Nagai, N. Yasuda, K. Noguchi, T. Matsumoto, H. Hirai and H. Kawagishi, *Angew. Chem., Int. Ed.*, 2012, **51**, 10820–10822, (*Angew. Chem.*, 2012, **124**, 10978–10980).
30 J. Wu, H. Kobori, M. Kawaide, T. Suzuki, J.-H. Choi, N. Yasuda, K. Noguchi, T. Matsumoto, H. Hirai and H. Kawagishi, *Biosci., Biotechnol., Biochem.*, 2013, **77**, 1779–1781.
31 H. T. Aung, A. Porta, M. Clericuzio, Y. Takaya and G. Vidari, *Chem. Biodivers.*, 2017, **14**, e1600421.
32 R. C. Heinze, D. Lentz and P. Heretsch, *Angew. Chem., Int. Ed.*, 2016, **55**, 11656–11659, (*Angew. Chem.*, 2016, **128**, 11828–11831).
33 S. Sato, Y. Fukuda, Y. Ogura, E. Kwon and S. Kuwahara, *Angew. Chem., Int. Ed.*, 2017, **56**, 10911–10914, (*Angew. Chem.*, 2017, **129**, 11051–11054).
34 Y.-P. Song, Z.-Z. Shi, F.-P. Miao, S.-T. Fang, X.-L. Yin and N.-Y. Ji, *Org. Lett.*, 2018, **20**, 6306–6309.

Appendix B

Synthesis of Swinhoeisterol A, Dankasterone A and B, and Periconiastone A by Radical Framework Reconstruction

Fenja L. Duecker, Robert C. Heinze, Philipp Heretsch[a]



a Institut für Chemie und Biochemie
Freie Universität Berlin
Takustraße 3, 14195 Berlin, Germany

This article is reproduced with permission from:
F. L. Duecker, R. C. Heinze, P. Heretsch, *J. Am. Chem. Soc.* **2020**, *142*, 104–108.
DOI: 10.1021/jacs.9b12899

Author contribution: This project was designed by Fenja L. Dücker, Robert C. Heinze and Philipp Heretsch. The synthetic work and analytical characterizations were carried out by Fenja L. Dücker. The manuscript was prepared by Fenja L. Dücker, Robert C. Heinze and Philipp Heretsch.

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
Cite This: J. Am. Chem. Soc. 2020, 142, 104−108
pubs.acs.org/JACS

Synthesis of Swinhoeisterol A, Dankasterone A and B, and Periconiastone A by Radical Framework Reconstruction

Fenja L. Duecker, Robert C. Heinze, and Philipp Heretsch*

Institute of Chemistry and Biochemistry, Freie Universität Berlin, Takustraße 3, 14195 Berlin, Germany

Supporting Information

ABSTRACT: A switchable radical framework reconstruction approach to structurally unique 13(14 → 8),14(8 → 7)di*abeo*-steroid swinhoeisterol A was developed. The conversion of an ergostane skeleton proceeded through the intermediacy of a 13(14 → 8)*abeo*-framework as present in the dankasterone and periconiastone family of natural products and features a β scission of a 14-alkoxy radical with concomitant generation of the C8−C13 bond. From this intermediate, and dependent on the conditions employed, the cascade continues with a Dowd−Beckwith rearrangement and leads to the formation of the 13(14 → 8),14(8 → 7)di*abeo*-framework of the swinhoeisterol class of natural products. The synthesis of these frameworks then allowed for efficient access to swinhoeisterol A (**1**), dankasterone A (Δ^4-**2**), dankasterone B (**2**), and periconiastone A (**3**).

Understanding the biogenesis of natural products provides the synthetic organic chemist with inspiration and a benchmark when designing and executing a laboratory synthesis.[1] Within this respect, the *abeo*-steroids, a class of steroid-derived compounds that exhibit one or more C−C bond migrations, still hold much ambiguity. Whether the formation of *abeo*-steroids from the classical steroid backbone involves multiple steps and enzymes or a rearrangement cascade, typically, remains speculative in the absence of biosynthetic intermediates from the producing organism. Quite frequently, polar reactions and pathways are then evoked to account for C−C bond breaking and migratory events while radical alternatives are rarely brought forward.[2,3]

However, radical cyclization events were recently shown to competently allow for diverse framework manipulations in our syntheses of 15(14 → 22)*abeo*-steroid strophasterol A[4] and 11(9 → 7)*abeo*-steroid pleurocin A/matsutakone.[5] In continuation, and to collect more such reactivity evidence for potential radical alternatives in *abeo*-steroid biosynthesis, we now initiate our search for processes in which a cascade of radical rearrangements profoundly alters the steroid framework. With this in mind, the swinhoeisterol class of natural products[6−8] with its unprecedented 6/6/5/7 ring system presented itself as a target and a yet unmet synthetic challenge.[9] These marine metabolites were first isolated and structurally elucidated in 2014 from the sponge *Theonella swinhoei* endemic to the South China Sea.[6] Swinhoeisterol A−F vary in their degree of oxidation with swinhoeisterol A (**1**, Figure 1) and E (not shown) possessing the lowest oxidation level of the class.[6−8] Biological activity has been reported with cytotoxicity toward A549 and MG-63 cells. Furthermore, a polar biogenesis proposal was put forward consisting of the oxidative cleavage of the C8−C14 bond in a steroid precursor, an aldol step, as well as a β scission of an alkoxide, followed by further addition and elimination steps.

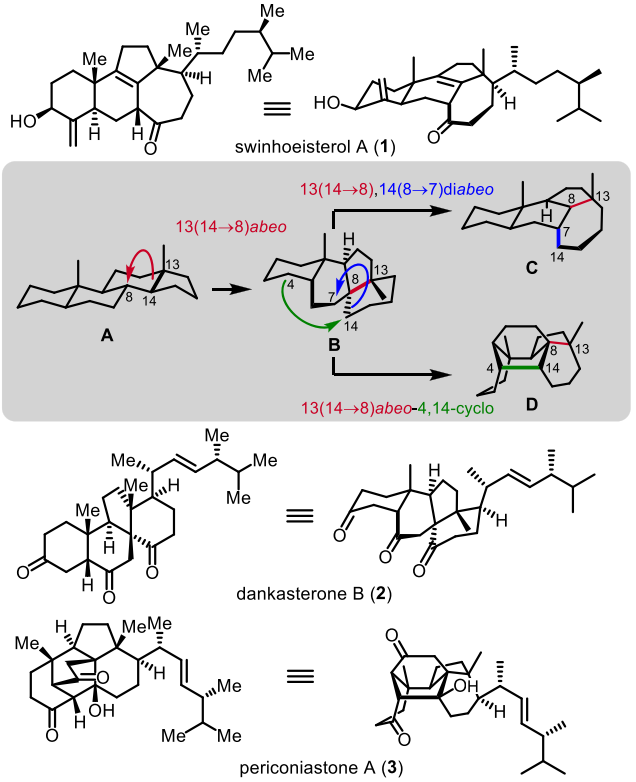


Figure 1. Structures of swinhoeisterol A (**1**), dankasterone B (**2**), and periconiastone A (**3**) and their formal origin.

Formally, the steroidal descent of the swinhoeisterols can be revealed by two migratory events (Figure 1), i.e. (1) cleavage of the C13−C14 bond in a steroid **A** and reconnection of C13 to C8 to furnish **B**, and (2) cleavage of the C8−C14 bond in **B** and reconnection of C14 to C7 to yield **C**. The intriguing structure of intermediate **B** was found in a small collection of natural products[10] with the dankasterones[10a,b] being the most prevalent examples. Dankasterone A (Δ^4-**2**) was isolated in

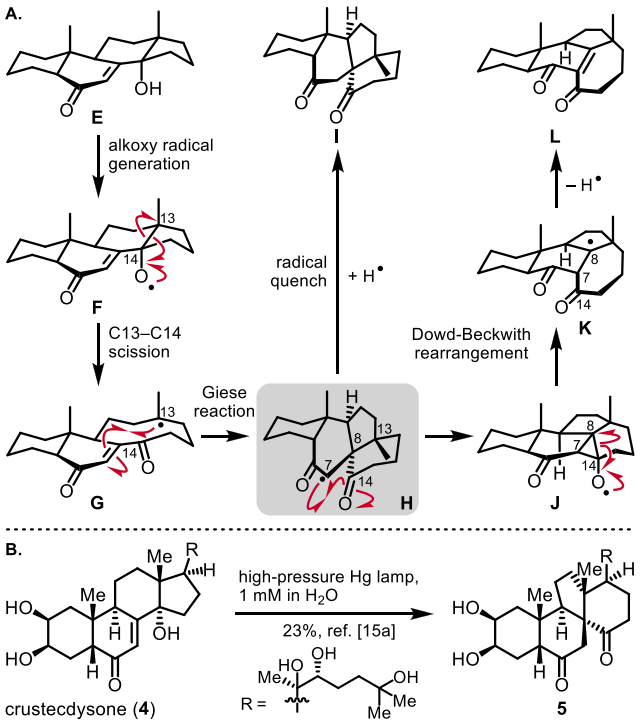
Received: November 29, 2019
Published: December 24, 2019

DOI: 10.1021/jacs.9b12899
J. Am. Chem. Soc. 2020, 142, 104−108

1999 from the *Halichondria* sponge-derived fungus *Gymnascella dankaliensis* endemic to the Sea of Japan,[10a] while dankasterone B (**2**) was isolated in 2007 and has the lowest oxidation level of this class.[10b] Thus, also a certain geographical proximity between the respective grounds of isolation of these and the former natural products is evident. Cytotoxic activities in murine P388 as well as human cancer cell lines CT26 and K562 have been reported.[11] Very recently, periconiastone A (**3**) was isolated from cultures of the endophytic fungus *Periconia* sp. TJ403-rc01 and showed significant antibacterial properties against MRSA (4 μg/mL).[12] Its 13(14 → 8)*abeo*-4,14-cyclo-system **D** was interpreted to derive from dankasterone B (**2**).[13]

We now envisioned the radical cascade shown in Scheme 1A to translate the formal framework reconstruction into a

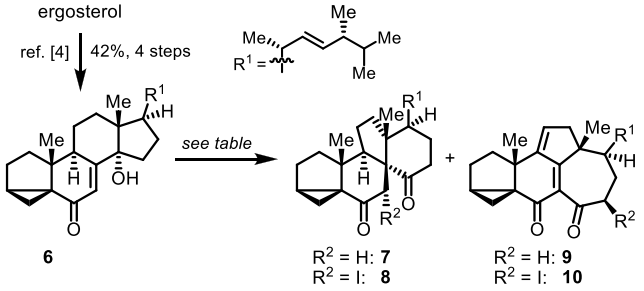
Scheme 1. (A) Mechanistic Rationale of Proposed Radical Rearrangement Leading to the Dankasterone or Swinhoeisterol Frameworks; (B) Danieli's Rearrangement of Crustecdysone (4)[15]



chemical access to all three families of natural products from one precursor. A 14-hydroxy steroid enone of type **E** could thus undergo alkoxy radical initiated β scission of the C13–C14 bond (**F** → **G**), followed by attack of the so-generated C13 centered radical to the enone to give α-keto radical **H**.[14] Radical **H** would act as a hub for accessing either (and selectively) the dankasterone and periconiastone or the swinhoeisterol class of natural products. The former would derive from radical quench of **H** to give the 13(14 → 8)*abeo*-framework **I**. Down this line, Danieli reported a rearrangement of crustecdysone (**4**) to the 13(14 → 8)*abeo*-product **5** under UV-irradiation (Scheme 1B).[15a] If **H** remains unquenched and is persistent for long enough, the cascade could continue via a Dowd–Beckwith rearrangement,[16] consisting of an attack of said α-keto radical to the adjacent oxo functionality to furnish a second tertiary alkoxy radical **J**. This intermediate could undergo another β scission of the cyclopropane and give tertiary radical **K**. Abstraction of an H atom then furnishes the ene dione system **L** possessing the desired 13(14 → 8),14(8 → 7)di*abeo*-structure.

Following this plan, we chose our previously described 14-hydroxy steroid **6**,[4] which we obtained from ergosterol (not shown) in four steps and 42% overall yield, to explore several options for the generation of the 14-alkoxy radical. When treating **6** with $Pb(OAc)_4$ and I_2 under $CaCO_3$-buffered conditions in refluxing benzene,[17] we obtained a complex mixture containing four major products **7**–**10** (Table 1, entry

Table 1. Radical Framework Rearrangement of 14-Hydroxy Steroid 6



		isolated yields			
no.	reagents[a]	7	8	9	10
1	$Pb(OAc)_4$, I_2[b]	15%	8%	52%	10%
2	$PhI(OAc)_2$, I_2	n.o.	76%	n.o.	n.o.
3	HgO, I_2	n.o.	<5%	68%	n.o.

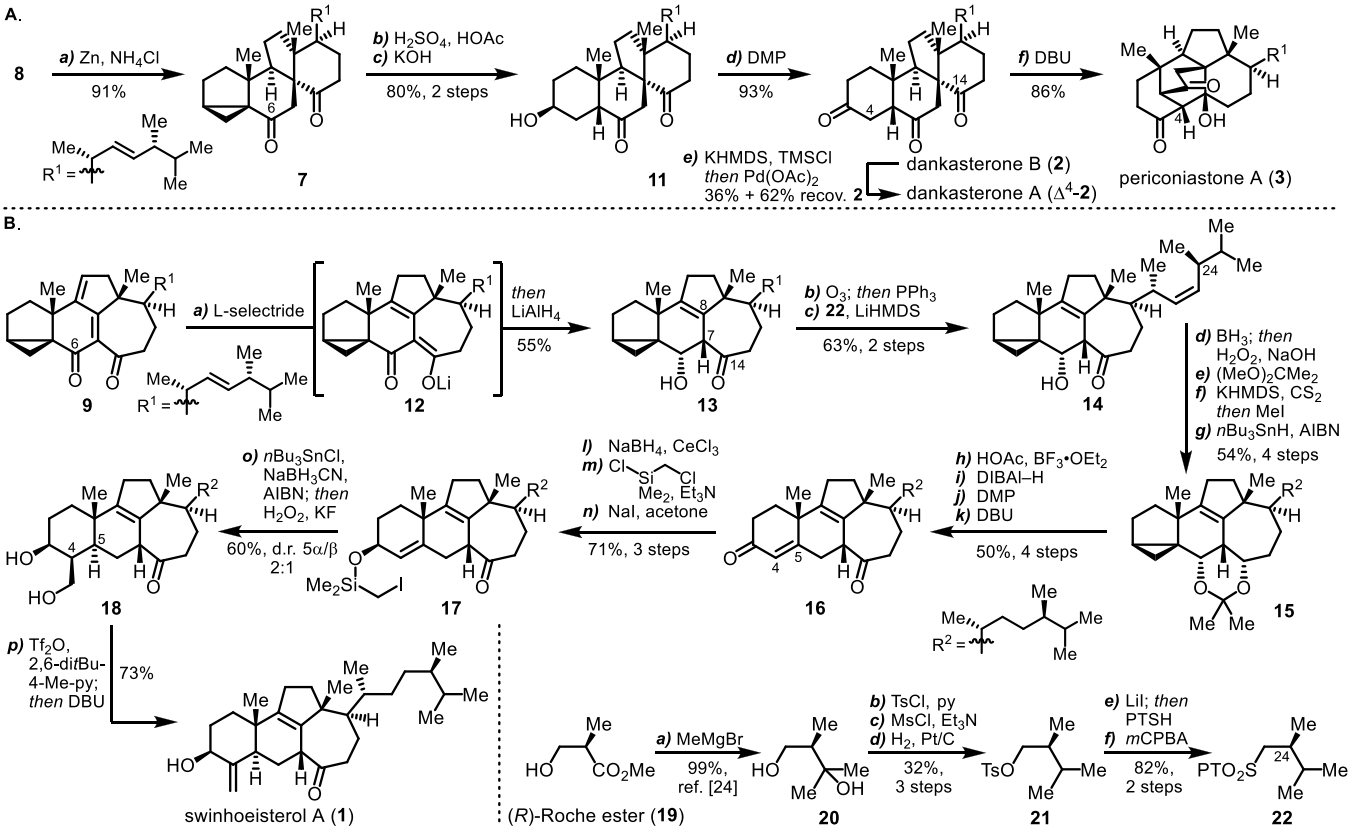
[a]Conditions: C_6H_6, 0.025 M. [b]$CaCO_3$ was added. n.o.: not observed.

1). Careful separation and analysis confirmed the formation of two 13(14 → 8)*abeo*-ergostanes **7** and **8** as minor products of the reaction (for X-ray crystallographic data, see Supporting Information), wherein **8** is the 7-iodo derivative of **7**. Furthermore, **9** was isolated as the main product comprising the desired 13(14 → 8),14(8 → 7)di*abeo*-skeleton but with an additional degree of unsaturation (compared to **L**). Another minor product observed was 15-iodo derivative **10**, which, as **8**, was obtained as a single diastereomer. With this result closely following our initial hypothesis, we aimed at identifying conditions to improve both the yield and selectivity of the cascade. Exposing **6** to (diacetoxyiodo)benzene and iodine in benzene[18] led to complete conversion of the starting material after only 30 min at 25 °C and furnished **8** as the only isolable product in 76% yield (entry 2). Using the same reagents but more forcing conditions only led to complex mixtures, and di*abeo*-products were never observed. On the other hand, selective generation of **9** was achieved when using mercuric oxide and iodine instead (68% of **9**, only trace amounts of **8**, entry 3).[19]

We were now in a position to selectively access key intermediates to synthesize dankasterone and periconiastone as well as swinhoeisterol. Thus, spiro-compound **8** was deiodinated using dissolving metal conditions (Zn, NH_4Cl)[20] to furnish **7** (Scheme 2A). Opening of the *i*-steroid while retaining the oxo functionality at C6 was achieved by applying a strong Brønsted acid (H_2SO_4 in HOAc),[21] and immediate saponification of the so-obtained mixture of partly acetylated **11** gave the desired 5β-isomer in 80% yield (d.r. 19:1, β/α) over two steps. Oxidation of the 3-hydroxy group using Dess–

DOI: 10.1021/jacs.9b12899
J. Am. Chem. Soc. 2020, 142, 104–108

Scheme 2. (A) Synthesis of Dankasterone A (Δ^4-2) and B (2), and Periconiastone A (3); (B) Synthesis of Swinhoeisterol A (1)[a]



[a]See Supporting Information for reagents and conditions; AIBN = 2,2′-azobis(isobutyronitrile), DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAl–H = diisobutylaluminum hydride, DMAP = 4-(dimethylamino)pyridine, DMP = Dess–Martin periodinane, HMDS = 1,1,1,3,3,3-hexamethyldisilazide, *m*CPBA = 3-chloroperbenzoic acid, Ms = methanesulfonyl, PT = 1-phenyl-1*H*-tetrazol-5-yl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, Ts = 4-methylbenzenesulfonyl.

Martin periodinane completed an efficient synthesis of dankasterone B (**2**) in nine steps and 22% total yield from ergosterol. All analytical data matched reported data; furthermore, single-crystal X-ray diffraction analysis allowed for an unequivocal confirmation of the originally assigned structure of **2** (see Supporting Information). From this natural product, dankasterone A (Δ^4-**2**) and periconiastone A (**3**) could be reached in one step. Thus, Saegusa–Ito oxidation [$Pd(OAc)_2$] of a mixture of silyl enol ethers obtained from **2** by treatment with KHMDS and TMSCl/Et_3N gave dankasterone A (Δ^4-**2**, 36% yield) together with recovered dankasterone B (**2**, 62%). On the other hand, when treating **2** with DBU in toluene, intramolecular aldol addition between C4 and C14 occurred and resulted in the formation of periconiastone A (**3**) as a single diastereomer in 86% yield. This supported the original biosynthetic hypothesis and suggests dankasterone B (**2**) to be the precursor of **3**. Furthermore, the easy access to periconiastone A (**3**, 10 steps, 19% total yield from ergosterol) puts us in a position to investigate the biological properties of this structurally unique antibiotic agent.

For the synthesis of swinhoeisterol A (**1**) we employed rearrangement product **9**, being aware that the ergostane-derived stereoconfiguration of remote C24 was inverse to the one in the natural product and, thus, had to be adjusted.[22] Ozonolytic cleavage of steroid side chains and Julia–Kocienski olefination of so-obtained aldehydes with sulfones of type **22** (Scheme 2B) have been reported.[23] The dense functionality of **9** as well as of several downstream intermediates, though, required careful consideration and probing for the right opportunity, if tedious redox or protecting group operations were to be minimized. The required sulfone **22**[23] was accessible through standard transformations starting from (*R*)-Roche ester (**19**), shortening a previously reported sequence to tosylate **21**[24] via diol **20**.[25]

Attempted Julia–Kocienski olefination on most downstream intermediate-derived aldehydes revealed mainly aldol reactivity, an intramolecular process between readily enolizable C7 and the C22 aldehyde (see Supporting Information). Interestingly, and likely attributed to a less favorable conformation, C7 was less prone to engage in such aldol reactions, when the *i*-steroid was still present. Thus, to remove some reactive sites of the diene dione system **9**, a 1,6-reduction with L-selectride was employed to deliver the desired Δ^8 bond and furnish enolate **12**. The lability of the latter toward oxygen required immediate reduction in the same pot ($LiAlH_4$) and gave hydroxy ketone **13**. The enolate in the former intermediate was thus preventing further reduction by masking the 14-oxo moiety, which also inhibited isomerization of the Δ^8 bond. Protonation during workup took place selectively from the β-face. Controlled ozonolysis of the Δ^{22} bond then gave an aldehyde, which was successfully merged with sulfone **22** to yield exclusively (*Z*)-olefin **14** in 63% yield over two steps.[23]

DOI: 10.1021/jacs.9b12899
J. Am. Chem. Soc. 2020, 142, 104–108

Under a variety of conditions, we tried to effect hydrogenation of the (22*Z*)-double bond, which only occurred at elevated hydrogen pressure and when using Pd or Pt catalysts, and was in all cases accompanied by extensive epimerization of C24 (for Pd/C up to 50% epimerization; for Pt/C 25%, see Supporting Information). Since radical methods for hydrogenation also failed,[26] we circumvented this problem via a hydroboration/oxidation−defunctionalization sequence. Thus, hydroboration (giving predominantly 23-OH, as judged by 2D NMR), accompanied by desired reduction of the 14-oxo moiety, oxidative workup, acetonide protection of the 6,14-diol, and, eventually, Barton−McCombie reaction, furnished **15** with the desired saturated side chain and no epimerization. Applying acidic conditions (BF_3·OEt_2, HOAc) then led to the cleavage of the acetonide under concomitant *i*-steroid opening.[27] Removal of the 3-acetyl group in thus-obtained material using nonbasic conditions (DIBAl−H) to prevent reformation of the *i*-steroid was followed by oxidation of the 3- and 14-hydroxy groups and furnished a dione, of which the Δ^5 bond could now readily be isomerized with DBU to provide enone **16**. All that remained was installation of the 4-*exo*-methylene motif under concomitant generation of the 5α-stereoconfiguration. Initially, we explored reductive alkylation protocols. However, this option had been quickly abandoned since the desired 4-(hydroxymethylated) 3-oxo derivative could only be obtained in low and irreproducible yield owing to a high propensity to undergo retro-aldol reaction.[28]

Instead, we aimed for a Nishiyama−Stork radical cyclization[29] and, toward this reaction, selectively reduced enone **16** ($NaBH_4$, $CeCl_3$, complete diastereocontrol for the 3β-isomer) and functionalized the thus-obtained allylic alcohol with (chloromethyl)chlorodimethylsilane. Finkelstein reaction provided necessary iodide **17** and set the stage for cyclization onto the 4-position, for which a protocol employing catalytic quantities of tinhydride (AIBN, $n$$Bu_3$SnCl, $NaBH_3CN$)[30] was crucial for success. The resulting dimethyl oxasilolane (not shown) was directly converted to diol **18** by applying Tamao's conditions.[31] Eventually, treatment of **18** with Tf_2O and DBU effected elimination of the primary alcohol and furnished swinhoeisterol A (**1**) in 21 steps and 1% overall yield starting from ergosterol. Also, we were able to obtain 24-*epi*-swinhoeisterol (24-*epi*-**1**) in 16 steps and 3% overall yield for future biological comparison. In this case, (22*E*)-configurated compound **6** was reduced with H_2, Pt/C (5% epimerization), suggesting a pronounced influence of both, the configuration of Δ^{22} as well as the carbon backbone on the outcome of hydrogenation (see Supporting Information).

In summary, we here describe a switchable and divergent approach to *abeo*-steroids swinhoeisterol A (**1**), dankasterone A (Δ^4-**2**) and B (**2**), and periconiastone A (**3**) through radical framework reconstruction. The choice of reagents for alkoxy radical generation allows an intermediate radical to function as a hub of the whole sequence and lead to the dankasterone, periconiastone, or swinhoeisterol class of natural products. Ongoing work in our laboratory focuses on a synthetic access to the remaining members of each class and studies to reveal the biological target of novel and potent anti-MRSA agent periconiastone A.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b12899.

General methods; detailed experimental studies; experimental procedures and spectral data; comparison of synthetic and natural swinhoeisterol A (**1**), of synthetic and natural dankasterone A (Δ^4-**2**)and B (**2**), and of synthetic and natural periconiastone A (**3**); ^1H and ^{13}C NMR spectra; X-ray crystallographic data; and references (PDF)

X-ray crystallographic data for **8** (1900562) (CIF)

X-ray crystallographic data for **2** (1900563) (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*philipp.heretsch@fu-berlin.de

ORCID

Fenja L. Duecker: 0000-0002-1060-9309
Robert C. Heinze: 0000-0002-3431-816X
Philipp Heretsch: 0000-0002-9967-3541

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by Deutsche Forschungsgemeinschaft (Grant No. HE 7133/7-1), the Boehringer Ingelheim Stiftung (exploration grant to P.H.), and Studienstiftung des Deutschen Volkes (Ph.D. scholarship to R.C.H.). We acknowledge the assistance of the Core Facility BioSupraMol supported by the DFG. We are grateful to Mira Mueller for experimental assistance, to Christiane Groneberg for HPLC separations, and to Prof. Dr. Dieter Lentz for X-ray crystallographic analyses (Freie Universität Berlin).

■ REFERENCES

(1) (a) de la Torre, M. C.; Sierra, M. A. Comments on Recent Achievements in Biomimetic Organic Synthesis. *Angew. Chem., Int. Ed.* **2004**, *43*, 160−181. (b) Razzak, M.; De Brabander, J. K. Lessons and revelations from biomimetic syntheses. *Nat. Chem. Biol.* **2011**, *7*, 865−875. (c) Brown, P. D.; Lawrence, A. L. The importance of asking "how and why?" in natural product structure elucidation. *Nat. Prod. Rep.* **2017**, *34*, 1193−1202.

(2) Duecker, F. L.; Reuß, F.; Heretsch, P. Rearranged ergostane-type natural products: chemistry, biology, and medicinal aspects. *Org. Biomol. Chem.* **2019**, *17*, 1624−1633.

(3) (a) Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S. Radicals: Reactive Intermediates with Translational Potential. *J. Am. Chem. Soc.* **2016**, *138*, 12692−12714. (b) Smith, J. M.; Harwood, S. J.; Baran, P. S. Radical Retrosynthesis. *Acc. Chem. Res.* **2018**, *51*, 1807−1817. (c) Morcillo, S. P. Radical-Promoted C−C Bond Cleavage: A Deconstructive Approach for Selective Functionalization. *Angew. Chem., Int. Ed.* **2019**, *58*, 14044−14054.

(4) Heinze, R. C.; Lentz, D.; Heretsch, P. Synthesis of Strophasterol A Guided by a Proposed Biosynthesis and Innate Reactivity. *Angew. Chem., Int. Ed.* **2016**, *55*, 11656−11659.

(5) Heinze, R. C.; Heretsch, P. Translation of a Polar Biogenesis Proposal into a Radical Synthetic Approach: Synthesis of Pleurocin A/Matsutakone and Pleurocin B. *J. Am. Chem. Soc.* **2019**, *141*, 1222−1226.

(6) Gong, J.; Sun, P.; Jiang, N.; Riccio, R.; Lauro, G.; Bifulco, G.; Li, T.-J.; Gerwick, W. H.; Zhang, W. New Steroids with a Rearranged Skeleton as (h)P300 Inhibitors from the Sponge *Theonella swinhoei*. *Org. Lett.* **2014**, *16*, 2224−2227.

(7) Li, J.; Tang, H.; Kurtán, T.; Mándi, A.; Zhuang, C.-L.; Su, L.; Zheng, G.-L.; Zhang, W. Swinhoeisterols from the South China Sea Sponge *Theonella swinhoei*. *J. Nat. Prod.* **2018**, *81*, 1645−1650.

DOI: 10.1021/jacs.9b12899
J. Am. Chem. Soc. 2020, 142, 104−108

(8) In an earlier patent (Zhang, W.; Sun, P.; Gong, J.; Tang, H. Preparation of four-ring fused compounds as antitumor, antifungal, antibacterial, and antiinflammatory agents. PCT Int. Appl. WO 2015124037 A1, August 27, 2015), isolation and structural assignment of three additional swinhoeisterols was reported. These were then named swinhoeisterol C, D, and E. Reference 6 neither cites this patent nor does it adhere to this nomenclature.

(9) Takano, A.; Zhao, Y.; Ohyoshi, T.; Kigoshi, H. Synthetic studies toward swinhoeisterol A, a novel steroid with an unusual carbon skeleton. *Tetrahedron Lett.* **2019**, *60*, 591−593.

(10) (a) Amagata, T.; Doi, M.; Tohgo, M.; Minoura, K.; Numata, A. Dankasterone, a new class of cytotoxic steroid produced by a *Gymnascella* species from a marine sponge. *Chem. Commun.* **1999**, 1321−1322. (b) Amagata, T.; Tanaka, M.; Yamada, T.; Doi, M.; Minoura, K.; Ohishi, H.; Yamori, T.; Numata, A. Variation in Cytostatic Constituents of a Sponge-Derived *Gymnascella dankaliensis* by Manipulating the Carbon Source. *J. Nat. Prod.* **2007**, *70*, 1731−1740. (c) Miyata, Y.; Diyabalanage, T.; Amsler, C. D.; McClintock, J. B.; Valeriote, F. A.; Baker, B. J. Ecdysteroids from the Antarctic Tunicate *Synoicum adareanum*. *J. Nat. Prod.* **2007**, *70*, 1859−1864. (d) Hu, Z.; Wu, Y.; Xie, S.; Sun, W.; Guo, Y.; Li, X.-N.; Liu, J.; Li, H.; Wang, J.; Luo, Z.; Xue, Y.; Zhang, Y. Phomopsterones A and B, Two Functionalized Ergostane-Type Steroids from the Endophytic Fungus *Phomopsis* sp. TJ507A. *Org. Lett.* **2017**, *19*, 258−261.

(11) Lee, T.-H.; Chen, C.-C.; Chen, J.-J.; Liao, H.-F.; Chang, H.-S.; Sung, P.-J.; Tseng, M.-H.; Wang, S.-Y.; Ko, H.-H.; Kuo, Y.-H. New and Cytotoxic Components from Antrodia camphorata. *Molecules* **2014**, *19*, 21378−21385.

(12) Gao, W.; Chai, C.; He, Y.; Li, F.; Hao, X.; Cao, F.; Gu, L.; Liu, J.; Hu, Z.; Zhang, Y. Periconiastone A, an Antibacterial Ergosterol with a Pentacyclo[8.7.0.0^{1,5}.0^{2,14}.0^{10,15}]heptadecane System from *Periconia* sp. TJ403-rc01. *Org. Lett.* **2019**, *21*, 8469−8472.

(13) The authors of ref 12 do not indentify **2** as dankasterone B and do not cite its seminal isolation report (ref 10b).

(14) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P. Ed.; Academic Press: New York, 1980; Vol. I, p 161. (b) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. Some guidelines for radical reactions. *J. Chem. Soc., Chem. Commun.* **1980**, 482−483. (c) Giese, B. Formation of CC Bonds by Addition of Free Radicals to Alkenes. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753−764.

(15) (a) Canonica, L.; Danieli, B.; Lesma, G.; Palmisano, G. Unusual photochemical behaviour of the enone chromophore of the insect moulting hormone 20α-hydroxyecdysone. *J. Chem. Soc., Chem. Commun.* **1985**, 1321−1322. (b) Canonica, L.; Danieli, B.; Lesma, G.; Palmisano, G.; Mugnoli, A. Fe(II)-Induced Fragmentation Reaction of γ-Hydroperoxy-α,β-enones. Part 1. Synthesis of 13(14→8)-*abeo*-Steroids. *Helv. Chim. Acta* **1987**, *70*, 701−716. (c) For a recent example, see: Savchenko, R. G.; Kostyleva, S. A.; Apaeva, A. V.; Mesheryakova, E. S.; Tukhbatullin, A. A.; Odinokov, V. N.; Parfenova, L. V. Sonochemically assisted 2,3-dideoxygenation and skeletal rearrangement of ecdysteroid derivatives. *Ultrason. Sonochem.* **2019**, *52*, 505−511.

(16) (a) Dowd, P.; Choi, S.-C. Free radical ring expansion by three and four carbons. *J. Am. Chem. Soc.* **1987**, *109*, 6548−6549. (b) Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S.; Westwood, S. W. Cyano or acyl group migration by consecutive homolytic addition and β-fission. *J. Chem. Soc., Chem. Commun.* **1987**, 666−667. (c) Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. Rearrangement of suitably constituted aryl, alkyl, or vinyl radicals by acyl or cyano group migration. *J. Am. Chem. Soc.* **1988**, *110*, 2565−2575. (d) Dowd, P.; Zhang, W. Free radical-mediated ring expansion and related annulations. *Chem. Rev.* **1993**, *93*, 2091−2115.

(17) (a) Meystre, C.; Heusler, K.; Kalvoda, J.; Wieland, P.; Anner, G.; Wettstein, A. Reaktionen von Steroid-Hypojoditen II, Über die Herstellung 18-oxygenierter Pregnanverbindungen. *Helv. Chim. Acta* **1962**, *45*, 1317−1343. (b) Khripach, V. A.; Zhabinskii, V. N.; Fando, G. P.; Khripach, N. B.; Schneider, B. Synthesis of radical oxidation of steroidal 1-oxo-5α-alcohols. *ARKIVOC* **2008**, *ix*, 20−28.

(18) (a) Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. Intramolecular Hydrogen Abstraction. Iodosobenzene Diacetate, An Efficient and Convenient Reagent for Alkoxy Radical Generation. *Tetrahedron Lett.* **1984**, *25*, 1953−1956. (b) Ellwood, C. W.; Pattenden, G. Sequential Alkoxy Radical Fragmentation−Transannular Radical Cyclisation−Ring Expansion Reactions. A New Approach to Bicyclo[5.3.0]decanones and to Bicyclo[6.3.0]-undecanones. *Tetrahedron Lett.* **1991**, *32*, 1591−1594. (c) Mowbray, C. E.; Pattenden, G. Polycycle Contruction *via* Cascade Radical Fragmentation-Transannulation-Cyclisation Processes. *Tetrahedron Lett.* **1993**, *34*, 127−130.

(19) Akhtar, M.; Barton, D. H. R. Reactions at Position 19 in the Steroid Nucleus. A Convenient Synthesis of 19-Norsteroids. *J. Am. Chem. Soc.* **1964**, *86*, 1528−1536.

(20) (a) Inhoffen, H. H.; Zühlsdorff, G. Umwandlungsreaktionen von bromierten Derivaten des Cholesterins, VIII. Mitteil.: Versuche mit 2.2- und 2.4-Dibromiden der Androstan-Reihe. *Ber. Dtsch. Chem. Ges. B* **1943**, *76*, 233−245. (b) Noyori, R.; Hayakawa, Y. Reductive dehalogenation of polyhalo ketones with low-valent metals and related reducing agents. *Org. Reactions* **1983**, *29*, 163−344.

(21) Takatsuto, S. Synthesis of Teasterone and Typhasterol, Brassinolide-related Steroids with Plant-growth-promoting Activity. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1833−1836.

(22) The correctly configurated series of steroid starting materials, *i.e.* campestanes, are neither commercially available nor isolable from a natural source in sufficient purity; see: Kircher, H. W.; Rosenstein, F. U. Purification of Campesterol and Preparation of 7-Dehydrocampesterol, 7-Campestenol and Campestanol. *Lipids* **1974**, *9*, 333−337.

(23) Yakimchyk, V. S.; Kazlova, V. V.; Hurski, A. L.; Savchenko, R. G.; Kostyleva, S. A.; Zhabinskii, V. N.; Khripach, V. A. Enantioselective catalytic approach to the C23-C28 subunit of 24α-methyl steroids. *Steroids* **2019**, *148*, 82−90.

(24) O'Connell, N. M.; O'Callaghan, Y. C.; O'Brien, N. M.; Maguire, A. R.; McCarthy, F. O. Synthetic routes to campesterol and dihydrobrassicasterol: a first reported synthesis of the key phytosterol dihydrobrassicasterol. *Tetrahedron* **2012**, *68*, 4995−5004.

(25) Kutner, A.; Perlman, K. L.; Lago, A.; Sicinski, R. R.; Schnoes, H. K.; DeLuca, H. F. Novel Convergent Synthesis of Side-Chain-Modified Analogues of 1α,25-Dihydroxycholecalciferol and 1α,25-Dihydroxyergocalciferol. *J. Org. Chem.* **1988**, *53*, 3450−3457.

(26) Obradors, C.; Martinez, R. M.; Shenvi, R. A. Ph(*i*-PrO)SiH$_2$: An Exceptional Reductant for Metal-Catalyzed Hydrogen Atom Transfers. *J. Am. Chem. Soc.* **2016**, *138*, 4962−4971.

(27) Hosoda, H.; Yamashita, K.; Chino, N.; Nambara, T. Synthesis of 15-hydroxylated Dehydroepiandrosterone and Androstenediol. *Chem. Pharm. Bull.* **1976**, *24*, 1860−1864.

(28) Trost, B.; Hiemstra, H. Synthetic Studies Toward Taxanes. A Sulfur Based Approach to the Benzilic Acid Rearrangement. *Tetrahedron* **1986**, *42*, 3323−3332.

(29) (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. Silylmethyl Radical Cyclization: New Stereoselective Method for 1,3-Diol Synthesis from Allylic Alcohols. *J. Org. Chem.* **1984**, *49*, 2298−2300. (b) Stork, G.; Kahn, M. Control of ring junction stereochemistry via radical cyclization. *J. Am. Chem. Soc.* **1985**, *107*, 500−501.

(30) (a) Sawamura, M.; Kawaguchi, Y.; Nakamura, E. Conversion of Alkyl Halides into Alcohols Using a Near Stoichiometric Amount of Molecular Oxygen: An Efficient Route to ^{18}O- and ^{17}O-Labeled Alcohols. *Synlett* **1997**, *1997*, 801−802. (b) Corey, E. J.; Suggs, J. W. Method for catalytic dehalogenations via trialkyltin hydrides. *J. Org. Chem.* **1975**, *40*, 2554−2555.

(31) Tamao, K.; Ishida, N.; Kumada, M. (Diisopropoxymethylsilyl)-methyl Grignard Reagent: A New, Practically Useful Nucleophilic Hydroxymethylating Agent. *J. Org. Chem.* **1983**, *48*, 2120−2122.

DOI: 10.1021/jacs.9b12899
J. Am. Chem. Soc. 2020, 142, 104−108

Synthesis of Swinhoeisterol A, Dankasterone A and B, and Periconiastone A by Radical Framework Reconstruction

Fenja L. Duecker, Robert C. Heinze, Philipp Heretsch*

Institute of Chemistry and Biochemistry, Freie Universität Berlin, Takustraße 3, 14195 Berlin, Germany

*Correspondence to: philipp.heretsch@fu-berlin.de

Supporting Information

Table of Contents

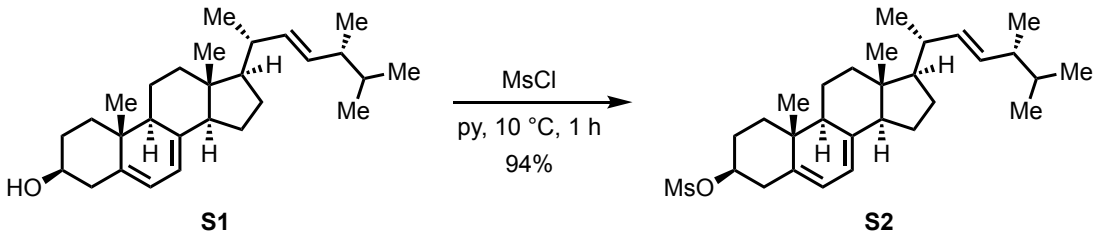
1 General Methods

All reactions sensitive to moisture and/or air were carried out using heat gun dried glassware, an argon atmosphere, and dry solvents. Dry dichloromethane, toluene, and Et_2O were taken from a M. Braun GmbH MB SPS-800 solvent purification system. THF was distilled from sodium and stored over 4 Å molecular sieves. Triethylamine was distilled from CaH_2 and stored over KOH. Ethyl acetate and *n*hexane were purified by distillation on a rotary evaporator. All other solvents and commercially available reagents were used without further purification unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck Silica Gel 50 F245-plates and visualized by fluorescence quenching under UV-light or an aqueous solution of cerium sulfate and phosphomolybdic acid and heat as developing agent. Column chromatographic purification was performed on Macherey-Nagel Silica Gel 60 M (40–60 μm). HPLC separation was performed on a Knauer system with DAD detection at 254 nm. Concentration under reduced pressure was performed by rotary evaporation at 45 °C and appropriate pressure, followed by exposure to high vacuum (10^{-3} mbar) at 25 °C. NMR spectra were recorded on either a Jeol ECX400 (400 MHz), a Jeol ECP500 (500 MHz), a Bruker AVANCE III 500 (500 MHz), a Varian INOVA600 (600 MHz) or a Bruker AVANCE III 700 (700 MHz, with CryoProbe) spectrometer. Chemical shifts δ are reported in parts per million (ppm) and are referenced using residual undeuterated solvent ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; pyridine-d_5: δ_H = 8.74 ppm, δ_C = 150.35 ppm; unless otherwise stated) as an internal reference at 298 K. The given multiplicities are phenomenological; thus the actual appearance of the signals is stated and not the theoretically expected one. The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, and combinations thereof. In case no multiplicity could be identified, the chemical shift range of the signal is given (m = multiplet). Infrared (IR) spectra were measured on a Jasco FT/IR-4100 Type A spectrometer with a TGS detector. Wavenumbers $\tilde{\nu}$ are given in cm^{-1} and intensities are as follows: s = strong, m = medium, w = weak. High-resolution mass spectra (HRMS) were recorded using an Agilent 6210 ESI-TOF or an Ionspec QFT-7 ESI-TOF spectrometer. Optical rotations were measured on a JASCO P-2000 polarimeter at 589 nm using 100 mm cells and the solvent and concentration (g/100 mL) indicated. Melting points were measured on a Stuart SMP30.

2 Experimental Procedures and Characterization Data

2.1 Synthesis of γ-Hydroxy Enone **6**

Ergosterol mesylate (**S2**)



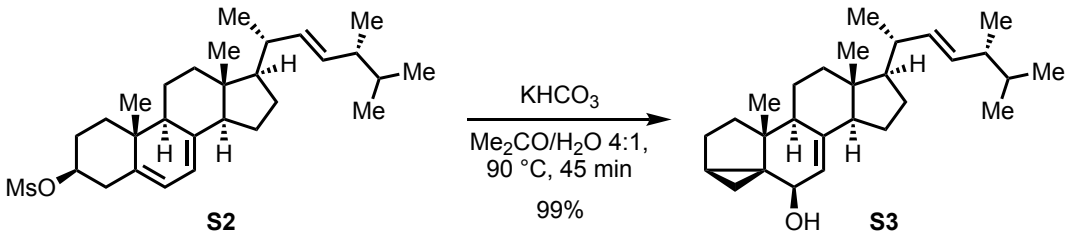
S1 **S2**

To a stirred solution of ergosterol (**S1**) (53.7 g, 135 mmol, 1.0 eq.) in pyridine (1.0 L) was added methanesulfonyl chloride (52.4 mL, 677 mmol, 5.0 eq.) dropwise at 10 °C. After stirring at this temperature for 1 h, the reaction mixture was poured into a mixture of ice and H_2O (1.5 L) under stirring. The precipitate was filtered off, washed with H_2O (3 × 1 L), and dried under vacuum to give mesylate **S2** (60.0 g, 126 mmol, 94%) as a colorless solid, which was used in the next step without further purification.

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.60 (dd, *J* = 5.7, 2.3 Hz, 1H), 5.39 (dt, *J* = 5.3, 2.6 Hz, 1H), 5.23 (dd, *J* = 15.2, 7.1 Hz, 1H), 5.17 (dd, *J* = 15.2, 7.8 Hz, 1H), 4.63 (tt, *J* = 11.4, 4.7 Hz, 1H), 3.02 (s, 3H), 2.65 (ddd, *J* = 14.4, 5.1, 2.4 Hz, 1H), 2.62 – 2-50 (m, 1H), 2.15 – 1.21 (m, 18H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.95 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.62 (s, 3H).

All characterization data were consistent with those reported in the literature.[1]

(22*E*)-3α,5-Cyclo-5α-ergosta-7,22-dien-6β-ol (**S3**)



S2 **S3**

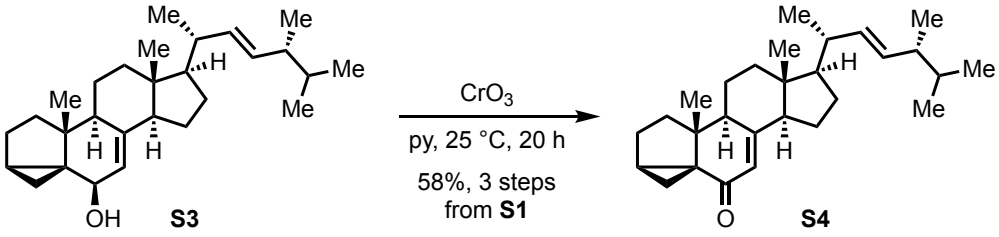
Finely powdered mesylate **S2** (60.0 g, 126 mmol, 1.0 eq.) was added portion wise to a refluxing solution of $KHCO_3$ (14.6 g, 145 mmol, 1.15 eq.) in acetone/ H_2O (4:1, 1.8 L) at 80 °C. After stirring for 45 min at 90 °C, the reaction mixture was allowed to cool to 40 °C and a mixture of ice and H_2O (1 L) was added. After further cooling to 0 °C, the precipitate was filtered off, washed with H_2O (2 × 500 mL), and dried under vacuum to

give *i*-sterol **S3** (49.6 g, 125 mmol, 99%) as a colorless solid, which was used in the next step without further purification.

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.52 – 5.42 (m, 1H), 5.23 (dd, *J* = 15.2, 7.3 Hz, 1H), 5.17 (dd, *J* = 15.3, 8.1 Hz, 1H), 3.42 (s, 1H), 2.10 – 1.18 (m, 20H), 1.08 (s, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz), 3H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.66 – 0.60 (m, 4H), 0.48 (dd, *J* = 7.9, 5.0 Hz, 1H).

All characterization data were consistent with those reported in the literature.[1]

(22*E*)-3α,5-Cyclo-5α-ergosta-7,22-dien-6-one (**S4**)

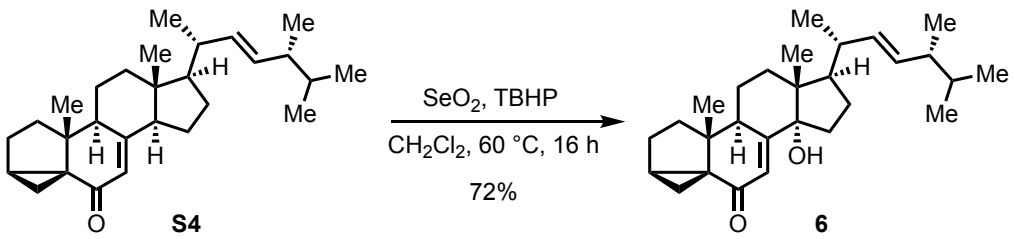


Under stirring CrO_3 (50.0 g, 500 mmol, 4.0 eq.) was added portion wise to pyridine (500 mL). To the resulting red-brown suspension was added *i*-sterol **S3** (49.6 g, 125 mmol, 1.0 eq.) in pyridine (500 mL) *via* cannula over 10 min. After stirring at 25 °C for 20 h, Et_2O (1.2 L) was added, the resulting mixture was filtered through Celite® and rinsed with Et_2O (2 × 200 mL). The filtrate was washed sequentially with H_2O (2 × 1 L) and brine (sat., 1 L), dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization from acetone (250 mL) gave enone **S4** (30.9 g, 78.3 mmol, 58% over 3 steps) as a crystalline solid.

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.82 (t, *J* = 2.2 Hz, 1H), 5.27 (dd, *J* = 15.3, 7.6 Hz, 1H), 5.20 (dd, *J* = 15.7, 8.3 Hz, 1H), 2.28 (ddd, *J* = 11.7, 7.2, 2.3 Hz, 1H), 2.19 – 2.05 (m, 3H), 2.00 (tdd, *J* = 12.3, 8.0, 4.4 Hz, 1H), 1.93 – 1.85 (m, 1H), 184 – 1.64 (m, 8H), 1.58 – 1.47 (m, 2H), 1.47 – 1.33 (m, 3H), 1.19 – 1.13 (m, 1H), 1.12 (s, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.78 (t, *J* = 4.6 Hz, 1H), 0.71 (s, 3H).

All characterization data were consistent with those reported in the literature.[1]

(22*E*)-14-Hydroxy-3α,5-cyclo-5α-ergosta-7,22-dien-6-one (**6**)



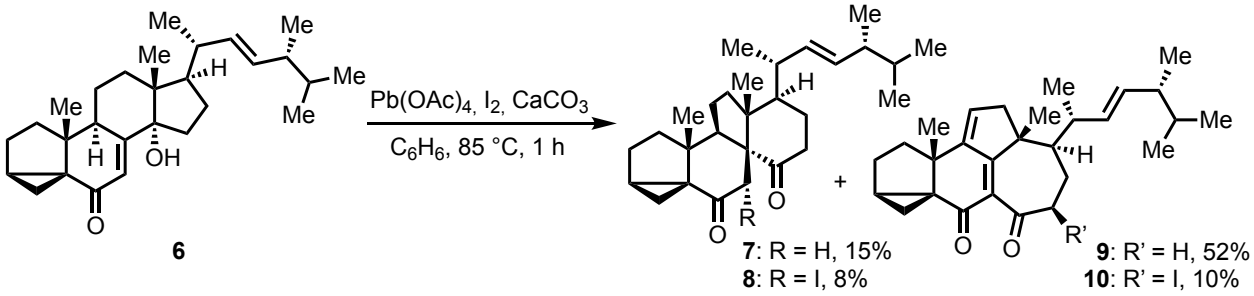
To a stirred suspension of SeO_2 (1.13 g, 10.2 mmol, 0.5 eq.) in CH_2Cl_2 (18 mL) was added *t*BuOOH (70% in H_2O, 11.2 mL, 81.8 mmol, 4.0 eq.) at 0 °C. After stirring at 25°C for 15 min, enone **S4** (8.07 g, 20.4 mmol, 1.0 eq.) in CH_2Cl_2 (22 mL) was added. The vessel was sealed, and the mixture was stirred at 60 °C for 16 h. The reaction mixture was allowed to cool to 25 °C and was carefully added to $NaHSO_3$ (10% *w/w* in H_2O, 200 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (2 × 250 mL) and the combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 250 mL) and brine (sat., 250 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was adsorbed on silica and the mixture was purified by column chromatography (silica gel, *n*hexane/EtOAc 5:1 → 4:1) to give γ-hydroxy enone **6** (6.05 g, 14.7 mmol, 72%) as a crystalline solid.

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.97 (d, *J* = 2.7 Hz, 1H), 5.27 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.20 (ddd, *J* = 15.2, 8.5, 0.9 Hz, 1H), 2.79 – 2.75 (m, 1H), 2.13 – 1.84 (m, 7H), 1.80 (dt, *J* = 8.8, 4.6 Hz, 1H), 1.75 – 1.65 (m, 6H), 1.55 (ddd, *J* = 13.7, 9.8, 5.1 Hz, 1H), 1.48 (qd, *J* = 6.8, 5.7 Hz, 1H), 1.43 (s, 1H), 1.43 – 1.37 (m, 1H), 1.15 – 1.11 (m, 1H), 1.10 (s, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.79 (t, *J* = 4.7 Hz, 1H), 0.76 (s, 3H).

All characterization data were consistent with those reported in the literature.[2]

2.2 Studies on the Radical Rearrangement

Reaction Conditions for Entry 1, Table 1



Through a solution of γ-hydroxy enone **6** (1.00 g, 2.44 mmol, 1.0 eq.) in benzene (100 mL) was bubbled argon *via* cannula for 10 min. $CaCO_3$ (487 mg, 4.87 mmol, 2.0 eq.), iodine (1.24 g, 4.87 mmol, 2.0 eq.), and $Pb(OAc)_4$ (2.16 g, 4.87 mmol, 2.0 eq.) were added and the reaction mixture was stirred at 85 °C for 1 h. It was cooled to 25 °C, filtered through a plug of Celite®, and rinsed with EtOAc (50 mL). The organic phase was washed sequentially with $Na_2S_2O_3$ (sat. aq., 150 mL) and brine (sat., 150 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 9:1 → 3:1) gave dione **7** (147 mg, 358 μmol, 15%) as a colorless solid, iodo dione **8** (107 mg, 199 μmol, 8%) as colorless needles, diene dione **9** (517 mg, 1.27 mmol, 52%) as a light-yellow foam, and iodo diene dione **10** (130 mg, 244 μmol, 10%) as a colorless solid.

Characterization data for (22*E*)-13(14→8)*abeo*-3α,5-Cyclo-5α-ergosta-22-en-6,14-dione (**7**)

M.p.: 66–67 °C ($CHCl_3$).

TLC: R_f = 0.39 (*n*hexane/EtOAc 9:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.27 – 5.24 (m, 2H), 2.93 (dd, *J* = 11.0, 8.2 Hz, 1H), 2.73 (d, *J* = 14.5 Hz, 1H), 2.61 (ddd, *J* = 17.1, 6.0, 3.2 Hz, 1H), 2.52 (d, *J* = 14.6 Hz, 1H), 2.38 – 2.31 (m, 1H), 2.28 – 2.18 (m, 2H), 1.91 – 1.82 (m, 2H), 1.82 – 1.75 (m, 3H), 1.75 – 1.70 (m, 1H), 1.67 – 1.61 (m, 3H), 1.51 (dd, *J* = 8.3, 4.3 Hz, 1H), 1.50 – 1.44 (m, 1H), 1.31 (td, *J* = 12.0, 6.3 Hz, 1H), 1.20 – 1.12 (m, 1H), 1.10 (s, 3H), 1.09 – 1.03 (m, 1H), 1.03 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.84 – 0.82 (m, 1H), 0.82 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 215.5, 210.6, 134.7, 133.1, 61.4, 52.9, 52.5, 45.2, 44.9, 44.2, 43.4, 41.9, 41.3, 38.9, 38.3, 38.1, 37.9, 33.3, 25.6, 25.2, 23.2, 22.3, 21.7, 20.2, 19.8, 17.8, 17.5 (2C).

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2922 (s), 2853 (m), 1697 (w), 1461 (w), 1376 (w), 1158 (w), 972 (w).

HRMS: (ESI-TOF) *m/z* calcd. for $C_{28}H_{42}O_2Na^+$ $[M+Na]^+$: 433.3077, found: 433.3088.

Opt. act. $[\alpha]_D^{21}$ = +34.0 (*c* = 1.00, $CHCl_3$).

Characterization data for (22*E*)-7α-Iodo-13(14→8)*abeo*-3α,5-Cyclo-5α-ergosta-22-en-6,14-dione (**8**)

M.p.: 102–103 °C (EtOAc).

TLC: R_f = 0.27 (*n*hexane/EtOAc 9:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.40 (dd, *J* = 15.3, 7.8 Hz, 1H), 5.29 (dd, *J* = 15.4, 8.2 Hz, 1H), 5.13 (s, 1H), 2.73 (dd, *J* = 19.2, 4.9 Hz, 1H), 2.56 (t, *J* = 7.3 Hz, 1H), 2.53 (d, *J* = 9.3 Hz, 1H), 2.24 (dt, *J* = 8.3, 5.2 Hz, 1H), 2.16 – 2.08 (m, 1H), 2.07 – 2.03 (m, 1H), 2.00 (td, *J* = 12.9, 5.1 Hz, 1H), 1.93 – 1.85 (m, 2H), 1.78 – 1.71 (m, 2H), 1.69 (dd, *J* = 8.4, 4.2 Hz, 1H), 1.65 (dd, *J* = 13.2, 7.6 Hz, 1H), 1.63 – 1.57 (m, 2H), 1.53 – 1.47 (m, 2H), 1.42 (s, 3H), 1.35 (d, *J* = 12.4 Hz, 1H), 1.19 – 1.14 (m, 1H), 1.13 (s, 3H), 1.09 (d, *J* = 7.1 Hz, 3H), 0.97 – 0.95 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 216.2, 200.0, 135.0, 132.5, 69.3, 55.4, 51.7, 48.5, 48.4, 44.8, 43.5, 42.3, 41.3, 41.1, 39.1, 37.9, 37.5, 33.3, 24.6, 24.5, 23.9, 23.0, 21.8, 20.2, 19.9, 19.7, 19.0, 17.8.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (s), 2871 (m), 2360 (s), 2341 (m), 1699 (s), 1456 (m), 1364 (w), 1288 (w), 1162 (w), 1082 (w), 983 (m).

HRMS: (ESI-TOF) *m/z* calcd. for $C_{28}H_{41}IO_2Na^+$ $[M+Na]^+$: 559.2043, found: 559.2055.

Opt. act. $[\alpha]_D^{21}$ = +41.6 (*c* = 1.01, $CHCl_3$).

Characterization data for (22*E*)-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α-ergosta-7,9(11),22-trien-6,14-dione (**9**)

TLC: R_f = 0.32 (*n*hexane/EtOAc 3:1),

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 6.34 (t, *J* = 2.9 Hz, 1H), 5.36 (dd, *J* = 15.3, 8.4 Hz, 1H), 5.28 (dd, *J* = 15.3, 7.9 Hz, 1H), 2.78 (dd, *J* = 17.7, 2.4 Hz, 1H), 2.74 – 2.68 (m, 1H), 2.62 – 2.54 (m, 2H), 2.45 (dd, *J* = 17.6, 3.4 Hz, 1H), 2.11 – 2.03 (m, 1H), 2.03 – 1.95 (m, 1H), 1.93 – 1.81 (m, 4H), 1.77 – 1.72 (m, 2H), 1.69 (dd, *J* = 12.9, 7.6 Hz, 1H), 1.50 – 1.37 (m, 2H), 1.16 (s, 6H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.77 (t, *J* = 7.1 Hz, 1H).

^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 204.3, 193.1, 168.6, 145.9, 136.9, 135.4, 132.0, 130.9, 53.4, 49.9, 47.7, 45.3, 43.5, 43.4, 41.2, 39.7, 36.3, 35.4, 33.2, 26.4, 26.3, 23.9, 23.0, 22.2, 20.2, 19.9, 17.6, 12.8.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2957 (m), 2867 (w), 1691 (m), 1636 (m), 1588 (w), 1454 (w), 1373 (m), 1260 (m), 1010 (s), 796 (s).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{38}O_2Na^+$ $[M+Na]^+$: 429.2764, found: 429.2777.

Opt. act. $[\alpha]_D^{23} = -13.6$ (*c* = 1.00, $CHCl_3$).

Characterization data for (22*E*)-15β-Iodo-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α-ergosta-7,9(11),22-trien-6,14-dione (**10**)

M.p.: 155–157 °C (Et_2O).

TLC: R_f = 0.26 (*n*hexane/EtOAc 5:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 6.39 (dd, *J* = 3.3, 2.5 Hz, 1H), 5.32 – 5.28 (m, 2H), 4.91 (dd, *J* = 4.5, 3.4 Hz, 1H), 2.91 (dd, *J* = 17.8, 2.5 Hz, 1H), 2.70 – 2.65 (m, 1H), 2.48 (dd, *J* = 17.8, 3.3 Hz, 1H), 2.21 – 2.18 (m, 1H), 2.10 – 2.02 (m, 3H), 1.94 – 1.87 (m, 3H), 1.82 – 1.75 (m, 2H), 1.72 (dd, *J* = 12.9, 7.5 Hz, 1H), 1.50 – 1.44 (m, 1H), 1.17 (s, 3H), 1.14 (s, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.85 – 0.81 (m, 7H).

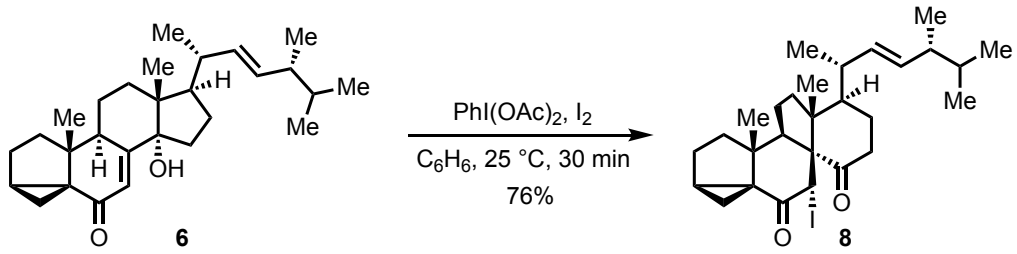
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 195.6, 192.9, 167.1, 145.7, 138.1, 136.0, 132.0, 128.2, 52.6, 47.2, 45.5, 43.4 (2C), 40.7, 39.4, 39.0, 36.0, 35.6, 33.2, 31.5, 26.5, 26.3, 22.8, 22.1, 20.2, 19.9, 17.6, 12.4.

FT-IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (m), 2867 (w), 1685 (s), 1640 (m), 1586 (m), 1452 (m), 1373 (m), 1294 (m), 1136 (m), 1011 (s), 988 (m), 880 (m), 806 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{37}IO_2Na^+$ $[M+Na]^+$: 555.1730, found: 555.1738.

Opt. act. $[\alpha]_D^{23} = +42.0$ (*c* = 0.41, $CHCl_3$).

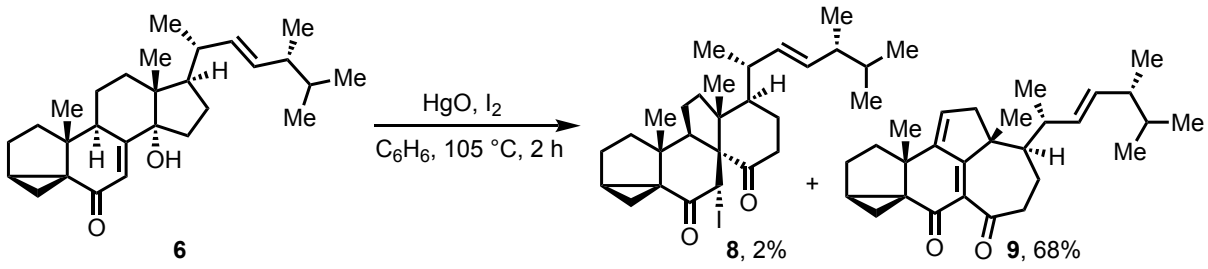
Reaction Conditions for Entry 2, Table 1



A solution of γ-hydroxy enone **6** (30 mg, 73 μmol, 1.0 eq.) in benzene (1.5 mL) was degassed applying three freeze-pump-thaw cycles. (Diacetoxyiodo)benzene (47.0 mg, 146 μmol, 2.0 eq.) and iodine (18 mg, 73 μmol, 1.0 eq.) were added, and the resulting mixture was stirred at 25 °C for 30 min. $Na_2S_2O_3$ (sat. aq., 5 mL) was added and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (sat., 15 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and column chromatography (silica gel, *n*hexane/EtOAc 19:1 → 9:1) gave iodo ketone **8** (30 mg, 55 mmol, 76%) as colorless needles.

Characterization data for iodo ketone **8** see page S7.

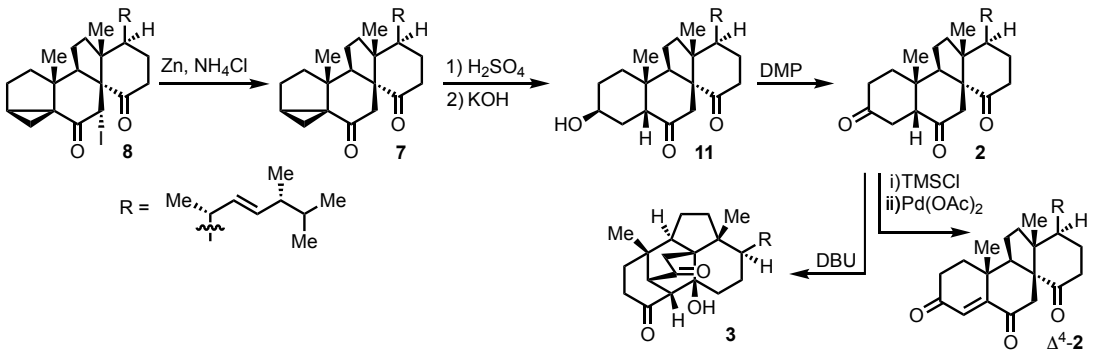
Reaction Conditions for Entry 3, Table 1



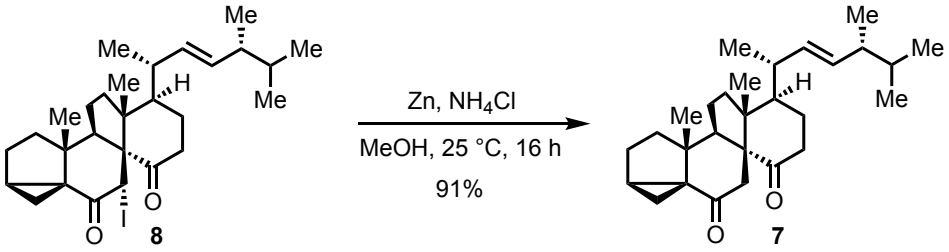
Through a solution of γ-hydroxy enone **6** (3.00 g, 7.31 mmol, 1.0 eq.) in benzene (300 mL) was bubbled argon *via* cannula for 10 min. Iodine (4.45 g, 17.5 mmol, 2.4 eq.) and HgO (yellow, 4.27 g, 19.7 mmol, 2.7 eq.) were added at 60 °C and the resulting mixture was stirred at 105 °C for 3 h. The reaction mixture was cooled to 25 °C, filtered through a plug of Celite®, and rinsed with EtOAc (100 mL). The organic phase was washed sequentially with $Na_2S_2O_3$ (sat. aq., 250 mL) and brine (sat., 250 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1 → 3:1) gave iodo ketone **8** (78 mg, 146 μmol, 2%) as colorless needles and diene dione **9** (2.02 g, 4.97 mmol, 68%) as a light-yellow foam.

Characterization data for iodo ketone **8** and diene dione **9** see page S7–8.

2.3 Synthesis of Dankasterone A (Δ^4-**2**) and B (**2**), and Periconiastone A (**3**)



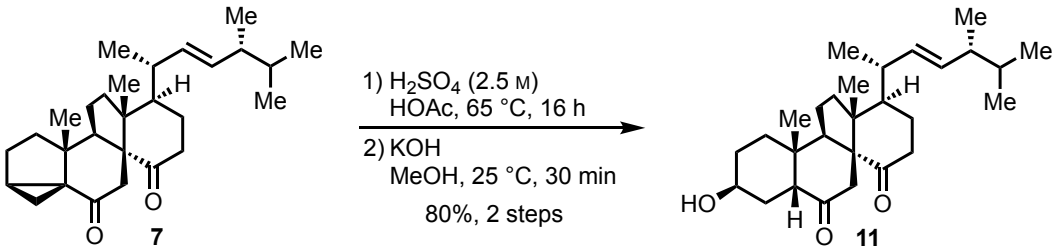
(22*E*)-13(14→8)*abeo*-3α,5-Cyclo-5α-ergosta-22-en-6,14-dione (**7**)



To a solution of iodo ketone **8** (107 mg, 199 μmol, 1.0 eq.) in MeOH (4 mL) were added NH_4Cl (50.0 mg, 935 μmol, 4.7 eq.) and zink powder (208 mg, 3.18 mmol, 16 eq.), and the resulting mixture was stirred at 25 °C for 16 h. The reaction mixture was filtered through a plug of Celite®, rinsed with EtOAc (10 mL), and H_2O (10 mL) was added to the resulting filtrate. The aqueous phase was extracted with EtOAc (2 × 10 mL) and the combined organic phases were washed with brine (sat., 30 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 9:1) gave dione **7** (74 mg, 181 μmol, 91%) as a colorless solid.

Characterization data for dione **7** see page S6–7.

(22*E*)-3β-Hydroxy-13(14→8)*abeo*-5β-ergosta-22-en-6,14-dione (**11**)



To a solution of dione **7** (133 mg, 327 *μ*mol, 1.0 eq.) in acetic acid (26 mL) was added H_2SO_4 (2.5 M in H_2O, 6.5 mL, 16 mmol, 49 eq.) and the resulting solution was stirred at 65 °C for 16 h. After cooling to 25 °C, the reaction mixture was poured into H_2O (50 mL), before NaOH (20% *w/w* in H_2O, 8.7 mL) was carefully added. The aqueous phase was extracted with Et_2O (3 × 25 mL) and the combined organic phases were washed with brine (sat., 75 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was then dissolved in KOH (5% *w/w* in MeOH, 5 mL) and the reaction mixture was stirred at 25 °C for 30 min. After diluting with H_2O (5 mL), it was neutralized with HCl (0.5 M in H_2O), and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (sat., 30 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 1:1) gave 3β-hydroxy dione **11** (112 mg, 262 *μ*mol, 80% over 2 steps) as a colorless solid.

M.p.: 167–168 °C ($CHCl_3$).

TLC: R_f = 0.36 (*n*hexane/EtOAc 1:2).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.26 – 5.19 (m, 2H), 3.79 – 3.72 (m, 1H), 2.94 – 2.90 (m, 1H), 2.83 (dd, *J* = 14.0, 2.0 Hz, 1H), 2.81 – 2.75 (m, 1H), 2.46 – 2.43 (m, 1H), 2.43 – 2.37 (m, 1H), 2.37 – 2.31 (m, 2H), 2.25 – 2.17 (m, 1H), 2.08 (ddd, *J* = 14.0, 9.9, 4.2 Hz, 1H), 2.03 – 1.99 (m, 1H), 1.98 – 1.93 (m, 2H), 1.89 (d, *J* = 13.8 Hz, 1H), 1.85 – 1.81 (m, 1H), 1.67 – 1.58 (m, 3H), 1.55 (ddd, *J* = 14.0, 12.3, 6.0 Hz, 1H), 1.48 – 1.41 (m, 2H), 1.33 (ddd, *J* = 12.8, 11.3, 4.8 Hz, 1H), 1.20 (td, *J* = 13.3, 4.0 Hz, 1H), 1.14 – 1.11 (m, 6H), 1.09 (dq, *J* = 13.3, 3.7 Hz, 1H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.74 (s, 3H).

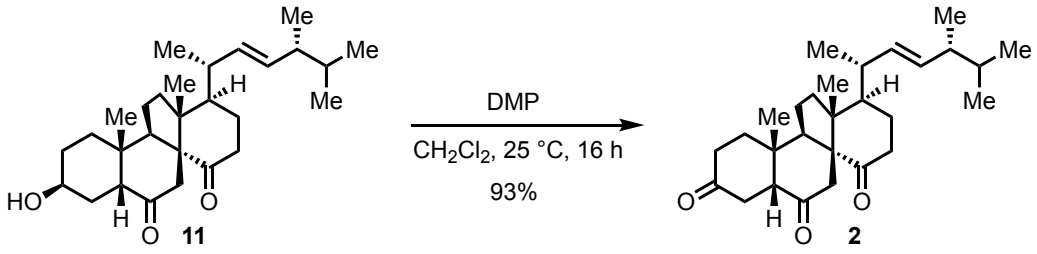
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 215.9, 209.4, 135.2, 132.3, 66.3, 65.0, 59.7, 53.7, 49.5, 45.8, 43.4, 40.3, 40.0, 38.8, 36.9, 34.1, 33.7, 33.2, 30.4, 29.4, 27.3, 25.7, 24.2, 24.1, 20.2, 19.8, 17.7, 15.5.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3412 (br w), 2954 (m), 2924 (s), 2854 (m), 1709 (m), 1459 (w), 1379 (w), 1161 (w), 1059 (w), 976 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{44}O_3Na^+$ [M+Na]$^+$: 451.3183, found: 451.3198.

Opt. act. $[\alpha]_D^{21}$ = +6.1 (*c* = 1.00, $CHCl_3$).

Dankasterone B (**2**)



To a solution of 3β-hydroxy dione **11** (15 mg, 35 μmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) was added Dess–Martin periodinane (22 mg, 53 μmol, 1.5 eq.) and the reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (2 mL) and $Na_2S_2O_3$ (sat. aq., 5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 15 mL) and brine (sat., 15 mL). It was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 1:1) gave dankasterone B (**2**) (13.9 mg, 32.6 μmol, 93%) as colorless needles.

M.p.: 182–189 °C ($CHCl_3$).

TLC: R_f = 0.33 (*n*hexane/EtOAc 1:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.28 – 5.19 (m, 2H), 3.05 (t, *J* = 9.9 Hz, 1H), 2.95 (dd, *J* = 13.2, 1.8 Hz, 1H), 2.90 – 2.87 (m, 1H), 2.84 (dt, *J* = 16.5, 2.0 Hz, 1H), 2.79 (ddd, *J* = 14.3, 12.8, 5.9 Hz, 1H), 2.42 (p, *J* = 6.9 Hz, 1H), 2.36 (ddd, *J* = 12.7, 4.2, 2.5 Hz, 1H), 2.33 – 2.26 (m, 2H), 2.22 (dt, *J* = 5.7, 2.1 Hz, 1H), 2.20 (d, *J* = 6.1 Hz, 1H), 2.18 – 2.14 (m, 1H), 2.12 – 2.07 (m, 1H), 2.02 – 1.93 (m, 3H), 1.88 – 1.81 (m, 1H), 1.69 – 1.61 (m, 2H), 1.54 (td, *J* = 12.9, 5.7 Hz, 1H), 1.48 – 1.42 (m, 1H), 1.31 (ddt, *J* = 13.3, 6.8, 2.4 Hz, 1H), 1.27 (s, 3H), 1.15 (d, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.75 (s, 3H).

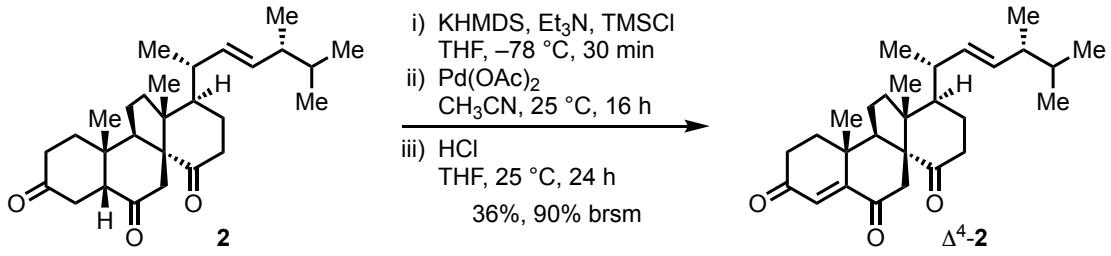
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 214.9, 208.6, 207.7, 135.4, 132.2, 65.8, 60.2, 53.4, 50.2, 45.6, 43.4, 40.7, 40.1, 38.7, 37.0, 36.9, 35.9, 34.2, 33.2, 32.8, 27.4, 25.7, 24.3, 23.5, 20.2, 19.8, 17.7, 15.3.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2922 (s), 2852 (m), 1740 (w), 1459 (m), 1377 (w), 1167 (w), 722 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_3Na^+$ $[M+Na]^+$: 449.3026, found: 449.3030.

Opt. act. $[\alpha]_D^{24}$ = +28.2 (*c* = 1.00, $CHCl_3$).

Dankasterone A (Δ^4-**2**)



To a solution of dankasterone B (**2**) (10 mg, 23 μmol, 1.0 eq.) in THF (0.6 mL) at –78 °C were added Et_3N (64 μL, 0.46 mmol, 20 eq.), TMSCl (58 μL, 0.46 mmol, 20 eq.) and KHMDS (0.5 M in toluene, 140 μL, 70 μmol, 3.0 eq.) and the reaction mixture was stirred at this temperature for 30 min. It was diluted with EtOAc (5 mL) and phosphate buffer (aq., pH ~7.4, 5 mL) was added. The aqueous phase was extracted with EtOAc (3 × 10 mL), the combined organic phases were washed with brine (sat., 20 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure.

The residue was taken up in CH_3CN (0.5 mL), $Pd(OAc)_2$ (26.0 mg, 115 μmol, 5.0 eq.) was added and the reaction mixture was stirred at 25 °C for 16 h. It was filtered through Celite®, rinsed with CH_2Cl_2 (15 mL), and the solvent was removed under reduced pressure. The residue was taken up in THF (1 mL) and HCl (1 M in H_2O, 1 mL) and stirred at 25 °C for 24 h. It was diluted with EtOAc (5 mL) and H_2O (5 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with $NaHCO_3$ (sat. aq., 20 mL) and brine (sat., 20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 3:1 → 1:1) gave dankasterone A (Δ^4-**2**) (3.5 mg, 8.2 μmol, 36%) as a colorless solid and re-isolated dankasterone B (**2**) (6.1 mg, 14 μmol, 62%).

M.p.: 128–129 °C (CH_3OH).

TLC: R_f = 0.27 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 6.36 (d, *J* = 0.8 Hz, 1H), 5.31 – 5.22 (m, 2H), 2.84 – 2.79 (m, 1H), 2.65 (dd, *J* = 16.8, 1.6 Hz, 1H), 2.56 – 2.43 (m, 5H), 2.41 (td, *J* = 7.4, 2.6 Hz, 1H), 2.10 – 1.98 (m, 3H), 1.92 – 1.82 (m, 3H), 1.77 (dt, *J* = 13.0, 7.4 Hz, 1H), 1.74 – 1.66 (m, 2H), 1.50 – 1.46 (m, 2H), 1.26 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.98 (s, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

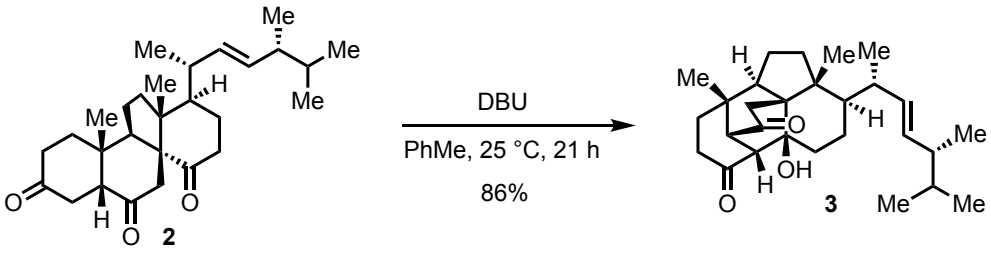
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 214.9, 200.1, 199.2, 156.2, 135.3, 132.5, 126.7, 62.3, 54.1, 49.5, 49.5, 43.4, 41.0, 39.1, 38.5, 38.1, 37.4, 36.2, 34.5, 33.2, 25.3, 24.2, 23.8, 23.3, 20.2, 19.8, 17.8, 17.2.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (m), 2923 (s), 2853 (m), 1739 (w), 1698 (w), 1461 (w), 1377 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{40}O_3Na^+$ $[M+Na]^+$: 447.2870, found: 4472892.

Opt. act. $[\alpha]_D^{21}$ = +43.3 (*c* = 0.7, $CHCl_3$).

Periconiastone A (**3**)



To a solution of dankasterone B (**2**) (8.1 mg, 19 μmol, 1.0 eq.) in toluene (1 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (28 μL, 190 μmol, 10 eq.) over 5 h at 25 °C and the reaction mixture was stirred for 16 h at this temperature before NH_4Cl (sat. aq., 10 mL) was added. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed sequentially with HCl (1 M in H_2O, 20 mL), $NaHCO_3$ (sat. aq., 20 mL), and brine (sat., 20 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 1:1) gave periconiastone A (**3**) (7.0 mg, 16 μmol, 86%) as colorless needles.

M.p. 175–176 °C (EtOAc)

TLC: R_f = 0.16 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (600 MHz, pyridine-d_5); δ [ppm] = 6.64 (s, 1H), 5.52 (dd, *J* = 15.4, 8.1 Hz, 1H), 5.30 (dd, *J* = 15.4, 8.2 Hz, 1H), 3.21 (d, *J* = 18.5 Hz, 1H), 3.12 (d, *J* = 3.9 Hz, 1H), 2.87 (ddd, *J* = 19.9, 11.8, 9.0 Hz, 1H), 2.80 (t, *J* = 10.0 Hz, 1H), 2.52 – 2.42 (m, 3H), 2.16 – 2.10 (m, 2H), 2.03 (ddd, *J* = 14.2, 9.7, 5.3 Hz, 1H), 1.98 – 1.91 (m, 1H), 1.90 – 1.77 (m, 5H), 1.61 – 1.41 (m, 5H), 1.22 (s, 3H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.99 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.87 – 0.83 (m, 6H).

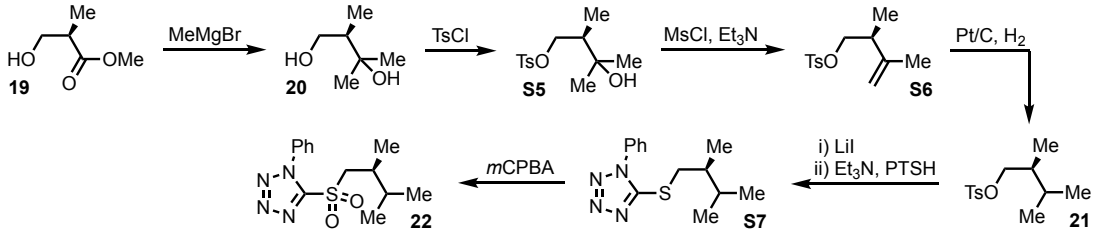
^{13}C-NMR: (151 MHz, pyridine-d_5); δ [ppm] = 213.1, 209.2, 134.6, 134.5, 73.1, 65.3, 58.8, 56.0, 48.2, 47.8, 44.0, 42.3, 38.5, 37.6, 37.4, 37.4, 36.8, 34.3, 33.9, 33.6, 26.5, 24.4, 22.7, 20.7, 20.6, 20.3, 19.3, 18.3.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3456 (br w), 2956 (s), 2925 (s), 2871 (m), 1718 (s), 1685 (s), 1455 (w), 1384 (w), 1206 (w), 956 (w), 761 (w).

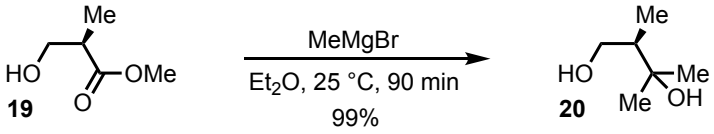
HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_3Na^+$ $[M+Na]^+$: 449.3026, found: 449.3034.

Opt. act. $[\alpha]_D^{21}$ = –8.8 (*c* = 0.1, CH_3OH).

2.4 Synthesis of Sulfone **22**



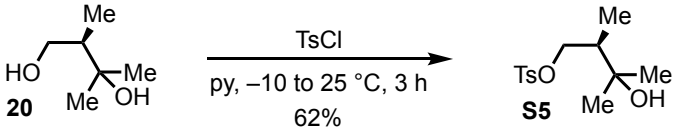
(*R*)-2,3-Dimethylbutane-1,3-diol (**20**)



To a solution of (*R*)-Roche ester (**19**) (180 mg, 1.52 mmol, 1.0 eq.) in Et_2O (5 mL) was added methylmagnesium bromide (3 M in Et_2O, 9.3 mL, 28 mmol, 3.3 eq.) at 0 °C and the reaction mixture was stirred at 25 °C for 1.5 h. It was cooled to 0 °C and HCl (1 M in H_2O, 10 mL) and Et_2O (10 mL) were added dropwise. The aqueous phase was neutralized and a continuous extraction with Et_2O (250 mL) was performed for 48 h. The solvent was removed under reduced pressure giving diol **20** (178 mg, 1.51 mmol, 99%) as a colorless oil, which was used in the next step without further purification.

TLC:	R_f = 0.28 (*n*pentane/Et_2O 1:2).
^{1}H-NMR:	(500 MHz, $CDCl_3$); δ [ppm] = 3.89 (br s, 1H), 3.73 – 3.56 (m, 3H), 1.84 – 1.71 (m, 1H), 1.22 (s, 3H), 1.15 (s, 3H), 0.82 (d, *J* = 7.1 Hz, 3H).
^{13}C-NMR:	(126 MHz, $CDCl_3$); δ [ppm] = 74.7, 66.2, 44.0, 29.8, 24.1, 13.1.
IR:	(neat); $\tilde{\nu}$ [cm^{-1}] = 3335 (br m), 2973 (m), 2934 (w), 2885 (w), 1717 (w), 1458 (m), 1366 (m), 1174 (m), 1024 (s), 946 (m), 904 (m), 857 (w).
HRMS:	(ESI-TOF); *m/z* calcd. for $C_6H_{14}O_2Na^+$ $[M+Na]^+$: 141.0886, found: 141.0898.
Opt. act.	$[\alpha]_D^{26}$ = –4.0 (*c* = 1.00, $CHCl_3$).

(*R*)-3-Hydroxy-2,3-dimethylbutyl 4-methylbenzenesulfonate (**S5**)



To a solution of diol **20** (200 mg, 1.69 mmol, 1.0 eq.) in pyridine (1.5 mL) at –10 °C was added tosyl chloride (806 mg, 4.23 mmol, 2.5 eq.) and the reaction mixture was allowed to warm to 25 °C over 4 h. A mixture of ice and H_2O (5 mL) was added and the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic phases were washed sequentially with H_2O (25 mL), HCl (1 M in H_2O, 25 mL), and brine (sat., 25 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 3:1) gave toslyate **S5** (287 mg, 1.06 mmol, 62%) as a colorless oil.

TLC: R_f = 0.29 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 7.78 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 4.25 – 4.21 (m, 1H), 3.93 – 3.89 (m, 1H), 2.44 (s, 3H), 1.90 – 1.77 (m, 1H), 1.54 – 1.42 (m, 1H), 1.18 (s, 3H), 1.11 (s, 3H), 0.95 (d, *J* = 7.0 Hz, 3H).

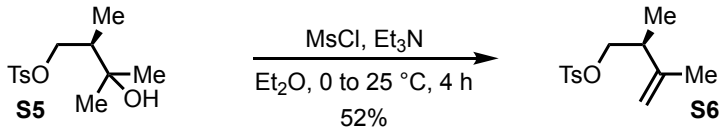
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 144.9, 133.1, 130.0, 128.0, 72.7, 72.1, 43.5, 28.7, 26.2, 21.8, 12.8.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3541 (br w), 2974 (w), 2925 (w), 2857 (w), 1598 (w), 1463 (w), 1353 (m), 1173 (s), 1097 (m), 950 (s), 837 (m), 813 (m), 735 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{13}H_{20}O_4SNa^+$ [M+Na]$^+$: 295.0975, found: 295.0987.

Opt. act. $[\alpha]_D^{26}$ = +17.4 (*c* = 1.00, $CHCl_3$).

(*S*)-2,3-Dimethylbut-3-en-1-yl 4-methylbenzenesulfonate (**S6**)



To a solution of tosylate **S5** (4.21 g, 15.5 mmol, 1.0 eq.) in Et_2O (300 mL) at 25 °C was added methanesulfonyl chloride (6.0 mL, 77 mmol, 5.0 eq.). It was cooled to 0 °C, triethylamine (43 mL, 0.31 mol, 20 eq.) was added dropwise and the reaction mixture was stirred at 25 °C for 4 h. HCl (20% in H_2O *w/w*, 6 mL) was added at 0 °C and the organic phase was separated. The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic phases were washed sequentially with HCl (1 M in H_2O, 25 mL), $NaHCO_3$ (sat. aq., 25 mL), and brine (sat., 25 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 12:1 → 9:1) gave unsaturated tosylate **S6** (2.03 g, 8.01 mmol, 52%) as a colorless oil.

TLC: R_f = 0.28 (*n*hexane/EtOAc 50:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 7.78 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.79 – 4.76 (m, 1H), 4.69 – 4.68 (m, 1H), 3.98 (dd, *J* = 9.5, 6.6 Hz, 1H), 3.86 (dd, *J* = 9.5, 7.2 Hz, 1H), 2.50 – 2.45 (m, 1H), 2.44 (s, 3H), 1.61 (s, 3H), 1.01 (d, *J* = 7.0 Hz, 3H).

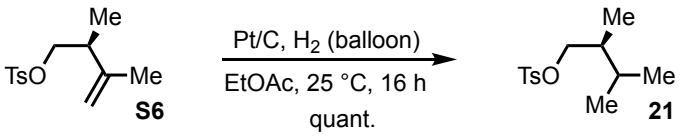
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 145.0, 144.8, 133.3, 129.9, 128.0, 112.1, 73.2, 40.2, 21.7, 20.2, 16.0.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2972 (w), 1650 (w), 1598 (w), 1454 (w), 1357 (m), 1174 (s), 1096 (m), 966 (s), 895 (m), 834 (m), 813 (s), 767 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{13}H_{18}O_3SNa^+$ [M+Na]$^+$: 277.0869, found: 277.0885.

Opt. act. $[\alpha]_D^{26}$ = +6.9 (*c* = 1.00, $CHCl_3$).

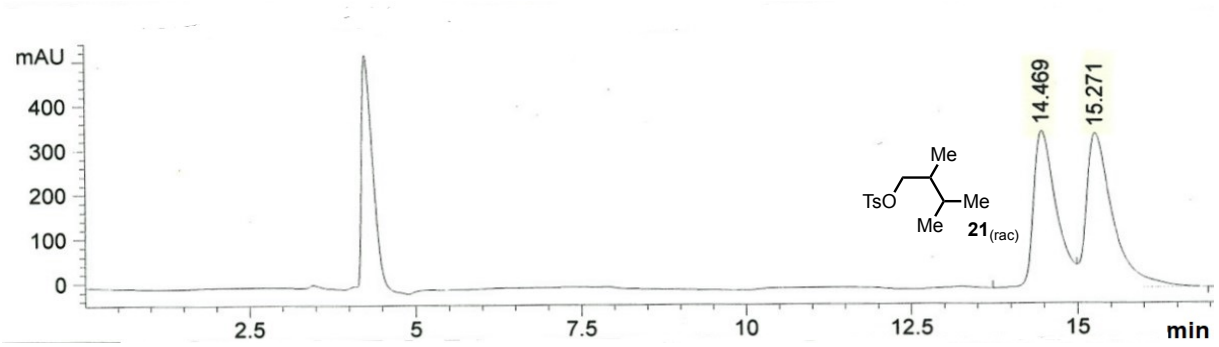
(*S*)-2,3-Dimethylbutyl 4-methylbenzenesulfonate (**21**)

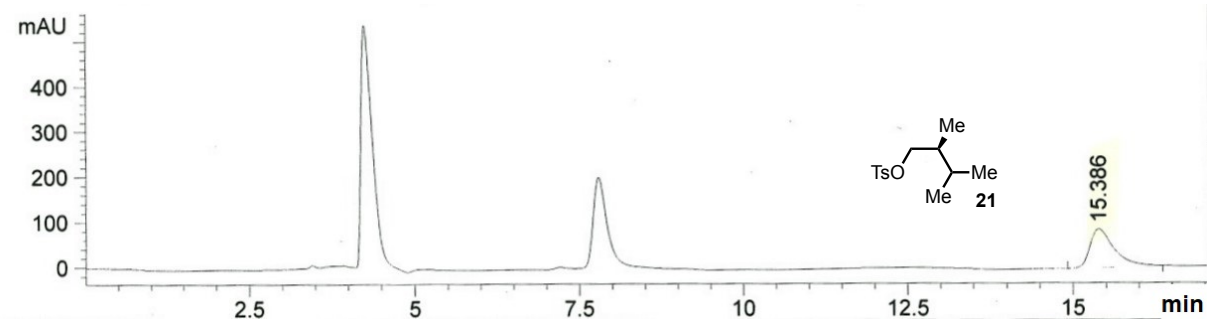


To a solution of olefin **S6** (0.99 g, 3.9 mmol, 1.0 eq.) in EtOAc (40 mL) was added Pt/C (10% *w/w*, 767 mg, 390 *µ*mol, 0.1 eq.), the atmosphere was exchanged to hydrogen, and the reaction mixture was stirred at 25 °C for 18 h. It was filtered through Celite® and the solvent was removed under reduced pressure. Tosylate **21** (925 mg, 3.90 mmol, quant.) was obtained as a colorless oil and used in the next step without further purification.

The enantiomeric excess was determined by HPLC using a Chiralpak® IC column, λ = 210.4 nm, *n*hexane/*i*PrOH 199:1, flow rate = 1 mL/min; t_R = 14.47 min (minor, epi-**21**, not shown), 15.27 min (major, **21**) (*ee* > 99%).

HPLC traces of racemic tosylate **21**$_{(rac)}$ (top) and enantiopure tosylate **21** (bottom)





TLC: R_f = 0.30 (*n*hexane/EtOAc 50:1).

^{1}H-NMR: (400 MHz, $CDCl_3$); δ [ppm] = 7.79 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 3.94 (dd, *J* = 9.4, 5.7 Hz, 1H), 3.84 (dd, *J* = 9.4, 6.5 Hz, 1H), 2.45 (s, 3H), 1.73 – 1.59 (m, 2H), 0.87 – 0.79 (m, 6H), 0.76 (d, *J* = 6.6 Hz, 3H).

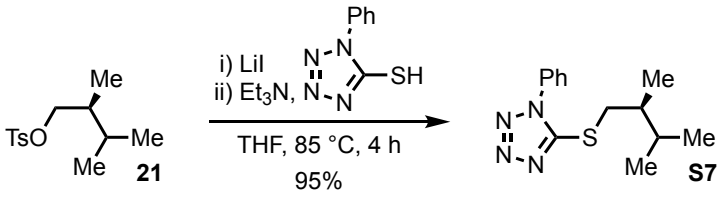
^{13}C-NMR: (101 MHz, $CDCl_3$); δ [ppm] = 144.8, 133.3, 129.9, 128.0, 73.9, 38.5, 28.9, 21.8, 20.3, 18.0, 12.7.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2961 (w), 1598 (w), 1466 (w), 1358 (m), 1174 (s), 1097 (m), 960 (s), 929 (m), 837 (m), 813 (m), 759 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{13}H_{20}O_3SNa^+$ [M+Na]$^+$: 279.1025, found: 279.1026.

Opt. act. $[\alpha]_D^{26}$ = +5.2 (*c* = 1.00, $CHCl_3$).

(*S*)-5-((2,3-Dimethylbutyl)thio)-1-phenyl-1*H*-tetrazole (**S7**)



To a solution of tosylate **21** (462 mg, 1.80 mmol, 1.0 eq.) in THF (20 mL) was added lithium iodide (previously dried under reduced pressure at 120 °C for 24 h, 522 mg, 3.60 mmol, 2.0 eq.) and the reaction mixture was heated to reflux for 1 h. It was cooled to 25 °C and triethylamine (810 µL, 5.85 mmol, 3.0 eq.) and 1-phenyl-1*H*-tetrazole-5-thiol (729 mg, 3.60 mmol, 2.0 eq.) were added before the solution was again heated to reflux for 3 h and then stirred at 25 °C for 16 h. The precipitate was filtered off, the solvent was removed under reduced pressure, and the resulting residue was taken up in Et_2O (20 mL) and brine (sat., 20 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic phases were washed with brine (sat., 20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 12:1) gave thioether **S7** (448 mg, 1.71 mmol, 95%) as a colorless oil.

TLC: R_f = 0.35 (*n*hexane/EtOAc 9:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 7.61 – 7.50 (m, 5H), 3.52 (dd, *J* = 12.5, 5.3 Hz, 1H), 3.23 (dd, *J* = 12.6, 8.3 Hz, 1H), 1.85 – 1.72 (m, 2H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

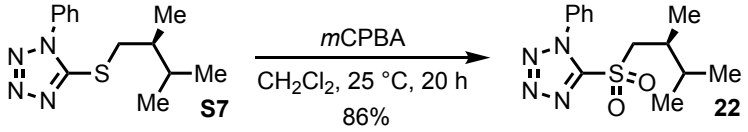
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 154.9, 134.0, 130.2, 129.9, 124.0, 38.8, 38.6, 31.6, 20.4, 17.8, 15.1.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2958 (m), 2924 (m), 2872 (w), 2853 (w), 1735 (w), 1597 (w), 1499 (m), 1463 (m), 1385 (m), 1239 (m), 1974 (w), 1014 (m), 978 (w), 912 (w), 759 (s), 733 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{13}H_{18}N_4SNa^+$ [M+Na]$^+$: 285.1144, found: 285.1162.

Opt. act. $[\alpha]_D^{26}$ = +13.4 (*c* = 0.92, $CHCl_3$).

(*S*)-5-((2,3-Dimethylbutyl)sulfonyl)-1-phenyl-1*H*-tetrazole (**22**)



To a solution of thioether **S7** (407 mg, 1.55 mmol, 1.0 eq.) in CH_2Cl_2 (16 mL) was added *m*CPBA (70% *w/w*, 804 mg, 4.66 mmol, 3.0 eq.) and the reaction was stirred at 25 °C for 24 h. The reaction mixture was filtered, the filtrate was cooled to 0 °C and H_2O (3 mL), $NaHSO_3$ (5% aq., 15 mL) and $NaHCO_3$ (sat. aq., 15 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 15 mL) and brine (sat., 15 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 9:1) gave sulfone **22** (393 mg, 1.34 mmol, 86%) as a colorless oil.

TLC: R_f = 0.32 (*n*hexane/EtOAc 12:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 7.70 – 7.66 (m, 2H), 7.65 – 7.57 (m, 3H), 3.85 (dd, *J* = 14.4, 3.7 Hz, 1H), 3.52 (dd, *J* = 14.4, 9.0 Hz, 1H), 2.32 – 2.23 (m, 1H), 1.89 – 1.80 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H).

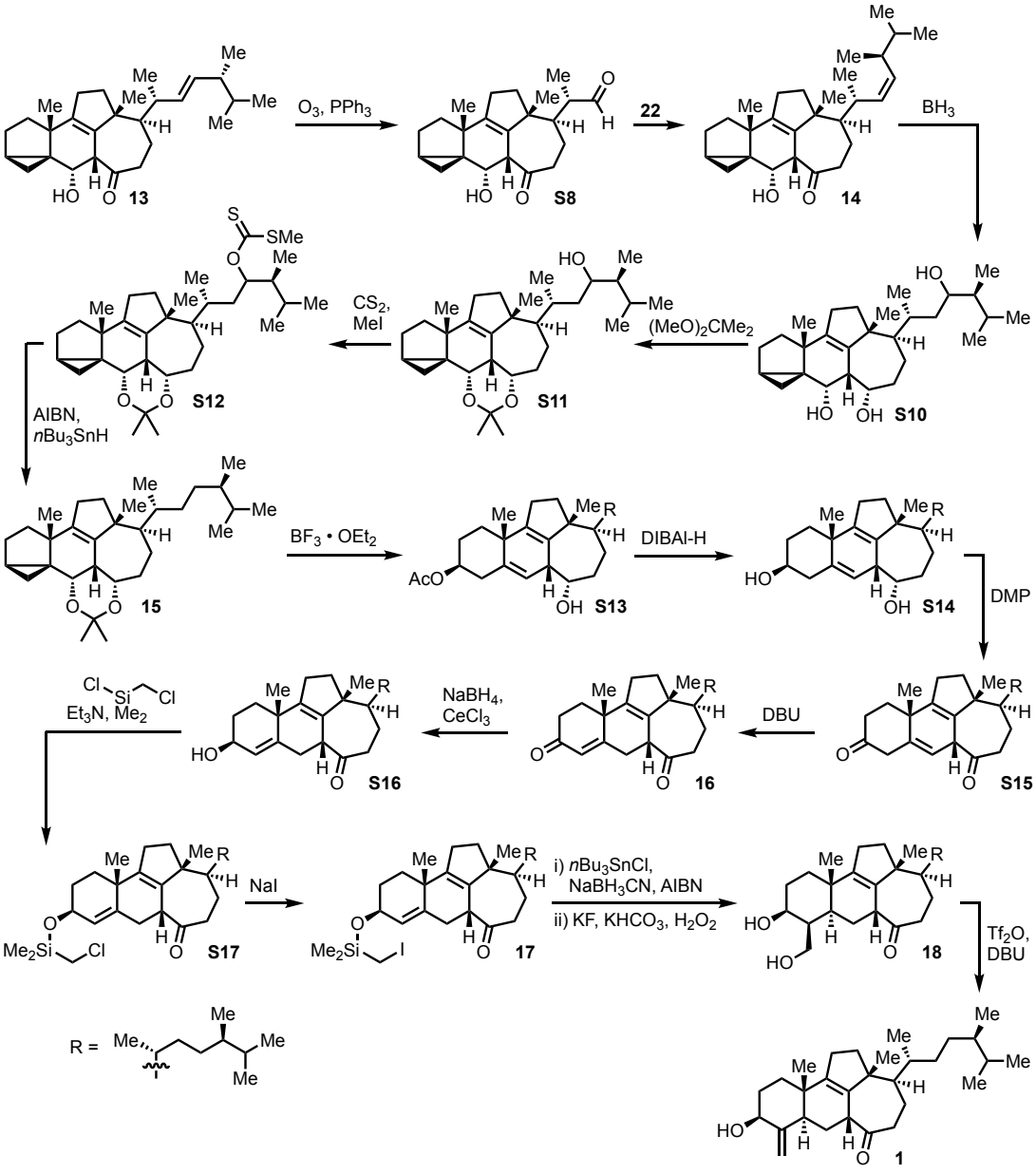
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 154.2, 133.2, 131.6, 129.8, 125.3, 60.2, 33.4, 32.5, 19.5, 17.8, 15.8.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2960 (m), 2923 (m), 2853 (m), 1497 (m), 1462 (m), 1336 (s), 1150 (s), 763 (s).

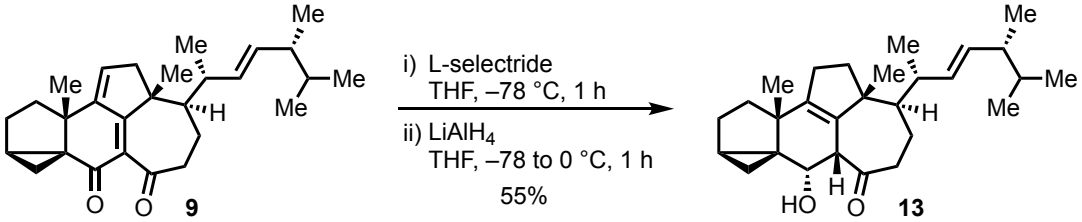
HRMS: (ESI-TOF); *m/z* calcd. for $C_{13}H_{18}N_4O_2SNa^+$ [M+Na]$^+$: 317.1043, found: 317.1064.

Opt. act. $[\alpha]_D^{27}$ = +8.1 (*c* = 1.00, $CHCl_3$).

2.5 Synthesis of Swinhoeisterol A (**1**)



(22*E*)-6α-Hydroxy-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α,7β(H)-ergosta-8,22-dien-14-one (**13**)



A solution of diene dione **9** (1,31 g, 3.23 mmol, 1.0 eq.) in THF (32 mL) was degassed applying three freeze-pump-thaw cycles. After cooling to –78 °C, L-selectride (1 M in THF, 6.5 mL, 6.5 mmol, 2.0 eq.) was added dropwise over 30 min and the resulting solution was stirred at this temperature for 30 min. Lithium aluminum hydride (1 M in THF, 6.5 mL, 6.5 mmol, 2.0 eq.) was added dropwise over 30 min, and the reaction mixture was warmed to 0 °C. After stirring for 30 min at this temperature, EtOAc (20 mL) and Rochelle's salt (½ sat. aq., 30 mL) were added carefully, and the mixture was vigorously stirred at 25 °C for 16 h. A solution of $NaBO_3 \cdot 4H_2O$ (1.24 g, 8.08 mmol, 2.5 eq.) in H_2O (10 mL) was added and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc (3 × 25 mL) and the combined organic phases were washed with brine (sat., 50 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 50:1 → 19:1) gave β-hydroxy ketone **13** (731 mg, 1.78 mmol, 55%) as a colorless oil.

TLC: R_f = 0.44 (*n*hexane/EtOAc 9:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.31 – 5.21 (m, 2H), 4.44 (d, *J* = 8.5 Hz, 1H), 4.25 – 4.19 (m, 1H), 3.16 (d, *J* = 6.4 Hz, 1H), 2.60 – 2.52 (m, 1H), 2.51 – 2.40 (m, 2H), 2.35 – 2.26 (m, 1H), 2.21 – 2.13 (m, 2H), 2.12 – 2.06 (m, 1H), 1.87 – 1.82 (m, 1H), 1.74 – 1.67 (m, 1H), 1.66 – 1.62 (m, 1H), 1.62 – 1.58 (m, 2H), 1.58 – 1.54 (m, 1H), 1.53 – 1.47 (m, 2H), 1.46 – 1.39 (m, 2H), 1.09 (s, 3H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.98 (s, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.77 – 0.73 (m, 1H), 0.31 (t, *J* = 4.2 Hz, 1H).

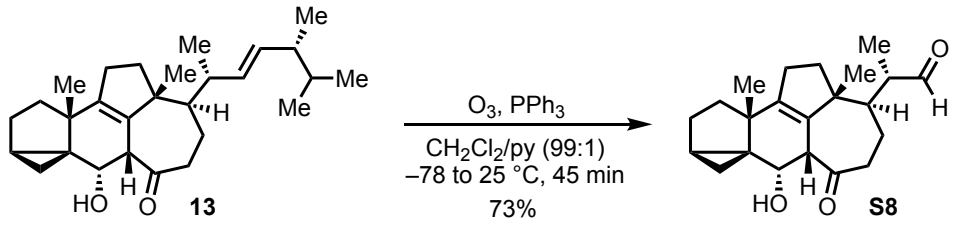
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 219.7, 144.8, 137.6, 134.9, 132.3, 68.2, 53.6, 53.5, 48.3, 46.1, 45.3, 43.5, 38.5, 37.9, 37.8, 33.2, 33.1, 28.1, 26.6, 22.9, 22.6, 21.5, 20.9, 20.2, 19.9, 19.9, 17.8, 7.7.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3441 (br w), 2955 (s), 2924 (s), 2867 (m), 1738 (w), 1684 (m), 1457 (m), 1375 (w), 1070 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_2Na^+$ $[M+Na]^+$: 433.3077, found: 433.3099.

Opt. act. $[\alpha]_D^{25}$ = +54.9 (*c* = 1.00, $CHCl_3$).

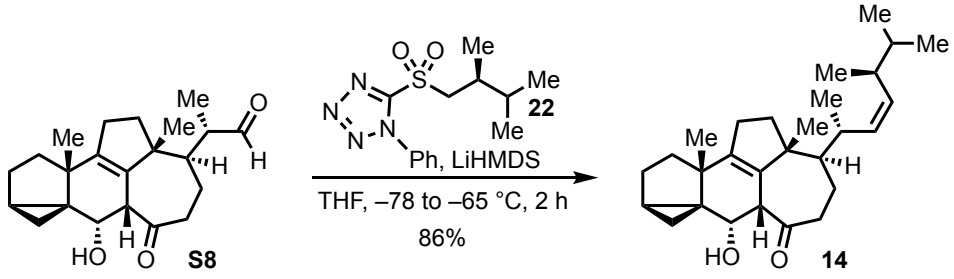
6α-Hydroxy-14-oxo-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α,7β(H)-pregn-8-en-20α-carboxaldehyde (**S8**)



A stream of ozone-rich oxygen was passed through a solution of β-hydroxy ketone **13** (574 mg, 1.40 mmol, 1.0 eq.) in CH_2Cl_2/pyridine (99:1, 14 mL) at –78 °C for 45 min. PPh_3 (732 mg, 2.80 mmol, 2.0 eq.) was added and the reaction mixture was allowed to warm to 25 °C over 16 h. The solvent was removed, the residue was adsorbed on silica gel and column chromatography (silica gel, *n*hexane/EtOAc 5:1) gave aldehyde **S8** (349 mg, 1.02 mmol, 73%) as a crystalline solid.

M.p.	122–124 °C ($CHCl_3$)
TLC:	R_f = 0.19 (*n*hexane/EtOAc 5:1).
^{1}H-NMR:	(600 MHz, $CDCl_3$); δ [ppm] = 9.77 (d, *J* = 2.4 Hz, 1H), 4.37 (d, *J* = 8.6 Hz, 1H), 4.29 – 4.19 (m, 1H), 3.22 (d, *J* = 6.3 Hz, 1H), 2.76 – 2.66 (m, 1H), 2.56 – 2.46 (m, 2H), 2.37 – 2.30 (m, 1H), 2.24 (ddt, *J* = 16.1, 9.2, 2.1 Hz, 1H), 2.04 (ddd, *J* = 12.7, 7.7, 2.3 Hz, 1H), 1.82 – 1.77 (m, 1H), 1.70 (dt, *J* = 12.7, 9.2 Hz, 1H), 1.65 – 1.60 (m, 4H), 1.52 – 1.44 (m, 1H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 1.08 – 1.04 (m, 2H), 0.98 (dd, *J* = 8.4, 4.9 Hz, 1H), 0.33 (t, *J* = 4.3 Hz, 1H).
^{13}C-NMR:	(151 MHz, $CDCl_3$); δ [ppm] = 218.3, 205.0, 146.1, 136.3, 68.1, 53.5, 53.0, 48.6, 48.4, 46.1, 45.4, 37.9, 37.8, 33.1, 28.1, 26.6, 22.6, 21.6, 21.3, 20.0, 15.7, 7.8.
IR:	(neat); $\tilde{\nu}$ [cm^{-1}] = 3446 (br w), 2954 (s), 2925 (s), 2857 (m), 1718 (m), 1684 (m), 1456 (w), 1418 (w), 1378 (w), 1281 (w), 1069 (w), 1029 (w).
HRMS:	(ESI-TOF); *m/z* calcd. for $C_{22}H_{30}O_3Na^+$ [M+Na]$^+$: 365.2087, found: 365.2104.
Opt. act.	$[\alpha]_D^{28}$ = +56.0 (*c* = 1.00, $CHCl_3$).

(22*Z*)-6α-Hydroxy-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α,7β(H)-campesta-8,22-dien-14-one (**14**)



To a solution of hexamethyldisilazane (520 μL, 2.52 mmol, 3.26 eq.) in THF (1 mL) at 0 °C was added *n*BuLi (1.6 M in *n*hexane, 1.5 mL, 2.40 mmol, 3.1 eq.) and it was stirred for 15 min at this temperature before the solution was added to sulfone **22** (1.14 g, 3.87 mmol, 5.0 eq.) in THF (3 mL) at –78 °C. The resulting bright yellow solution was stirred at –65 °C for 1 h and a solution of aldehyde **S8** (265 mg, 774 μmol, 1.0 eq.) in THF (2 mL) was added to the reaction mixture over 30 min. The reaction was stirred at –65 °C for further 30 min before EtOAc (3 mL) and H_2O (5 mL) were added to the reaction mixture. The aqueous phase was

extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed sequentially with HCl (1 M in H_2O, 20 mL), $NaHCO_3$ (sat. aq., 20 mL) and brine (sat., 20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 19:1) gave (22*Z*)-olefin **14** (273 mg, 665 μmol, 86%) as a crystalline solid and aldol product **S9** (11 mg, 23 μmol, 3%) as a colorless solid and re-isolated sulfone **22** (855 mg, 2.90 mmol, 3.75 eq.) as a colorless oil.

M.p. 88–90 °C ($CHCl_3$)

TLC: R_f = 0.33 (*n*hexane/EtOAc 9:1).

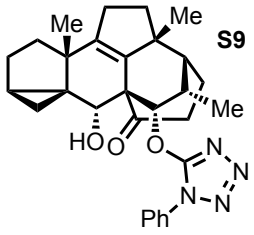
^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.25 (t, *J* = 10.7 Hz, 1H), 5.06 (t, *J* = 10.8 Hz, 1H), 4.42 – 4.35 (m, 1H), 4.25 – 4.17 (m, 1H), 3.26 – 3.18 (m, 1H), 2.83 – 2.72 (m, 1H), 2.57 – 2.51 (m, 1H), 2.50 – 2.45 (m, 1H), 2.34 – 2.27 (m, 1H), 2.24 – 2.15 (m, 2H), 2.12 (ddd, *J* = 12.4, 7.8, 2.6 Hz, 1H), 1.88 – 1.82 (m, 1H), 1.66 – 1.59 (m, 3H), 1.55 – 1.47 (m, 2H), 1.46 – 1.42 (m, 1H), 1.40 – 1.35 (m, 1H), 1.12 – 1.07 (m, 4H), 1.07 – 1.03 (m, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 4.9 Hz, 1H), 0.96 (s, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.31 (t, *J* = 4.3 Hz, 1H).

^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 219.2, 144.9, 137.6, 133.5, 131.8, 68.2, 54.2, 53.3, 48.5, 46.2, 45.3, 38.4, 38.1, 37.8, 33.6, 33.4, 33.1, 28.2, 26.5, 23.0, 22.7, 21.0, 20.3, 20.3, 20.1, 20.0, 17.7, 7.7.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2952 (m), 2924 (s), 2854 (m), 1740 (w), 1685 (w), 1458 (w), 1377 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_2Na^+$ [M+Na]$^+$: 433.3077, found: 433.3085.

Opt. act. $[\alpha]_D^{28}$ = +28.5 (*c* = 1.00, $CHCl_3$).



S9

M.p. 190–193 °C ($CHCl_3$)

TLC: R_f = 0.33 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 7.82 (d, *J* = 8.3 Hz, 2H), 7.57 – 7.51 (m, 2H), 7.44 – 7.40 (m, 1H), 5.70 (d, *J* = 9.7 Hz, 1H), 4.30 (d, *J* = 9.3 Hz, 1H), 4.15 (d, *J* = 9.3 Hz, 1H), 3.32 – 3.24 (m, 1H), 3.15 (dt, *J* = 13.5, 10.9 Hz, 1H), 2.61 (ddd, *J* = 16.1, 10.5, 5.8 Hz, 1H), 2.30 – 2.20 (m, 2H), 2.15 – 2.07 (m, 2H), 1.98 – 1.86 (m, 2H), 1.79 – 1.71 (m, 2H), 1.65 – 1.57 (m, 2H), 1.39 – 1.32 (m, 1H), 1.26 (s, 3H), 1.09 – 1.05 (m, 1H), 1.04 (s, 3H), 1.02 – 0.98 (m, 1H), 0.87 (d, *J* = 7.5 Hz, 3H), 0.22 (t, *J* = 4.5 Hz, 1H).

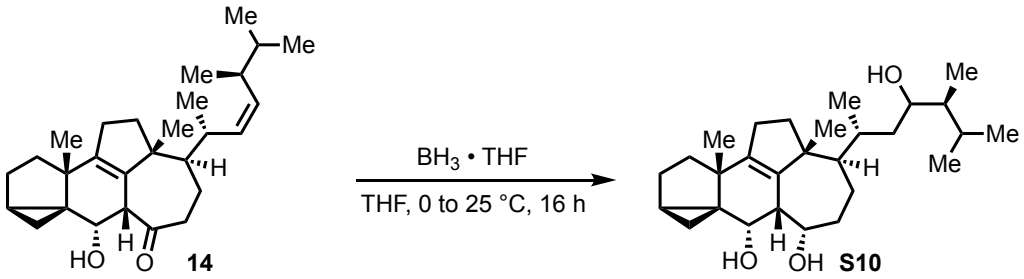
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 218.6, 160.4, 145.1, 140.8, 133.8, 129.7, 128.8, 121.2, 83.2, 72.1, 57.0, 48.8, 45.5, 43.9, 40.2, 38.1, 37.8, 33.0, 32.0, 29.2, 26.9, 24.1, 23.6, 20.6, 18.6, 14.7, 7.0.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] =2954 (m), 2923 (s), 2853 (m), 1740 (w), 1558 (w), 1459 (w), 1377 (w).

HRMS: (ESI-TOF); *m/z* calcd. $C_{29}H_{34}N_4O_3Na^+$ $[M+Na]^+$: 509.2523, found: 509.2518.

Opt. act. $[\alpha]_D^{20} = -41.6$ (*c* = 1.00, $CHCl_3$).

13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α,7β(H)-Campesta-8-en-6α,14α,23-triol (**S10**)



To a solution of (22*Z*)-olefin **14** (339 mg, 825 μmol, 1.0 eq.) in THF (8.3 mL) was added BH_3•THF (1 M in THF, 8.3 mL, 8.3 mmol, 10 eq.) at 0 °C and the reaction mixture was allowed to warm to 25 °C over 16 h. It was diluted with Et_2O (10 mL) at 0 °C, NaOH (10% *w/w* in H_2O, 5 mL) and H_2O_2 (35% *w/w* in H_2O, 5 mL) were carefully added and it was stirred at 25 °C for 1 h. It was neutralized with HCl (1 M in H_2O, 5 mL) and the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 30 mL) and brine (sat., 30 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude mixture of regio- and diastereomers (303 mg, 704 μmol, combined yield 85%) was used in the next step without further purification.

Analytically pure triol **S10** (major product, C23-OH, configuration at C23 was not elucidated) could be obtained by column chromatography (silica gel, *n*hexane/EtOAc 5:1 → 3:1) as a colorless foam.

TLC: R_f = 0.24 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 4.27 (d, *J* = 6.3 Hz, 1H), 4.23 (d, *J* = 6.2 Hz, 1H), 3.52 (ddd, *J* = 10.6, 7.0, 1.6 Hz, 1H), 2.68 (d, *J* = 6.3 Hz, 1H), 2.29 – 2.18 (m, 2H), 2.01 – 1.94 (m, 2H), 1.94 – 1.87 (m, 1H), 1.87 – 1.81 (m, 1H), 1.79 – 1.74 (m, 1H), 1.73 – 1.66 (m, 1H), 1.65 – 1.57 (m, 4H), 1.57 – 1.48 (m, 3H), 1.47 – 1.39 (m, 2H), 1.35 – 1.29 (m, 1H), 1.10 – 1.07 (m, 1H), 1.04 (s, 3H), 1.03 (s, 3H), 0.93 – 0.89 (m, 6H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.9 Hz, 3H), 0.69 (dd, *J* = 8.4, 5.0 Hz, 1H), 0.28 (t, *J* = 4.5 Hz, 1H).

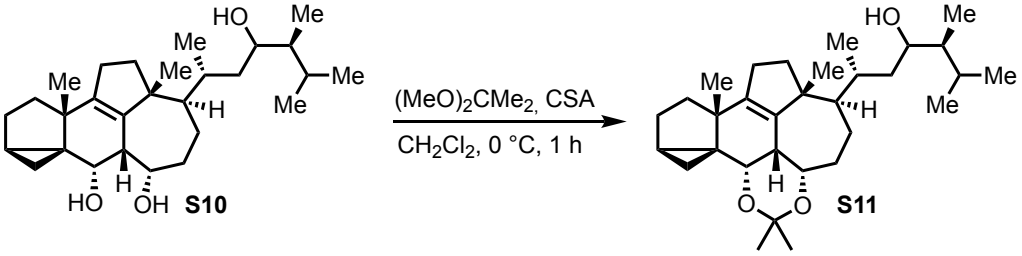
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 144.7, 140.1, 72.4, 66.4, 64.2, 53.8, 51.8, 45.7, 45.5, 42.5, 39.5, 37.4, 36.3, 35.8, 33.2, 30.1, 28.5, 28.2, 26.1, 23.9, 21.7, 21.6, 20.8, 20.5, 18.5, 17.8, 10.5, 7.1.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3320 (br w), 2953 (s), 2925 (w), 2870 (m), 1740 (m), 1463 (m), 1367 (m), 1217 (w), 1045 (m), 754 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{46}O_3Na^+$ $[M+Na]^+$: 453.3339, found: 453.3318.

Opt. act. $[\alpha]_D^{19}$ = +101.3 (*c* = 1.00, $CHCl_3$).

6,14-(1-Methylethylidene acetal)-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α,7β(H)-campesta-8-en-6α,14α,23-triol (**S11**)



To a solution of the crude mix of regio- and diastereomers **S10** (296 mg, 687 μmol, 1.0 eq) in CH_2Cl_2/2,2-dimethoxy propane (5:1, 6.6 mL) was added camphorsulfonic acid (192 mg, 825 μmol, 1.2 eq.) at 0°C. The reaction mixture was stirred at this temperature for 1 h before $NaHCO_3$ (sat. aq., 5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine (sat., 30 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was used without further purification in the next step.

Analytically pure C23-hydroxy epimers **S11a** and **S11b** could be obtained by column chromatography (silica gel, *n*hexane/EtOAc 19:1 → 9:1) as colorless oils.

S11a

TLC: R_f = 0.20 (*n*hexane/EtOAc 9:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 4.48 (d, *J* = 7.2 Hz, 1H), 3.95 (ddd, *J* = 11.5, 9.5, 2.0 Hz, 1H), 3.54 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.04 (ddt, *J* = 9.6, 7.3, 2.3 Hz, 1H), 2.27 – 2.18 (m, 1H), 2.11 (dd, *J* = 12.2, 6.6 Hz, 1H), 2.09 – 2.04 (m, 1H), 2.00 (ddd, *J* = 15.5, 8.8, 2.3 Hz, 1H), 1.86 – 1.78 (m, 1H), 1.71 – 1.65 (m, 2H), 1.60 – 1.51 (m, 5H), 1.49 (s, 3H), 1.39 – 1.33 (m, 2H), 1.32 – 1.27 (m, 2H), 1.24 (s, 3H), 1.22 – 1.18 (m, 1H), 1.14 (dd, *J* = 12.9, 2.7 Hz, 1H), 1.10 – 1.05 (m, 1H), 1.03 (s, 3H), 0.98 (s, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.8 Hz,

3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.79 (dd, *J* = 8.0, 4.6 Hz, 1H), 0.75 (d, *J* = 6.9 Hz, 3H), 0.27 (t, *J* = 4.1 Hz, 1H).

^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 142.9, 140.3, 96.8, 72.4, 72.0, 68.7, 54.1, 49.8, 45.9, 44.6, 38.0, 36.9, 36.5, 33.4, 33.1, 32.9, 30.3, 30.1, 28.2, 27.9, 26.0, 25.7, 23.8, 22.2, 21.6, 21.3, 21.2, 20.5, 17.9, 10.5, 6.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2923 (s), 2854 (m), 1739 (w), 1461 (m), 1378 (m), 1244 (w), 1212 (w), 1094 (w), 1050 (w), 873 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{31}H_{50}O_3Na^+$ [M+Na]$^+$: 493.3652, found: 493.3630.

Opt. act. $[\alpha]_D^{22}$ = +74.3 (*c* = 1.00, $CHCl_3$).

S11b

TLC: R_f = 0.23 (*n*hexane/EtOAc 5:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 4.49 (d, *J* = 7.2 Hz, 1H), 3.97 – 3.91 (m, 1H), 3.82 – 3.76 (m, 1H), 3.04 (dt, *J* = 9.7, 5.0 Hz, 1H), 2.26 – 2.18 (m, 1H), 2.09 – 1.97 (m, 2H), 1.77 – 1.66 (m, 3H), 1.65 – 1.53 (m, 5H), 1.50 (s, 3H), 1.36 – 1.29 (m, 1H), 1.28 – 1.25 (m, 1H), 1.24 (s, 3H), 1.23 – 1.17 (m, 1H), 1.14 – 1.06 (m, 3H), 1.04 (s, 3H), 1.03 (d, *J* = 7.6 Hz, 3H), 1.00 – 0.97 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.94 – 0.90 (m, 6H), 0.88 (d, *J* = 6.8 Hz, 1H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.80 (dd, *J* = 8.2, 4.5 Hz, 1H), 0.28 (t, *J* = 4.1 Hz, 1H).

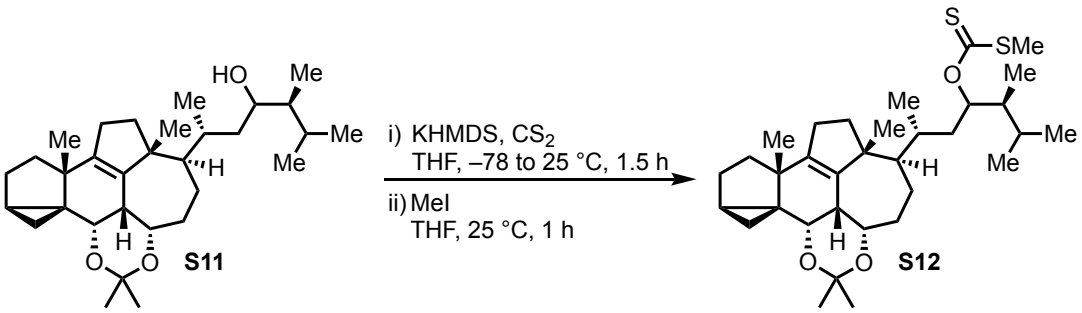
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 143.0, 140.3, 96.8, 72.9, 72.3, 68.7, 53.7, 50.7, 44.6, 43.2, 38.8, 38.0, 36.5, 33.5, 33.1, 33.0, 32.5, 30.7, 30.2, 27.9, 26.0, 25.7, 23.9, 22.3, 22.2, 21.3, 21.3, 20.4, 20.4, 9.9, 6.7.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2952 (m), 2922 (s), 2853 (m), 1740 (w), 1460 (m), 1377 (w), 1244 (w), 1171 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{31}H_{50}O_3Na^+$ [M+Na]$^+$: 493.3652, found: 493.3646.

Opt. act. $[\alpha]_D^{22}$ = +58.4 (*c* = 1.00, $CHCl_3$).

23-(*S*-Methyl carbonodithioate)-6,14-(1-methylethylidene acetal)-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α,7β(H)-campesta-8-en-6α,14α,23-triol (**S12**)



A solution of crude acetonides **S11** (687 μmol, 1.0 eq.) in THF (6.9 mL) was cooled to 78 °C and KHMDS (0.5 M in toluene, 2.75 mL, 1.37 mmol, 2.0 eq.) and CS_2 (208 μL, 3.44 mmol, 5 eq.) were added dropwise. After stirring at this temperature for 20 min, the mixture was warmed to 25 °C and stirred for 1 h. MeI (321 μL, 5.15 mmol, 7.5 eq.) was added and stirring was continued at 25 °C for 45 min before it was diluted with H_2O (5 mL) and Et_2O (5 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic phases were washed with brine (sat., 40 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. A mixture of xanthates **S12** was obtained by filtering through a plug of silica with *n*hexane/EtOAc (9:1).

Analytically pure xanthate C23-epimers **S12a** and **S12b** could be obtained by column chromatography (silica gel, *n*hexane/EtOAc 50:1) as colorless oils.

S12a

TLC: R_f = 0.35 (*n*hexane/EtOAc 19:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.98 (ddd, *J* = 11.4, 5.3, 1.5 Hz, 1H), 4.49 (d, *J* = 7.2 Hz, 1H), 4.00 – 3.95 (m, 1H), 3.05 (ddt, *J* = 9.6, 7.5, 2.3 Hz, 1H), 2.56 (s, 3H), 2.23 – 2.15 (m, 1H), 2.03 – 1.95 (m, 2H), 1.88 – 1.82 (m, 1H), 1.81 – 1.75 (m, 1H), 1.74 – 1.67 (m, 3H), 1.60 – 1.52 (m, 8H), 1.51 (s, 3H), 1.35 – 1.28 (m, 1H), 1.25 (s, 3H), 1.15 – 1.10 (m, 2H), 1.03 (s, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.98 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.82 – 0.78 (m, 1H), 0.28 (t, *J* = 4.0 Hz, 1H).

^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 216.3, 143.0, 140.2, 96.8, 85.8, 72.4, 68.7, 53.8, 49.7, 44.6, 42.8, 37.9, 36.5, 33.4, 33.2, 33.1, 32.9, 30.2, 29.9, 29.7, 27.9, 26.0, 25.7, 23.5, 22.2, 21.6, 21.3, 21.2, 20.3, 19.8, 19.0, 11.5, 6.7.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2923 (s), 2854 (m), 1738 (w), 1460 (w), 1378 (w), 1219 (s), 1172 (w), 1095 (w), 1049 (s), 874 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{33}H_{52}O_3S_2Na^+$ $[M+Na]^+$: 583.3250, found: 583.3252.

Opt. act. $[\alpha]_D^{23}$ = +57.5 (*c* = 0.44, $CHCl_3$).

S12b

TLC: R_f = 0.27 (*n*hexane/EtOAc 19:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.94 (ddd, *J* = 9.3, 5.2, 1.9 Hz, 1H), 4.49 (d, *J* = 7.2 Hz, 1H), 3.94 (ddd, *J* = 11.2, 9.5, 2.2 Hz, 1H), 3.03 (ddt, *J* = 9.5, 7.3, 2.3 Hz, 1H), 2.54 (s, 3H), 2.26 – 2.17 (m, 1H), 2.09 – 1.97 (m, 2H), 1.77 – 1.66 (m, 4H), 1.61 – 1.53 (m, 10H), 1.53 – 1.50 (m, 1H), 1.49 (s, 3H), 1.43 (ddd, *J* = 13.5, 12.0, 5.2 Hz, 1H), 1.38 – 1.31 (m, 2H), 1.26 (d, *J* = 3.1 Hz, 1H), 1.24 (s, 3H), 1.23 – 1.20 (m, 1H), 1.11 (dd, *J* = 12.7, 3.0 Hz, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.96 (s, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.90 – 0.85 (m, 1H), 0.80 (dd, *J* = 8.3, 4.5 Hz, 1H), 0.28 (t, *J* = 4.1 Hz, 1H).

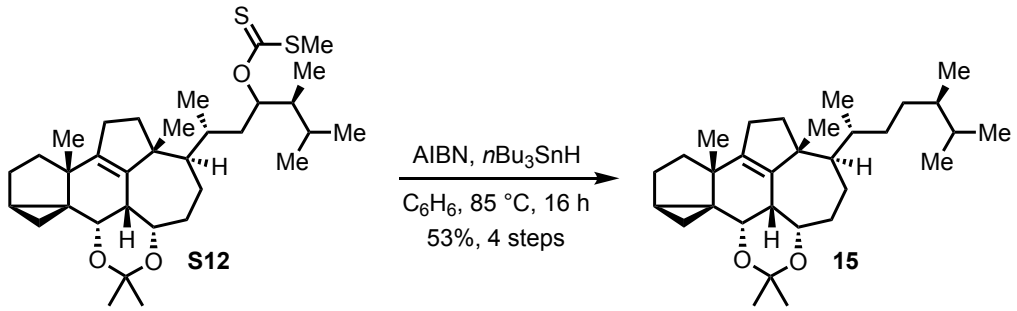
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 215.3, 143.1, 140.1, 96.8, 86.0, 72.3, 68.7, 53.6, 50.6, 44.6, 41.3, 38.0, 36.5, 34.0, 33.4, 33.1, 32.9, 31.6, 30.9, 30.1, 27.9, 26.0, 25.7, 23.8, 22.3, 21.5, 21.4, 21.1, 20.5, 20.3, 18.8, 11.6, 6.7.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2924 (s), 2854 (m), 1739 (w), 1459 (w), 1379 (w), 1218 (m), 1094 (w), 1050 (m), 874 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{33}H_{52}O_3S_2Na^+$ $[M+Na]^+$: 583.3250, found: 583.3242.

Opt. act. $[\alpha]_D^{24}$ = +53.2 (*c* = 0.22, $CHCl_3$).

6,14-(1-Methylethylidene acetal)-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α,7β(H)-campesta-8-en-6α,14α-diol (**15**)



Azobisisobutyronitrile (56 mg, 344 μmol, 0.5 eq.) and $n$$Bu_3SnH$ (927 μL, 3.44 mmol, 5 eq.) were dissolved in benzene (3.3 mL) and the solution was degassed applying three freeze-pump-thaw cycles. This mixture was added to a degassed solution (also three freeze-pump-thaw cycles) of xanthates **S12** (687 μmol, 1.0 eq.) in benzene (6.8 mL) at 85 °C over 3 h. The reaction mixture was then allowed to cool to 25 °C and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 50:1 → 19:1 → 12:1) gave acetonide **15** (200 mg, 440 μmol, 53% over 4 steps) as a colorless oil.

TLC: R_f = 0.33 (*n*hexane/EtOAc 19:1).

^{1}H-NMR: (400 MHz, $CDCl_3$); δ [ppm] = 4.49 (d, *J* = 7.2 Hz, 1H), 3.96 (ddd, *J* = 11.4, 9.5, 2.1 Hz, 1H), 3.04 (ddt, *J* = 9.5, 7.5, 2.3 Hz, 1H), 2.26 – 2.16 (m, 1H), 2.07 – 1.95 (m, 2H), 1.72 – 1.64 (m, 2H), 1.62 – 1.51 (m, 6H), 1.50 (s, 3H), 1.45 – 1.42 (m, 1H), 1.37 – 1.26 (m, 3H), 1.24 (s, 3H), 1.23 – 1.13 (m, 3H), 1.09 (dd, *J* = 12.6, 2.9 Hz, 2H), 1.03 (s, 3H), 1.01 – 0.96 (m, 1H), 0.94 – 0.90 (m, 6H), 0.90 – 0.87 (m, 1H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.82 – 0.76 (m, 6H), 0.28 (t, *J* = 4.1 Hz, 1H).

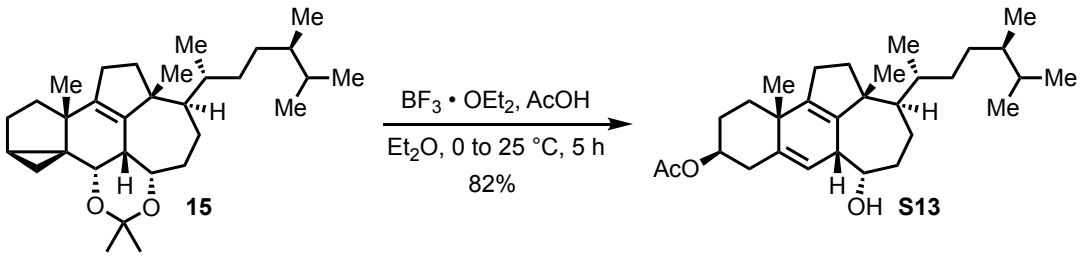
^{13}C-NMR: (101 MHz, $CDCl_3$); δ [ppm] = 142.8, 140.3, 96.8, 72.4, 68.7, 53.9, 50.2, 44.6, 39.2, 38.0, 36.5, 35.3, 33.5, 33.4, 33.1, 33.0, 32.2, 30.9, 30.5, 30.2, 27.9, 26.0, 25.7, 23.7, 22.3, 21.3, 20.4, 20.3, 18.2, 15.7, 6.7.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2989 (w), 2954 (s), 2867 (m), 2359 (w), 1458 (w), 1377 (m), 1244 (m), 1212 (m), 1094 (m), 747 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{31}H_{50}O_2Na^+$ [M+Na]$^+$: 477.3703, found: 477.3699.

Opt. act. $[\alpha]_D^{24}$ = +27.8 (*c* = 1.00, $CHCl_3$).

14α-Hydroxy-13(14→8),14(8→7)di*abeo*-7β(H)-campesta-5,8-dien-3β-yl acetate (**S13**)



To a solution of acetonide **15** (200 mg, 440 μmol, 1.0 eq.) in Et_2O (4.4 mL) were added acetic acid (2.2 mL) and BF_3•OEt_2 (2.2 mL) at 0 °C. The resulting solution was warmed to 25 °C and stirred for 5 h, before diluting with EtOAc (10 mL). The reaction mixture was then carefully poured into $NaHCO_3$ (sat. aq., 100 mL) and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 50 mL) and brine (sat., 50 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1) gave acetate **S13** (165 mg, 361 μmol, 82%) as a colorless oil.

TLC: R_f = 0.25 (*n*hexane/EtOAc 5:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.43 – 5.34 (m, 1H), 4.64 (tt, *J* = 11.4, 5.0 Hz, 1H), 3.84 – 3.76 (m, 1H), 3.02 – 2.95 (m, 1H), 2.47 (ddd, *J* = 12.5, 5.3, 1.8 Hz, 1H), 2.44 – 2.36 (m, 1H), 2.35 – 2.28 (m, 1H), 2.23 (dddd, *J* = 15.8, 8.7, 2.7, 1.4 Hz, 1H), 2.03 (s, 3H), 1.95 – 1.88 (m, 3H), 1.82 (ddd, *J* = 12.0, 7.5, 2.6 Hz, 1H), 1.73 – 1.66 (m, 2H), 1.65 – 1.57 (m, 3H), 1.56 – 1.51 (m, 3H), 1.40 – 1.32 (m, 2H), 1.30 – 1.23 (m, 2H), 1.15 (s, 3H), 1.01 – 0.97 (m, 1H), 0.96 (s, 3H), 0.94 – 0.91 (m, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H).

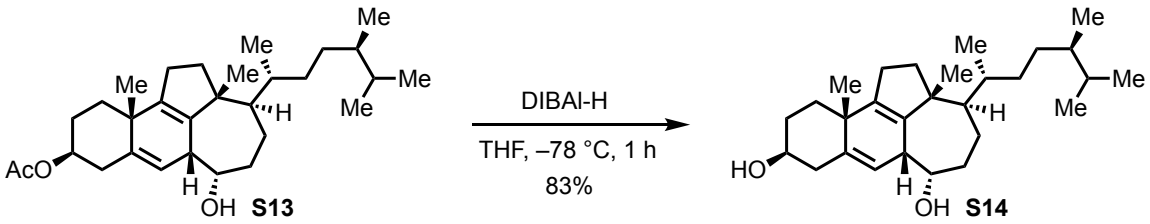
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 170.5, 143.7, 139.9, 137.8, 124.2, 74.2, 72.5, 53.9, 52.0, 39.8, 39.3, 39.1, 37.3, 36.8, 36.4, 35.6, 35.1, 33.5, 32.2, 30.5, 27.8, 27.7, 22.8, 21.8, 21.7, 21.5, 20.4, 19.1, 18.2, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (m), 2923 (s), 2853 (m), 1739 (w), 1458 (w), 1378 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{30}H_{48}O_3Na^+$ [M+Na]$^+$: 479.3496, found: 479.3482.

Opt. act. $[\alpha]_D^{22}$ = +41.3 (*c* = 1.00, $CHCl_3$).

13(14→8),14(8→7)di*abeo*-7β(H)-Campesta-5,8-dien-3β,14α-diol (**S14**)



To a solution of acetate **S13** (102 mg, 223 μmol, 1.0 eq.) in THF (2.2 mL) at –78 °C was added DIBAl-H (1 M in hexanes, 1.1 mL, 1.1 mmol, 5.0 eq.) and the resulting solution was stirred at this temperature for 1 h. EtOAc (1 mL) and Rochelle's salt (½ sat. aq., 5 mL) were added carefully and the mixture was vigorously stirred for 30 min while warming to 25 °C. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic phases were washed with brine (sat., 15 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 1:1) gave diol **S14** (76.7 mg,185 μmol, 83%) as a colorless oil.

TLC: R_f = 0.29 (*n*hexane/EtOAc 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.34 (dd, *J* = 3.2, 1.6 Hz, 1H), 3.83 – 3.75 (m, 1H), 3.62 – 3.51 (m, 1H), 3.03 – 2.94 (m, 1H), 2.44 – 2.37 (m, 1H), 2.37 – 2.28 (m, 2H), 2.28 – 2.20 (m, 1H), 2.00 – 1.93 (m, 1H), 1.93 – 1.86 (m, 2H), 1.83 (ddd, *J* = 12.0, 7.5, 2.3 Hz, 1H), 1.73 – 1.65 (m, 2H), 1.65 – 1.57 (m, 3H), 1.57 – 1.46 (m, 5H), 1.40 – 1.33 (m, 2H), 1.27 – 1.22 (m, 1H), 1.22 – 1.15 (m, 3H), 1.14 (s, 3H), 0.96 (s, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.79 (dd, *J* = 6.8, 0.8 Hz, 3H), 0.77 (d, *J* = 6.3 Hz, 3H).

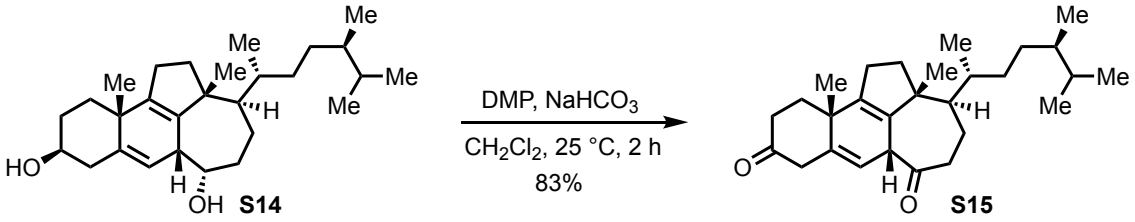
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 144.4, 141.0, 137.4, 123.2, 72.5, 72.4, 53.9, 52.3, 41.4, 39.7, 39.3, 39.1, 36.8, 36.7, 35.7, 35.1, 33.5, 32.2, 31.6, 30.4, 27.9, 23.0, 21.8, 21.6, 20.4, 19.0, 18.2, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3380 (br w), 2954 (s), 2927 (s), 2869 (m), 1706 (m), 1459 (m), 1376 (m), 1216 (w), 1058 (m), 1007 (m), 758 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{46}O_2Na^+$ $[M+Na]^+$: 437.3390, found: 437.3388.

Opt. act. $[\alpha]_D^{22}$ = +45.3 (*c* = 1.00, $CHCl_3$).

13(14→8),14(8→7)di*abeo*-7β(H)-Campesta-5,8-dien-3,14-dione(**S15**)



To a solution of diol **S14** (64.4 mg, 155 μmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) were added $NaHCO_3$ (84.6 mg, 1.01 mmol, 6.5 eq.) and Dess–Martin periodinane (197 mg, 465 μmol, 3.0 eq.), and the resulting suspension was stirred at 25 °C. After 45 min, $Na_2S_2O_3$ (sat. aq., 3 mL) was added and after further stirring for 15 min, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 15 mL) and brine (sat., 15 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1) gave dione **S15** (53.0 mg, 129 μmol, 83%) as a colorless oil.

TLC: R_f = 0.25 (*n*hexane/EtOAc 5:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.22 (t, *J* = 2.7 Hz, 1H), 3.54 (t, *J* = 3.2 Hz, 1H), 3.36 (dt, *J* = 16.1, 3.2 Hz, 1H), 2.97 (dd, *J* = 16.1, 2.2 Hz, 1H), 2.59 (ddd, *J* = 15.4, 13.6, 6.5 Hz, 1H), 2.45 – 2.32 (m, 4H), 2.23 – 2.11 (m, 2H), 2.03 (ddd, *J* = 13.2, 6.5, 2.4 Hz, 1H), 1.80 – 1.72 (m, 1H), 1.66 – 1.60 (m, 1H), 1.60 – 1.55 (m, 1H), 1.54 – 1.50 (m, 1H), 1.50 – 1.45 (m, 1H), 1.40 (s, 3H), 1.35 – 1.29 (m, 1H), 1.29 – 1.23 (m, 2H), 1.22 – 1.13 (m, 3H), 0.95 – 0.91 (m, 6H), 0.89 – 0.85 (m, 1H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.3 Hz, 3H).

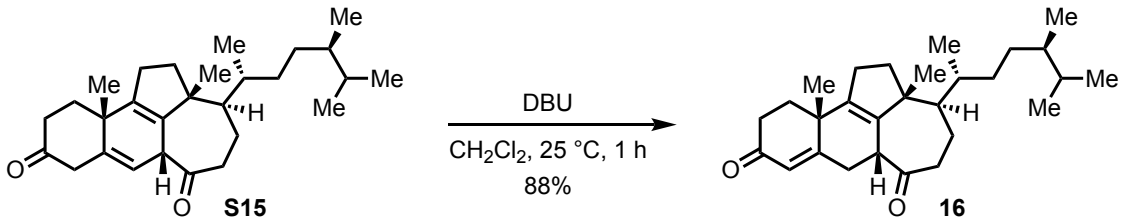
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 211.8, 207.9, 142.3, 139.7, 135.8, 119.2, 53.7, 51.5, 50.4, 48.2, 41.2, 39.1, 38.1, 38.0, 37.1, 35.9, 35.4, 33.4, 32.2, 30.8, 27.6, 22.6, 22.1, 21.4, 20.4, 19.6, 18.2, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2923 (s), 2853 (m), 1717 (m), 1459 (w), 1377 (w), 1239 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_2Na^+$ $[M+Na]^+$: 433.3077, found: 433.3074.

Opt. act. $[\alpha]_D^{21}$ = –27.1 (*c* = 1.00, $CHCl_3$).

13(14→8),14(8→7)di*abeo*-7β(H)-Campesta-4,8-dien-3,14-dione(**16**)



To a solution of dione **S15** (36.9 mg, 89.9 μmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (2.7 mg, 18 μmol, 0.2 eq.) and the resulting solution was stirred at 25 °C for 1 h. The reaction mixture was diluted with CH_2Cl_2 (2 mL) and NH_4Cl (sat. aq., 5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine (sat., 25 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 4:1 → 3:1) gave enone **16** (32.4 mg, 78.9 μmol, 88%) as a light-yellow oil.

M.p. 148–150 °C ($CHCl_3$)

TLC: R_f = 0.26 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.88 – 5.84 (m, 1H), 3.26 – 3.19 (m, 1H), 2.86 (dd, *J* = 13.1, 1.6 Hz, 1H), 2.57 – 2.47 (m, 3H), 2.47 – 2.38 (m, 2H), 2.32 – 2.27 (m, 2H), 2.21 – 2.12 (m, 1H), 2.00 – 1.93 (m, 2H), 1.76 – 1.69 (m, 2H), 1.65 – 1.61 (m, 2H), 1.58 – 1.50 (m, 2H), 1.40 – 1.31 (m, 1H), 1.29 (s, 3H), 1.26 – 1.22 (m, 2H), 1.21 – 1.18 (m, 2H), 1.08 (s, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.4 Hz, 3H).

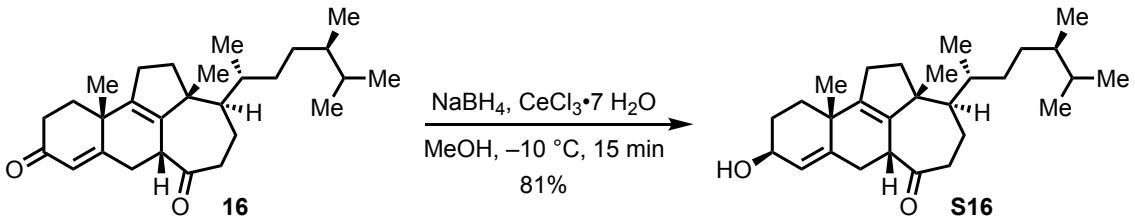
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 211.3, 198.5, 166.8, 143.3, 137.7, 126.0, 55.1, 53.6, 46.0, 44.9, 39.1, 38.0, 37.5, 35.0, 34.1, 33.6, 33.4, 32.8, 32.1, 30.4, 27.1, 22.3, 21.4, 20.3 (2C), 19.9, 18.1, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (s), 2926 (s), 2867 (m), 1707 (s), 1669 (s), 1456 (m), 1376 (m), 1235 (m), 1183 (w), 999 (w), 948 (w), 869 (w).

HRMS: (ESI-TOF); *m/z* calcd. $C_{28}H_{42}O_2Na^+$ $[M+Na]^+$: 433.3077, found: 433.3074.

Opt. act. $[\alpha]_D^{23}$ = +173.8 (*c* = 1.00, $CHCl_3$).

3β-Hydroxy-13(14→8),14(8→7)di*abeo*-7β(H)-campesta-4,8-dien-14-one(**S16**)



To a solution of enone **16** (32.4 mg, 78.9 *µ*mol, 1.0 eq.) in MeOH (2 mL) at –10 °C were added $CeCl_3 \bullet 7\ H_2O$ (73.5 mg, 197 *µ*mol, 2.5 eq.) and $NaBH_4$ (1.8 mg, 47 *µ*mol, 0.6 eq.) in three portions over 15 min. The reaction mixture was diluted with EtOAc (2 mL) and HCl (1 M in H_2O, 5 mL) was added. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 15 mL) and brine (sat., 15 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 2:1) gave allylic alcohol **S16** (26.4 mg, 63.9 *µ*mol, 81%) as a colorless oil.

TLC: R_f = 0.28 (*n*hexane/EtOAc 2:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.36 (q, *J* = 1.7 Hz, 1H), 4.20 – 4.12 (m, 1H), 3.00 – 2.94 (m, 1H), 2.61 (dd, *J* = 12.9, 1.6 Hz, 1H), 2.42 – 2.33 (m, 2H), 2.26 – 2.15 (m, 3H), 2.03 – 1.93 (m, 2H), 1.68 (dt, *J* = 13.1, 3.6 Hz, 1H), 1.64 – 1.53 (m, 6H), 1.53 – 1.48 (m, 2H), 1.38 – 1.31 (m, 2H), 1.26 – 1.21 (m, 2H), 1.19 (s, 3H), 1.00 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.89 – 0.86 (m, 1H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.3 Hz, 3H).

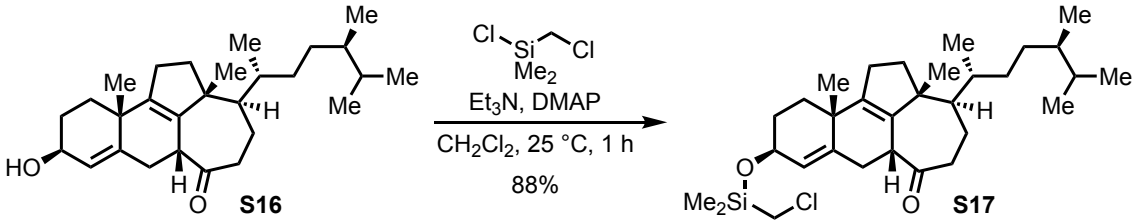
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 214.2, 145.2, 142.8, 137.4, 125.7, 67.8, 54.1, 53.5, 46.6, 45.5, 39.1, 37.9, 36.4, 35.1, 33.4, 33.1, 32.8, 32.2, 30.5, 28.8, 27.1, 23.9, 21.4, 20.4 (2C), 20.3, 18.2, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3383 (br w), 2954 (s), 2929 (s), 2868 (m), 1707 (m), 1458 (m), 1375 (w), 1066 (w), 1012 (w), 860 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{44}O_2Na^+$ $[M+Na]^+$: 435.3234, found: 435.3229.

Opt. act. $[\alpha]_D^{21}$ = +41.4 (*c* = 1.00, $CHCl_3$).

3β-(Chloromethyl)dimethylsilyloxy-13(14→8),14(8→7)di*abeo*-7β(H)-campesta-4,8-dien-14-one (**S17**)



To a solution of allylic alcohol **S16** (17.6 mg, 42 μmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) at 0 °C were added Et_3N (116 μL, 840 μmol, 20 eq.), 4-(dimethylamino)pyridine (1.0 mg, 8.4 μmol, 0.2 eq.) and (chloromethyl)-chlorodimethylsilane (83 μL, 0.63 mmol, 15 eq.), and the resulting solution was stirred at 25 °C for 1 h. The mixture was diluted with CH_2Cl_2 (2.5 mL) and NH_4Cl (sat. aq., 5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were washed sequentially with NH_4Cl (sat. aq., 4 × 20 mL), $NaHCO_3$ (sat. aq., 15 mL), and brine (sat., 15 mL). The organic phase was dried over $MgSO_4$, the solvent was removed under reduced pressure, and column chromatography (silica gel, *n*hexane/EtOAc 19:1) gave chloride **S17** (19.3 mg, 37.2 μmol, 88%) as a colorless oil.

TLC: R_f = 0.19 (*n*hexane/EtOAc 19:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.31 – 5.25 (m, 1H), 4.24 (ddt, *J* = 8.6, 6.5, 1.9 Hz, 1H), 3.00 – 2.94 (m, 1H), 2.78 (s, 2H), 2.60 (dd, *J* = 12.9, 1.5 Hz, 1H), 2.44 – 2.32 (m, 2H), 2.26 – 2.15 (m, 3H), 1.96 (ddd, *J* = 12.6, 7.4, 3.6 Hz, 1H), 1.92 – 1.86 (m, 1H), 1.72 – 1.57 (m, 6H), 1.57 – 1.48 (m, 3H), 1.38 – 1.30 (m, 2H), 1.26 – 1.20 (m, 2H), 1.18 (s, 3H), 1.00 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.90 – 0.86 (m, 1H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.3 Hz, 3H), 0.24 (s, 6H).

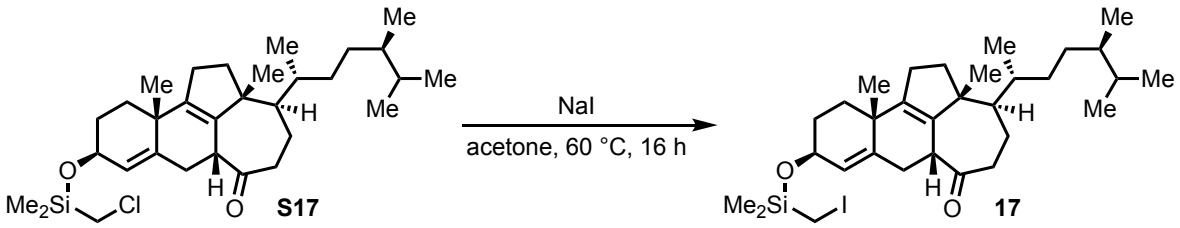
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 214.1, 145.2, 142.5, 137.3, 125.5, 69.1, 54.2, 53.4, 46.6, 45.4, 39.0, 37.9, 36.3, 35.1, 33.4, 33.1, 32.7, 32.1, 30.4, 30.1, 28.9, 27.0, 23.7, 21.3, 20.3, 20.3 (2C), 18.1, 15.6, –2.7, –2.8.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2923 (s), 2853 (m), 1739 (m), 1711 (m), 1458 (m), 1376 (m), 1253 (w), 1217 (w), 1074 (m), 986 (w), 888 (w), 822 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{31}H_{51}ClO_2SiNa^+$ [M+Na]$^+$: 541.3239, found: 541.3225

Opt. act. $[\alpha]_D^{23}$ = +25.7 (*c* = 1.00, $CHCl_3$).

3β-(Iodomethyl)dimethylsilyloxy-13(14→8),14(8→7)di*abeo*-7β(H)-campesta-4,8-dien-14-one (**17**)



Sodium iodide (previously dried under reduced pressure at 120 °C for 24 h, 279 mg, 1.86 mmol, 50 eq.) was added to a solution of chloride **S17** (19.3 mg, 37.2 μmol, 1.0 eq.) in acetone (2 mL) and the mixture was stirred at 60 °C for 16 h. The reaction mixture was allowed to cool to 25 °C, diluted with H_2O (5 mL) and EtOAc (5 mL), and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (sat., 30 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product **17** was used in the next step without further purification.

TLC: R_f = 0.20 (*n*hexane/EtOAc 19:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.29 (dt, *J* = 2.6, 1.4 Hz, 1H), 4.23 (ddt, *J* = 9.1, 6.7, 2.0 Hz, 1H), 3.00 – 2.94 (m, 1H), 2.60 (dd, *J* = 12.8, 1.6 Hz, 1H), 2.43 – 2.32 (m, 2H), 2.24 – 2.17 (m, 3H), 2.03 (s, 2H), 1.96 (ddd, *J* = 12.7, 7.5, 3.4 Hz, 1H), 1.93 – 1.86 (m, 1H), 1.68 – 1.57 (m, 6H), 1.54 – 1.46 (m, 2H), 1.36 – 1.30 (m, 3H), 1.26 – 1.21 (m, 2H), 1.18 (s, 3H), 1.00 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.90 – 0.86 (m, 1H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.4 Hz, 3H), 0.30 (d, *J* = 1.1 Hz, 6H).

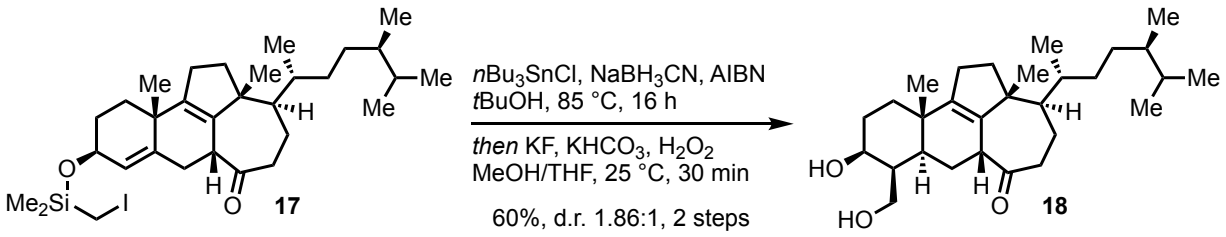
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 214.2, 145.2, 142.5, 137.3, 125.6, 69.2, 54.2, 53.5, 46.6, 45.5, 39.1, 37.9, 36.3, 35.1, 33.4, 33.1, 32.8, 32.2, 30.5, 29.0, 27.1, 23.8, 21.4, 20.4, 20.4 (2C), 18.2, 15.6, -1.8, -1.9, –13.9.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (s), 2924 (s), 2853 (m), 1708 (m), 1458 (m), 1376 (w), 1254 (m), 1070 (m), 884 (w), 834 (m), 803 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{31}H_{51}IO_2SiNa^+$ [M+Na]$^+$: 633.2595, found: 633.2565.

Opt. act. $[\alpha]_D^{24}$ = +18.0 (*c* = 1.00, $CHCl_3$).

3β-Hydroxy-4β-(hydroxymethyl)-13(14→8),14(8→7)di*abeo*-5α(H),7β(H)-campesta-4,8-dien-14-one (**18**)



A solution of crude iodide **17** (37.2 μmol, 1.0 eq.), azobisisobutyronitrile (0.6 mg, 3.7 μmol, 0.1 eq.), *n*Bu_3SnCl (2.0 μL, 7.4 μmol, 0.2 eq.) and $NaBH_3CN$ (4.7 mg, 74 μmol, 2.0 eq.) in *t*BuOH was degassed applying three freeze-pump-thaw cycles and stirred at 85 °C for 16 h. The reaction mixture was cooled to 25 °C and diluted with EtOAc (5 mL) and brine (sat., 15 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (sat., 30 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was taken up in MeOH/THF (2:1, 1 mL) and KF (21.6 mg, 372 μmol, 10 eq.), $KHCO_3$ (37.2 mg, 372 μmol, 10 eq.), and H_2O_2 (35% w/w, 0.75 mL) were added at 25 °C and the reaction mixture was stirred at this temperature for 30 min. It was diluted with EtOAc (5 mL) and cooled in a H_2O bath to maintain the temperature at 25 °C before $Na_2S_2O_3$ (sat. aq., 5 mL) was added carefully. The aqueous phase was extracted with EtOAc (3 × 10 mL), the combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 30 mL) and brine (sat., 30 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 2:1 → 1:1 → 1:2) gave 5α-epimer **18** (6.4 mg, 14 μmol, 39%) and 5β-epimer **S18** (3.5 mg, 7.8 μmol, 21%) as colorless oils.

major 5α-epimer **18**

TLC: R_f = 0.29 (*n*hexane/EtOAc 1:2).

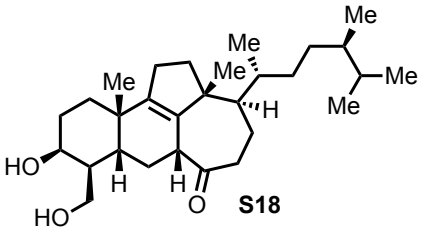
^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 4.02 (t, *J* = 10.4 Hz, 1H), 3.94 (dt, *J* = 9.1, 6.2 Hz, 1H), 3.55 (d, *J* = 11.0 Hz, 1H), 3.14 – 3.08 (m, 1H), 2.54 (ddd, *J* = 16.5, 6.1, 2.3 Hz, 1H), 2.37 – 2.28 (m, 2H), 2.17 (td, *J* = 7.3, 2.3 Hz, 2H), 1.99 (d, *J* = 11.5 Hz, 1H), 1.77 – 1.71 (m, 4H), 1.66 – 1.62 (m, 4H), 1.61 – 1.58 (m, 1H), 1.56 – 1.50 (m, 2H), 1.41 – 1.34 (m, 1H), 1.23 – 1.17 (m, 4H), 1.17 – 1.13 (m, 1H), 0.98 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.90 – 0.87 (m, 1H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.79 (s, 3H), 0.78 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 214.1, 147.1, 137.2, 74.5, 60.3, 55.8, 53.8, 48.2, 45.9, 45.5, 41.6, 39.1, 38.6, 35.2, 35.1, 34.7, 33.4, 32.2, 30.5, 27.6, 26.9, 26.9, 21.6, 20.4, 20.0, 19.9, 19.1, 18.2, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] =2952 (m), 2921 (s), 2852 (m), 1740 (w), 1459 (w), 1377 (w), 1243 (w), 1082 (w), 761 (w).

HRMS: (ESI-TOF); *m/z* calcd. $C_{29}H_{48}O_3Na^+$ [M+Na]$^+$: 467.3496, found:467.3486.

Opt. act. $[\alpha]_D^{22}$ = +40.6 (*c* = 0.54, $CHCl_3$).



S18

minor 5β-epimer **S18**

TLC: R_f = 0.26 (*n*hexane/EtOAc 1:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 4.16 – 4.10 (m, 1H), 3.85 (dd, *J* = 11.1, 5.2 Hz, 1H), 3.73 (dd, *J* = 11.1, 2.3 Hz, 1H), 2.80 (d, *J* = 8.0 Hz, 1H), 2.52 – 2.41 (m, 3H), 2.34 – 2.27 (m, 1H), 2.27 – 2.20 (m, 1H), 2.02 (ddd, *J* = 14.5, 8.0, 3.8 Hz, 1H), 1.96 (ddd, *J* = 13.0, 8.9, 4.2 Hz, 1H), 1.89 (dt, *J* = 11.7, 3.6 Hz, 1H), 1.73 (td, *J* = 13.9, 3.2 Hz, 1H), 1.70 – 1.61 (m, 3H), 1.61 – 1.57 (m, 1H), 1.52 – 1.45 (m, 2H), 1.37 – 1.32 (m, 2H), 1.30 – 1.24 (m, 3H), 1.23 – 1.16 (m, 3H), 1.07 (s, 3H), 1.02 – 0.99 (m, 1H), 0.97 (s, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.3 Hz, 3H).

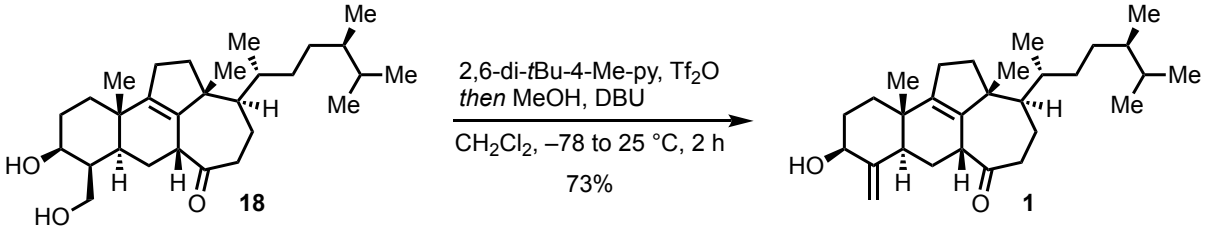
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 215.5, 143.5, 137.8, 70.7, 64.6, 56.8, 55.1, 45.3, 43.4, 41.5, 39.1, 38.0, 36.5, 35.4, 35.0, 33.4, 32.2, 30.6, 30.2, 29.4, 29.2, 28.3, 24.6, 21.6 (2C), 20.7, 20.4, 18.2, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3411 (br w), 2952 (m), 2924 (s), 2854 (m), 1738 (m), 1457 (w), 1376 (w), 1217 (w).

HRMS: (ESI-TOF); *m/z* calcd. $C_{29}H_{48}O_3Na^+$ [M+Na]$^+$: 467.3496, found: 467.3488.

Opt. act. $[\alpha]_D^{21}$ = +9.0 (*c* = 0.18, $CHCl_3$).

Swinhoeisterol A (**1**)



To a solution of diol **18** (4.0 mg, 9.0μmol, 1.0 eq) in CH_2Cl_2 (1.25 mL) was added 2,6-di-*tert*-butyl-4-methyl-pyridine (18.5 mg, 90.0 μmol, 10 eq.) and it was cooled to –78 °C. Triflic anhydride (1 M in CH_2Cl_2, 23 μL, 23 μmol, 2.6 eq.) was added dropwise and the reaction was stirred at this temperature for 5 min before

MeOH (20 μL, 0.50 mmol, 55 eq.) and DBU (30 μL, 0.20 μmol, 22 eq.) were added. The reaction mixture was allowed to warm to 25 °C over 1.5 h, and then stirred at this temperature for 1 h before HCl (1 M in H_2O, 5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed sequentially with HCl (1 M in H_2O, 20 mL), $NaHCO_3$ (sat. aq., 20 mL), and brine (sat., 20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 3:1) gave swinhoeisterol A (**1**) (2.8 mg, 6.6 μmol, 73%) as an amorphous powder.

TLC: R_f = 0.26 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.09 (s, 1H), 4.69 (s, 1H), 4.08 – 4.00 (m, 1H), 3.17 – 3.12 (m, 1H), 2.53 (ddd, *J* = 16.2, 6.1, 2.4 Hz, 1H), 2.36 (ddd, *J* = 15.9, 11.7, 3.5 Hz, 1H), 2.32 – 2.26 (m, 1H), 2.22 – 2.17 (m, 1H), 2.15 (d, *J* = 13.1 Hz, 1H), 2.06 – 2.02 (m, 1H), 2.00 (d, *J* = 12.6 Hz, 1H), 1.82 – 1.78 (m, 1H), 1.78 – 1.74 (m, 1H), 1.73 – 1.69 (m, 1H), 1.69 – 1.63 (m, 2H), 1.60 (dt, *J* = 12.8, 6.4 Hz, 1H), 1.57 – 1.55 (m, 2H), 1.48 (qd, *J* = 12.7, 4.3 Hz, 1H), 1.42 – 1.38 (m, 1H), 1.36 (td, *J* = 13.3, 4.2 Hz, 1H), 1.28 – 1.24 (m, 1H), 1.23 – 1.16 (m, 3H), 1.01 (s, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.92 – 0.90 (m, 1H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.5 Hz, 3H), 0.78 (s, 3H).

^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 213.6, 151.9, 146.9, 136.0, 102.9, 73.1, 55.8, 53.8, 45.4, 45.3, 44.4, 39.1, 38.7, 37.7, 35.2, 34.8, 33.5, 32.5, 32.2, 30.5, 27.8, 24.5, 21.6, 20.4, 20.1, 20.0, 18.2, 17.9, 15.6.

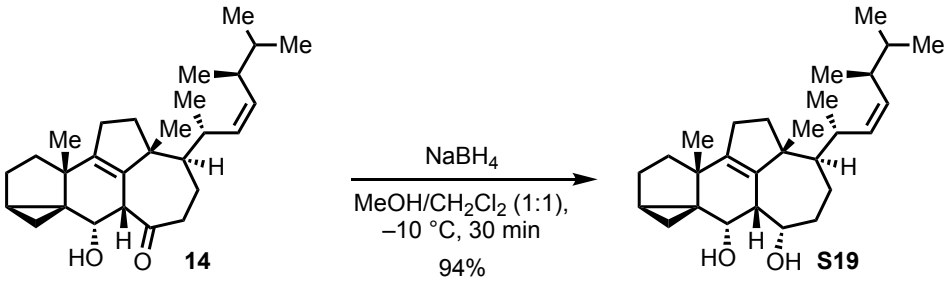
IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3488 (br w), 2953 (m), 2922 (s), 2853 (m), 1705 (w), 1458 (m), 1376 (w), 894 (w).

HRMS: (ESI-TOF); *m/z* calcd. $C_{29}H_{46}O_2Na^+$ $[M+Na]^+$: 449.3390, found: 449.3400.

Opt. act. $[\alpha]_D^{20}$ = +66.8 (*c* = 0.19, $CHCl_3$).

Attempted Hydrogenation of (22*Z*)-Diol **S19** and NMR Comparison with Epimers **S20** and **S26**

(22*Z*)-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α,7β(H)-Campesta-8,22-dien-6α,14α-diol (**S19**)



To a solution of 22*Z*-hydroxy ketone **14** (196 mg, 477 μmol, 1.0 eq.) in CH_2Cl_2/MeOH (1:1, 5.0 mL) was added $NaBH_4$ (45 mg, 1.2 mmol, 2.5 eq.) at –10 °C. After stirring for 30 min, the reaction mixture was diluted with CH_2Cl_2 (3 mL) and HCl (1 M in H_2O, 5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine (sat., 20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1) gave 22*Z*-diol **S19** (185 mg, 448 μmol, 94%) as a colorless solid.

M.p. 195–197 °C ($CHCl_3$)

TLC: R_f = 0.19 (*n*hexane/EtOAc 5:1).

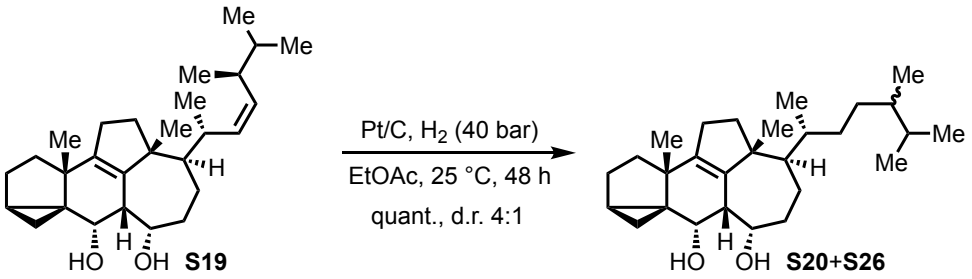
^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.39 (t, *J* = 10.7 Hz, 1H), 5.07 (t, *J* = 10.7 Hz, 1H), 4.34 – 4.23 (m, 2H), 2.78 – 2.71 (m, 1H), 2.68 (dd, *J* = 6.3, 2.3 Hz, 1H), 2.34 – 2.20 (m, 3H), 1.98 – 1.90 (m, 2H), 1.84 – 1.74 (m, 2H), 1.74 – 1.68 (m, 2H), 1.66 – 1.57 (m, 5H), 1.50 – 1.42 (m, 2H), 1.06 (s, 3H), 0.99 – 0.93 (m, 9H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.71 (dd, *J* = 8.4, 5.0 Hz, 1H), 0.31 (t, *J* = 4.6 Hz, 1H).

^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 144.5, 140.1, 132.8, 132.4, 66.2, 63.7, 53.3, 51.9, 45.4, 42.6, 39.4, 38.4, 37.3, 35.8, 33.6, 33.2, 32.6, 28.7, 26.1, 23.9, 22.6, 21.0, 20.4, 20.3, 20.3, 17.8, 17.0, 7.1.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3401 (w), 2953 (m), 2922 (s), 2852 (m), 1740 (w), 1459 (w), 1377 (w), 1244 (w), 1169 (w), 977 (w), 722 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{44}O_2Na^+$ $[M+Na]^+$: 435.3234, found: 435.3245.

13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α,7β(H)-Campesta-8-en-6α,14α-diol (**S20**+**S26**)



To a suspension of 22*Z*-diol **S19** (13.5 mg, 32.8 μmol 1.0 eq.) in EtOAc (1 mL) in a Parr reactor was added Pt/C (10% *w/w*, 6.4 mg, 3.3 μmol, 0.1 eq.). The reactor was purged with hydrogen gas three times before stirring the reaction mixture at 25 °C under 40 bar of hydrogen atmosphere for 48 h. The reactor was opened carefully, the reaction mixture was filtered through Celite®, rinsed with EtOAc (3 × 10 mL), and the solvent was removed under reduced pressure to give **S20** and **S26** as inseparable mixture of epimers (d.r. 4:1, determined by integration of C24' signals δ [ppm] = 18.2 (major, **S20**) and 17.9 (minor, **S26**) in ^{13}C-NMR of the crude product) as a colorless solid.

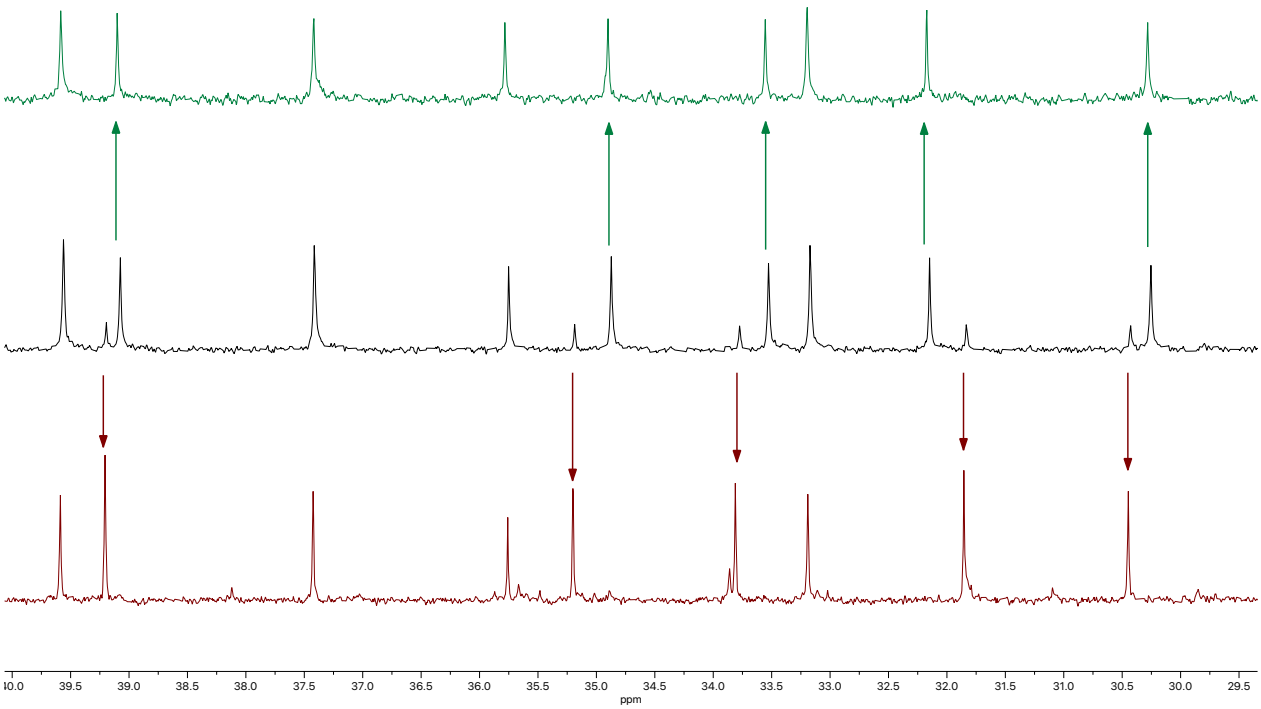
TLC: R_f = 0.20 (*n*hexane/EtOAc 5:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 4.27 (d, *J* = 6.3 Hz, 1H), 4.22 (d, *J* = 6.3 Hz, 1H), 2.69 (d, *J* = 6.0 Hz, 1H), 2.30 – 2.16 (m, 2H), 1.94 – 1.86 (m, 2H), 1.80 – 1.74 (m, 1H), 1.71 – 1.66 (m, 1H), 1.64 – 1.60 (m, 2H), 1.60 – 1.49 (m, 4H), 1.47 – 1.42 (m, 2H), 1.40 – 1.33 (m, 1H), 1.23 – 1.14 (m, 2H), 1.10 – 1.06 (m, 1H), 1.05 (s, 3H), 1.03 – 0.97 (m, 1H), 0.96 (s, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 6H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.69 (dd, *J* = 8.4, 5.0 Hz, 1H), 0.28 (t, *J* = 4.6 Hz, 1H).

^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 144.7, 140.1, 66.5, 64.3, 53.6, 52.3, 45.5, 42.5, 39.6, (39.2)*, 39.1, 37.5, 35.8, (35.2)*, 34.9, (33.8)*, 33.6, 33.2, 32.2, (31.8)*, (30.4)*, 30.3, 28.5, 26.1, 23.9, (22.0)*, 21.9, 20.8, 20.5, 20.4, 18.4, 18.2, (17.9)*, 15.6, 7.2. *minor epimer **S26**

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3382 (br w), 2953 (m), 2924 (s), 2854 (m), 1735 (w), 1459 (w), 1376 (w), 1215 (w), 760 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{46}O_2Na^+$ [M+Na]$^+$: 437.3390, found: 437.3404.

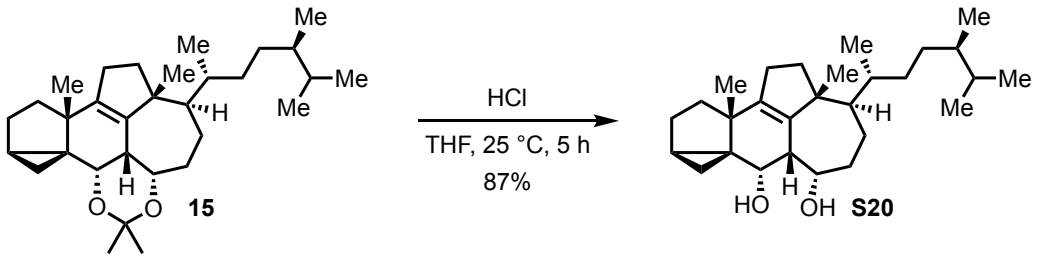


^{13}C-NMR Comparison of campestane **S20** (green), epimeric mixture (black) and ergostane **S26** (red), (shifts in ppm).

S20	39.6		39.1	37.4	35.8		34.9		33.6	33.2	32.2			30.3
mix	39.6	39.2	39.1	37.4	35.8	35.2	34.9	33.8	33.5	33.2	32.1	31.8	30.4	30.3
S26	39.6	39.2		37.4	35.8	35.2		33.8		33.2		31.9	30.4	

Campestane diol **S20** was synthesized to enable the assignment of signals in the ^{13}C-NMR spectrum of the epimeric mixture, for analytical data of ergostane diol **S26** see page S49–50.

13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α,7β(H)-Campesta-8-en-6α,14α-diol (**S20**)



Acetonide **15** was dissolved in THF (1 mL), HCl (1 m in H_2O, 1 mL) was added and the reaction mixture was stirred at 25 °C for 5 h. It was diluted with EtOAc (3 mL) and $NaHCO_3$ (sat. aq., 5 mL) was added carefully. The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic phases

were washed with brine (sat., 20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1) gave diol **S20** (87%) as a colorless solid.

M.p. 147–149 °C ($CHCl_3$)

TLC: R_f = 0.27 (*n*hexane/EtOAc 4:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 4.26 (d, *J* = 6.2 Hz, 1H), 4.22 (d, *J* = 6.1 Hz, 1H), 2.69 (d, *J* = 6.0 Hz, 1H), 2.29 – 2.16 (m, 2H), 1.93 – 1.85 (m, 2H), 1.79 – 1.73 (m, 1H), 1.72 – 1.65 (m, 2H), 1.65 – 1.58 (m, 3H), 1.58 – 1.50 (m, 4H), 1.48 – 1.40 (m, 3H), 1.40 – 1.31 (m, 1H), 1.20 – 1.14 (m, 2H), 1.09 – 1.05 (m, 1H), 1.04 (d, *J* = 2.3 Hz, 3H), 0.95 (s, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H), 0.69 (dd, *J* = 8.4, 5.0 Hz, 1H), 0.28 (t, *J* = 4.6 Hz, 1H).

^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 144.7, 140.1, 66.4, 64.4, 53.6, 52.3, 45.5, 42.5, 39.6, 39.1, 37.4, 35.8, 34.9, 33.6, 33.2, 32.2, 30.3, 28.5, 26.1, 23.9, 21.8, 20.8, 20.5, 20.4, 18.4, 18.1, 15.6, 7.1.

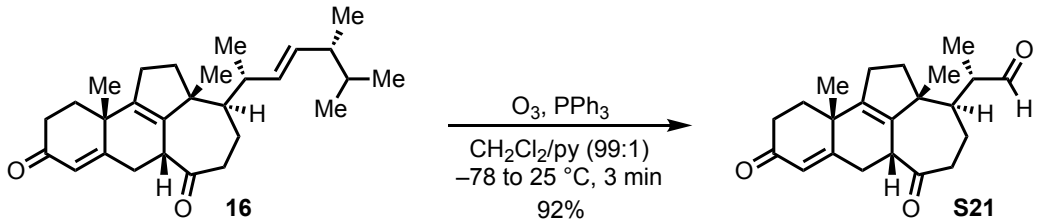
IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3393 (br w), 2953 (s), 2924 (s), 2854 (m), 1739 (w), 1456 (m), 1409 (m), 1370 (m), 1204 (w), 1073 (m), 1044 (w), 946 (w), 759 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{46}O_2Na^+$ [M+Na]$^+$: 437.3390, found: 437.3378

Opt. act. $[\alpha]_D^{22}$ = +95.0 (*c* = 1.00, $CHCl_3$).

Attempted late-stage Ozonolysis and Julia–Kocienski Olefination of Enone **16**

3,14-Dioxo-13(14→8),14(8→7)di*abeo*-7β(H)-pregn-4,8-dien-20α-carboxaldehyde (**S21**)



A stream of ozone-rich oxygen was passed through a solution of enone **16** (13.5 mg, 33.0 μmol, 1.0 eq.) in CH_2Cl_2/pyridine (99:1, 1 mL) at –78 °C for 3 min. PPh_3 (9.5 mg, 36 μmol, 1.1 eq.) was added and the reaction mixture was allowed to warm to 25 °C over 16 h. The solvent was removed, the residue was adsorbed on silica gel and column chromatography (silica gel, *n*hexane/EtOAc 1:1) gave aldehyde **S21** (10 mg, 30 μmol, 92%) as a colorless oil.

TLC: R_f = 0.30 (*n*hexane/EtOAc 1:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 9.79 (d, *J* = 2.5 Hz, 1H), 5.90 (s, 1H), 3.31 – 3.29 (m, 1H), 2.89 (dd, *J* = 13.2, 1.5 Hz, 1H), 2.70 – 2.66 (m, 1H), 2.57 – 2.51 (m, 2H), 2.49 (ddd, *J* = 13.1, 6.8, 1.8 Hz, 1H), 2.44 – 2.41 (m, 1H), 2.41 – 2.38 (m, 1H), 2.38 – 2.34 (m, 2H), 2.20 – 2.15 (m, 1H), 1.99 (ddd, *J* = 13.2, 5.2, 2.2 Hz, 1H), 1.93 (dd, *J* = 8.1, 5.5 Hz, 1H), 1.91 – 1.88 (m, 1H), 1.80 – 1.76 (m, 1H), 1.73 – 1.70 (m, 1H), 1.54 (dt, *J* = 11.3, 2.1 Hz, 1H), 1.30 (s, 3H), 1.18 (s, 3H), 1.16 (d, *J* = 7.0 Hz, 3H).

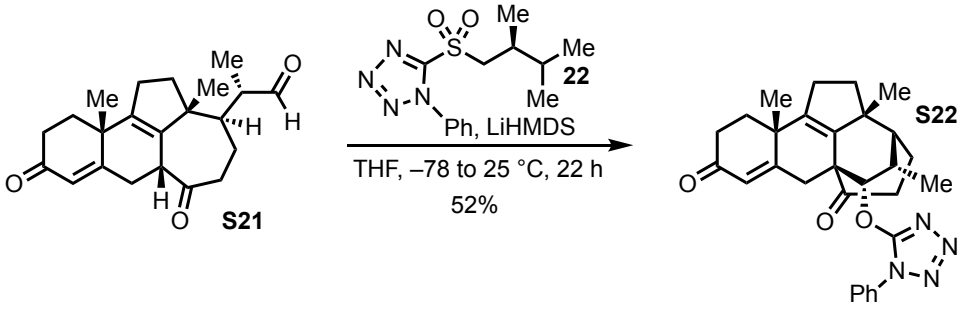
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 209.6, 205.0, 198.4, 166.2, 144.5, 136.3, 126.4, 55.0, 53.0, 48.4, 46.0, 44.8, 38.2, 37.6, 34.1, 33.6, 32.4, 27.4, 22.4, 21.2, 21.1, 15.7.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2958 (m), 2924 (s), 2853 (m), 1708 (s), 1667 (s), 1458 (m), 1377 (w), 1238 (w), 1186 (w), 870 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{22}H_{28}O_3Na^+$ [M+Na]$^+$: 363.1931, found: 363.1934.

Opt. act. $[\alpha]_D^{27}$ = +131.0 (*c* = 1.00, $CHCl_3$).

22α-((1-Phenyl-1*H*-tetrazol-5-yl)oxy)-13(14→8),14(8→7)di*abeo*-7β,22-cyclo-7β(H)-23,24-dinorchola-4,8-dien-3,14-dione (**S22**)



To a solution of hexamethyldisilazane (15 μL, 74 mmol, 5 eq.) in THF (0.2 mL) at 0 °C was added *n*BuLi (1.6 M in *n*hexane, 46 μL, 74 μmol, 5 eq.) and it was stirred for 15 min at this temperature before the solution was added to sulfone **22** (21 mg, 74 μmol, 5.0 eq.) in THF (1 mL) at –78 °C. The resulting bright yellow solution was stirred at –65 °C for 1 h and a solution of aldehyde **S21** (5 mg, 15 μmol, 1.0 eq.) in THF (0.5 mL) was added to the reaction mixture over 10 min, and the reaction mixture was allowed to warm to 25 °C over 20 h. EtOAc (3 mL) and H_2O (5 mL) were added to the reaction mixture and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 20 mL) and brine (sat., 20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 4:1) gave dione **S22** (3.8 mg, 7.8 μmol, 52%) as a colorless oil.

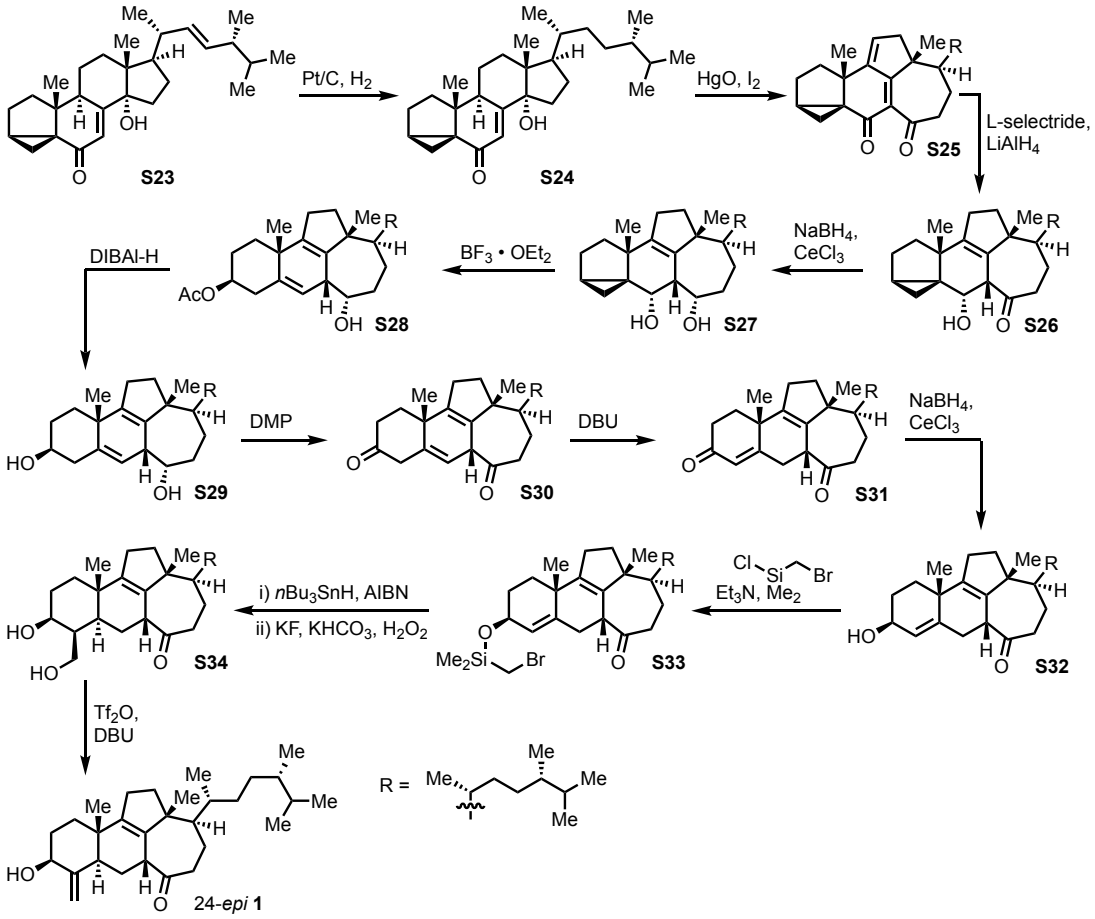
TLC: R_f = 0.35 (*n*hexane/EtOAc 1:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 7.94 – 7.91 (m, 2H), 7.61 – 7.58 (m, 2H), 7.48 – 7.45 (m, 1H), 5.77 (s, 1H), 5.41 (d, *J* = 9.7 Hz, 1H), 3.37 – 3.30 (m, 1H), 3.10 (d, *J* = 12.7 Hz, 1H), 2.76 – 2.67 (m, 2H), 2.59 – 2.52 (m, 1H), 2.47 (dd, *J* = 12.7, 1.8 Hz, 1H), 2.46 – 2.41 (m, 1H), 2.31 (dd, *J* = 15.9, 8.4 Hz, 1H), 2.24 (ddd, *J* = 14.8, 7.3, 2.7 Hz, 1H), 2.19 (dt, *J* = 6.8, 3.6 Hz, 1H), 2.16 – 2.11 (m, 1H), 2.05 – 2.01 (m, 1H), 1.94 – 1.89 (m, 2H), 1.81 (dd, *J* = 11.8, 5.8 Hz, 1H), 1.75 (td, *J* = 13.9, 4.9 Hz, 1H), 1.31 (s, 3H), 1.27 (s, 3H), 0.82 (d, *J* = 7.6 Hz, 3H).

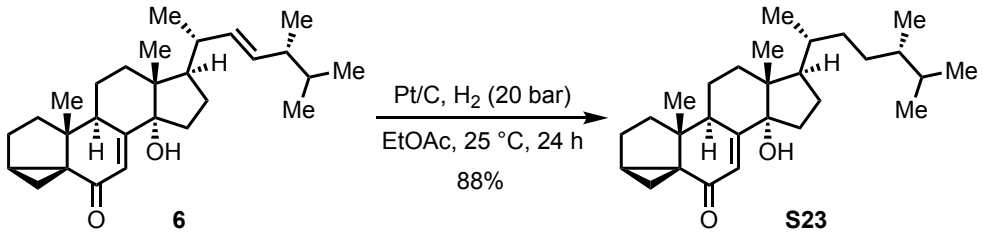
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 208.8, 198.3, 164.4, 160.1, 142.0, 142.0, 133.7, 129.9, 128.9, 128.3, 120.6, 83.9, 56.4, 48.0, 44.4, 38.9, 38.2, 37.7, 37.1, 34.2, 32.7, 31.7, 28.0, 24.3, 23.3, 18.5, 14.2.

HRMS: (ESI-TOF); *m/z* calcd. for $C_{29}H_{32}N_4O_3Na^+$ $[M+Na]^+$: 507.2367, found: 507.2375.

2.6 Synthesis of 24-*epi*-Swinhoeisterol A (24-*epi*-**1**)



14-Hydroxy-3α,5-cyclo-5α-ergosta-7-en-6-one (**S23**)



To a solution of γ-hydroxy enone **6** (3.90 g, 9.50 mmol, 1.0 eq.) in EtOAc (95 mL) in a Parr reactor was added Pt/C (10% *w/w*, 926 mg, 475 µmol, 0.05 eq.). The reactor was purged with hydrogen gas three times before stirring the reaction mixture at 25 °C under 20 bar of hydrogen atmosphere for 24 h. The reactor was opened carefully, the reaction mixture was filtered through Celite®, rinsed with EtOAc (100 mL), and the solvent was removed under reduced pressure. The crude product was adsorbed on silica gel and column

chromatography (silica gel, n hexane/EtOAc 5:1) gave γ-hydroxy enone **S23** (3.44 g, 8.33 mmol, 88%) as a colorless solid.

M.p.: 194–198 °C (EtOAc).

TLC: R_f = 0.40 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.97 (d, *J* = 2.6 Hz, 1H), 2.76 (ddd, *J* = 10.7, 7.6, 2.7 Hz, 1H), 2.14 – 1.98 (m, 3H), 1.98 – 1.90 (m, 2H), 1.80 (dt, *J* = 8.8, 4.6 Hz, 1H), 1.77 – 1.64 (m, 6H), 1.63 – 1.55 (m, 2H), 1.50 – 1.36 (m, 5H), 1.27 – 1.19 (m, 1H), 1.16 – 1.11 (m, 1H), 1.09 (s, 3H), 1.03 – 0.96 (m, 2H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.81 – 0.76 (m, 7H), 0.75 (s, 3H).

^{13}C-NMR: (101 MHz, $CDCl_3$); δ [ppm] = 198.4, 164.4, 123.4, 85.4, 50.6, 46.5, 45.3, 45.3, 44.0, 39.1, 37.9, 36.2, 35.6, 33.9, 33.7, 31.6, 31.0, 30.7, 26.9, 26.7, 21.9, 20.7, 19.4, 19.2, 17.7, 16.1, 15.5, 13.8.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3430 (br w), 2956 (s), 2929 (s), 2870 (m), 1648 (s), 1457 (w), 1377 (m), 1316 (m), 1174 (m), 1144 (w), 888 (w).

HRMS: (ESI-TOF) *m/z* calcd. for $C_{28}H_{44}O_2Na^+$ [M+Na]$^+$: 435.3234, found: 435.3256.

Opt. act. $[\alpha]_D^{20}$ = +110.6 (*c* = 1.00, $CHCl_3$).

13(14→8),14(8→7)Di*abeo*-3α,5-cyclo-5α-ergosta-7,9(11)-dien-6,14-dione (**S24**)

Through a solution of γ-hydroxy enone **S23** (2.70 g, 6.54 mmol, 1.0 eq.) in benzene (270 mL) in a pressure vessel at 60 °C was bubbled argon *via* cannula for 15 min. After addition of iodine (3.98 g, 15.7 mmol, 2.4 eq.) and HgO (yellow, 3.82 g, 17.6 mmol, 2.7 eq.) at the same temperature, the tube was sealed, transferred to a preheated oil bath, and the reaction was stirred at 105 °C for 2 h. After cooling to 25 °C, the mixture was filtered through Celite®, and was rinsed with EtOAc (100 mL). The organic phase was washed sequentially with $Na_2S_2O_3$ (sat. aq., 400 mL) and brine (sat., 400 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1 → 3:1) gave diene dione **S24** (1.82 g, 4.45 mmol, 68%) as a light-yellow foam.

TLC: R_f = 0.33 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 6.32 (t, *J* = 2.9 Hz, 1H), 2.74 – 2.65 (m, 2H), 2.59 (td, *J* = 11.4, 5.0 Hz, 1H), 2.41 (dd, *J* = 17.8, 3.3 Hz, 1H), 2.07 (dd, *J* = 13.6, 7.8 Hz, 1H), 1.95 – 1.89 (m, 2H), 1.89 – 1.81 (m, 2H), 1.78 (dd, *J* = 10.2, 4.2 Hz, 1H), 1.69 (dd, *J* = 12.8, 7.5 Hz, 1H), 1.65 – 1.61 (m, 1H), 1.58 – 1.53 (m, 2H), 1.48 – 1.37 (m, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.95 (q, *J* = 3.8 Hz, 1H), 0.93 – 0.89 (m, 2H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.80 – 0.76 (m, 7H).

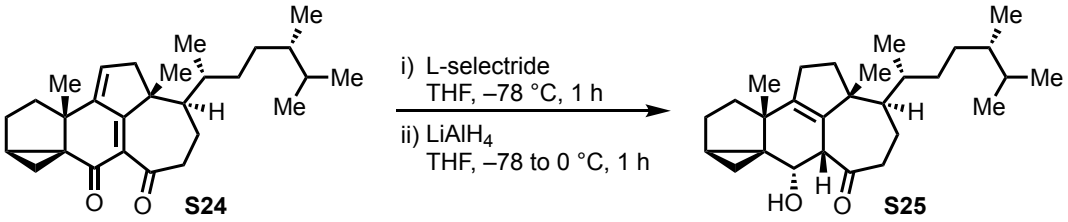
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 204.5, 193.0, 167.7, 145.8, 136.6, 131.2, 53.5, 50.5, 48.5, 45.5, 43.5, 41.1, 39.1, 36.3, 36.1, 35.4, 33.6, 31.8, 30.5, 26.4, 26.3, 23.6, 22.6, 21.4, 20.5, 17.8, 15.6, 12.9.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (s), 2924 (s), 2854 (m), 1732 (w), 1704 (m), 1648 (w), 1458 (w), 1377 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{40}O_2Na^+$ $[M+Na]^+$: 431.2921, found: 431.2930.

Opt. act. $[\alpha]_D^{23} = -8.4$ (*c* = 1.01, CH_2Cl_2).

6α-Hydroxy-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α,7β(H)-ergosta-8-en-14-one (**S25**)



A solution of diene dione **S24** (625 mg, 1.53 mmol, 1.0 eq.) in THF (15 mL) was degassed applying three freeze-pump-thaw cycles. After cooling to –78 °C, L-selectride (1 M in THF, 2.29 mL, 2.29 mmol, 1.5 eq.) was added dropwise over 15 min and the resulting solution was stirred at this temperature for 45 min. Lithium aluminum hydride (1 M in THF, 3.82 mL, 3.82 mmol, 2.5 eq.) was added, and the reaction mixture was warmed to 0 °C. After stirring for 30 min at this temperature, EtOAc (5 mL) was added dropwise and a solution of $NaBO_3 \cdot 4H_2O$ (1.18 g, 7.67 mmol, 5.0 eq.) in Rochelle's salt (½ sat. aq., 30 mL) was added carefully. The aqueous phase was extracted with EtOAc (3 × 25 mL) and the combined organic phases were washed with brine (sat., 50 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The obtained hydroxy ketone **S25** was used without further purification.

Analytically pure hydroxy ketone **S25** was obtained by column chromatography (silica gel, *n*hexane/EtOAc 50:1 → 19:1) as a colorless solid.

M.p.: 82–86 °C (EtOAc).

TLC: R_f = 0.37 (*n*hexane/EtOAc 9:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 4.45 (d, *J* = 8.3 Hz, 1H), 4.23 (t, *J* = 7.4 Hz, 1H), 3.17 (d, *J* = 6.4 Hz, 1H), 2.61 – 2.54 (m, 1H), 2.43 (dd, *J* = 13.6, 8.3 Hz, 1H), 2.33 – 2.26 (m, 1H), 2.19 – 2.12 (m, 1H), 2.07 – 2.01 (m, 1H), 1.70 – 1.64 (m, 1H), 1.64 – 1.59 (m, 2H), 1.58 – 1.51 (m, 4H), 1.49 – 1.45 (m, 1H), 1.45 – 1.41 (m, 2H), 1.33 (dd, *J* = 12.2, 2.5 Hz, 1H), 1.09 (s, 3H), 1.06 – 1.01 (m, 2H), 1.00 (s, 3H), 0.98 – 0.97 (m, 1H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.94 – 0.91 (m, 1H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.80 – 0.75 (m, 6H), 0.77 – 0.70 (m, 2H), 0.31 (t, *J* = 4.3 Hz, 1H).

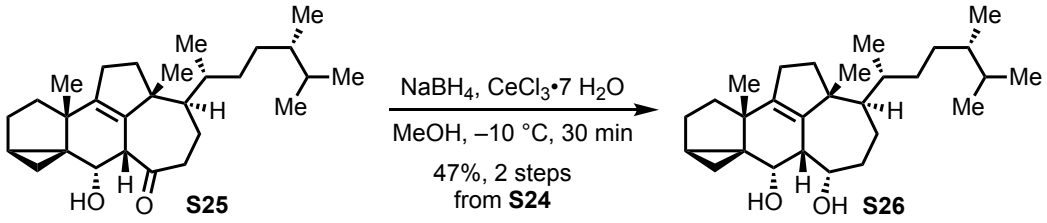
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 219.9, 144.9, 137.5, 68.2, 53.7, 53.7, 48.4, 46.1, 45.3, 39.2, 38.0, 37.8, 35.7, 33.7, 33.1, 31.9, 30.7, 28.0, 26.6, 22.7, 21.5, 20.8, 20.5, 20.4, 19.9, 17.9, 15.6, 7.8.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3443 (br w), 2954 (s), 2924 (s), 2855 (m), 1739 (w), 1685 (w), 1461 (w), 1377 (w), 1070 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{44}O_2Na^+$ $[M+Na]^+$: 435.3234, found: 435.3249.

Opt. act. $[\alpha]_D^{21}$ = +32.8 (*c* = 1.03, $CHCl_3$).

13(14→8),14(8→7)Di*abeo*-3α,5-cyclo-5α,7β(H)-ergosta-8-en-6α,14α-diol (**S26**)



To a solution of crude hydroxy ketone **S25** (631 mg, 1.53 mmol, 1.0 eq.) in MeOH (15 mL) were added $CeCl_3$•7 H_2O (1.42 g, 3.82 mmol, 2.5 eq.) and $NaBH_4$ (144 mg, 3.82 mmol, 2.5 eq.) at –10 °C. After stirring for 20 min, the reaction mixture was diluted with EtOAc (5 mL), and HCl (1 M in H_2O, 10 mL) was added. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic phases were washed with brine (sat., 50 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1) gave diol **S26** (297 mg, 716 μmol, 47% over two steps) as a colorless solid.

M.p.: 129–133 °C (EtOAc).

TLC: R_f = 0.22 (*n*hexane/EtOAc 5:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 4.28 (d, *J* = 6.3 Hz, 1H), 4.23 (d, *J* = 5.8 Hz, 1H), 2.70 (d, *J* = 6.0 Hz, 1H), 2.29 – 2.23 (m, 1H), 2.23 – 2.17 (m, 1H), 1.93 – 1.87 (m, 2H), 1.80 – 1.74 (m, 1H), 1.71 – 1.65 (m, 1H), 1.65 – 1.60 (m, 2H), 1.59 – 1.55 (m, 3H), 1.51 – 1.49 (m,

1H), 1.48 – 1.42 (m, 4H), 1.42 – 1.37 (m, 1H), 1.23 – 1.17 (m, 2H), 1.11 – 1.06 (m, 1H), 1.05 (s, 3H), 0.96 (s, 3H), 0.95 – 0.92 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H), 0.69 (dd, J = 8.4, 5.0 Hz, 1H), 0.29 (t, J = 4.6 Hz, 1H).

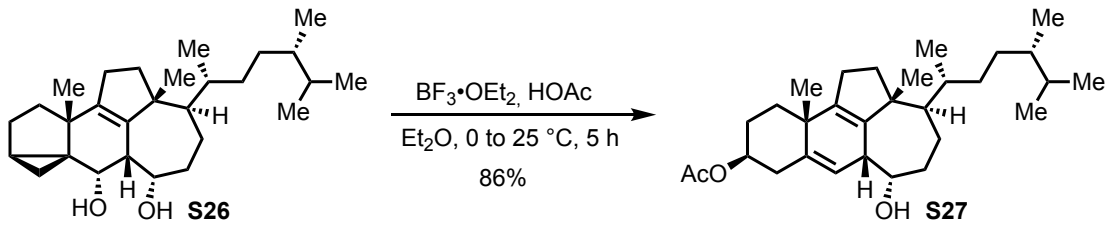
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 144.7, 140.0, 66.4, 64.3, 53.6, 52.3, 45.5, 42.5, 39.6, 39.2, 37.4, 35.8, 35.2, 33.8, 33.2, 31.9, 30.4, 28.5, 26.1, 24.0, 22.0, 20.8, 20.5, 20.5, 18.4, 17.9, 15.6, 7.1.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3405 (br w), 2952 (m), 2922 (s), 2854 (m), 1740 (w), 1456 (m), 1377 (w), 906 (m), 734 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{46}O_2Na^+$ [M+Na]$^+$: 437.3390, found: 437.3407.

Opt. act. $[\alpha]_D^{22}$ = +73.3 (c = 1.00, $CHCl_3$).

14α-Hydroxy-13(14→8),14(8→7)di*abeo*-7β(H)-ergosta-5,8-dien-3β-yl acetate (**S27**)



To a solution of diol **S26** (276 mg, 666 μmol, 1.0 eq.) in Et_2O (10 mL) were added acetic acid (5 mL) and BF_3•OEt_2 (5 mL) at 0 °C. The resulting solution was warmed to 25 °C and stirred for 5 h, before diluting with EtOAc (10 mL). The reaction mixture was then carefully poured into $NaHCO_3$ (sat. aq., 50 mL) and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 20 mL) and brine (sat., 20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1) gave acetate **S27** (263 mg, 576 μmol, 86%) as a colorless oil.

TLC: R_f = 0.24 (*n*hexane/EtOAc 5:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.38 (dd, J = 3.2, 1.6 Hz, 1H), 4.67 – 4.61 (m, 1H), 3.83 – 3.78 (m, 1H), 3.00 – 2.97 (m, 1H), 2.47 (ddd, J = 12.5, 5.2, 1.9 Hz, 1H), 2.43 – 2.38 (m, 1H), 2.34 – 2.28 (m, 1H), 2.26 – 2.21 (m, 1H), 2.04 (s, 3H), 1.98 – 1.89 (m, 3H), 1.82 (ddd, J = 12.0, 7.6, 2.6 Hz, 1H), 1.72 – 1.66 (m, 2H), 1.63 – 1.59 (m, 1H), 1.58 – 1.52 (m, 3H), 1.50 – 1.44 (m, 3H), 1.41 (dt, J = 12.9, 4.5 Hz, 1H), 1.39 – 1.36 (m, 1H), 1.30 – 1.24 (m, 2H), 1.22 – 1.18 (m, 1H), 1.16 (s, 3H), 0.96 (s, 3H), 0.95 – 0.91 (m, 1H), 0.90 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H), 0.79 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H).

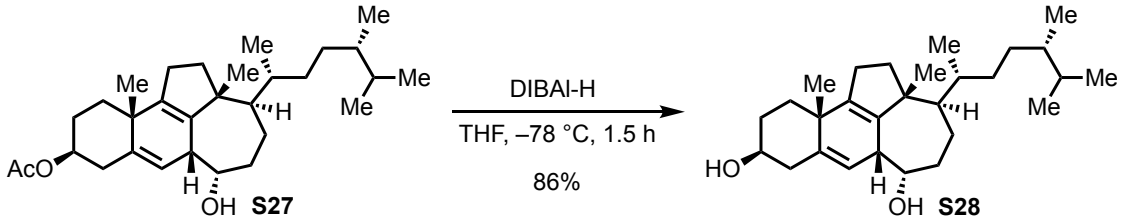
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 170.5, 143.8, 139.9, 137.8, 124.2, 74.3, 72.5, 53.9, 52.1, 39.8, 39.3, 39.2, 37.3, 36.8, 36.5, 35.6, 35.4, 33.8, 31.9, 30.7, 27.8, 27.7, 22.9, 22.0, 21.7, 21.5, 20.5, 19.1, 17.9, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3394 (br), 2953 (s), 2926 (s), 2869 (m), 1736 (w), 1464 (w), 1374 (w), 1241 (m), 1035 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{30}H_{48}O_3Na^+$ $[M+Na]^+$: 479.3496, found: 479.3512.

Opt. act. $[\alpha]_D^{23}$ = +26.5 (*c* = 1.00, $CHCl_3$).

13(14→8),14(8→7)Di*abeo*-7β(H)-ergosta-5,8-dien-3β,14α-diol (**S28**)



To a solution of acetate **S27** (209 mg, 458 μmol, 1.0 eq.) in THF (5 mL) at –78 °C was added DIBAl-H (1 M in hexanes, 2.29 mL, 2.29 mmol, 5.0 eq.) and the resulting solution was stirred at this temperature for 1 h. EtOAc (1 mL) and Rochelle's salt (½ sat. aq., 5 mL) were added carefully and the mixture was vigorously stirred for 30 min while warming to 25 °C. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic phases were washed with brine (sat., 15 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 1:1) gave diol **S28** (164 mg, 395 μmol, 86%) as a colorless solid.

M.p.: 120–122 °C (EtOAc).

TLC: R_f = 0.24 (*n*hexane/EtOAc 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.40 – 5.28 (m, 1H), 3.79 (d, *J* = 6.2 Hz, 1H), 3.61 – 3.52 (m, 1H), 3.03 – 2.95 (m, 1H), 2.41 (dd, *J* = 12.2, 5.0 Hz, 1H), 2.37 – 2.29 (m, 2H), 2.24 (dd, *J* = 15.5, 8.4 Hz, 1H), 2.00 – 1.93 (m, 1H), 1.93 – 1.86 (m, 2H), 1.86 – 1.80 (m, 2H), 1.74 – 1.63 (m, 2H), 1.62 – 1.51 (m, 6H), 1.49 – 1.44 (m, 2H), 1.41 (dt, *J* = 12.7, 4.1 Hz, 1H), 1.36 (d, *J* = 10.5 Hz, 1H), 1.24 – 1.16 (m, 2H), 1.14 (s, 3H), 0.96 (s, 3H), 0.95 – 0.91 (m, 1H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.80 – 0.76 (m, 6H).

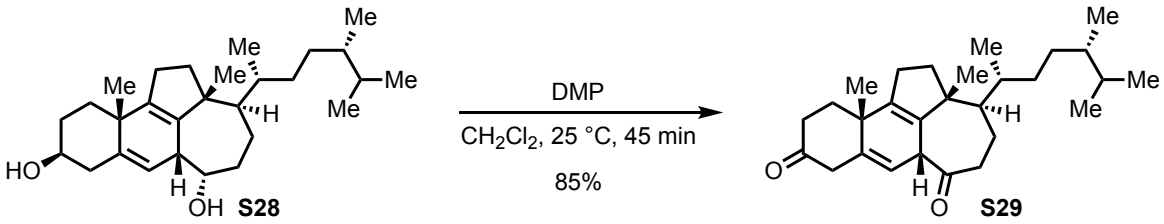
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 144.4, 141.0, 137.4, 123.2, 72.5, 72.4, 53.9, 52.4, 41.4, 39.7, 39.4, 39.2, 36.8, 36.7, 35.7, 35.4, 33.8, 31.9, 31.6, 30.6, 27.9, 23.0, 22.0, 21.6, 20.5, 19.0, 17.9, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3391 (br w), 2955 (s), 2928 (s), 2869 (m), 1739 (m), 1458 (m), 1375 (m), 1288 (w), 1217 (m), 1059 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{46}O_2Na^+$ [M+Na]$^+$: 437.3390, found: 437.3386.

Opt. act. $[\alpha]_D^{22}$ = +40.8 (*c* = 1.00, $CHCl_3$).

13(14→8),14(8→7)Di*abeo*-7β(H)-ergosta-5,8-dien-3,14-dione (**S29**)



To a solution of diol **S28** (164 mg, 395 μmol, 1.0 eq.) in CH_2Cl_2 (4 mL) were added $NaHCO_3$ (220 mg, 2.62 mmol, 6.6 eq.) and Dess–Martin periodinane (505 mg, 1.19 mmol, 3.0 eq.), and the resulting suspension was stirred at 25 °C. After 45 min, $Na_2S_2O_3$ (sat. aq., 3 mL) was added and after further stirring for 15 min, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 15 mL) and brine (sat., 15 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1) gave dione **S29** (138 mg, 336 μmol, 85%) as a colorless solid.

M.p.: 103–105 °C (EtOAc).

TLC: R_f = 0.19 (*n*hexane/EtOAc 5:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.23 (t, *J* = 2.7 Hz, 1H), 3.57 – 3.53 (m, 1H), 3.37 (dt, *J* = 16.2, 3.1 Hz, 1H), 2.98 (dd, *J* = 16.1, 2.2 Hz, 1H), 2.59 (ddd, *J* = 15.5, 13.8, 6.5 Hz, 1H), 2.46 – 2.29 (m, 5H), 2.20 (dd, *J* = 11.3, 7.9 Hz, 1H), 2.17 – 2.13 (m, 1H), 2.03 (ddd, *J* = 13.2, 6.6, 2.4 Hz, 1H), 1.79 – 1.72 (m, 1H), 1.62 – 1.52 (m, 5H), 1.52 – 1.46 (m, 2H), 1.44 – 1.41 (m, 2H), 1.40 (s, 3H), 0.97 – 0.93 (m, 6H), 0.93 – 0.88 (m, 1H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.9 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H).

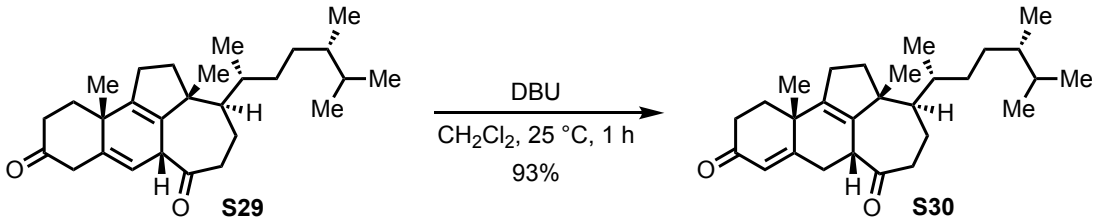
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 211.8, 207.8, 142.3, 139.7, 135.8, 119.3, 53.8, 51.6, 50.4, 48.2, 41.2, 39.2, 38.2, 38.0, 37.1, 36.0, 35.8, 33.8, 31.9, 31.0, 27.7, 22.6, 22.1, 21.5, 20.5, 19.6, 17.9, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (s), 2925 (s), 2854 (m), 1716 (m), 1458 (w), 1376 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_2Na^+$ [M+Na]$^+$: 433.3077, found: 433.3082.

Opt. act. $[\alpha]_D^{19}$ = –28.3 (*c* = 0.83, $CHCl_3$).

13(14→8),14(8→7)Di*abeo*-7β(H)-ergosta-4,8-dien-3,14-dione (**S30**)



To a solution of dione **S29** (138 mg, 336 μmol, 1.0 eq.) in CH_2Cl_2 (3.5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (10 mg, 66 μmol, 0.2 eq.) and the resulting solution was stirred at 25 °C for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (2 mL), and NH_4Cl (sat. aq., 5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine (sat., 25 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 4:1 → 3:1) gave enone **S30** (128 mg, 312 μmol, 93%) as a light-yellow oil.

TLC: R_f = 0.24 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.86 (s, 1H), 3.26 – 3.21 (m, 1H), 2.87 (d, *J* = 12.8 Hz, 1H), 2.57 – 2.48 (m, 2H), 2.46 (ddd, *J* = 15.8, 6.8, 1.9 Hz, 1H), 2.41 (dd, *J* = 17.8, 3.1 Hz, 1H), 2.32 – 2.27 (m, 2H), 2.21 – 2.13 (m, 1H), 2.00 – 1.93 (m, 2H), 1.76 – 1.70 (m, 2H), 1.66 – 1.60 (m, 1H), 1.60 – 1.51 (m, 3H), 1.51 – 1.40 (m, 2H), 1.30 (s, 3H), 1.27 – 1.17 (m, 3H), 1.08 (s, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.81 – 0.73 (m, 7H).

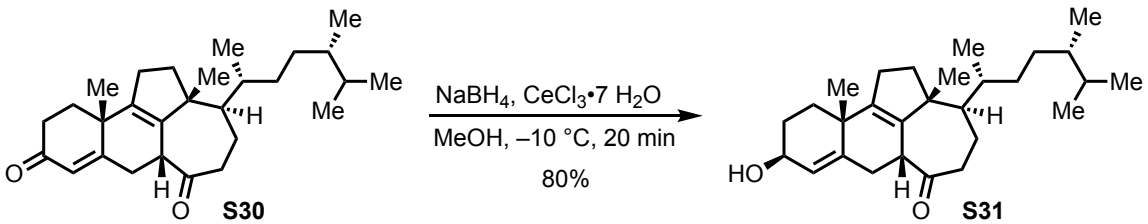
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 211.4, 198.6, 166.9, 143.4, 137.7, 126.1, 55.1, 53.6, 46.1, 45.0, 39.2, 38.0, 37.6, 35.4, 34.2, 33.7 (2C), 32.8, 31.9, 30.6, 27.2, 22.4, 21.6, 20.5, 20.4, 20.0, 17.9, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (s), 2927 (s), 2866 (m), 1739 (m), 1709 (m), 1672 (s), 1456 (m), 1375 (w), 1237 (m), 1046 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_2Na^+$ $[M+Na]^+$: 433.3077, found: 433.3087.

Opt. act. $[\alpha]_D^{24}$ = +106.7 (*c* = 1.00, $CHCl_3$).

3β-Hydroxy-13(14→8),14(8→7)di*abeo*-7β(H)-ergosta-4,8-dien-14-one (**S31**)



To a solution of enone **S30** (18 mg, 44 μmol, 1.0 eq.) in MeOH (1.5 mL) at –10 °C were added $CeCl_3 \cdot 7\ H_2O$ (41 mg, 110 μmol, 2.5 eq.) and $NaBH_4$ (1.0 mg, 26 μmol, 0.6 eq.) in three portions over 15 min at this temperature. The reaction mixture was diluted with EtOAc (2 mL), and HCl (1 M in H_2O, 5 mL) was added. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 15 mL) and brine (sat., 15 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 2:1) gave allylic alcohol **S31** (14.5 mg, 35.1 μmol, 80%) as a colorless oil.

TLC: R_f = 0.36 (*n*hexane/EtOAc 2:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.36 (s, 1H), 4.16 (t, *J* = 8.3 Hz, 1H), 2.98 (d, *J* = 6.7 Hz, 1H), 2.63 (d, *J* = 12.7 Hz, 1H), 2.42 – 2.34 (m, 2H), 2.29 – 2.16 (m, 3H), 2.04 – 1.94 (m, 2H), 1.68 (dt, *J* = 13.3, 3.5 Hz, 1H), 1.65 – 1.58 (m, 3H), 1.58 – 1.53 (m, 3H), 1.51 – 1.46 (m, 1H), 1.45 – 1.40 (m, 2H), 1.39 – 1.32 (m, 2H), 1.30 – 1.22 (m, 3H), 1.20 (s, 3H), 1.01 (s, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H).

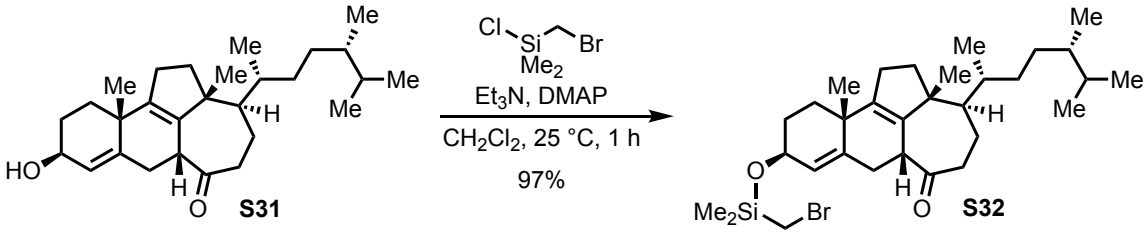
^{13}C-NMR: (101 MHz, $CDCl_3$); δ [ppm] = 214.2, 145.2, 142.8, 137.4, 125.7, 67.8, 54.2, 53.5, 46.6, 45.4, 39.2, 37.9, 36.4, 35.5, 33.7, 33.1, 32.8, 31.9, 30.6, 28.8, 27.1, 23.9, 21.5, 20.5, 20.4, 20.3, 17.9, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3406 (br w), 2953 (s), 2924 (s), 2854 (m), 1708 (m), 1458 (w), 1376 (w), 1065 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{44}O_2Na^+$ [M+Na]$^+$: 435.3234, found: 435.3255.

Opt. act. $[\alpha]_D^{23}$ = +34.9 (*c* = 1.00, $CHCl_3$).

3β-(Bromomethyl)dimethylsilyloxy-13(14→8),14(8→7)di*abeo*-7β(H)-ergosta-4,8-dien-14-one (**S32**)



To a solution of allylic alcohol **S31** (4.5 mg, 11 μmol, 1.0 eq.) in CH_2Cl_2 (1 mL) at 0 °C were added Et_3N (30 μL, 216 μmol, 20 eq.), 4-(dimethylamino)pyridine (0.3 mg, 2 μmol, 0.2 eq.) and (bromomethyl)-chlorodimethylsilane (22 μL, 165 μmol, 15 eq.) and the resulting solution was stirred at 25 °C for 1 h. The mixture was diluted with CH_2Cl_2 (2.5 mL), and NH_4Cl (sat. aq., 5 mL) was added. The aqueous phase was

extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were washed sequentially with NH_4Cl (sat. aq., 4 × 20 mL), $NaHCO_3$ (sat. aq., 15 mL) and brine (sat., 15 mL). The organic phase was dried over $MgSO_4$, the solvent was removed under reduced pressure and column chromatography (silica gel, *n*hexane/EtOAc 19:1) gave bromide **S32** (6.00 mg, 10.6 μmol, 97%) as a colorless oil.

TLC: R_f = 0.20 (*n*hexane/EtOAc 19:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.28 (s, 1H), 4.27 – 4.21 (m, 1H), 2.97 (d, *J* = 5.3 Hz, 1H), 2.60 (d, *J* = 11.8 Hz, 1H), 2.47 (s, 2H), 2.42 – 2.32 (m, 2H), 2.27 – 2.16 (m, 3H), 1.96 (ddd, *J* = 12.3, 7.5, 3.5 Hz, 1H), 1.92 – 1.86 (m, 1H), 1.72 – 1.63 (m, 2H), 1.63 – 1.45 (m, 6H), 1.45 – 1.38 (m, 2H), 1.37 – 1.30 (m, 1H), 1.25 – 1.21 (m, 1H), 1.18 (s, 3H), 1.00 (s, 3H), 0.95 – 0.91 (m, 4H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H), 0.75 – 0.69 (m, 1H), 0.27 (s, 6H).

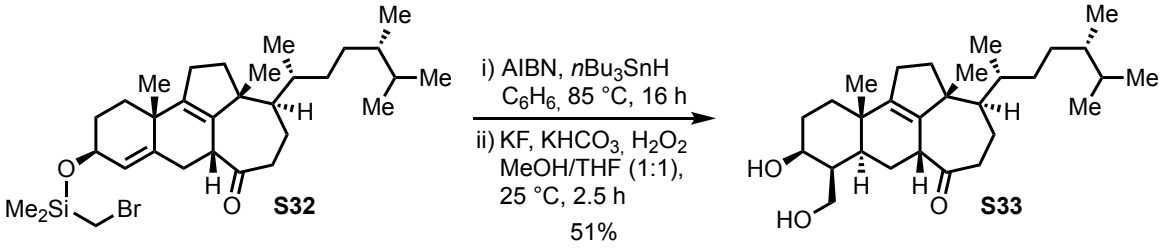
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 214.3, 145.2, 142.6, 137.3, 125.6, 69.2, 54.2, 53.4, 46.6, 45.4, 39.2, 37.9, 36.3, 35.4, 33.7, 33.1, 32.8, 31.9, 30.6, 29.0, 27.1, 23.8, 21.5, 20.5, 20.4, 20.3, 17.9, 16.6, 15.6, –2.3, –2.4.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (s), 2926 (s), 2856 (m), 1708 (m), 1460 (w), 1377 (w), 1254 (m), 1127 (w), 1073 (s), 887 (m), 839 (m), 815 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{31}H_{51}BrO_2SiNa^+$ [M+Na]$^+$: 585.2734, found: 585.2756.

Opt. act. $[\alpha]_D^{23}$ = +12.3 (*c* = 1.00, $CHCl_3$).

3β-Hydroxy-4β-(hydroxymethyl)-13(14→8),14(8→7)di*abeo*-5α(H),7β(H)-ergosta-4,8-dien-14-one (**S33**)



A solution of bromide **S32** (15 mg, 27 μmol, 1.0 eq.), AIBN (4.4 mg, 27 μmol, 1.0 eq.) and *n*Bu_3SnH (35.5 μL, 134 μmol, 5.0 eq.) in benzene (1.5 mL) was degassed applying three freeze-pump-thaw cycles. The reaction vessel was sealed, and it was heated to 85 °C for 16 h. After cooling to 25 °C, the solvent was removed under reduced pressure. The crude oxa-silolane was dissolved in MeOH/THF (1:1, 1 mL) and KF (15.6 mg, 270 μmol, 10 eq.), $KHCO_3$ (26.8 mg, 270 μmol, 10 eq.), and H_2O_2 (35% *w/w* in H_2O, 0.5 mL) were added. The mixture was stirred at 25 °C for 30 min before $Na_2S_2O_3$ (sat. aq., 2 mL) was carefully added. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic phases were washed with brine (sat., 15 mL). The organic phase was dried over $MgSO_4$, and the solvent was removed under

reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 2:1 → 1:1) gave diol **S33** (6.2 mg, 14 μmol, 51%) as a colorless oil in satisfactory purity for further transformation.

Analytically pure diol **S33** was obtained using preparative HPLC (MACHEREY-NAGEL VP 250/16 NUCLEOSIL® 50-5 Column; *n*-hexane/*i*PrOH 9:1; 1 mL/min)

TLC: R_f = 0.21 (*n*hexane/EtOAc 1:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 4.03 (t, *J* = 10.4 Hz, 1H), 3.94 (q, *J* = 7.3 Hz, 1H), 3.55 (t, *J* = 9.2 Hz, 1H), 3.14 – 3.09 (m, 1H), 2.72 – 2.67 (m, 1H), 2.54 (ddd, *J* = 16.5, 6.1, 2.2 Hz, 1H), 2.38 – 2.34 (m, 1H), 2.33 – 2.30 (m, 1H), 2.20 – 2.14 (m, 2H), 2.00 (d, *J* = 11.3 Hz, 1H), 1.78 – 1.69 (m, 5H), 1.68 – 1.60 (m, 5H), 1.53 – 1.49 (m, 1H), 1.49 – 1.45 (m, 1H), 1.42 (tt, *J* = 12.6, 4.3 Hz, 1H), 1.38 – 1.33 (m, 1H), 1.18 – 1.12 (m, 1H), 0.98 (s, 3H), 0.97 (s, 1H), 0.94 – 0.90 (m, 4H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.80 – 0.77 (m, 9H).

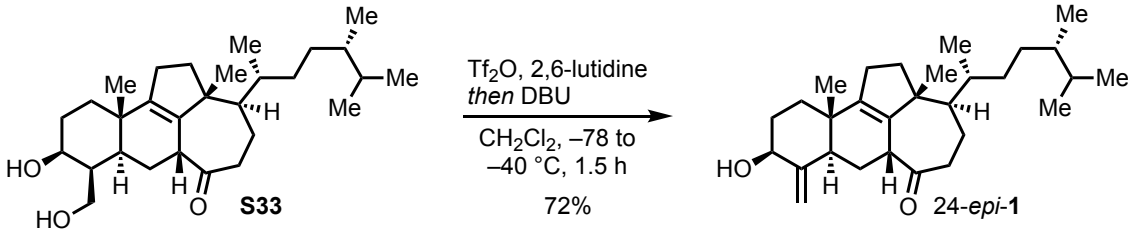
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 213.4, 147.1, 136.1, 74.5, 60.3, 55.8, 53.8, 48.2, 45.9, 45.5, 41.6, 39.2, 38.7, 35.5, 35.2, 34.7, 33.7, 31.9, 30.7, 27.6, 26.9 (2C), 21.7, 20.5, 20.0, 19.9, 19.1, 17.9, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3390 (br w), 2955 (s), 2925 (s), 2855 (m), 1704 (w), 1457 (m), 1376 (w), 1260 (w), 798 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{29}H_{48}O_3Na^+$ [M+Na]$^+$: 467.3496, found: 467.3473.

Opt. act. $[\alpha]_D^{20}$ = +19.4 (*c* = 0.35, $CHCl_3$).

24-*epi*-Swinhoeisterol A (24-*epi*-**1**)



A solution of diol **S33** (1.5 mg, 3.4 μmol, 1.0 eq.) and 2,6-lutidine (6 μL, 51 μmol, 15 eq.) in CH_2Cl_2 (0.5 mL) was cooled to –78 °C. Triflic anhydride (1 M in CH_2Cl_2, 34 μL, 34 μmol, 10 eq.) was added and the resulting mixture was stirred at this temperature for 10 min before MeOH (1.4 μL, 34 μmol, 10 eq.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (10 μL, 68 μmol, 20 eq.) were added. The reaction mixture was allowed to warm to –40 °C over 1.5 h before it was diluted with CH_2Cl_2 (1 mL) and HCl (1M in H_2O, 1 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 15 mL) and brine (sat., 15 mL), dried over $MgSO_4$, and the solvent was

removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 3:1) gave 24-*epi*-swinhoeisterol A (24-*epi*-**1**) (1.0 mg, 2.4 μmol, 72%) as a colorless oil.

TLC: R_f = 0.29 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.09 (s, 1H) , 4.69 (s, 1H) , 4.04 (dd, *J* = 11.9, 6.2 Hz, 1H), 3.16 – 3.12 (m, 1H), 2.53 (ddd, *J* = 16.3, 6.2, 2.2 Hz, 1H), 2.39 – 2.33 (m, 2H), 2.31 – 2.26 (m, 1H), 2.21 (ddd, *J* = 9.0, 6.3, 2.7 Hz, 1H), 2.14 (d, *J* = 13.2 Hz, 1H), 2.06 – 2.02 (m, 1H), 2.00 (d, *J* = 13.9 Hz, 1H), 1.80 – 1.74 (m, 3H), 1.71 – 1.69 (m, 1H), 1.67 – 1.63 (m, 2H), 1.62 – 1.60 (m, 1H), 1.60 – 1.58 (m, 1H), 1.48 – 1.46 (m, 1H), 1.38 – 1.36 (m, 1H), 1.36 – 1.34 (m, 1H), 1.34 – 1.32 (m, 1H), 1.22 – 1.18 (m, 3H), 1.01 (s, 3H), 0.94 – 0.92 (m, 4H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.80 – 0.77 (m, 9H).

^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 213.6, 151.9, 146.9, 135.9, 102.9, 73.1, 55.9, 53.8, 45.4, 45.3, 44.4, 39.2, 38.7, 37.7, 35.5, 34.8, 33.7, 32.5, 31.9, 30.7, 27.8, 24.5, 21.7, 20.5, 20.1, 20.0, 17.9, 17.9, 15.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2952 (m), 2924 (s), 2853 (m), 1739 (w), 1707 (w), 1459 (w), 1376 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{29}H_{46}O_2Na^+$ [M+Na]$^+$: 449.3390, found: 449.3410.

Opt. act. $[\alpha]_D^{23}$ = +44.1 (*c* = 0.1, $CHCl_3$).

3 NMR Comparisons

Table S1 NMR comparison of natural dankasterone B (**2**)[3] and synthetic material.

#	^{1}H-NMR		^{13}C-NMR	
	natural[3],a	**synthetic**b	**natural**[3],c	**synthetic**d
1	1.54 td (13.2, 5.7); 1.31 ddt (13.2, 6.9, 2.5)	1.54 td (12.9, 5.7); 1.31 ddt (13.3, 6.8, 2.4)	32.7	32.7
2	2.21 ddt (13.0, 5.7, 2.2); 2.29 td (13.0, 6.9)	2.22 dt (5.7, 2.1); 2.29 m	36.8	36.8
3	-	-	207.6	207.6
4	2.83 dt (16.2, 1.6); 2.19 dd (16.2, 2.6)	2.84 dt (16.5, 2.0); 2.20 d (6.1)	35.8	35.8
5	2.89 m	2.89 m	50.0	50.0
6	-	-	208.5	208.5
7	2.95 dd (13.2, 1.8); 1.95 d (13.2)	2.95 dd (13.2, 1.8); 1.95 d (13.5)	40.0	40.0
8	-	-	65.6	65.6
9	3.05 td (9.6, 1.8)	3.05 t (9.9)	53.2	53.2
10	-	-	40.5	40.5
11	2.31 m; 2.10 m	2.31 m; 2.10 m	25.5	25.5
12	2.14 m; 1.65 m	2.14 m; 1.65 m	34.1	34.1
13	-	-	60.1	60.0
14	-	-	214.7	214.7
15	2.78 ddd (13.0, 12.8, 5.9); 2.36 ddd (13.0, 4.3, 2.5)	2.79 ddd (14.3, 12.8, 5.9); 2.36 ddd (12.7, 4.2, 2.5)	38.5	38.5
16	1.99 m; 1.63 m	1.99 m; 1.64 m	27.2	27.2
17	1.95 m	1.95 m	45.4	45.4
18	0.75 s	0.75 s	15.2	15.1
19	1.27 s	1.27 s	23.4	23.4
20	2.42 m	2.42 p (6.9)	36.9	36.9
21	1.14 d (6.9)	1.15 d (7.1)	24.1	24.1
22	5.22 dd (15.3, 6.9)	5.23 m	132.0	132.0
23	5.25 dd (15.3, 6.8)	5.23 m	135.2	135.2
24	1.84 m	1.84 m	43.2	43.2
24[1]	0.88 d (6.8)	0.88 d (6.8)	17.5	17.5
25	1.45 m	1.45 m	33.0	33.0
26	0.79 d (6.8)	0.79 d (6.8)	19.7	19.7
27	0.81 d (6.8)	0.81 d (6.7)	20.0	20.0

All chemical shifts are reported in ppm. Coupling constants are in parentheses and are reported in Hz. m = centered multiplet. All spectra were measured in $CDCl_3$ and are referenced to the residual solvent peak at δ_H = 7.26 ppm and δ_C = 77.00 ppm. [a] Recorded at 500 MHz. [b] recorded at 700 MHz. [c] recorded at 126 MHz. [d] recorded at 176 MHz.

Table S2 NMR comparison of natural dankasterone A (Δ^4-**2**)[4] and synthetic material.

#	^{1}H-NMR		^{13}C-NMR	
	natural[4],a	**synthetic**b	**natural**[4],c	**synthetic**d
1	2.08 dd (13.3, 5.1); 2.04 m	2.08 m; 2.03 m	38.9	38.9
2	2.53 dt (17.6, 6.2); 2.46 m	2.53 m; 2.46 m	34.3	34.4
3	-	-	199.1	199.1
4	6.36 s	6.36 s	126.5	126.5
5	-	-	156.1	156.0
6	-	-	200.0	200.0
7	2.66 dd (16.8, 1.3); 2.50 d (16.8)	2.65 dd (16.8, 1.6); 2.50 m	40.8	40.9
8	-	-	62.2	62.2
9	2.81 td (9.0, 1.3)	2.81 m	49.4	49.4
10	-	-	36.0	36.0
11	2.02 m; 1.85 m	2.00 m; 1.85 m	25.1	25.1
12	1.77 dt (13.0, 7.2); 1.71 m	1.77 dt (13.0, 7.4); 1.71 m	38.3e	38.3
13	-	-	54.0e	54.0
14	-	-	214.8	214.7
15	2.48 m (2H)	2.48 m (2H)	37.9	37.9
16	1.90; 1.69 m	1.90 m; 1.69 m	23.2	23.2
17	1.48 dd (13.2, 4.2)	1.48 m	49.3	49.4
18	0.98 s	0.98 s	17.1	17.1
19	1.26 s	1.26 s	24.0	24.0
20	2.42 m	2.41 td (7.4, 2.6)	37.2	37.2
21	1.09 d (6.8)	1.09 d (7.0)	23.6	23.6
22	5.25 dd (15.1, 5.0)	5.27 m	132.3	132.3
23	5.29 dd (15.1, 3.5)	5.27 m	135.1	135.1
24	1.88 m	1.88 m	43.2	43.2
24[1]	0.91 d (6.8)	0.91 d (6.9)	17.6	17.6
25	1.47 octet (6.8)	1.48 m	33.0	33.1
26	0.84 d (6.8)	0.83 d (6.8)	20.0	20.0
27	0.81 d (6.8)	0.81 d (6.8)	19.7	19.7

All chemical shifts are reported in ppm. Coupling constants are in parentheses and are reported in Hz. m = centered multiplet. All spectra were measured in $CDCl_3$ and are referenced to the residual solvent peak at δ_H = 7.26 ppm and δ_C = 77.00 ppm. [a] Recorded at 500 MHz. [b] recorded at 700 MHz. [c] recorded at 126 MHz. [d] recorded at 176 MHz. [e] originally both assigned to C12.

Table S3 NMR comparison of natural periconiastone (**3**)[5] and synthetic material.

#	^{1}H-NMR		^{13}C-NMR	
	natural[5],a	**synthetic**b	**natural**[5],c	**synthetic**d
1	1.53 m; 1.81 m	1.51 m, 1.84 m	38.5	38.5
2	2.46 m, 2.87 m	2.46 m, 2.87 ddd (19.9, 11.8, 9.0)	36.8	36.8
3	-	-	209.2	209.2
4	3.12 d (4.0)	3.12 d (3.9)	65.3	65.3
5	2.45 d (4.0)	2.46 m	58.8	58.8
6	-	-	213.2	213.1
7	2.12 d (18.5); 3.21 dd (18.5, 2.4)	2.13 m, 3.21 d (18.5)	37.4	37.4
8	-	-	56.0	56.0
9	2.80 m	2.80 t (10.0)	42.3	42.3
10	-	-	33.7	33.6
11	1.85 m, 1.88 m	1.84 m (2H)	22.7	22.7
12	1.58 m, 2.04 m	1.51 m, 2.03 ddd (14.2, 9.7, 5.3)	37.6	37.6
13	-	-	47.9	47.8
14	-	-	73.1	73.1
15	1.88 m, 2.13 m	1.84 m, 2.13 m	34.3	34.3
16	1.48 m, 1.92 m	1.51 m, 1.94 m	20.6	20.6
17	1.55 m	1.51 m	48.2	48.2
18	1.22 s	1.22 s	19.3	19.3
19	0.99 s	0.99 s	26.6	26.5
20	2.49 m	2.47 m	37.4	37.4
21	1.13 d (7.1)	1.13 d (6.9)	24.5	24.4
22	5.52 dd (15.3, 7.9)	5.51 dd (15.4, 8.1)	134.6	134.6
23	5.30 dd (15.3, 8.2)	5.30 dd (15.4, 8.2)	134.5	134.5
24	1.86 m	1.84 m	44.0	44.0
24[1]	0.92 d (6.8)	0.92 d (6.8)	33.9	33.9
25	1.45 m	1.51 m	20.7	20.7
26	0.86 d (6.7)	0.85 (6.8)	20.4	20.3
27	0.84 d (6.7)	0.84 (7.3)	18.4	18.3
14-OH	6.63 s	6.64 s	-	-

All chemical shifts are reported in ppm. Coupling constants are in parentheses and are reported in Hz. m = centered multiplet. All spectra were measured in pyridine-d_5 and are referenced to the residual solvent peak at δ_H = 8.74 ppm and δ_C = 150.35 ppm. [a] Recorded at 400 MHz. [b] recorded at 600 MHz. [c] recorded at 100 MHz. [d] recorded at 151 MHz.

Table S4. ^{1}H-NMR comparison of synthetic swinhoeisterol A, natural swinhoeisterol A (**1**)[6], and synthetic 24-*epi*-swinhoeisterol A (24-*epi*-**1**).

#	**Synthetic**[a]	**Natural**[6],[b]	**Synthetic 24-*epi***[a]
1	1.71 m, 1.36 td (13.3, 4.2)	1.70 ov; 1.35 m	1.70 m; 1.35 m
2	2.04 m, 1.48 qd (12.7, 4.3)	2.05 m; 1.46 ov	2.05 m; 1.46 m
3	4.04 dd (11.9, 5.8)	4.03 dd (14.5, 5.8)	4.04 dd (11.9, 6.2)
4		-	-
5	2.00 d (12.6)	2.01 d (13.0)	2.00 d (13.9)
6	2.15 d (13.1), 1.60 dd (12.9, 6.4)	2.14 d (12.8); 1.61 dd (12.8, 6.3)	2.14 d (13.2); 1.61 m
7	3.14 m	3.14 m	3.14 m
8	-	-	-
9	-	-	-
10	-	-	-
11	2.29 m, 2.20 m	2.27 m; 2.21 ddd (9.1, 6.3, 2.9)	2.27 m; 2.21 ddd (9.0, 6.3, 2.7)
12	1.80 m, 1.76 m	1.80 ov; 1.77 ov	1.80 m; 1.77 m
13	-	-	-
14	-	-	-
15	2.53 ddd (16.3, 6.1, 2.4), 2.36 ddd (15.9, 11.7, 3.5)	2.54 m; 2.35 m	2.53 ddd (16.3, 6.2, 2.2); 2.35 m
16	1.68 m (2D), 1.66 m	1.68 ov; 1.65 ov	1.68 m; 1.65 m
17	1.26 m	1.25 ov	1.25 m
18	1.01 s	1.00 s	1.01 s
19	0.78 s	0.78 s	0.78 s
20	1.56 m	1.56 ov	1.59 m
21	0.93 d (6.9)	0.92 d (6.8)	0.93 d (6.9)
22	0.91 m; 1.39 m	0.91 m; 1.39 ov	0.91 m; 1.37 m
23	1.19 m	1.19 ov	1.19 m
24	1.20 m	1.20 ov	1.20 m
24[1]	0.78 d (6.5)	0.78 d (6.8)	0.78
25	1.55 m	1.55 ov	1.55 m
26	0.86 d (6.8)	0.85 d (6.8)	0.85 d (6.8)
27	0.80 d (6.8)	0.80 d (7.1)	0.79
28	5.09 s; 4.69 s	5.09 s; 4.68 s	5.09 s; 4.69 s

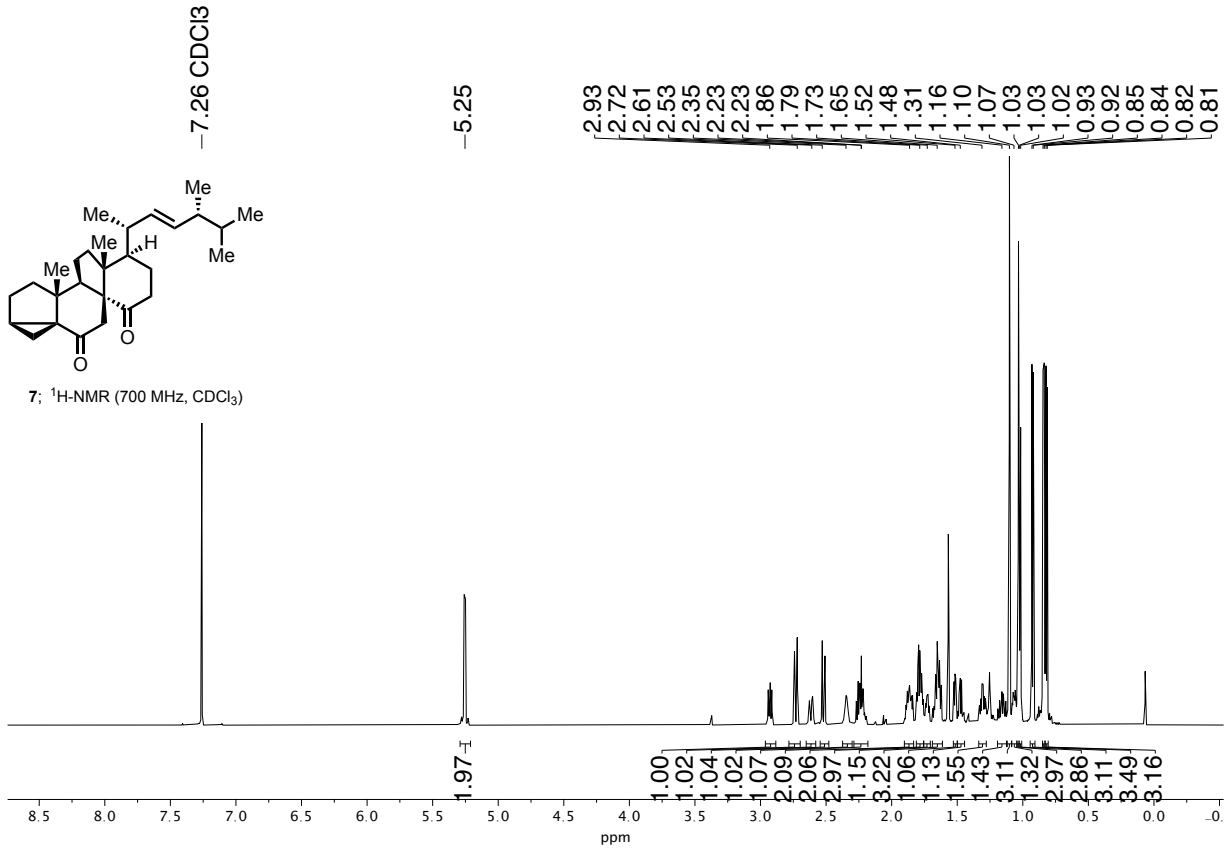
All chemical shifts are reported in ppm. Coupling constants are in parentheses and are reported in Hz. m = centered multiplet, ov = overlain. All spectra were measured in $CDCl_3$ and are referenced to the residual solvent peak at δ_H = 7.26 ppm. [a] Recorded at 700 MHz. [b] recorded at 500 MHz.

Table S5. ^{13}C-NMR comparison of synthetic swinhoeisterol A, natural swinhoeisterol A (**1**)[6] and synthetic 24-*epi*-swinhoeisterol A (24-*epi*-**1**).

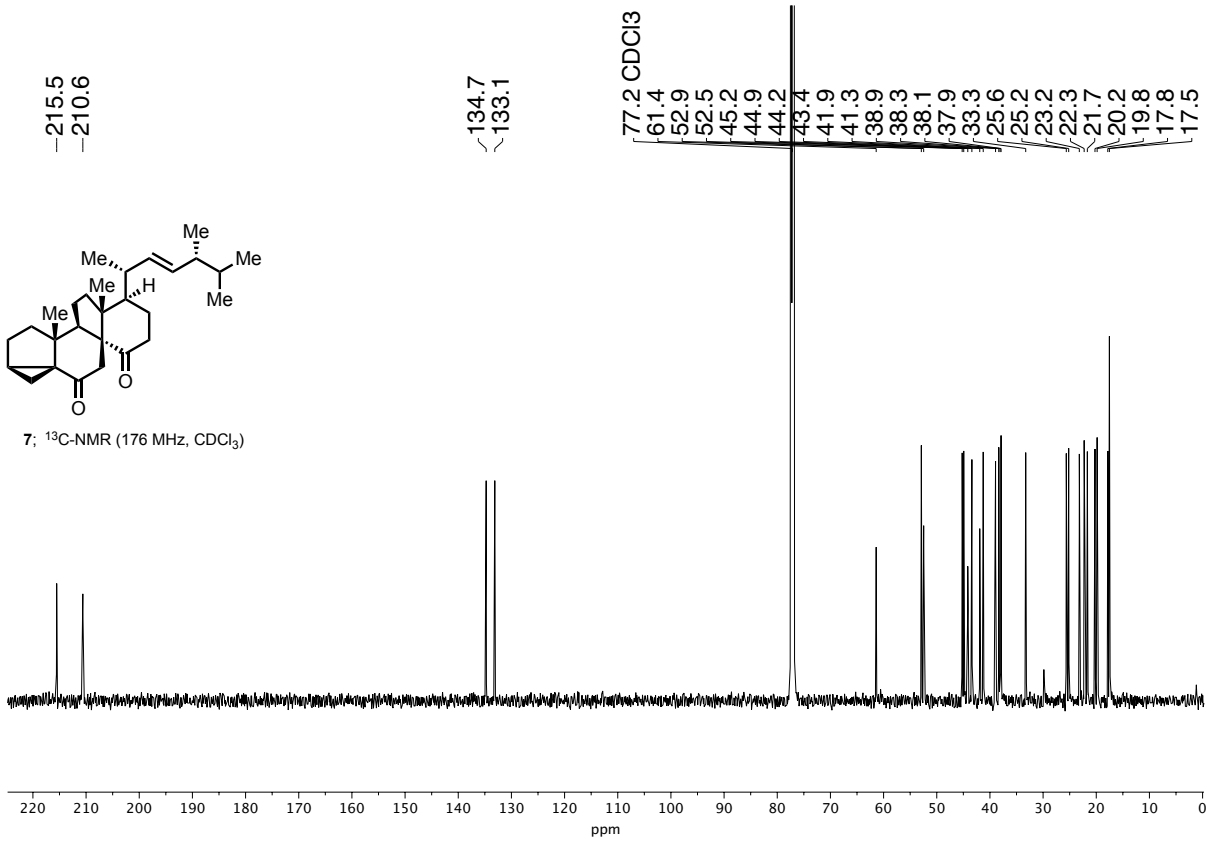
#	**Synthetic**[a]	**Natural**[6],[b]	**Synthetic 24-*epi***[a]
1	34.8	34.7	34.8
2	32.5	32.4	32.5
3	73.1	73.1	73.1
4	151.9	151.9	151.9
5	44.4	44.3	44.4
6	24.5	24.5	24.5
7	45.3	45.3	45.3
8	136.0	135.9	135.9
9	146.9	146.9	146.9
10	37.7	37.7	37.7
11	27.8	27.8	27.8
12	38.7	38.7	38.7
13	53.8	53.8	53.8
14	213.6	213.7	213.6
15	45.4	45.4	45.4
16	20.1	20.1	20.1
17	55.8	55.8	55.9
18	20.0	20.0	20.0
19	17.9	17.9	17.9
20	35.2	35.1	35.5
21	21.6	21.6	21.7
22	30.5	30.5	30.7
23	33.5	33.4	33.7
24	39.1	39.1	39.2
24[1]	15.6	15.6	15.6
25	32.2	32.3	31.9
26	20.4	20.4	20.5
27	18.2	18.2	17.9
28	102.9	102.9	102.9

All chemical shifts are reported in ppm. All spectra were measured in $CDCl_3$ and are referenced to the residual solvent peak at δ_C = 77.16 ppm. [a] Recorded at 176 MHz. [b] recorded at 126 MHz. Signals that are shifted due to different configuration at C24 are marked in light grey.

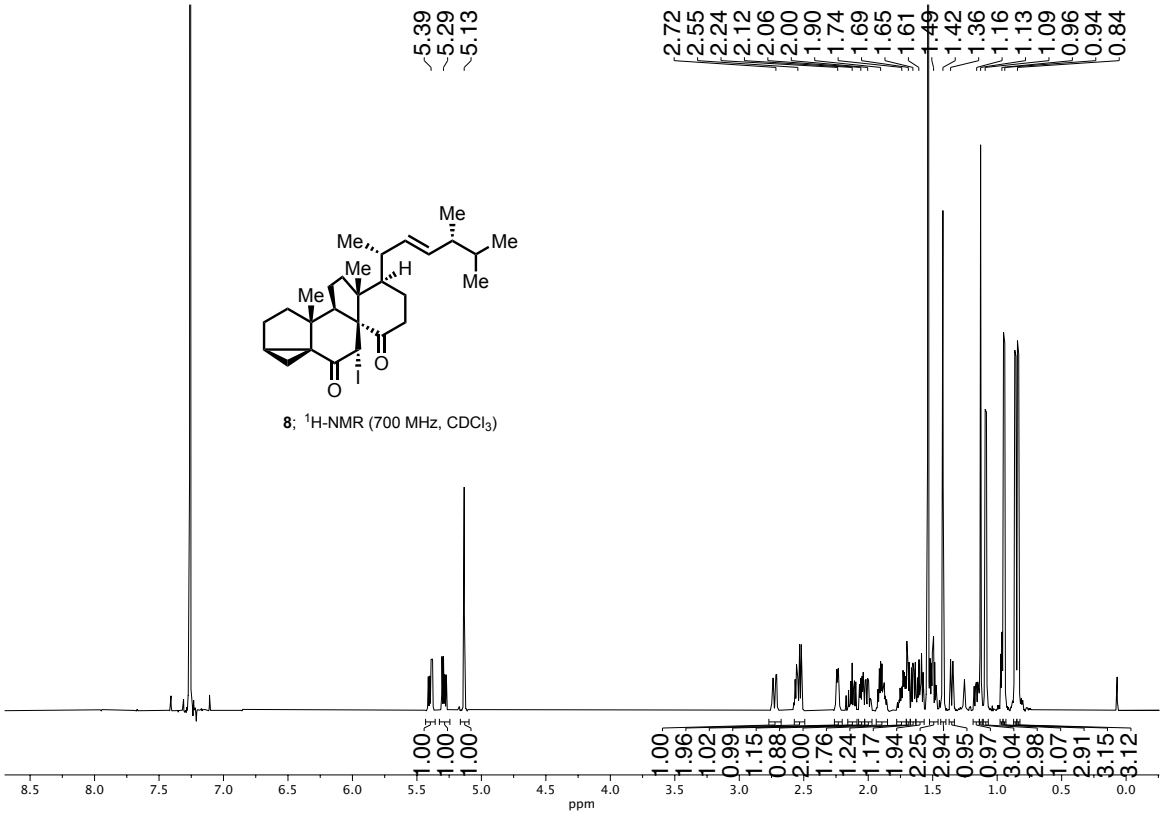
4 NMR Spectra



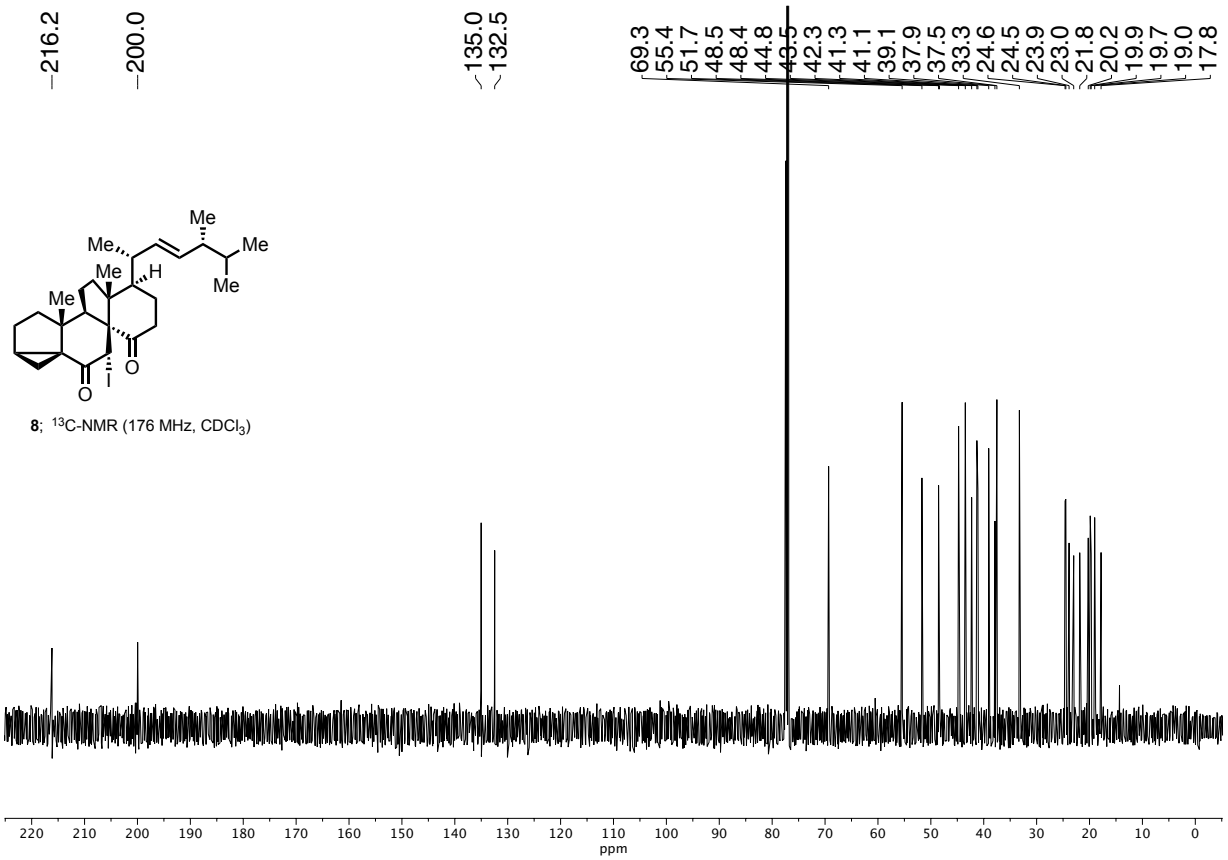
7; ^{1}H-NMR (700 MHz, $CDCl_3$)



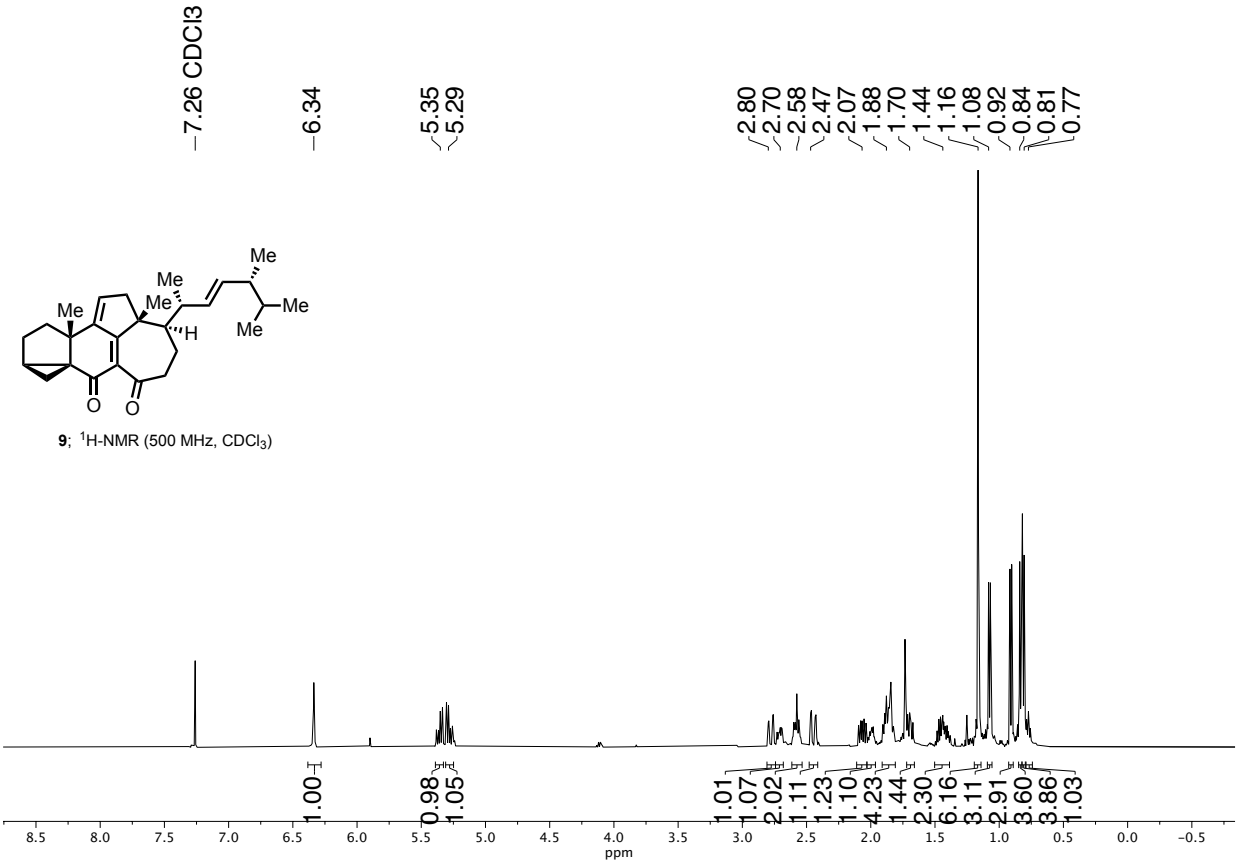
7; ^{13}C-NMR (176 MHz, $CDCl_3$)



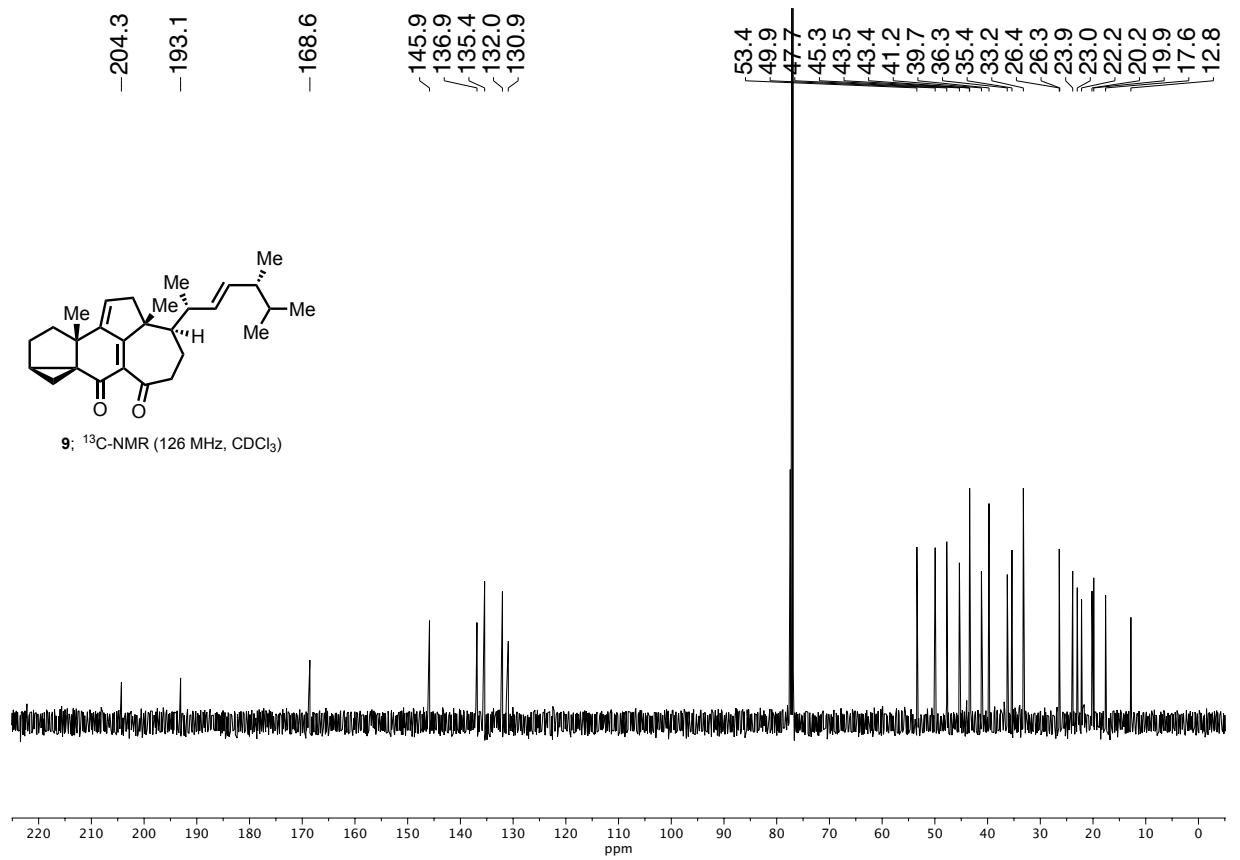
8; ^{1}H-NMR (700 MHz, $CDCl_3$)



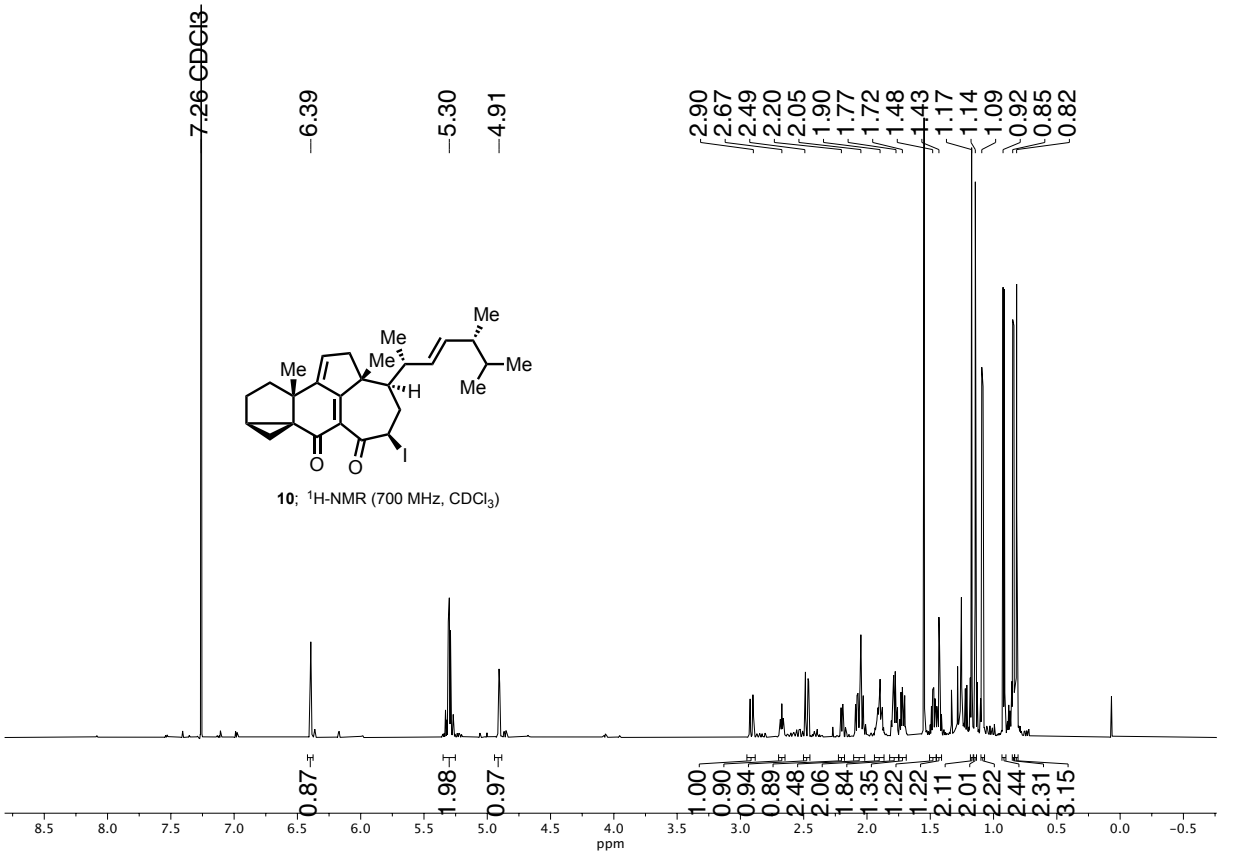
8; ^{13}C-NMR (176 MHz, $CDCl_3$)



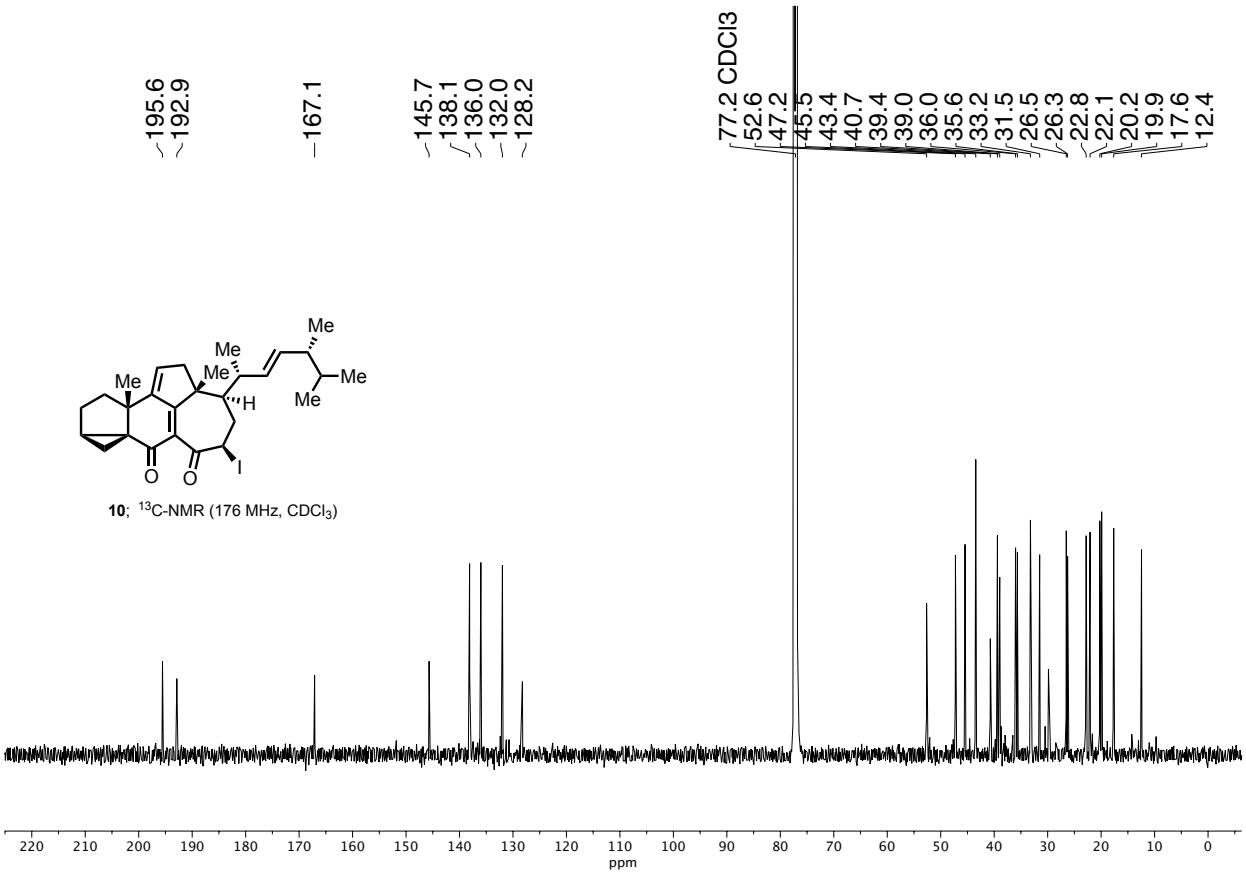
9; ^{1}H-NMR (500 MHz, $CDCl_3$)



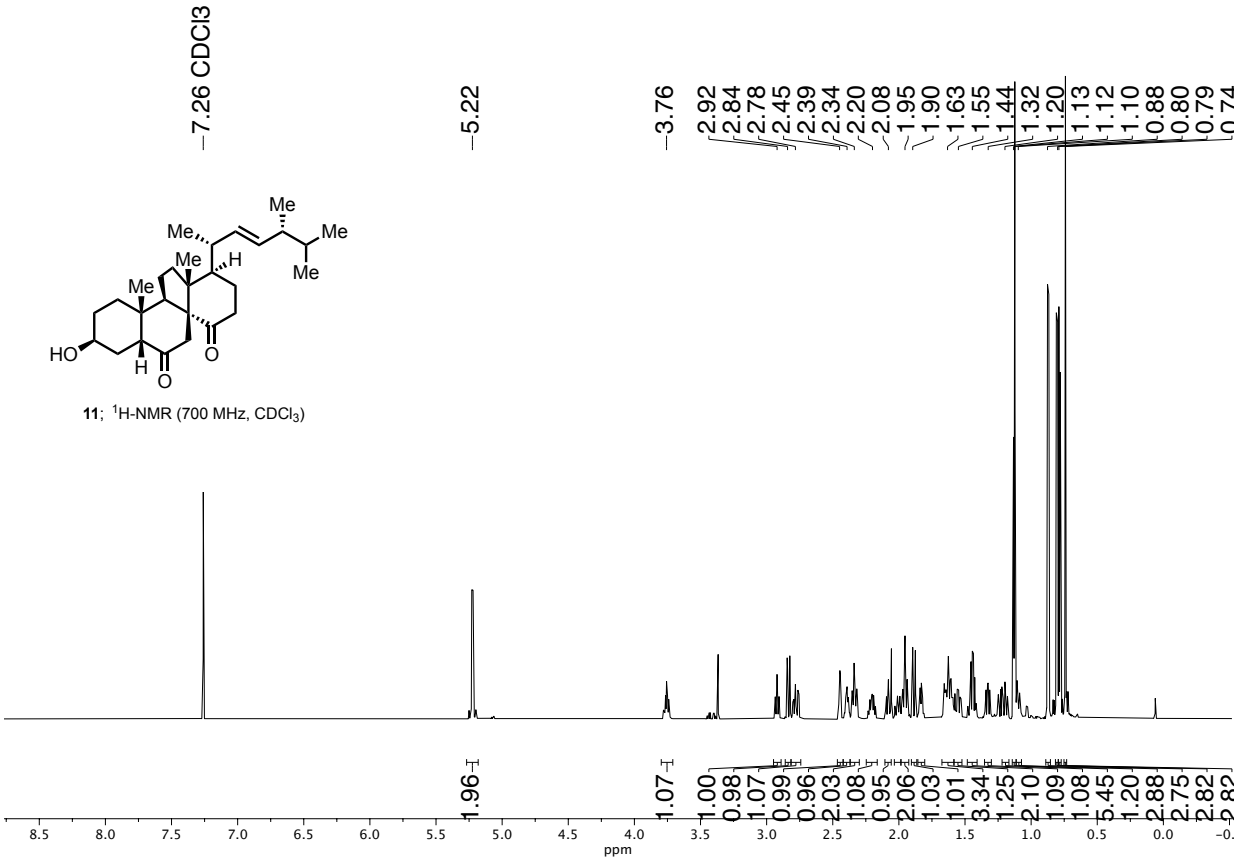
9; ^{13}C-NMR (126 MHz, $CDCl_3$)



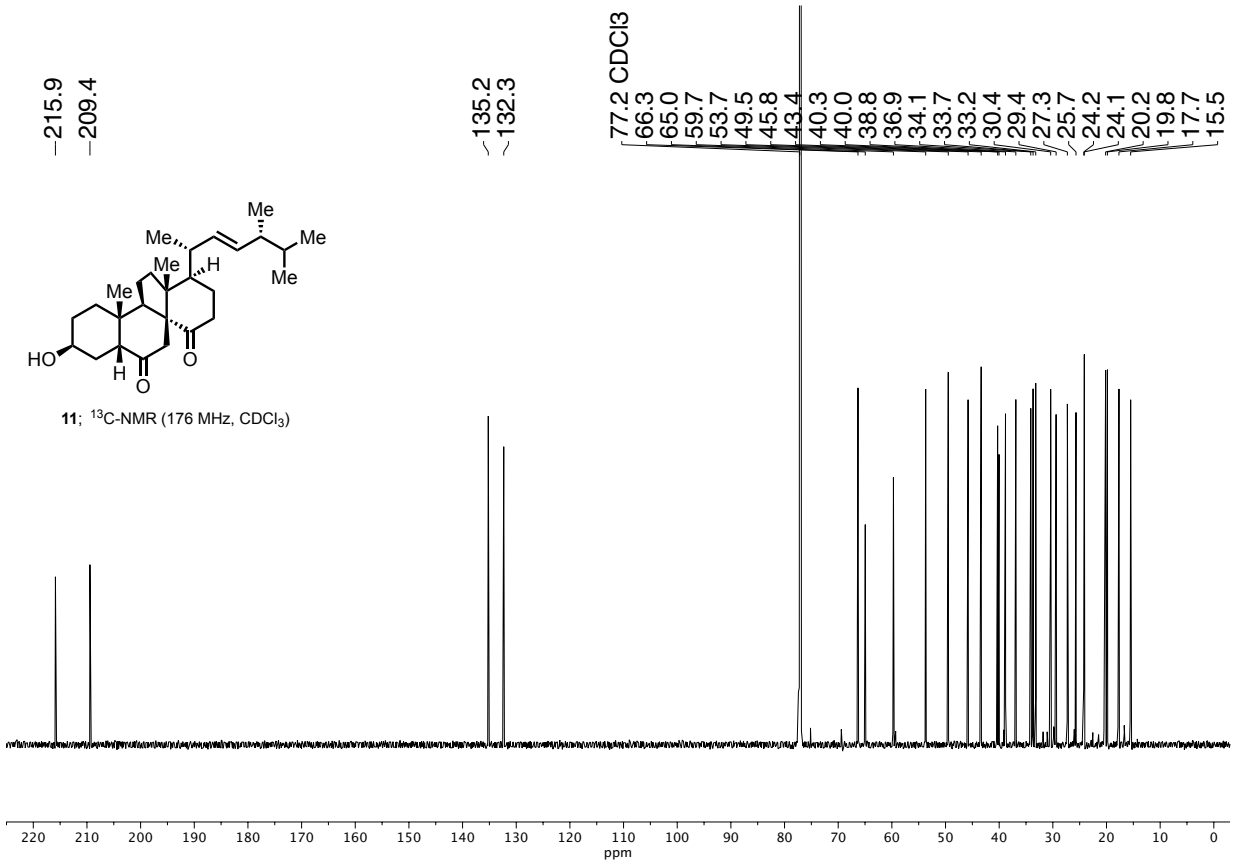
10; ^{1}H-NMR (700 MHz, $CDCl_3$)



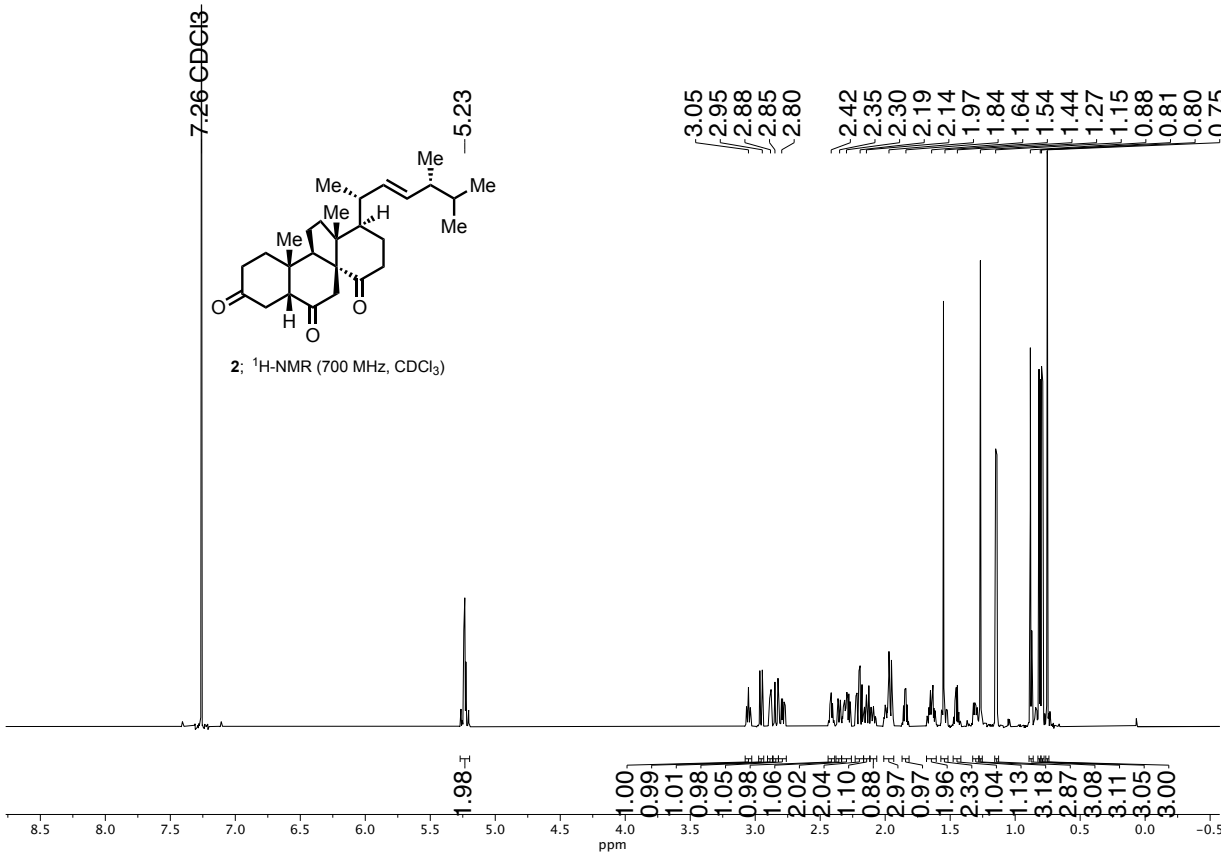
10; ^{13}C-NMR (176 MHz, $CDCl_3$)



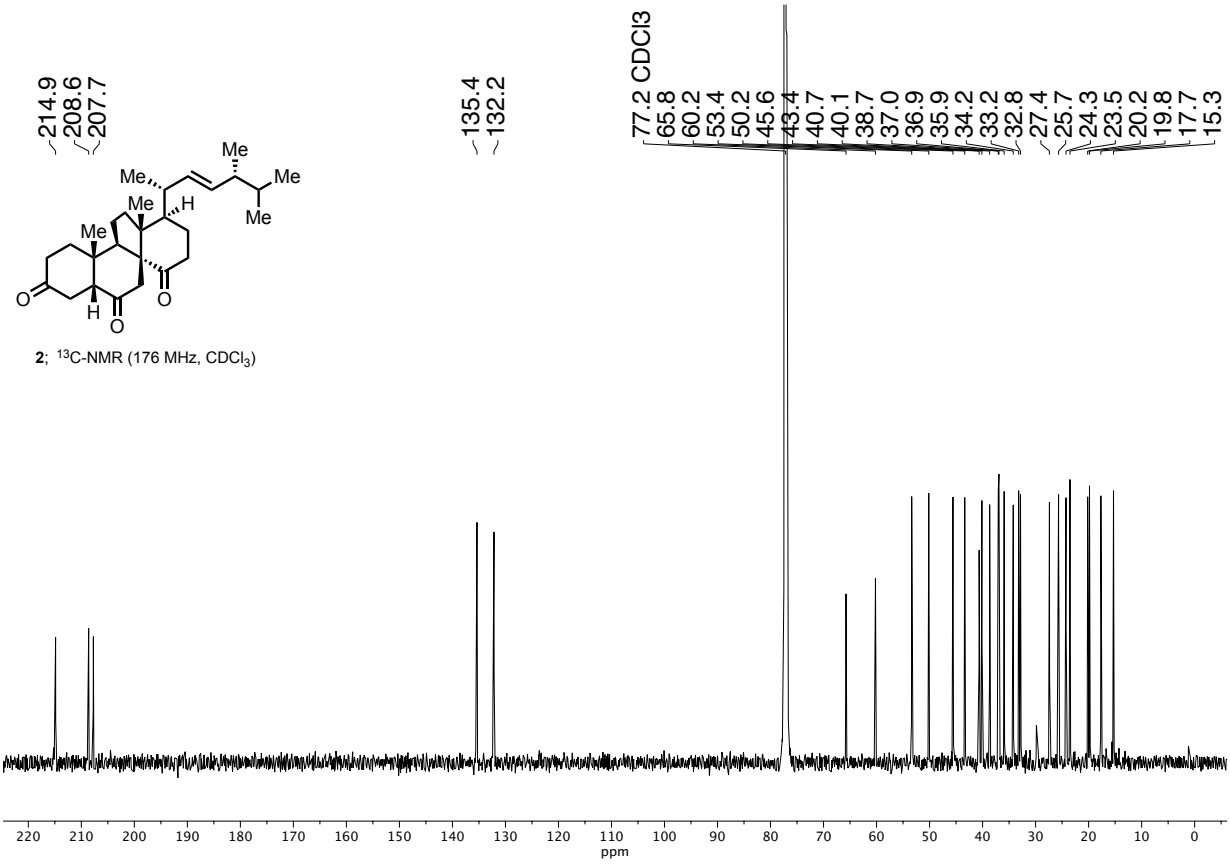
11; ^{1}H-NMR (700 MHz, $CDCl_3$)



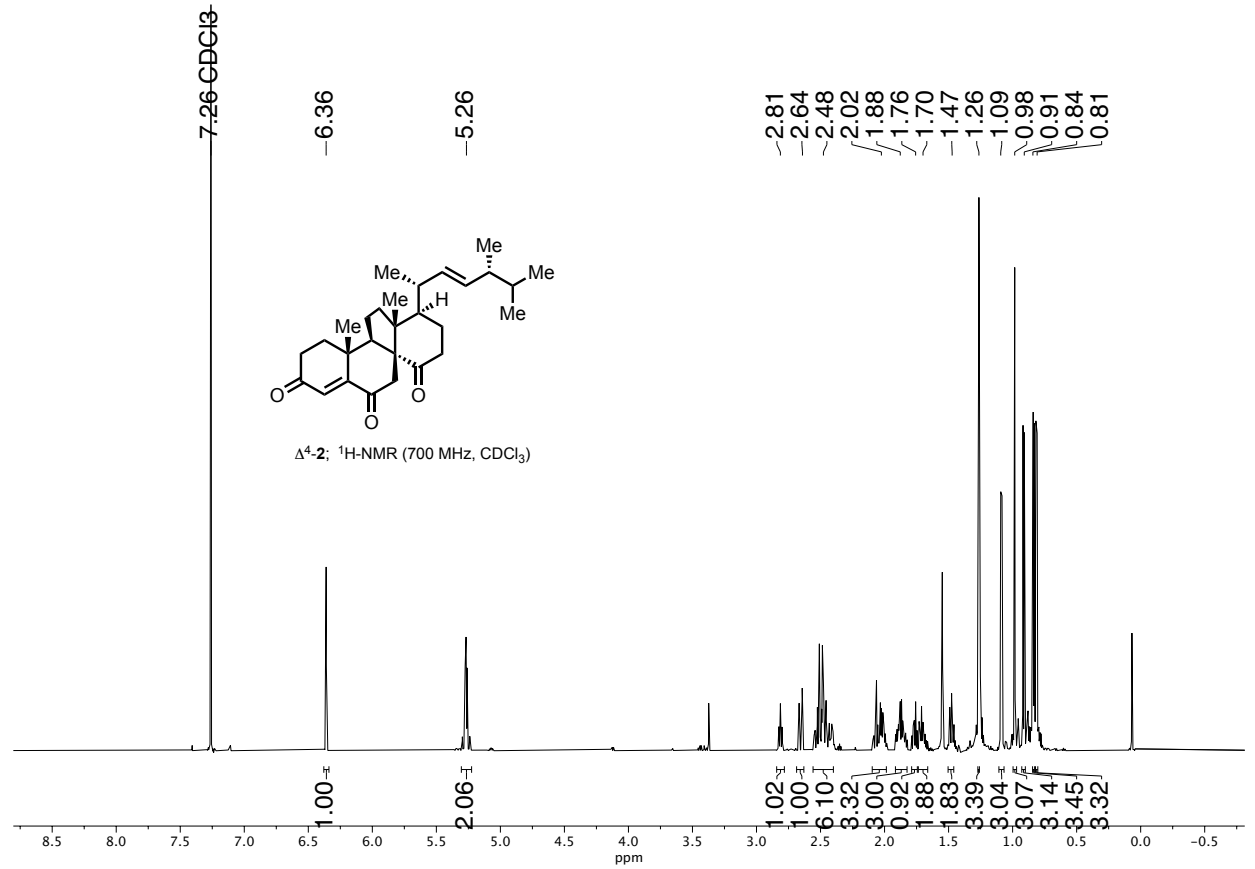
11; ^{13}C-NMR (176 MHz, $CDCl_3$)



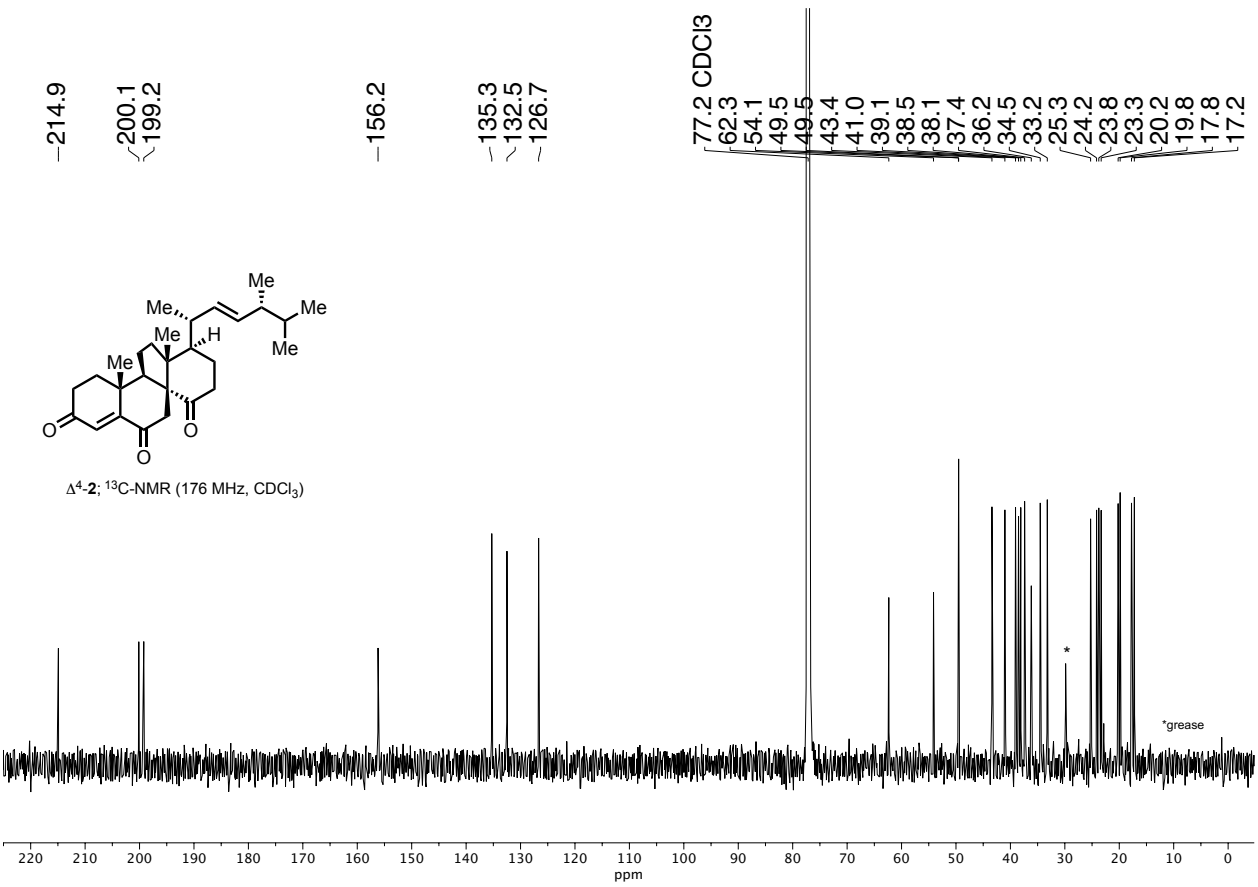
2; ^{1}H-NMR (700 MHz, $CDCl_3$)



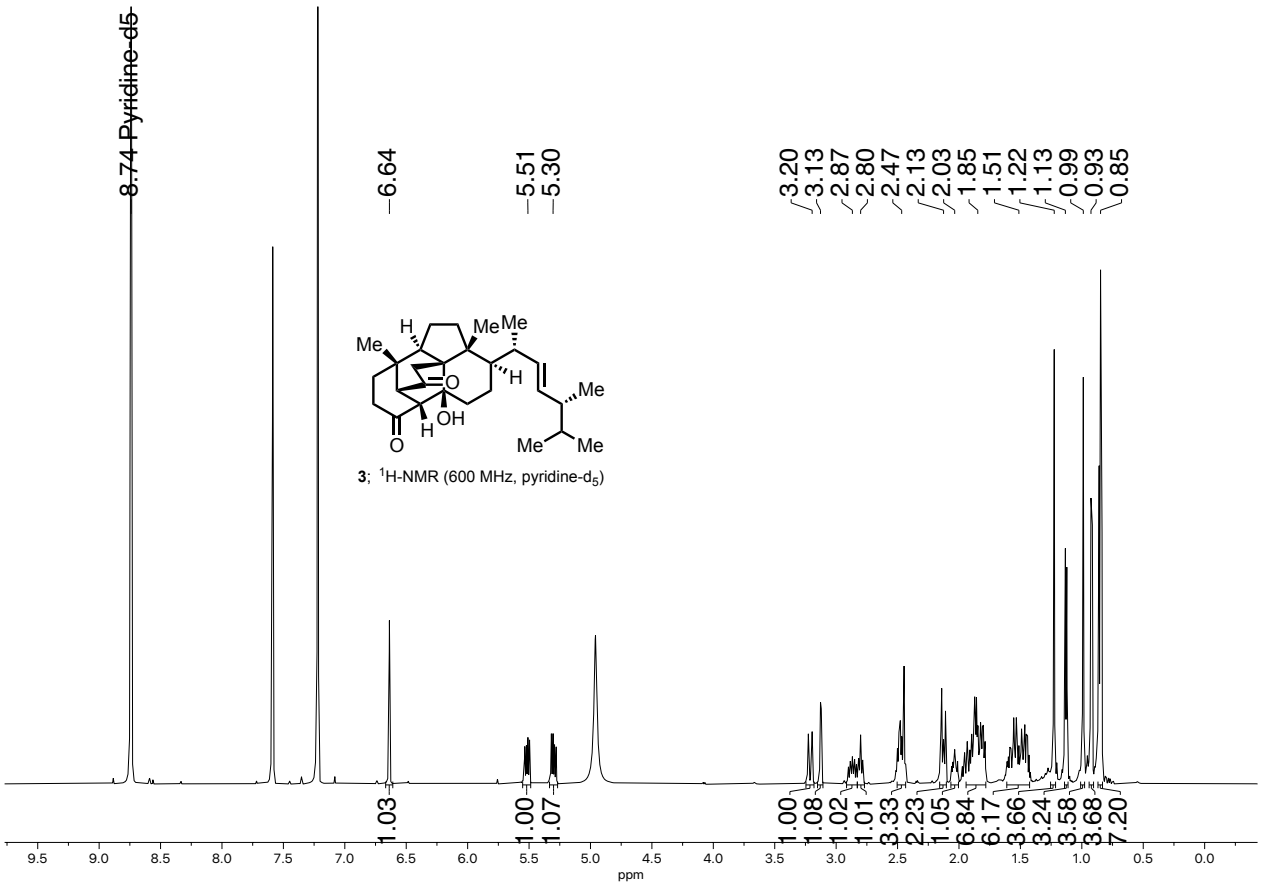
2; ^{13}C-NMR (176 MHz, $CDCl_3$)



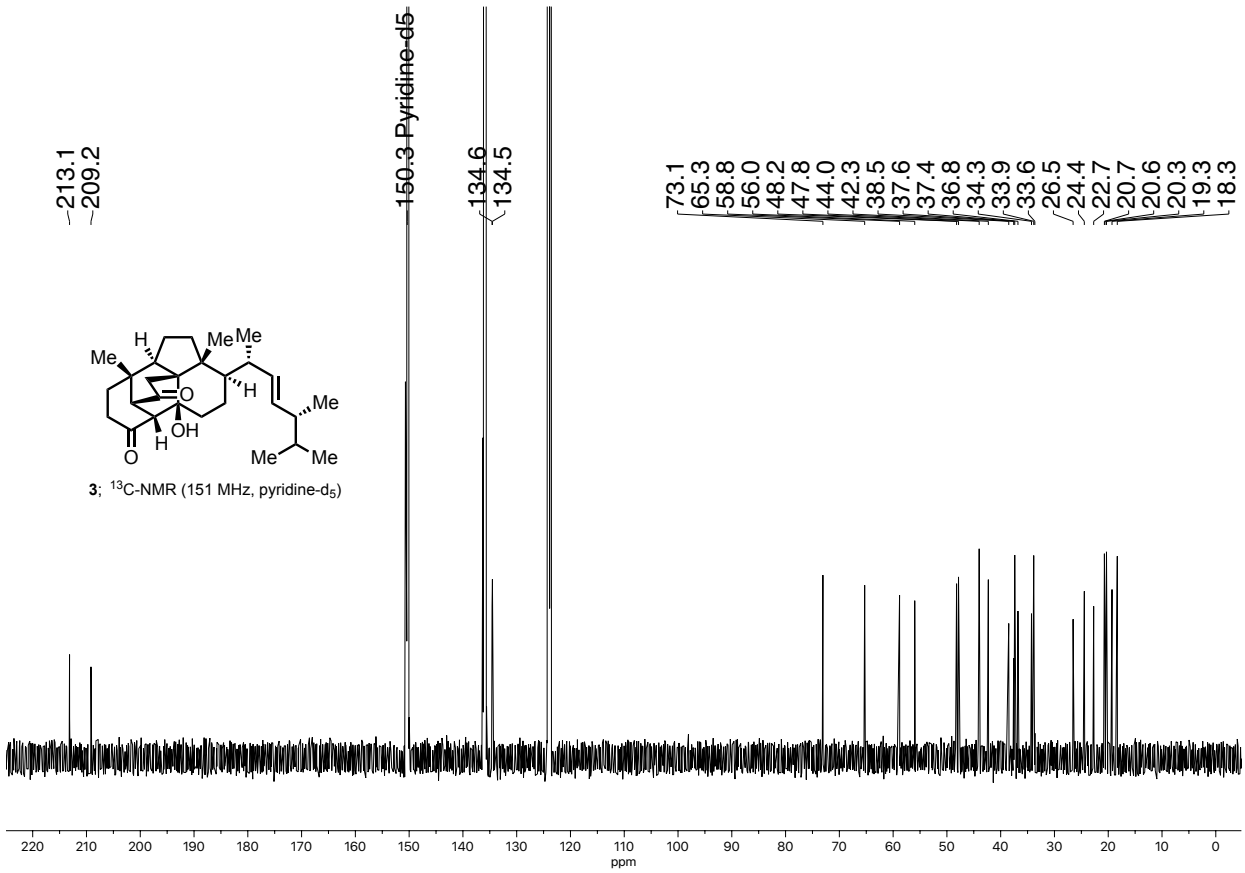
Δ^4-**2**; ^{1}H-NMR (700 MHz, $CDCl_3$)



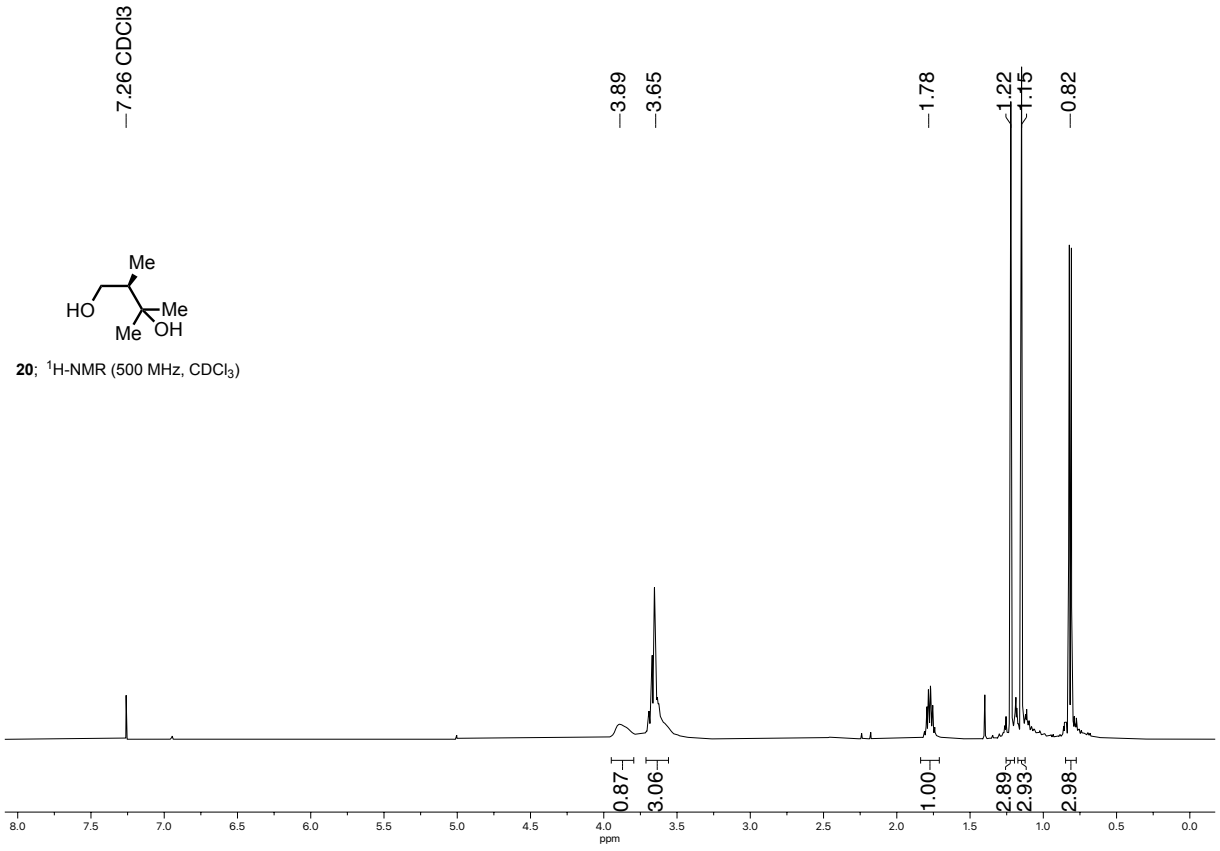
Δ^4-**2**; ^{13}C-NMR (176 MHz, $CDCl_3$)



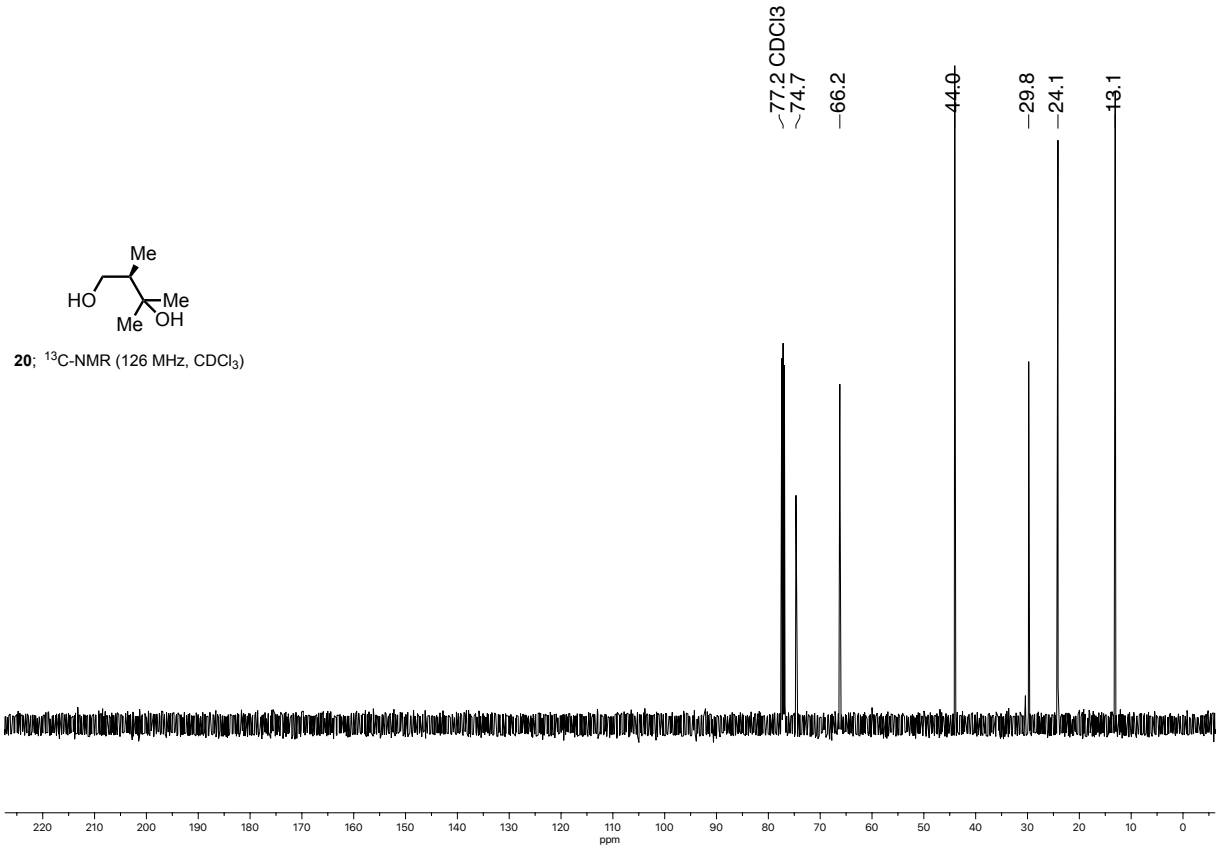
3; ^{1}H-NMR (600 MHz, pyridine-d_5)



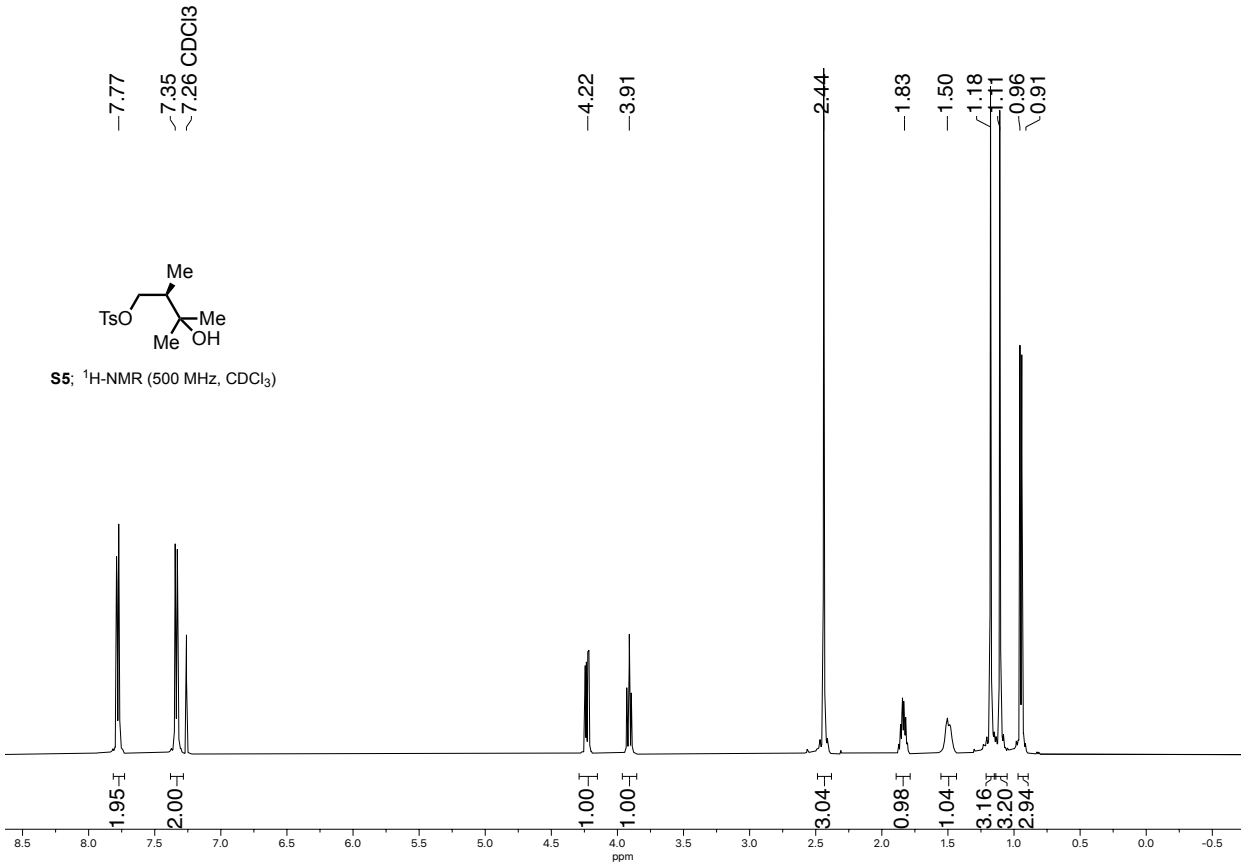
3; ^{13}C-NMR (151 MHz, pyridine-d_5)



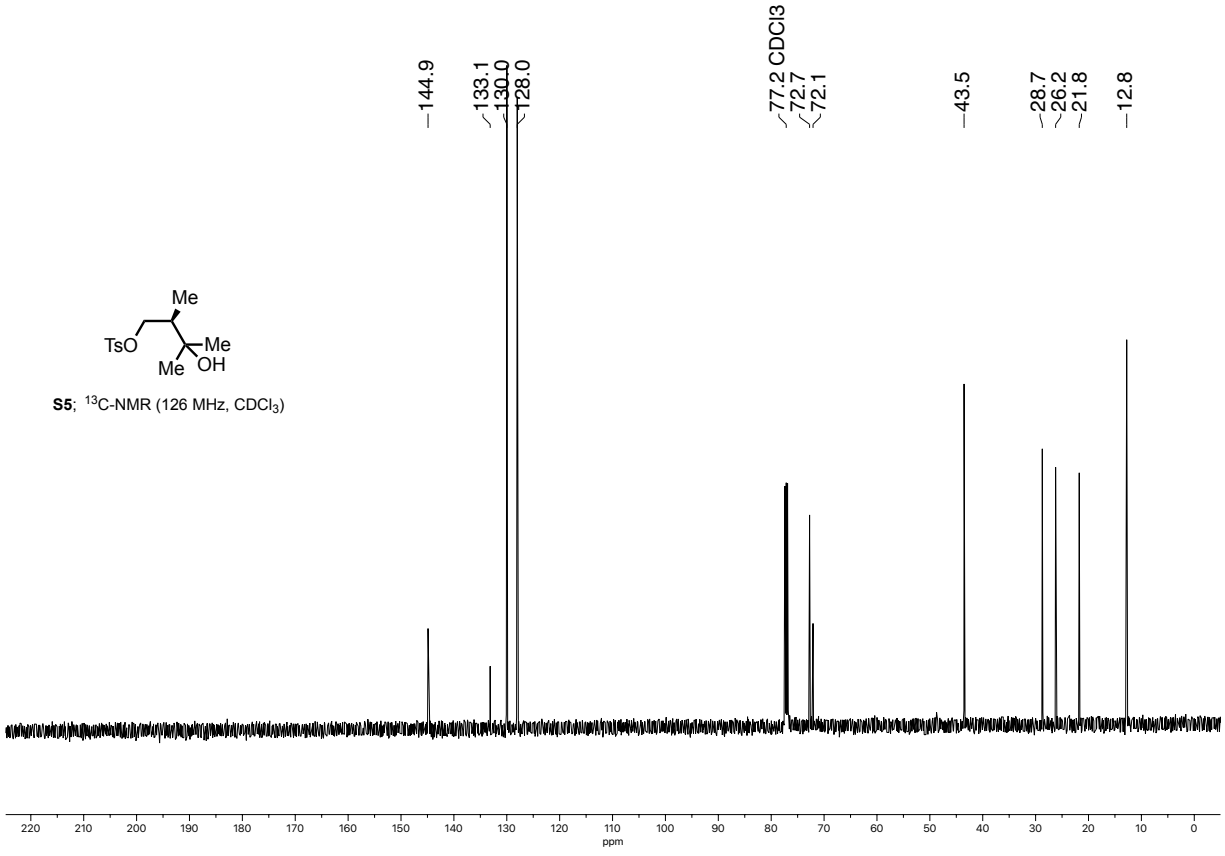
20; ^{1}H-NMR (500 MHz, $CDCl_3$)



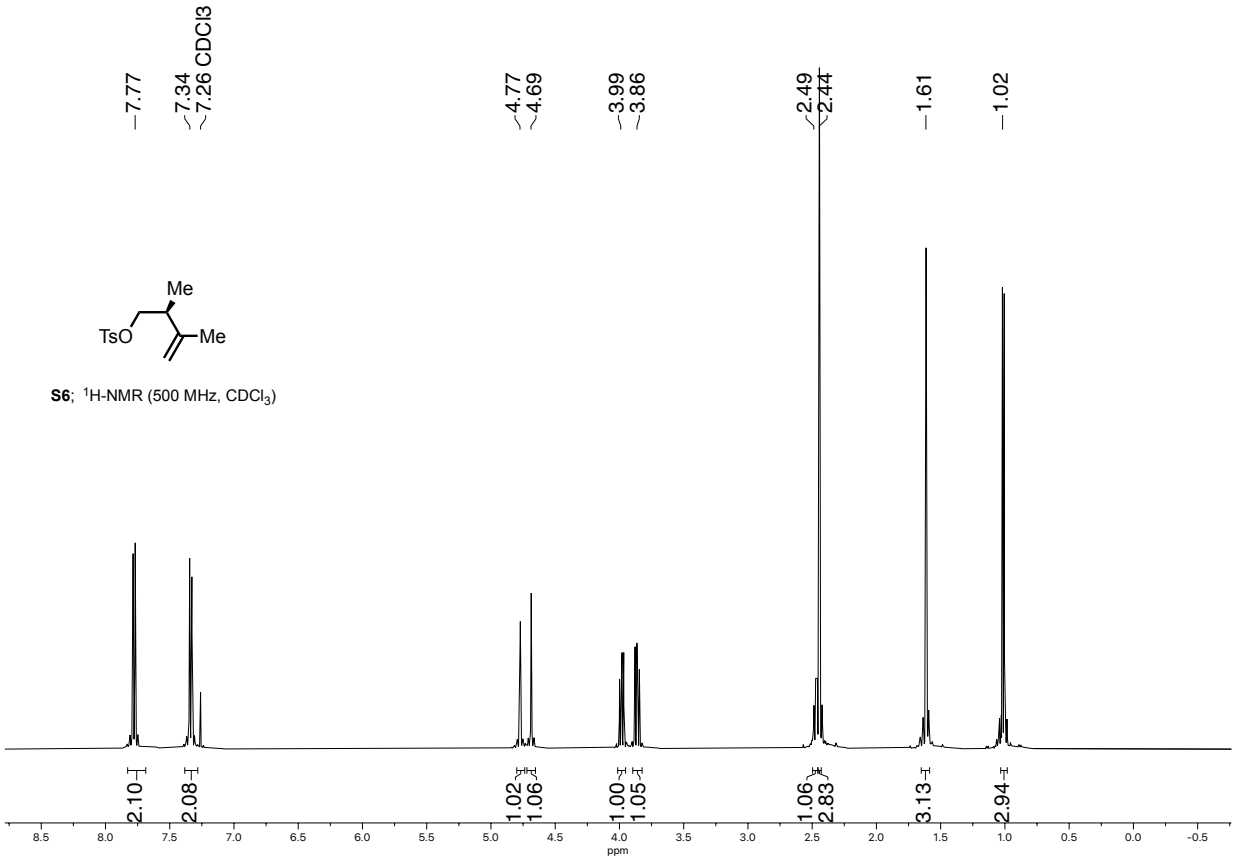
20; ^{13}C-NMR (126 MHz, $CDCl_3$)



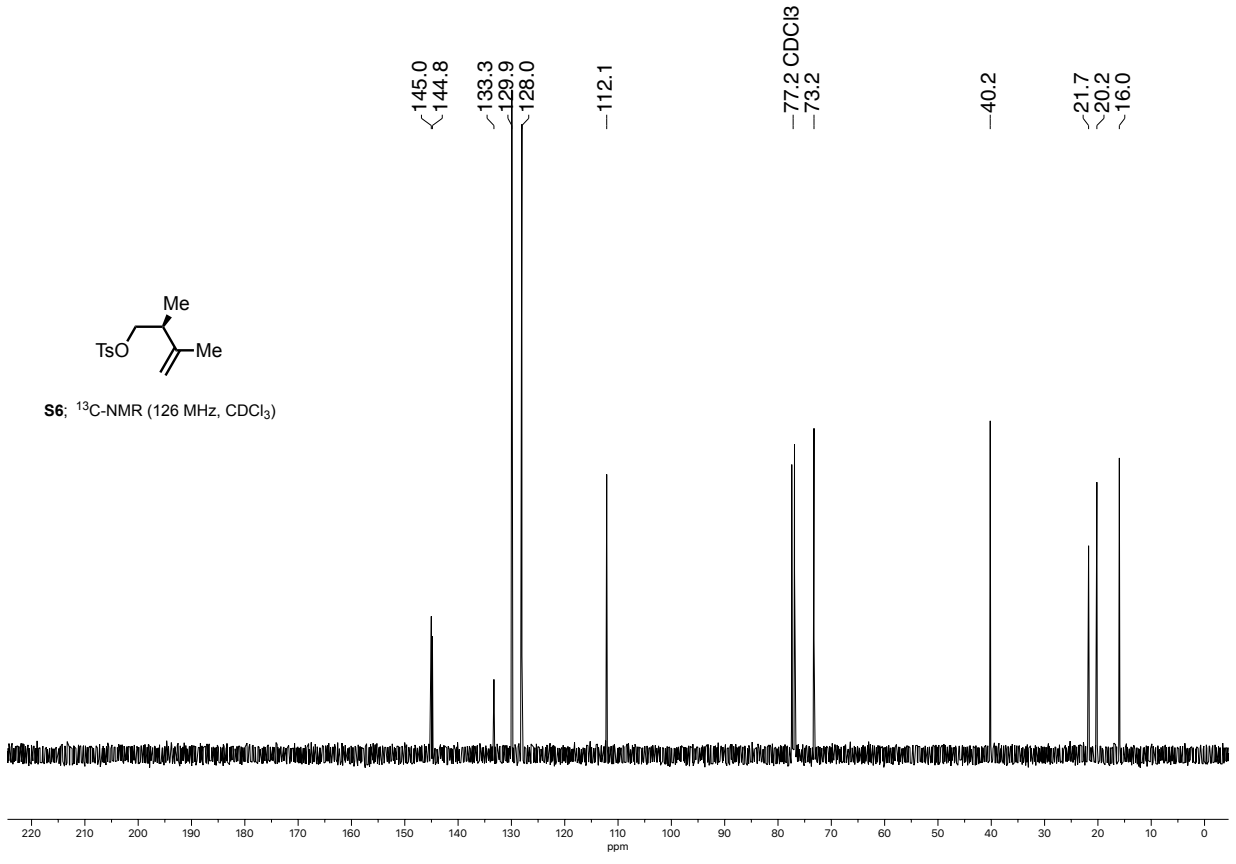
S5; ^{1}H-NMR (500 MHz, $CDCl_3$)



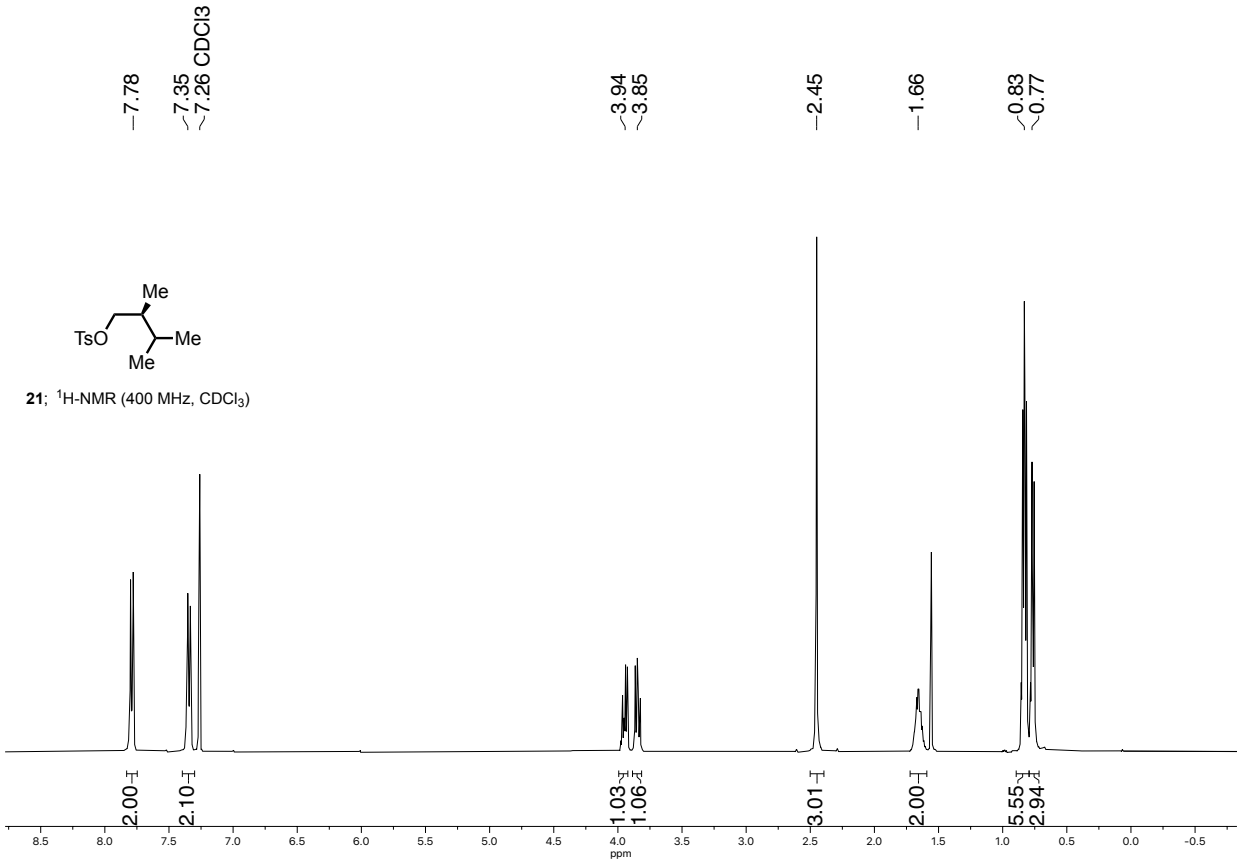
S5; ^{13}C-NMR (126 MHz, $CDCl_3$)



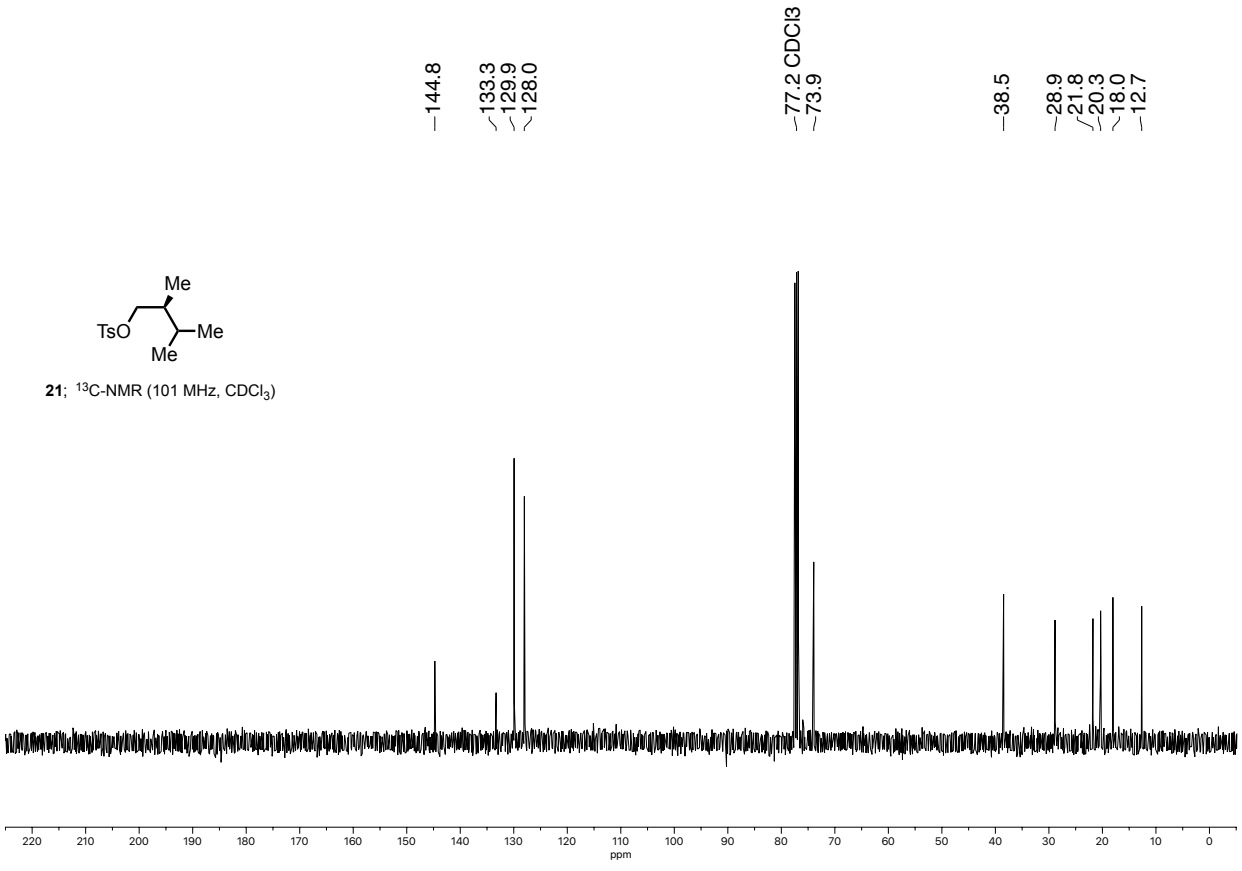
S6; ^{1}H-NMR (500 MHz, $CDCl_3$)



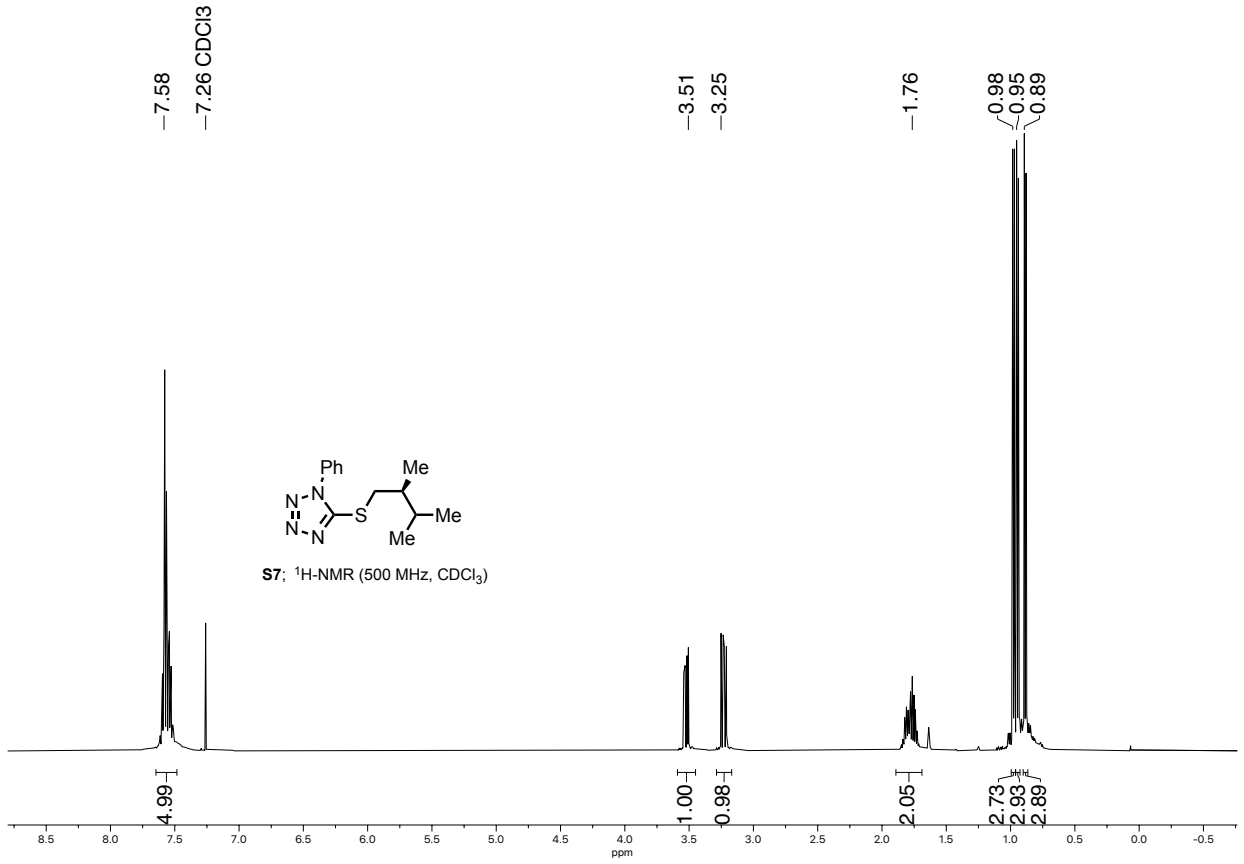
S6; ^{13}C-NMR (126 MHz, $CDCl_3$)



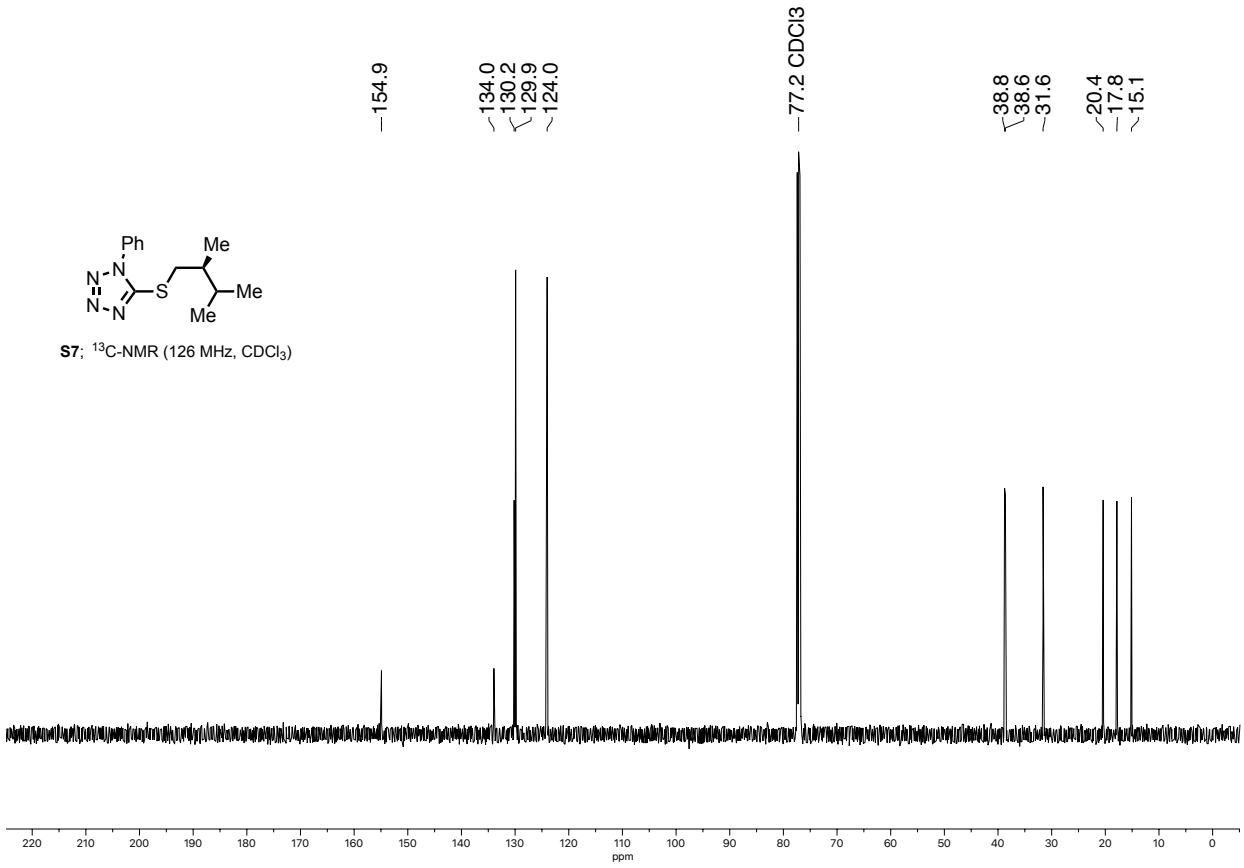
21; ^{1}H-NMR (400 MHz, $CDCl_3$)



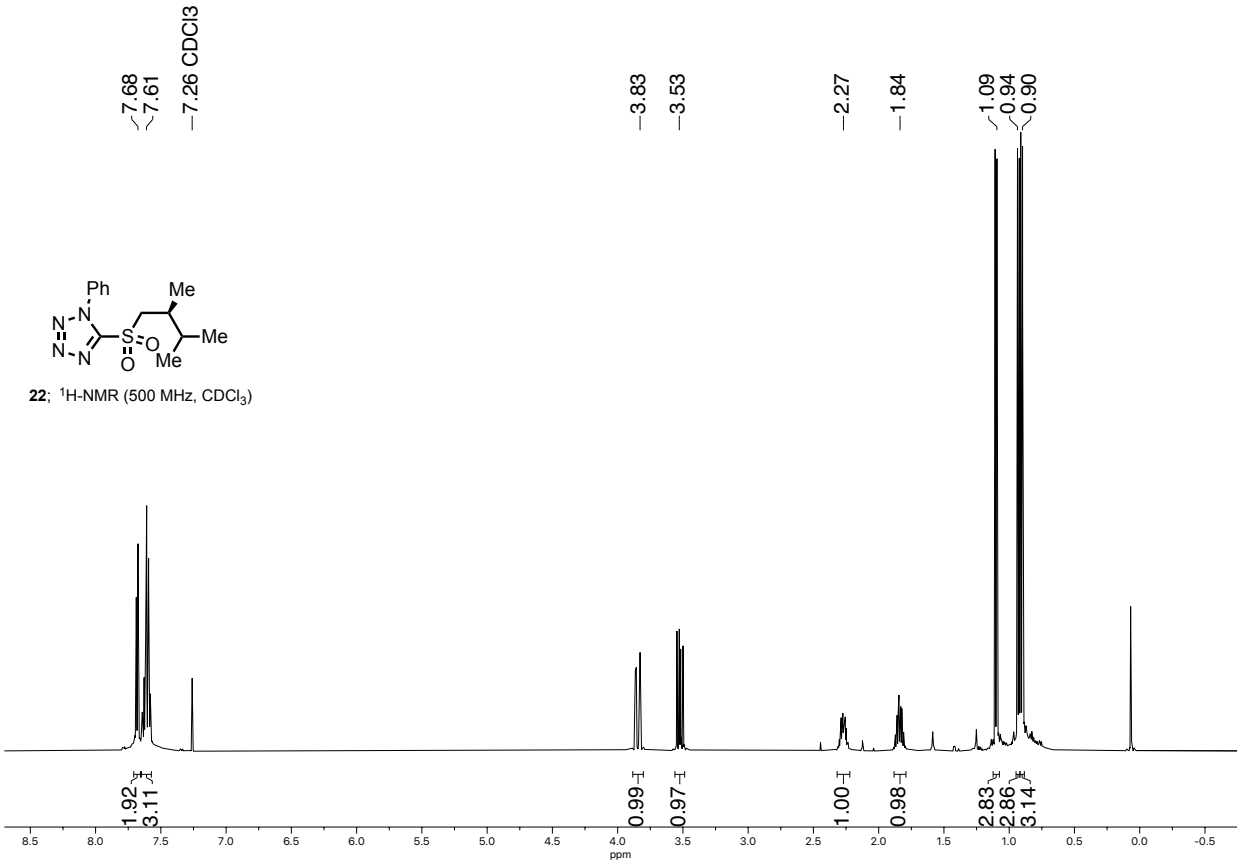
21; ^{13}C-NMR (101 MHz, $CDCl_3$)



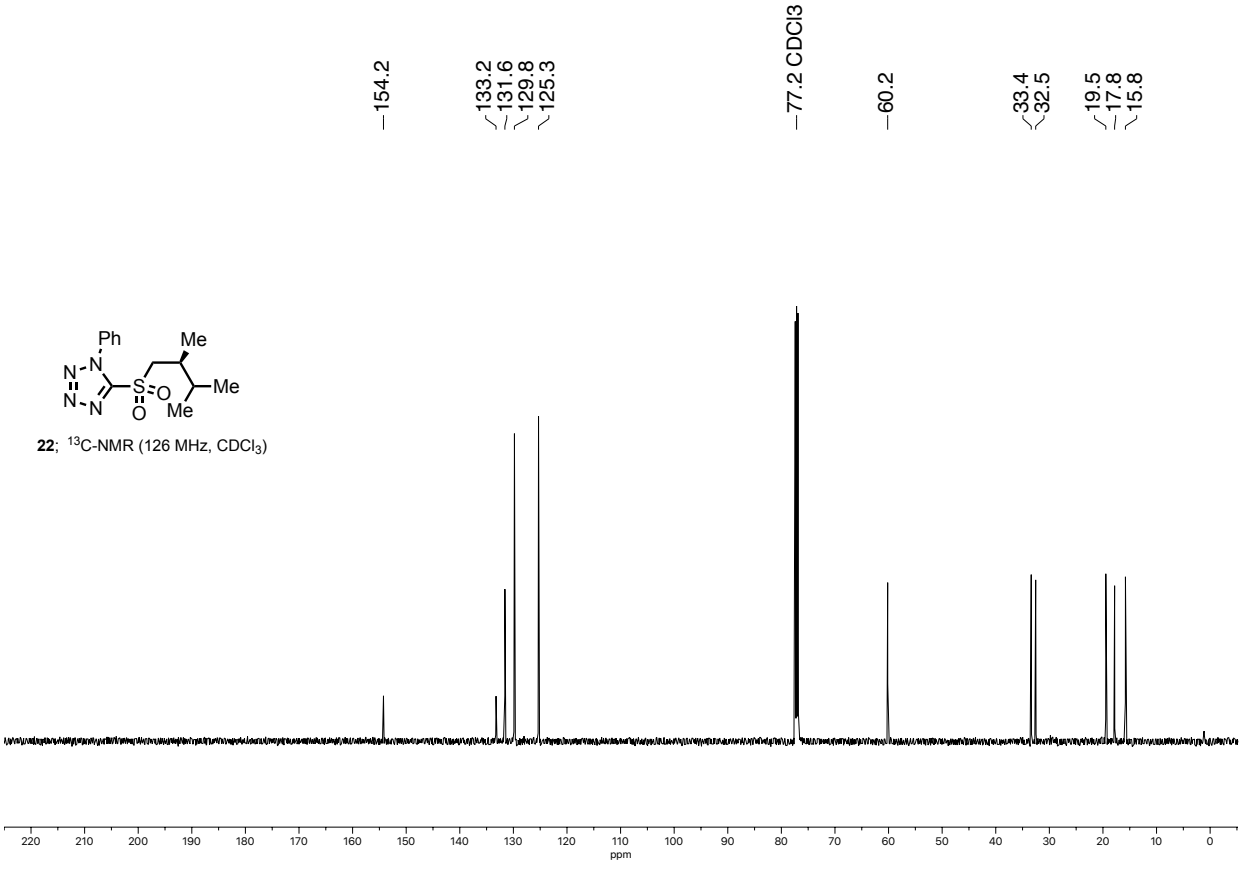
S7; ^{1}H-NMR (500 MHz, $CDCl_3$)



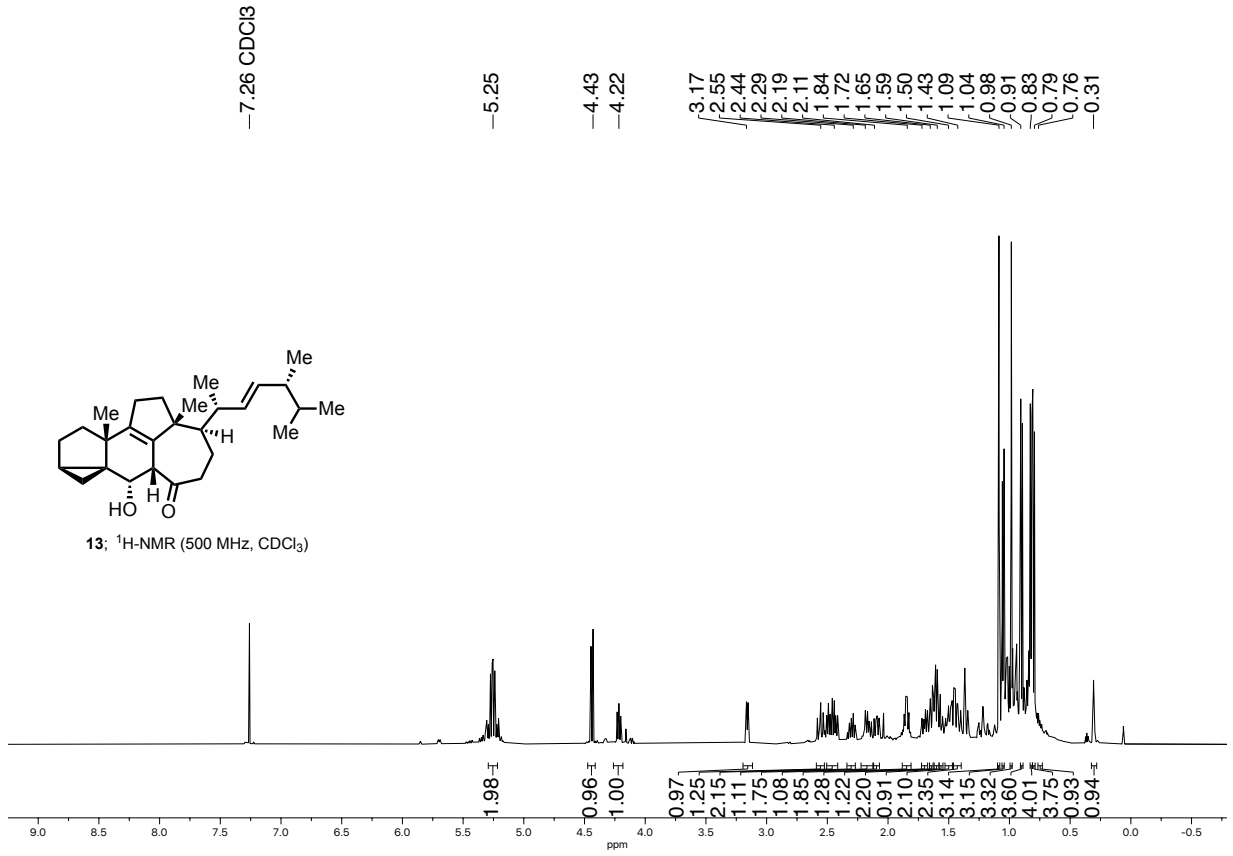
S7; ^{13}C-NMR (126 MHz, $CDCl_3$)



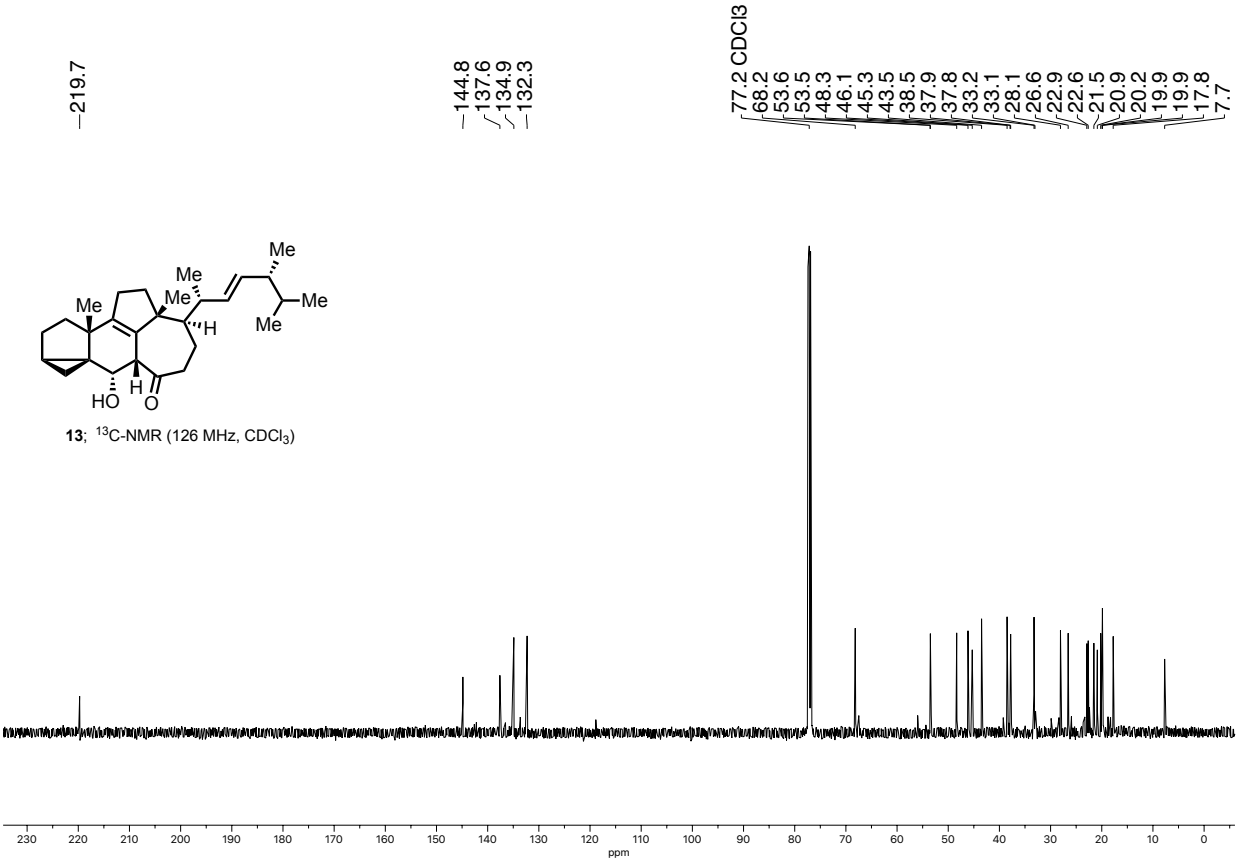
22; ^{1}H-NMR (500 MHz, $CDCl_3$)



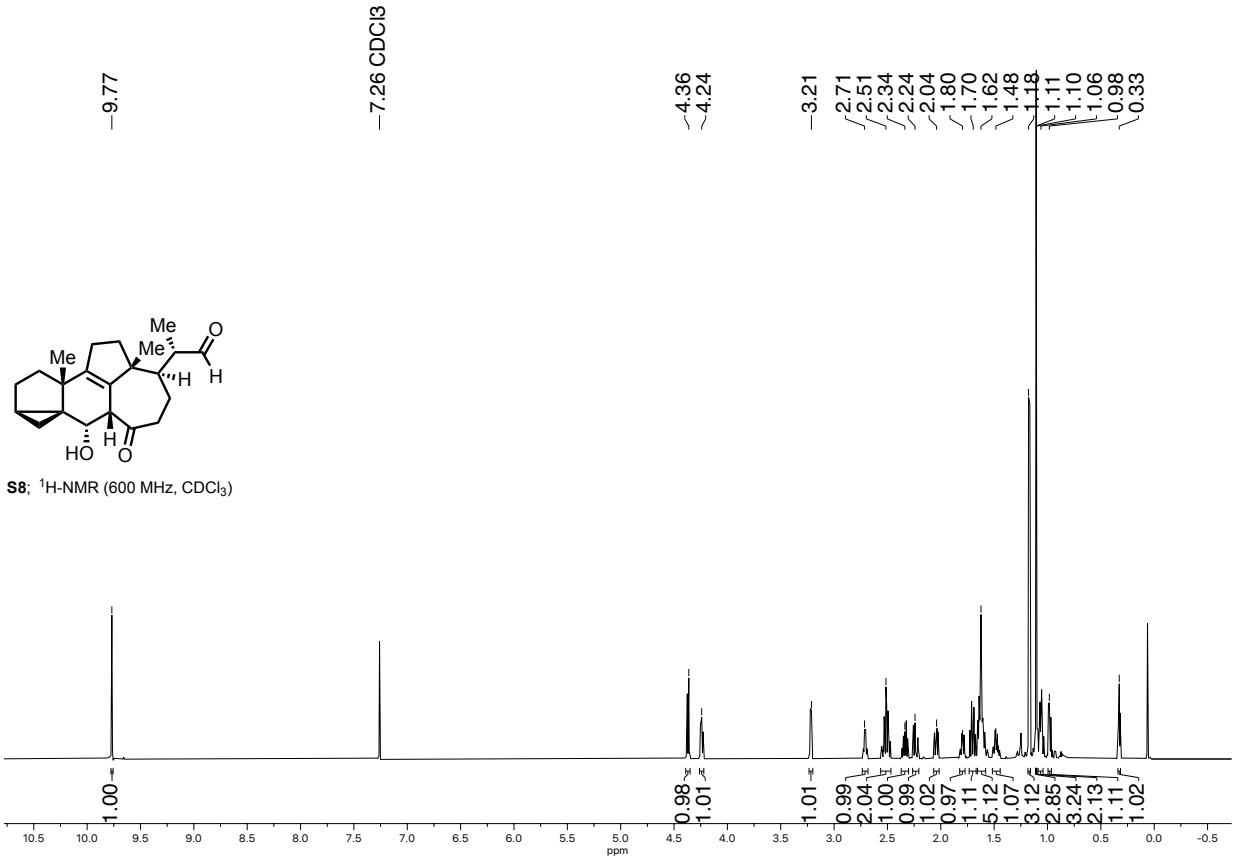
22; ^{13}C-NMR (126 MHz, $CDCl_3$)



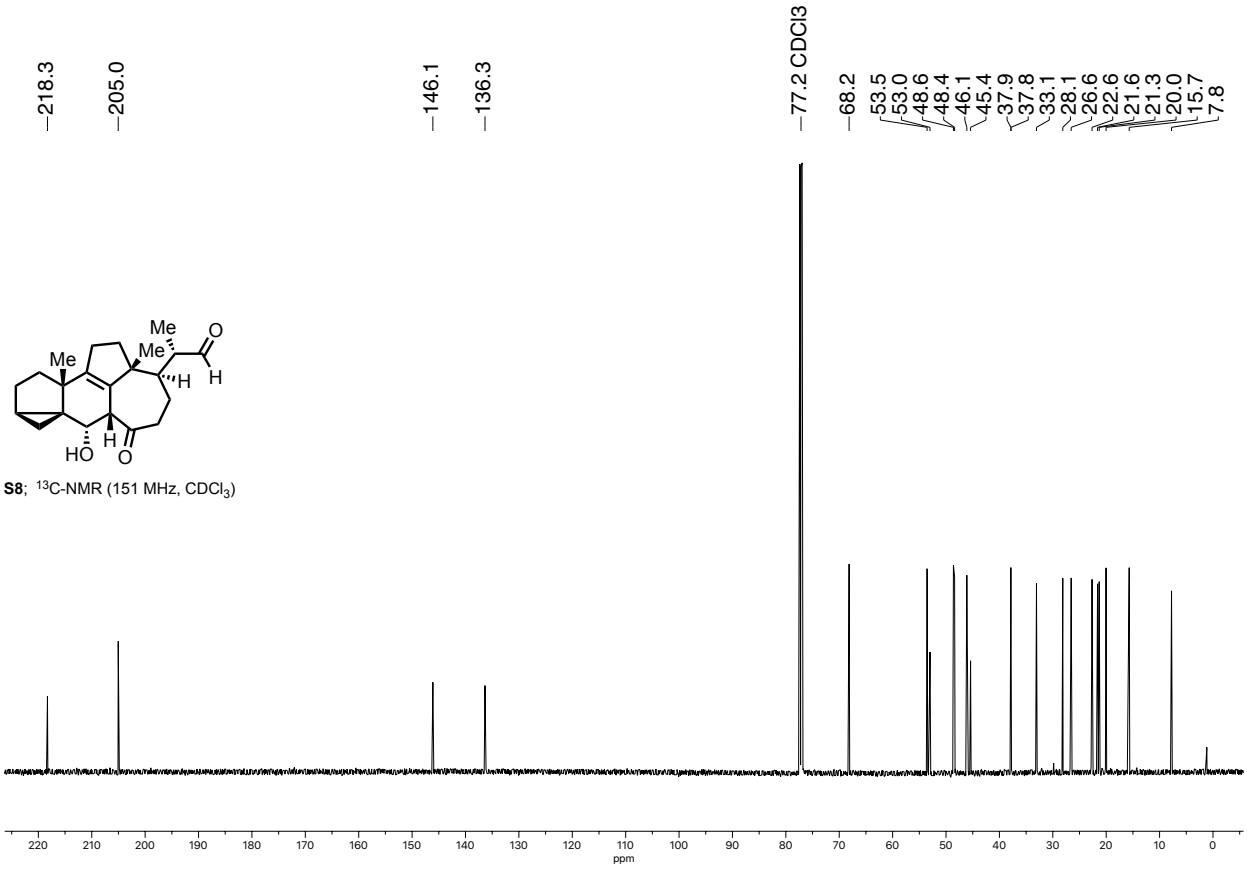
13; ^{1}H-NMR (500 MHz, $CDCl_3$)



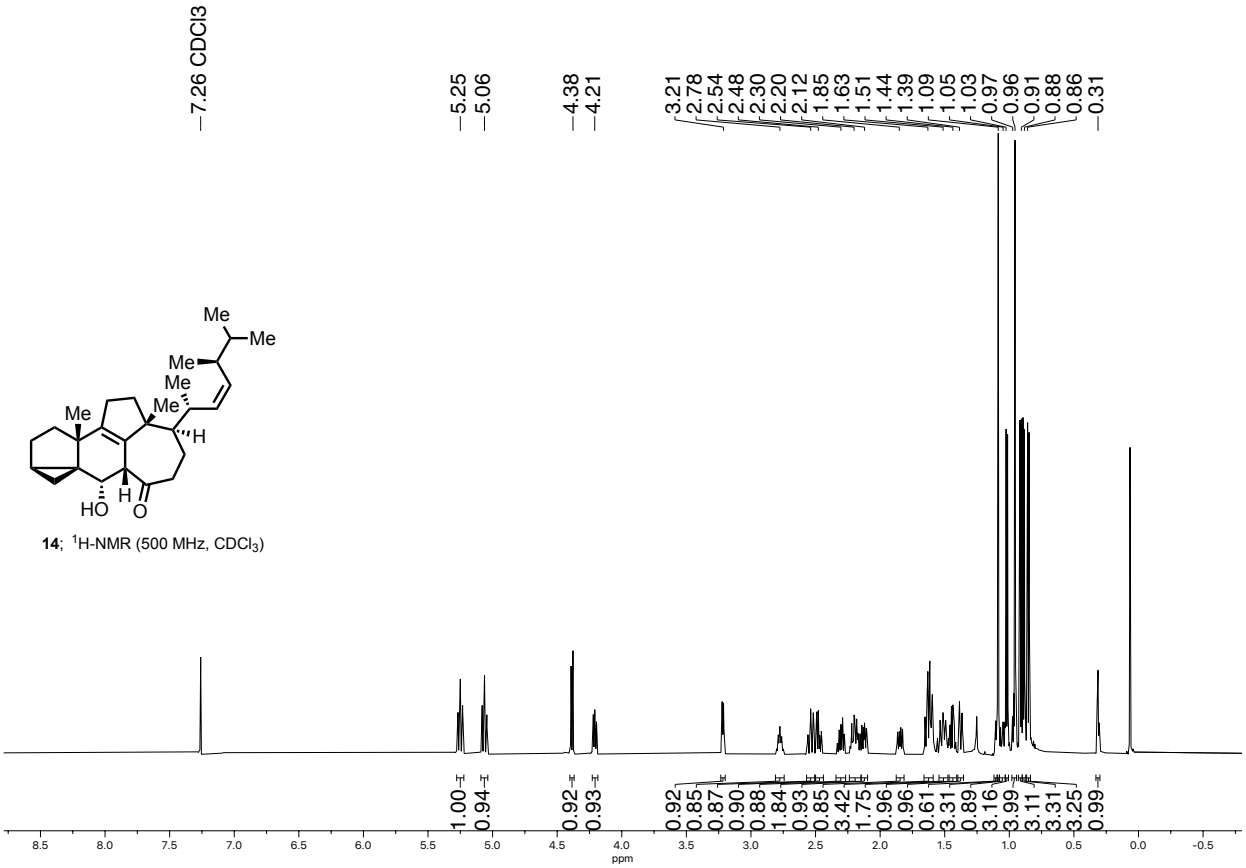
13; ^{13}C-NMR (126 MHz, $CDCl_3$)



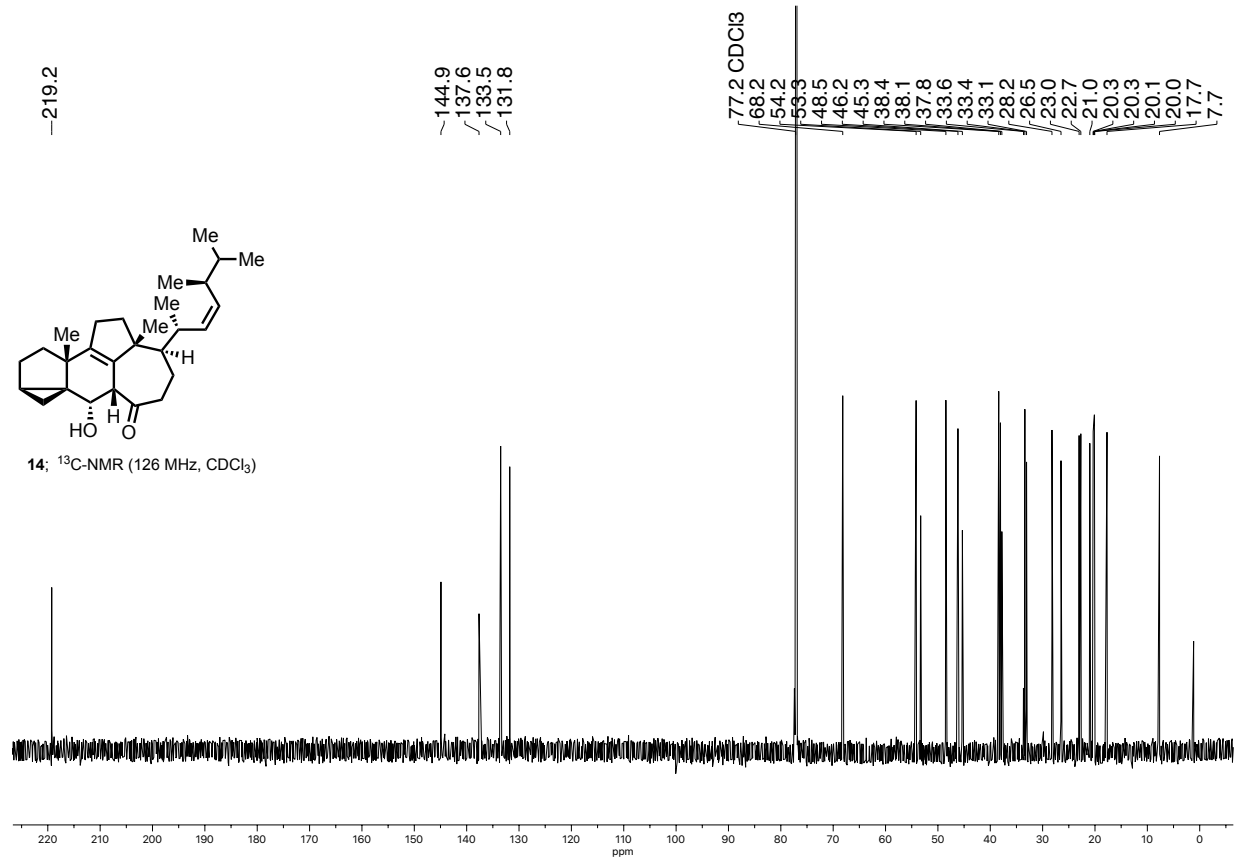
S8; ^{1}H-NMR (600 MHz, $CDCl_3$)



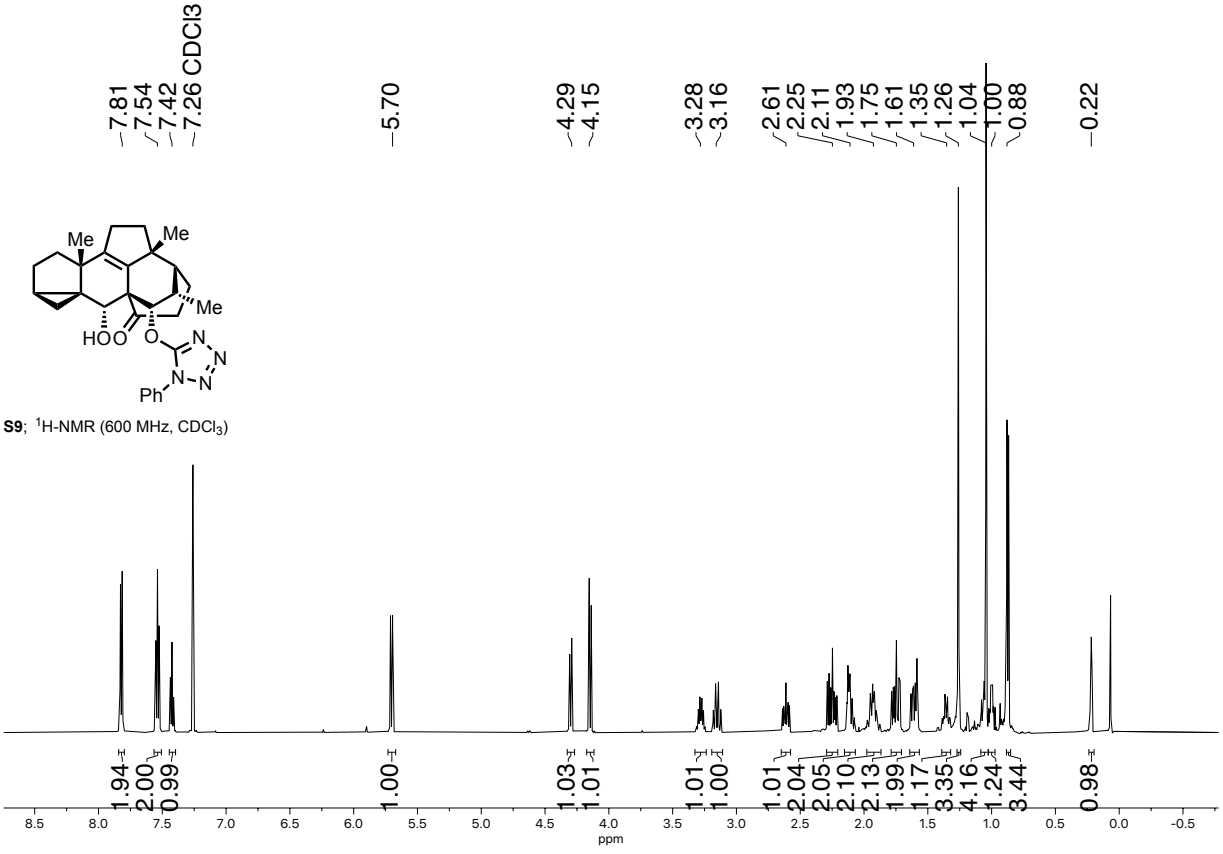
S8; ^{13}C-NMR (151 MHz, $CDCl_3$)



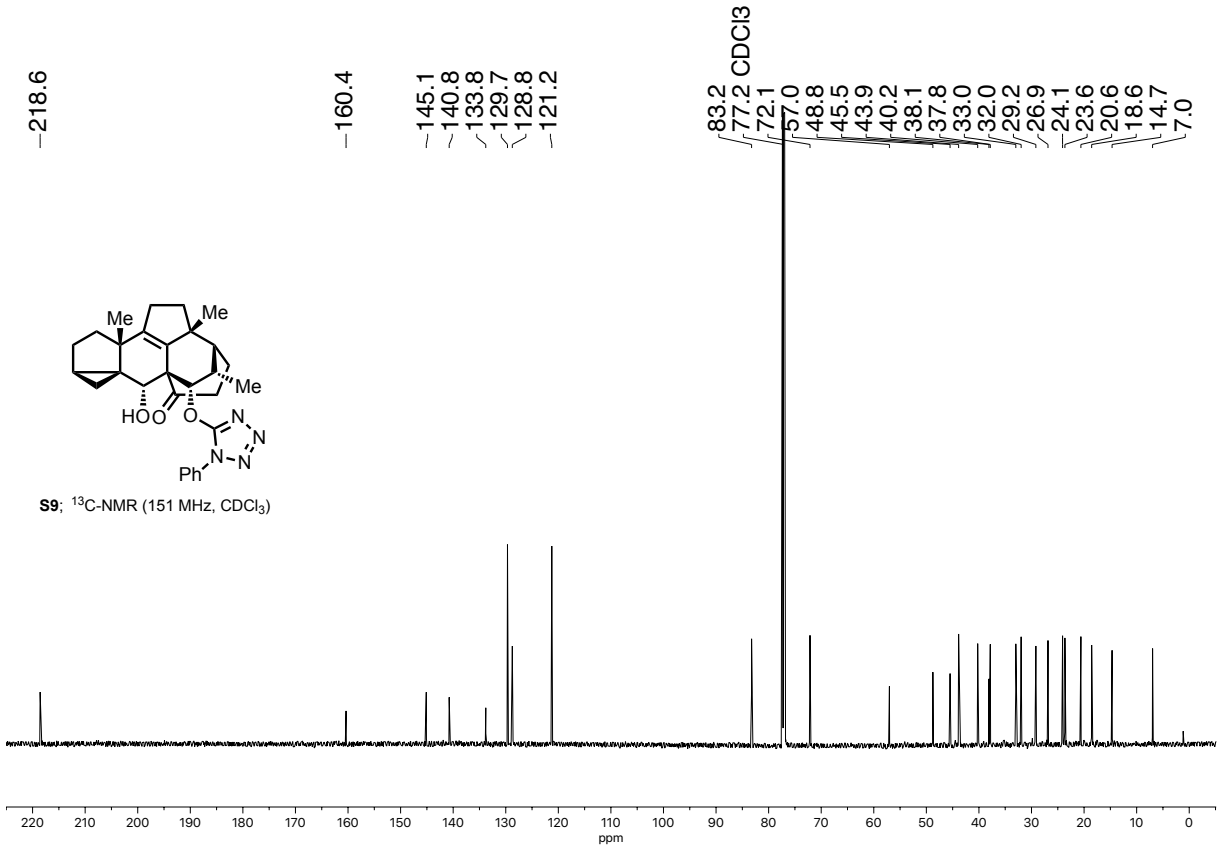
14; ^{1}H-NMR (500 MHz, $CDCl_3$)



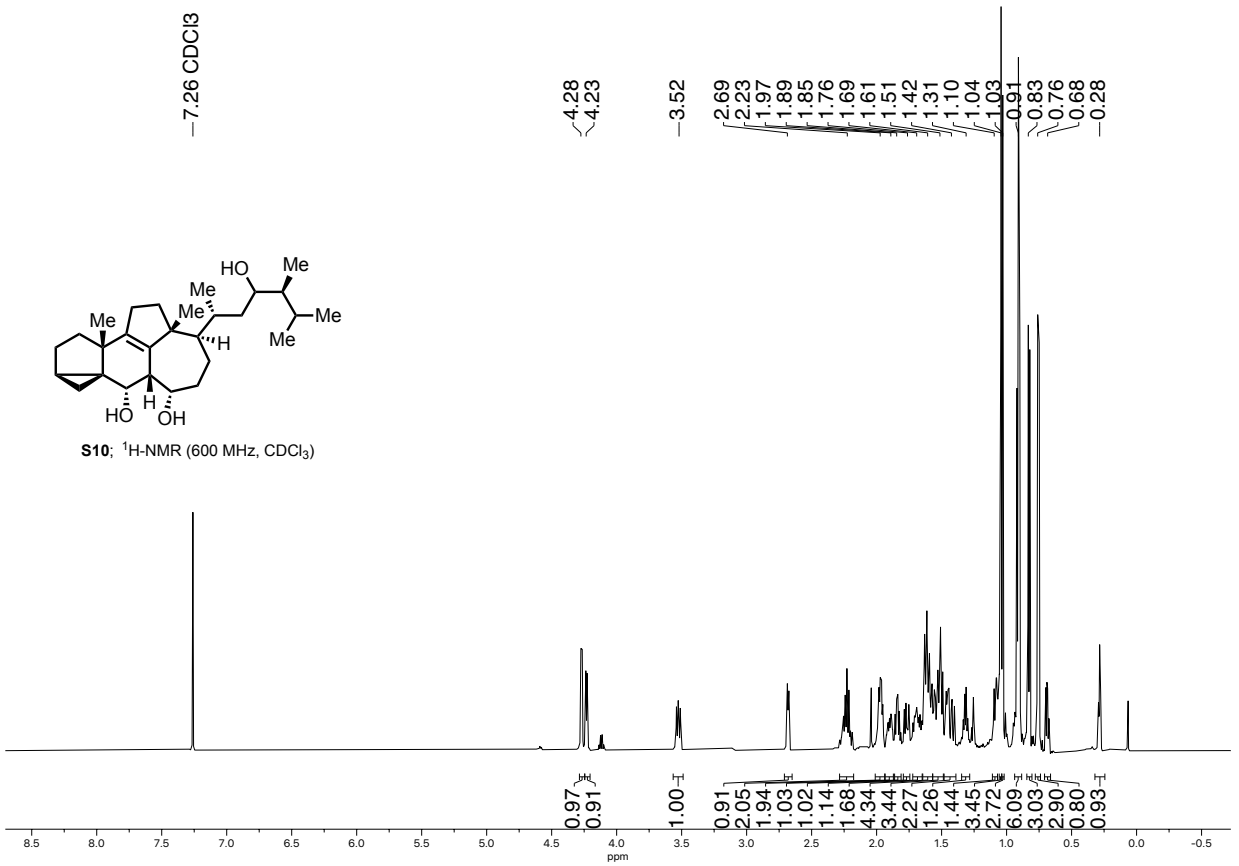
14; ^{13}C-NMR (126 MHz, $CDCl_3$)



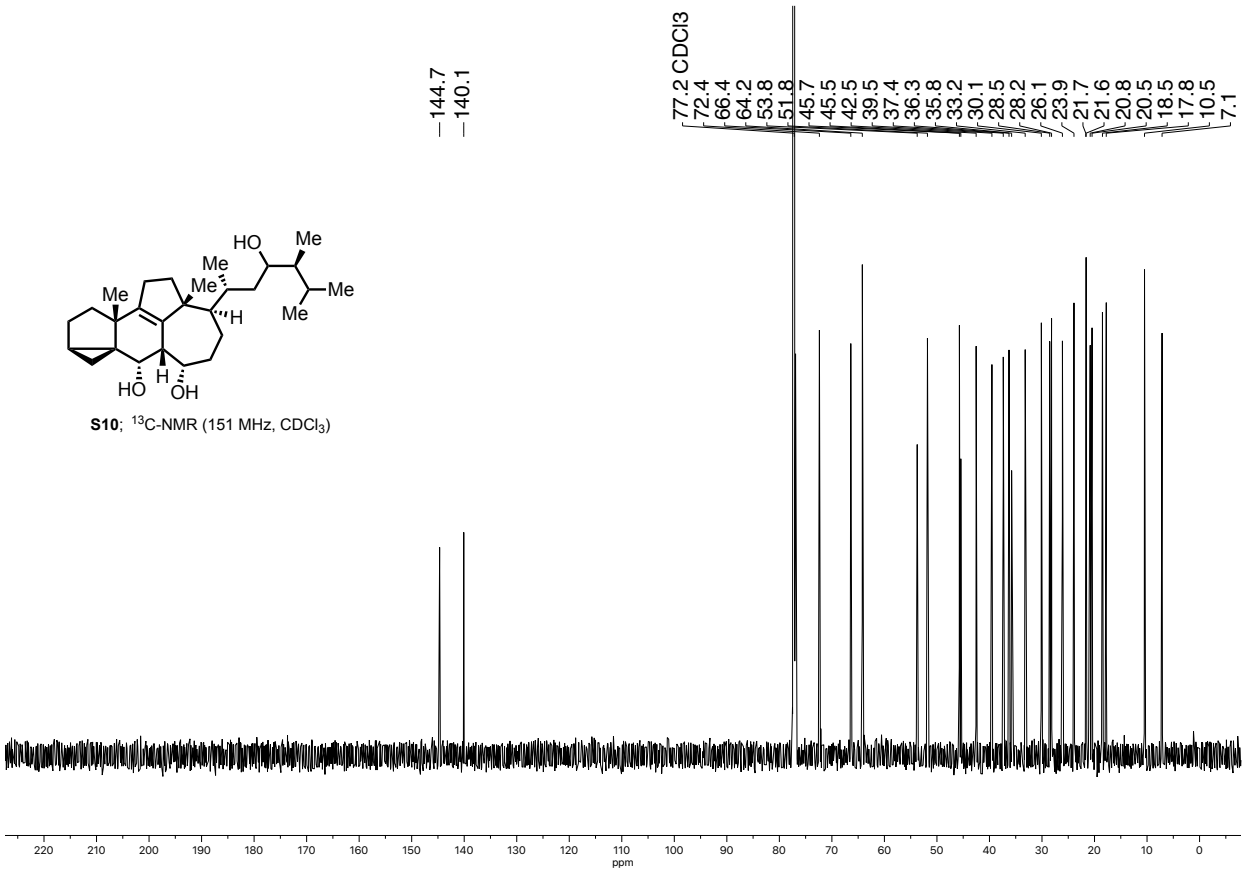
S9; ^{1}H-NMR (600 MHz, $CDCl_3$)



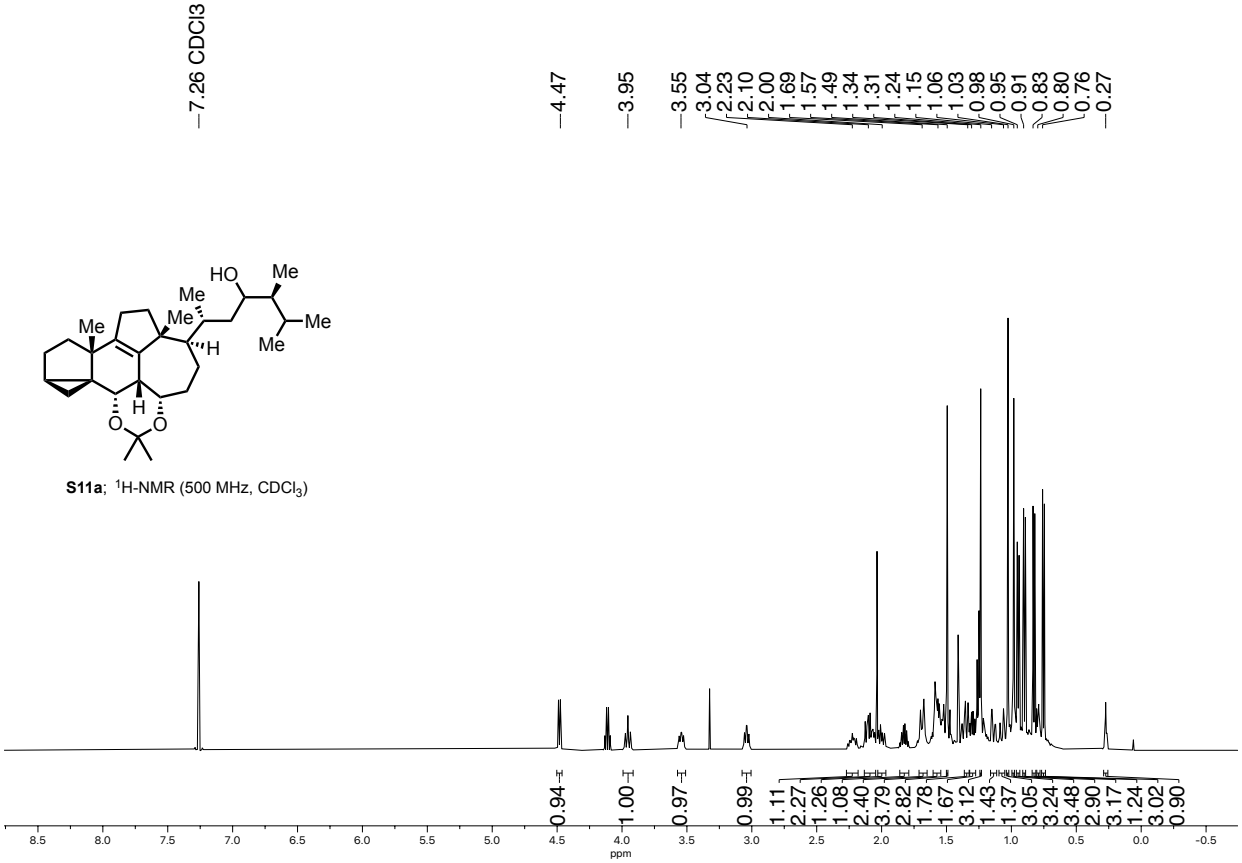
S9; ^{13}C-NMR (151 MHz, $CDCl_3$)



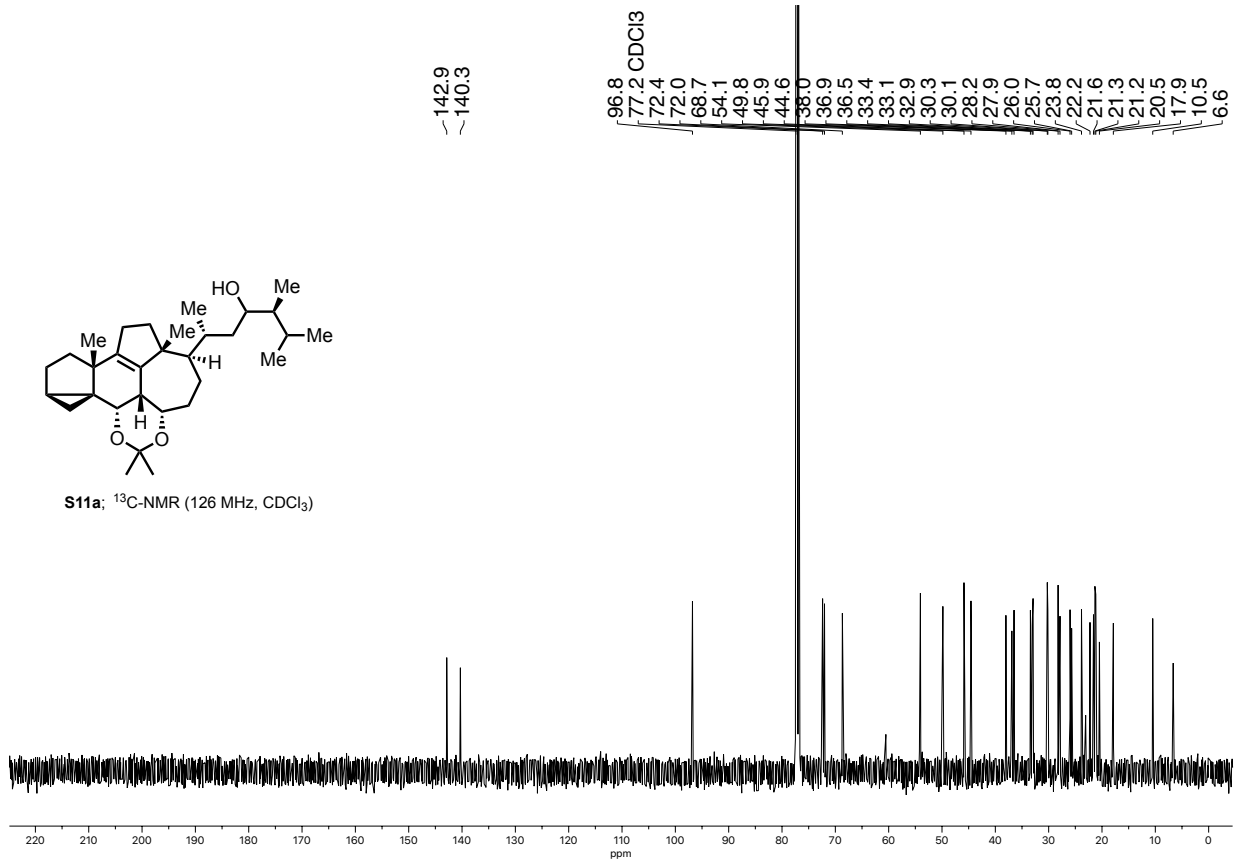
S10; ^{1}H-NMR (600 MHz, $CDCl_3$)



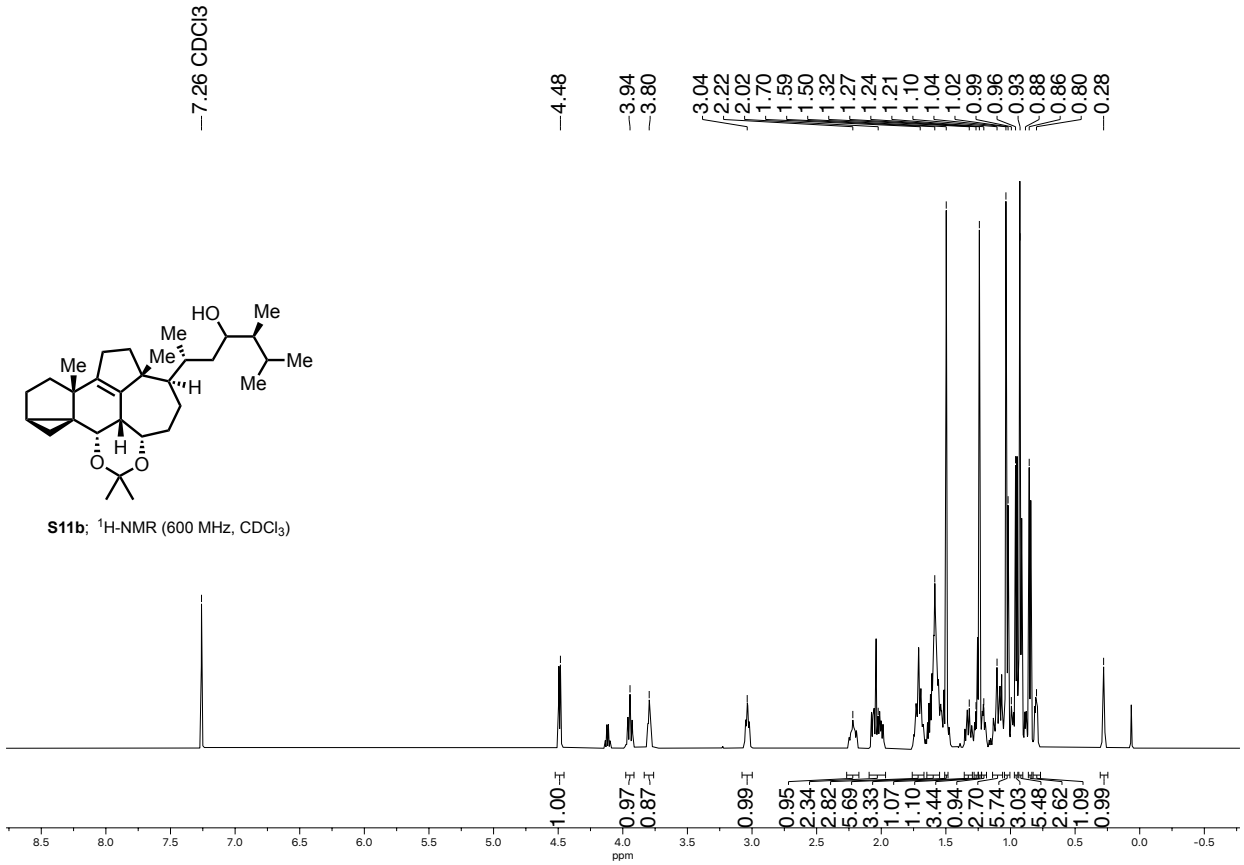
S10; ^{13}C-NMR (151 MHz, $CDCl_3$)



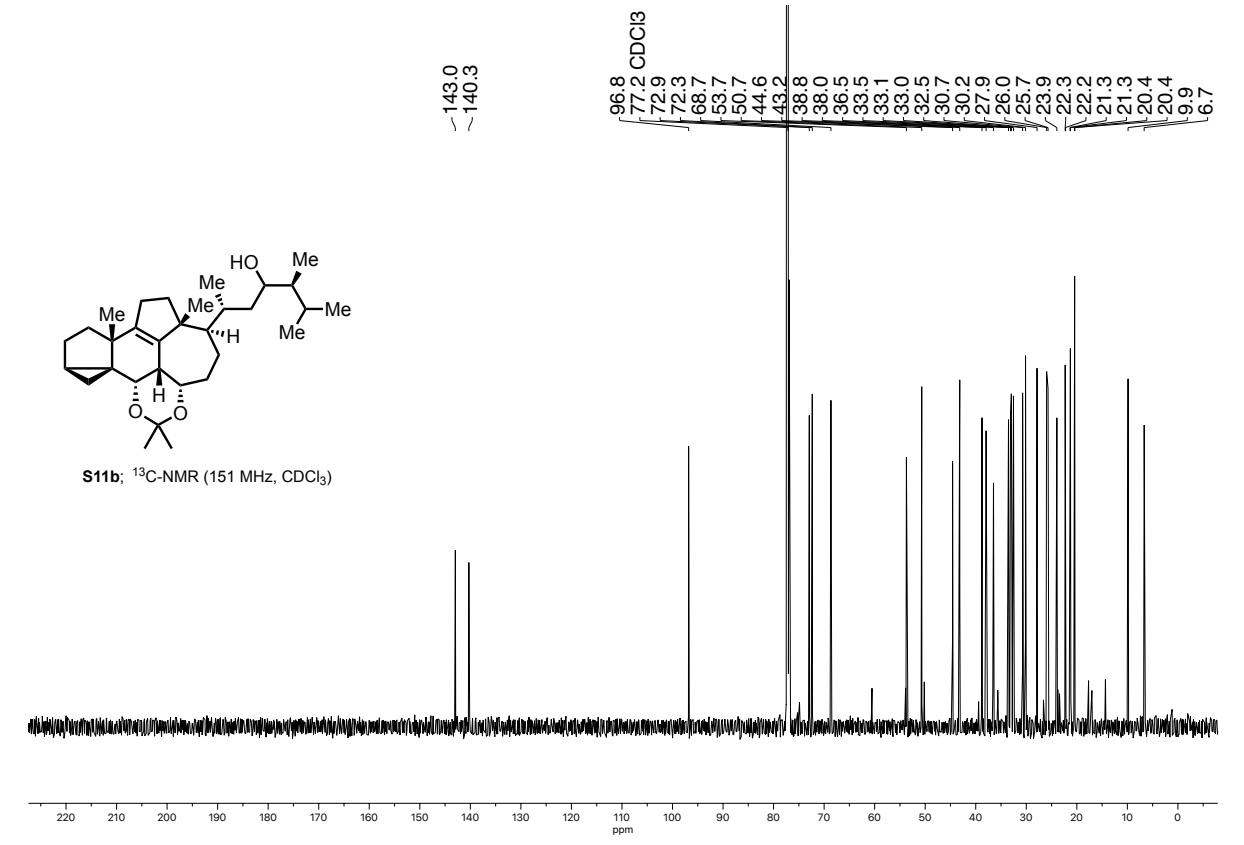
S11a; ^{1}H-NMR (500 MHz, $CDCl_3$)



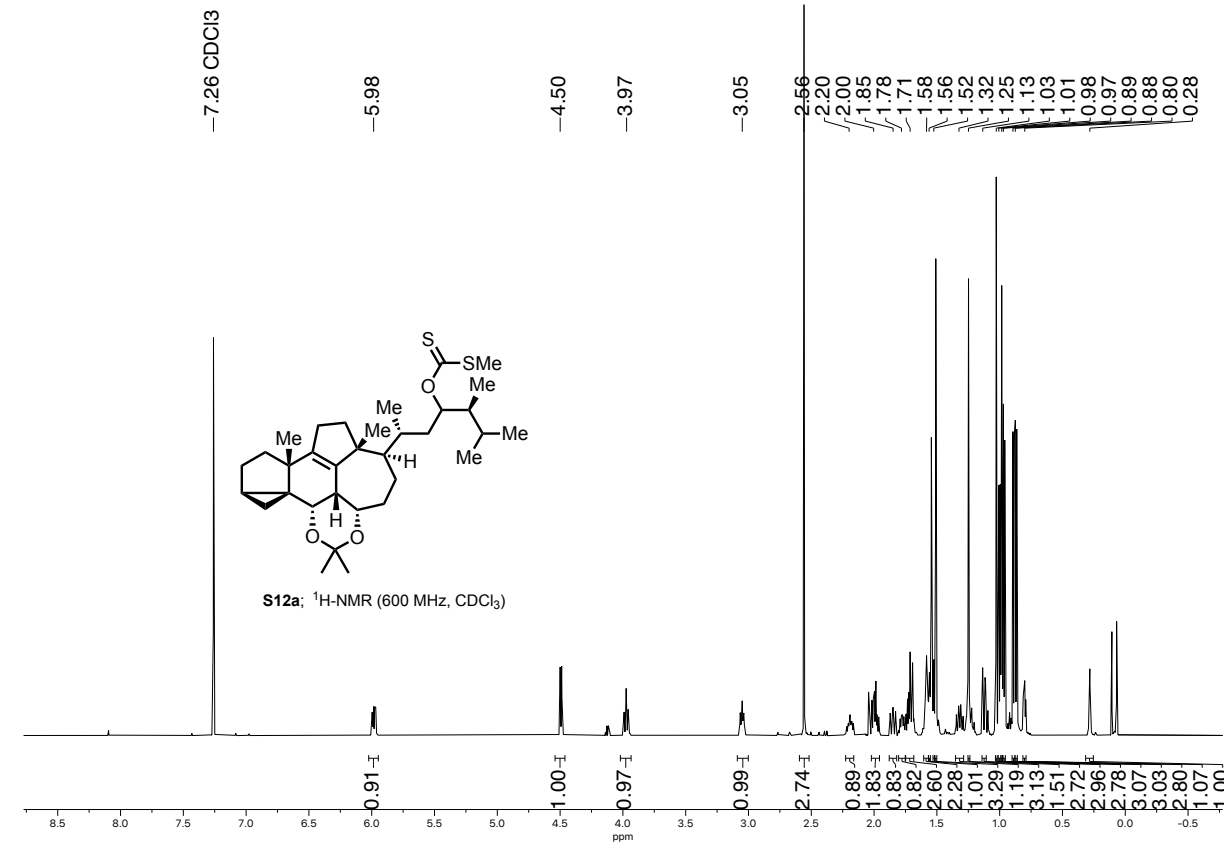
S11a; ^{13}C-NMR (126 MHz, $CDCl_3$)



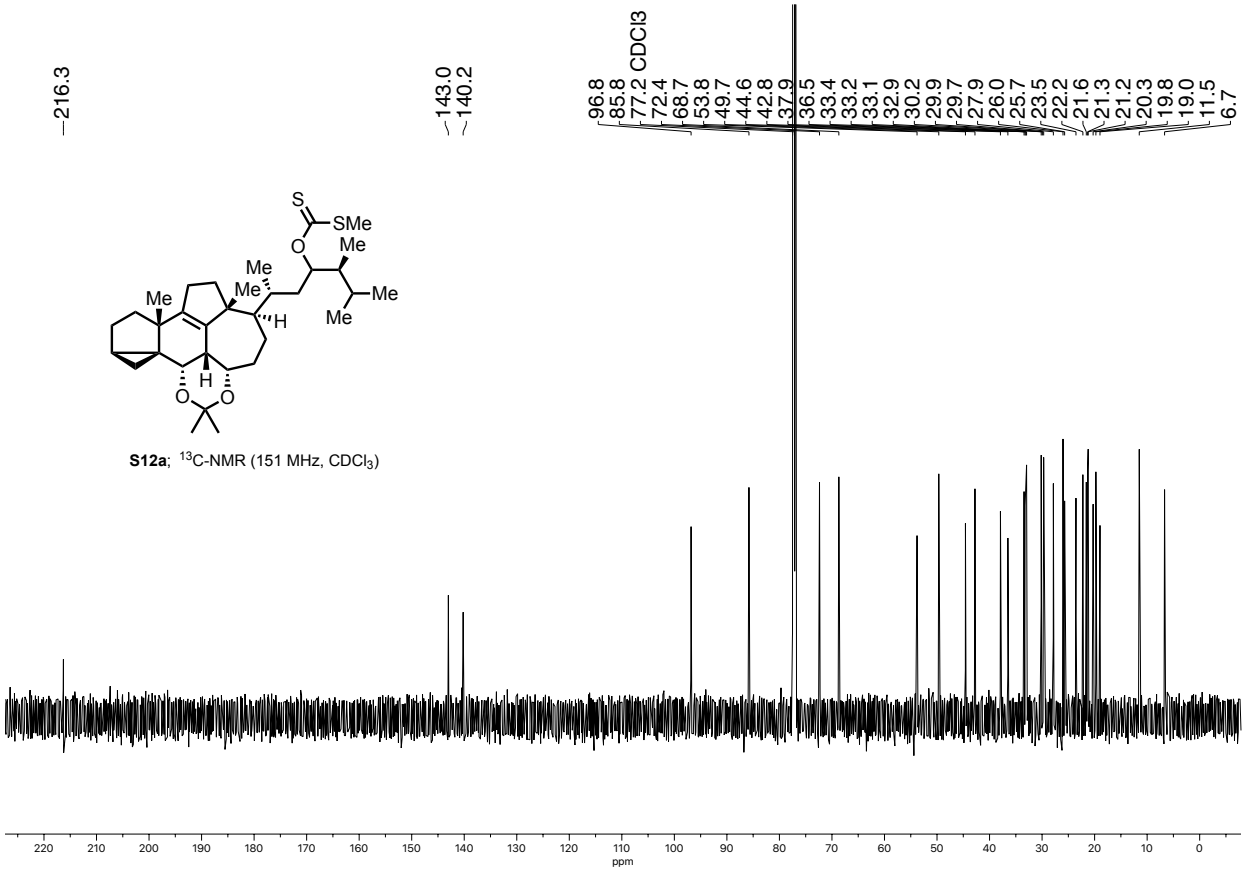
S11b; ^{1}H-NMR (600 MHz, $CDCl_3$)



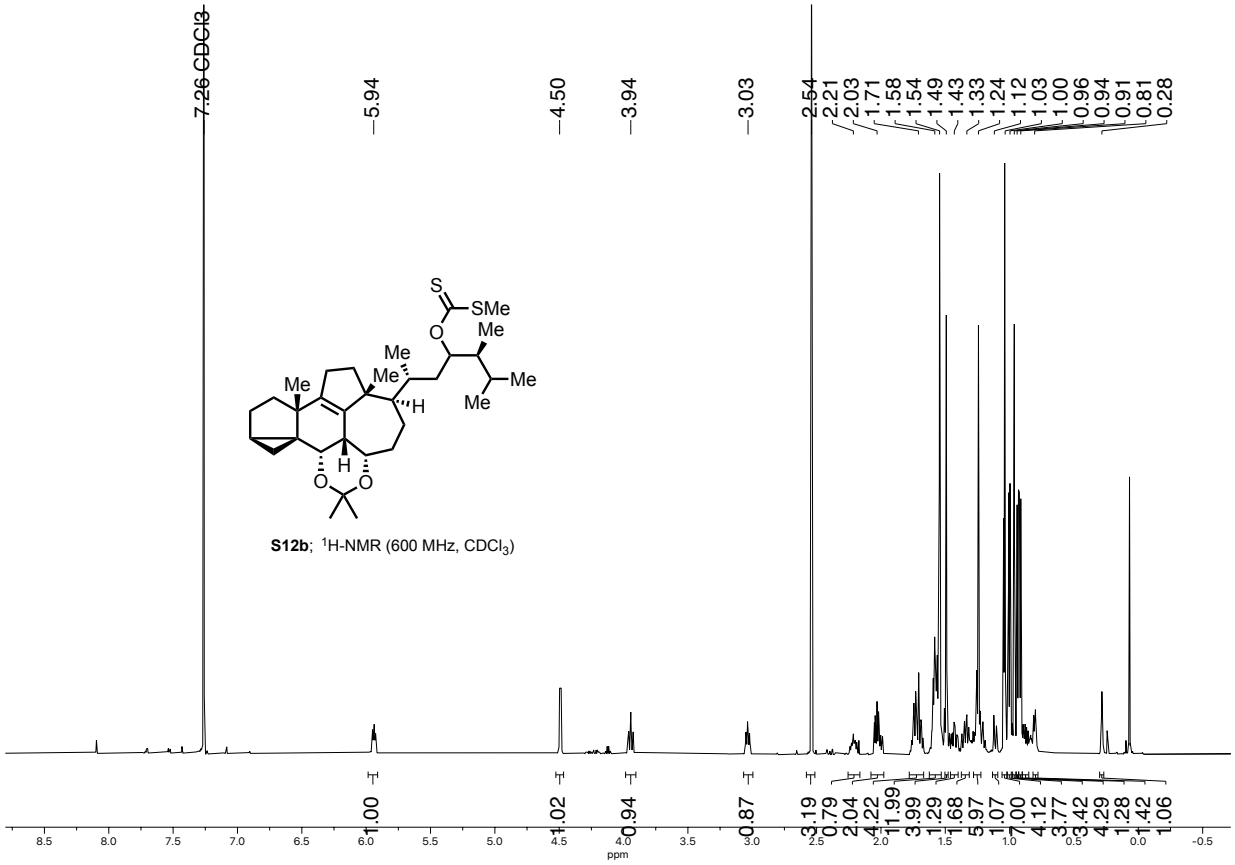
S11b; ^{13}C-NMR (151 MHz, $CDCl_3$)



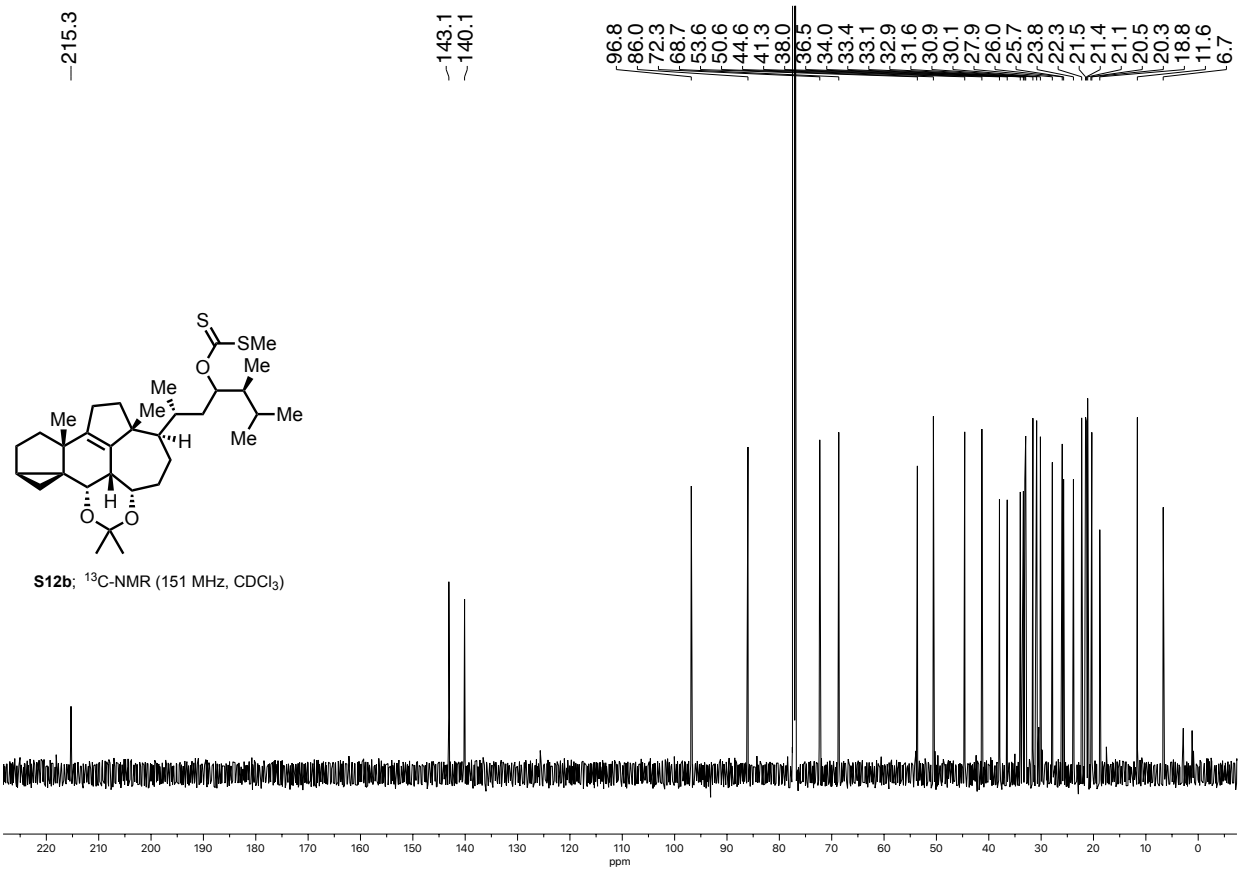
S12a; ^{1}H-NMR (600 MHz, $CDCl_3$)



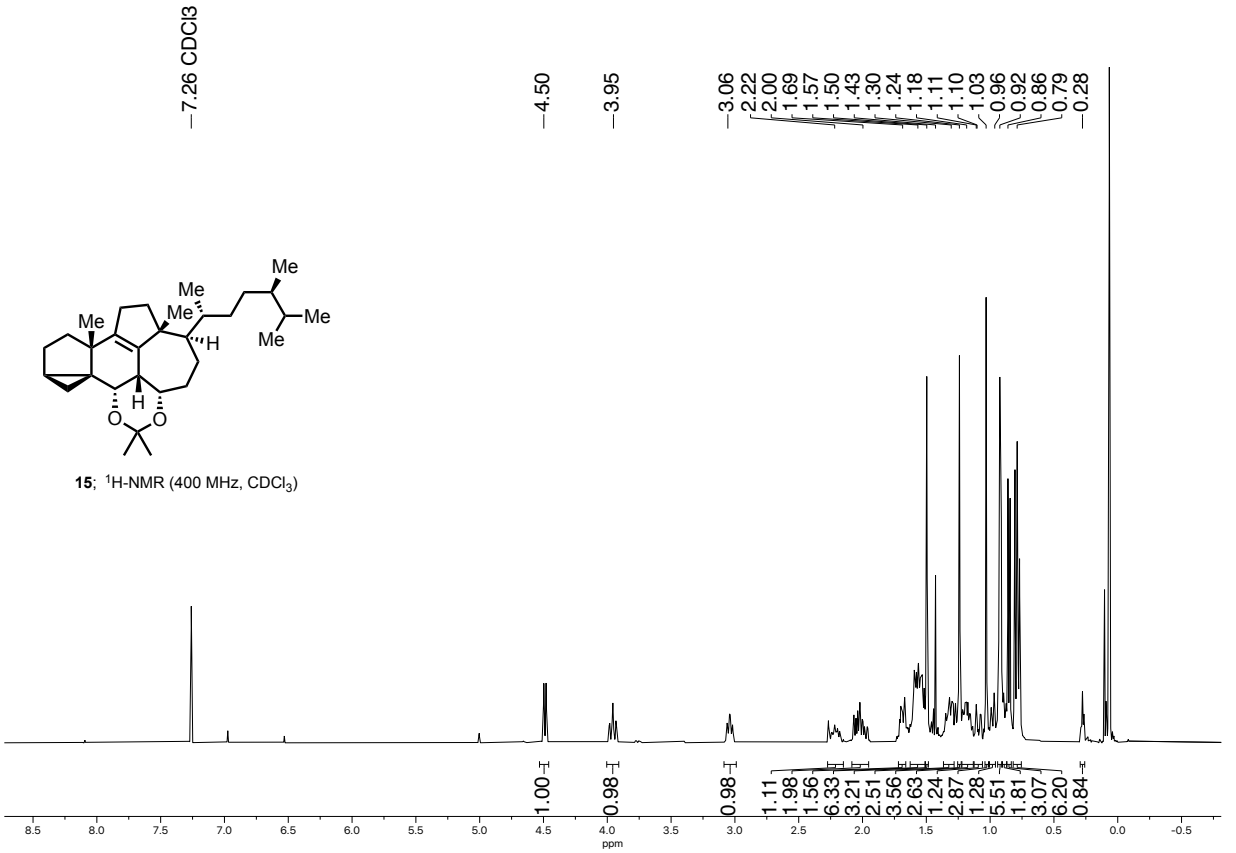
S12a; ^{13}C-NMR (151 MHz, $CDCl_3$)



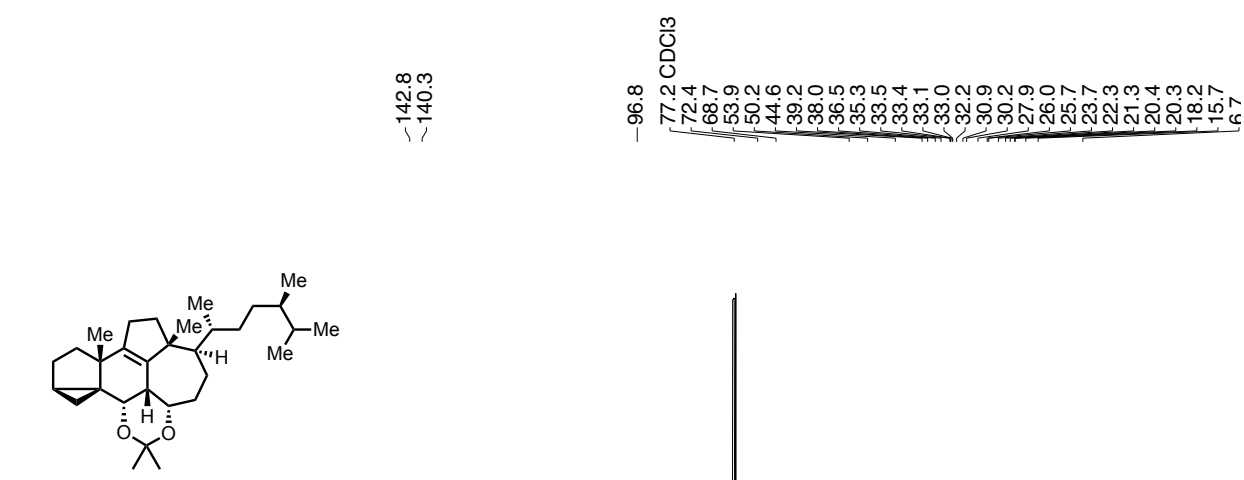
S12b; ^{1}H-NMR (600 MHz, $CDCl_3$)



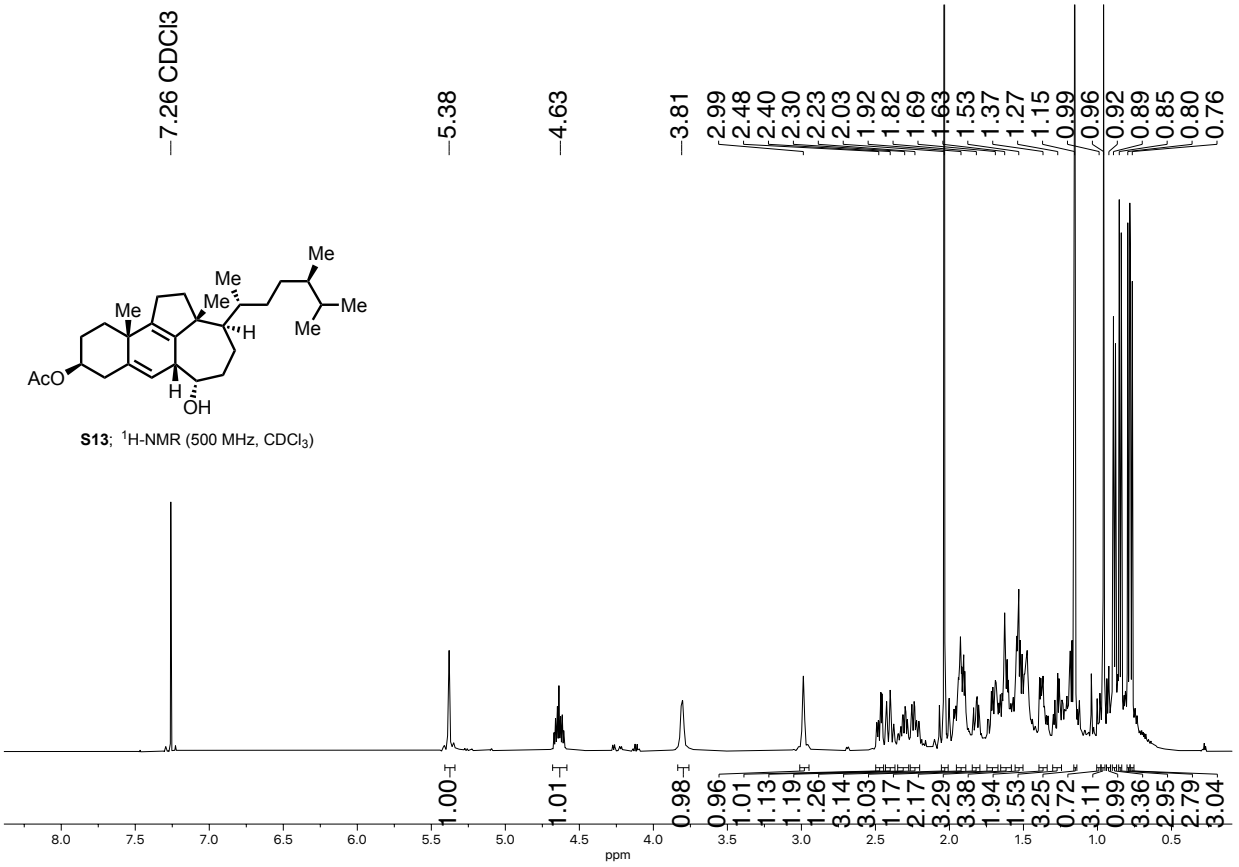
S12b; ^{13}C-NMR (151 MHz, $CDCl_3$)



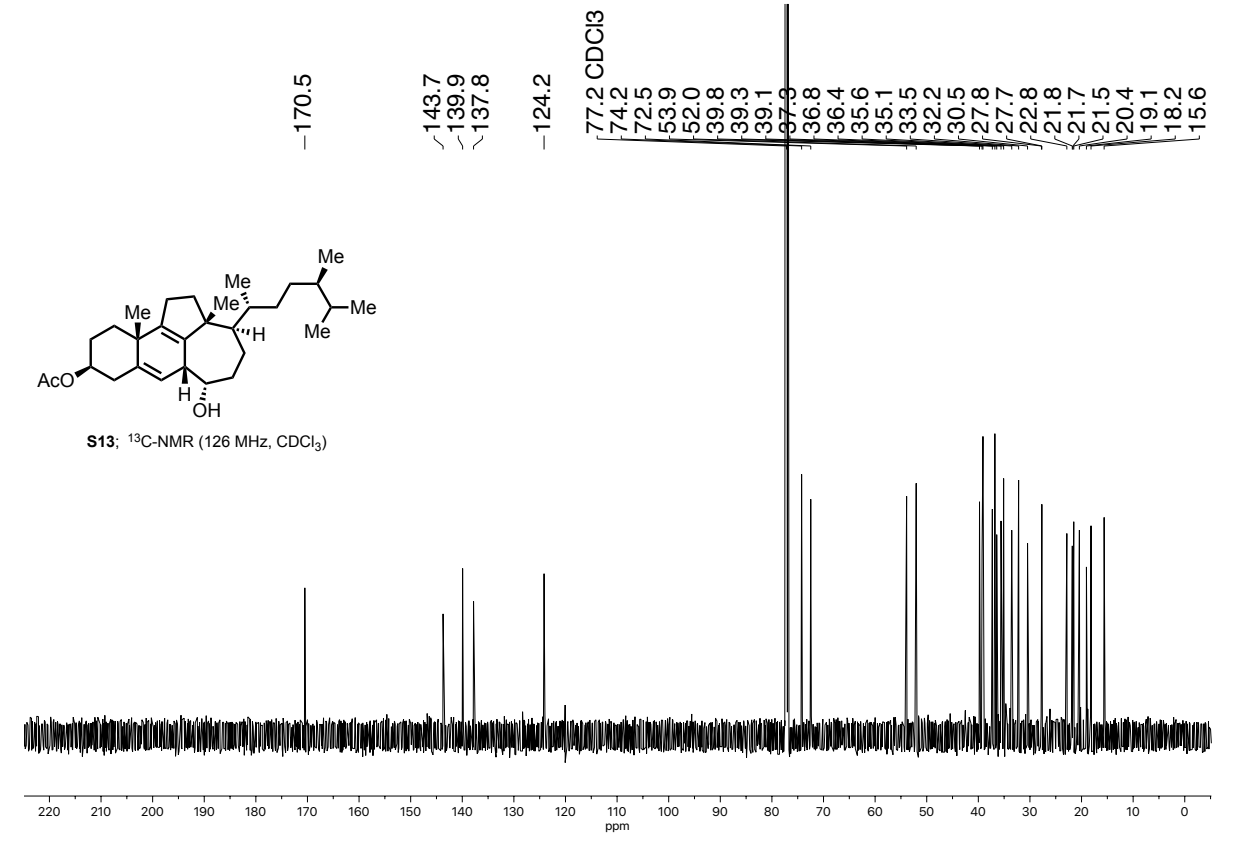
15; ^{1}H-NMR (400 MHz, $CDCl_3$)



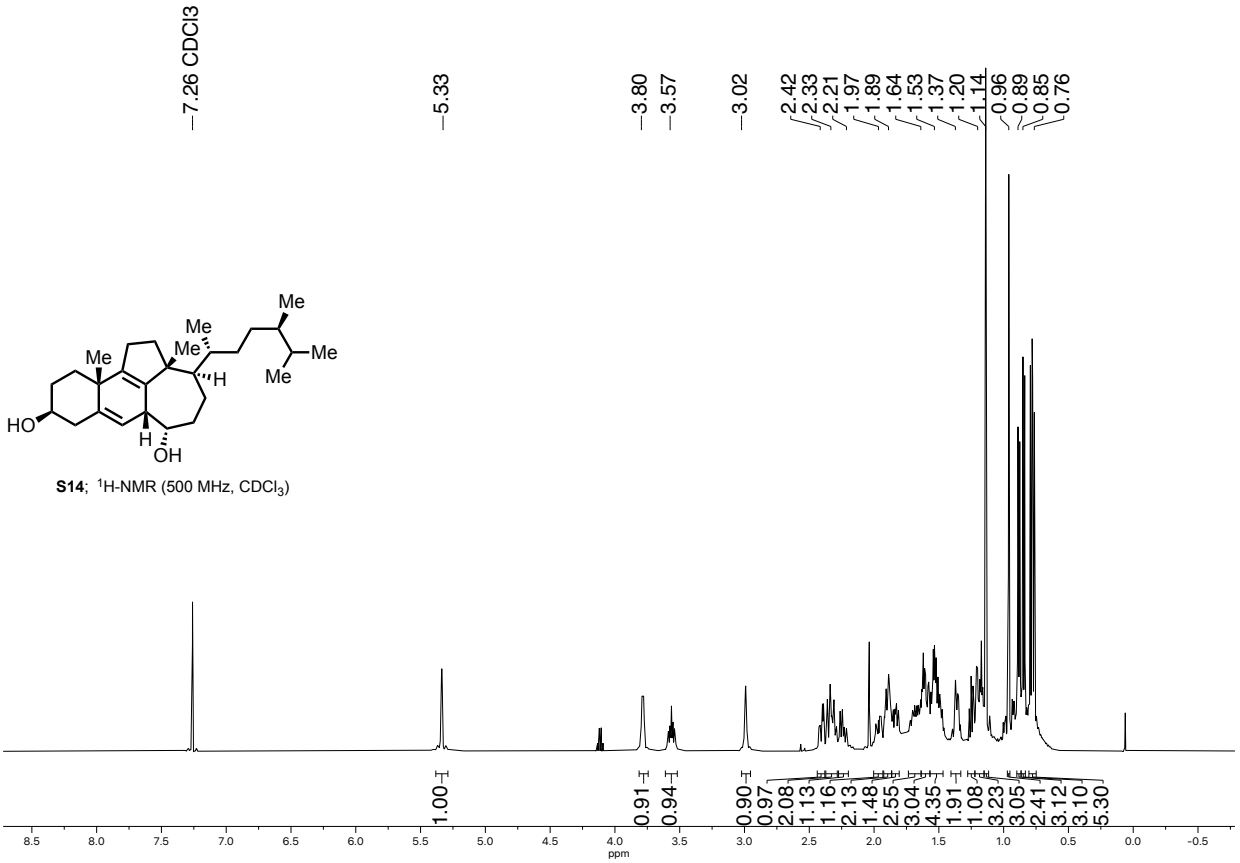
15; ^{13}C-NMR (101 MHz, $CDCl_3$)



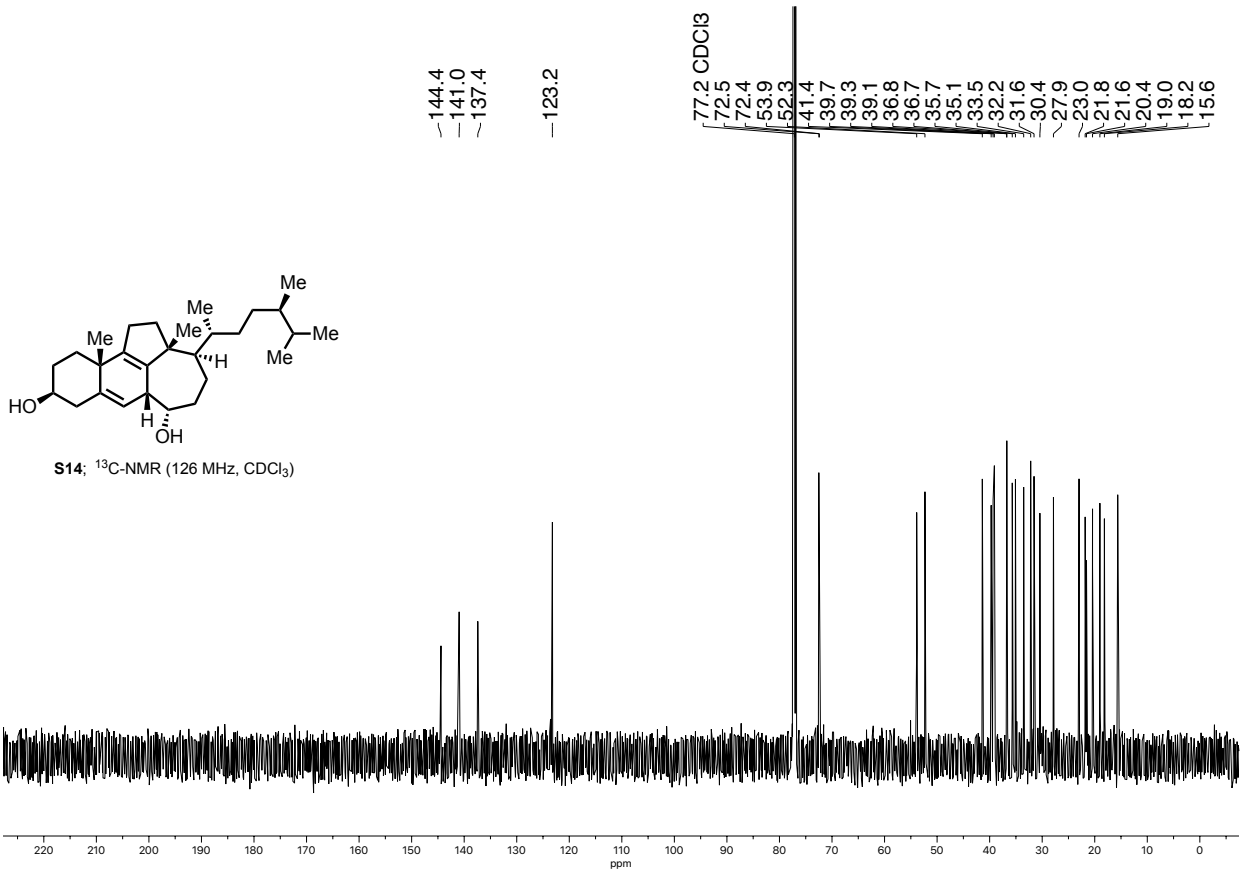
S13; ^{1}H-NMR (500 MHz, $CDCl_3$)



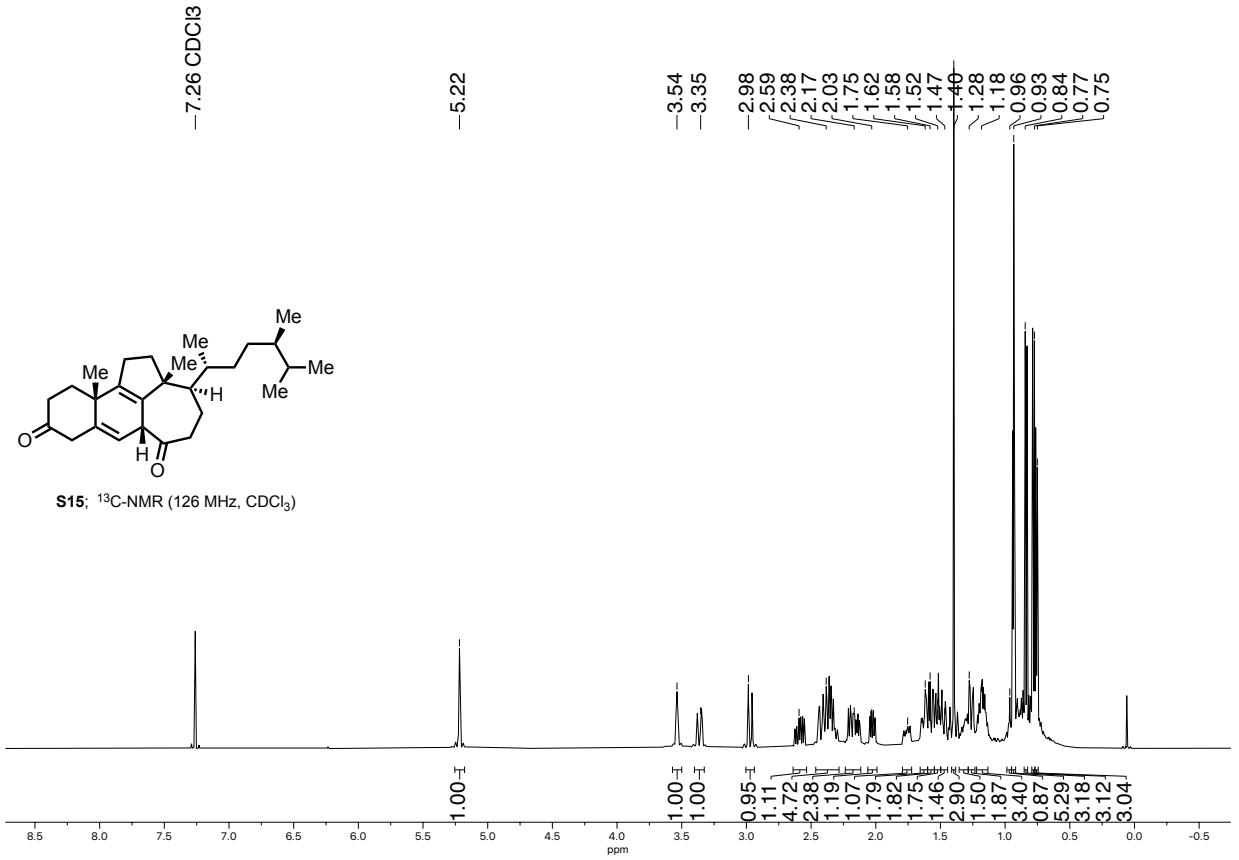
S13; ^{13}C-NMR (126 MHz, $CDCl_3$)



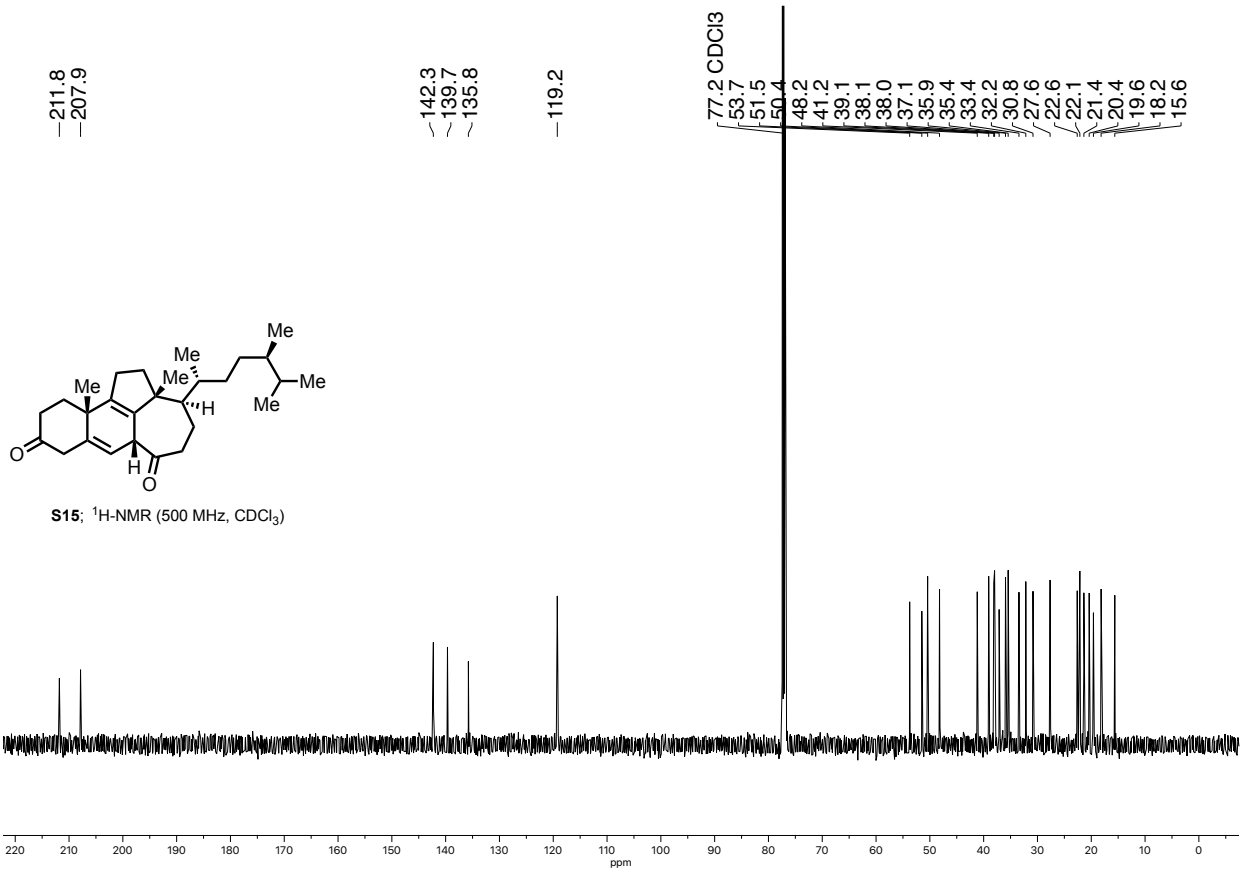
S14; ^{1}H-NMR (500 MHz, $CDCl_3$)



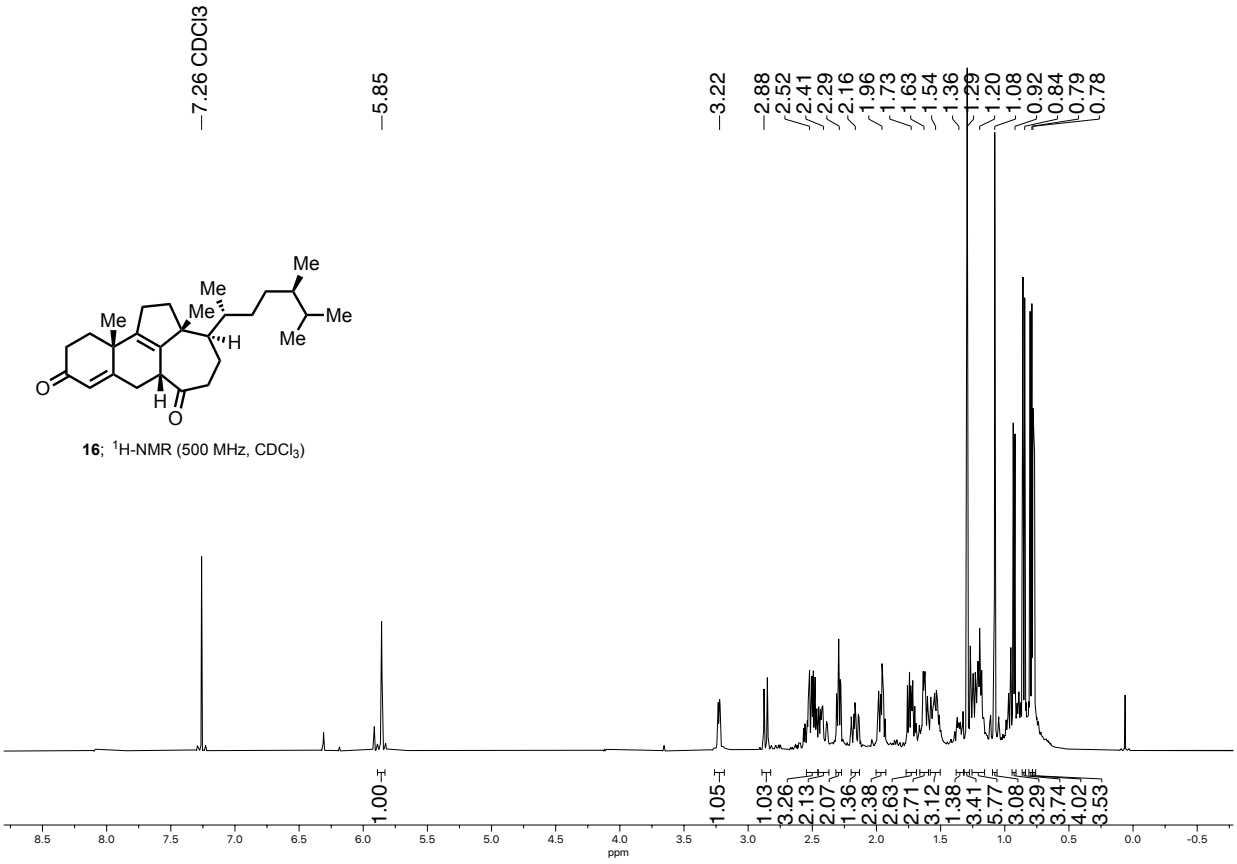
S14; ^{13}C-NMR (126 MHz, $CDCl_3$)



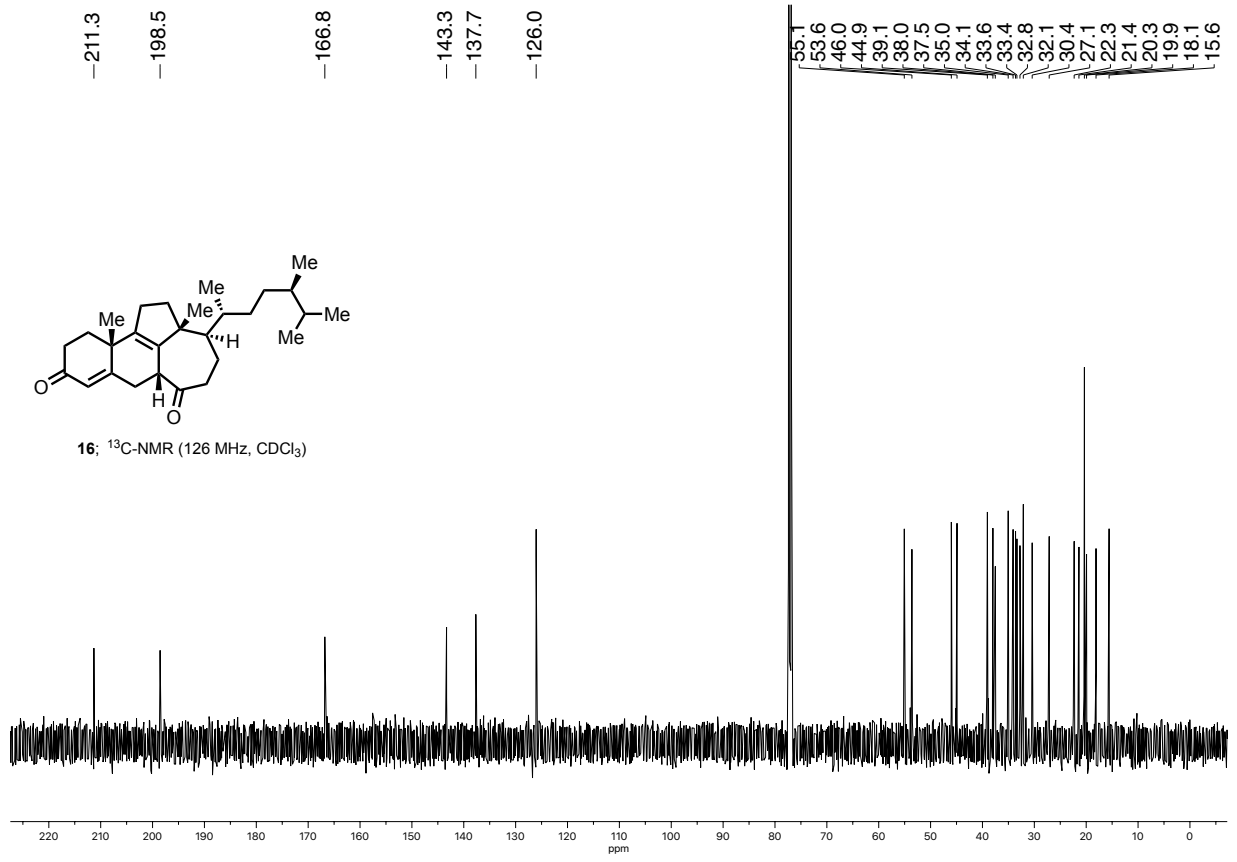
S15; ^{13}C-NMR (126 MHz, $CDCl_3$)



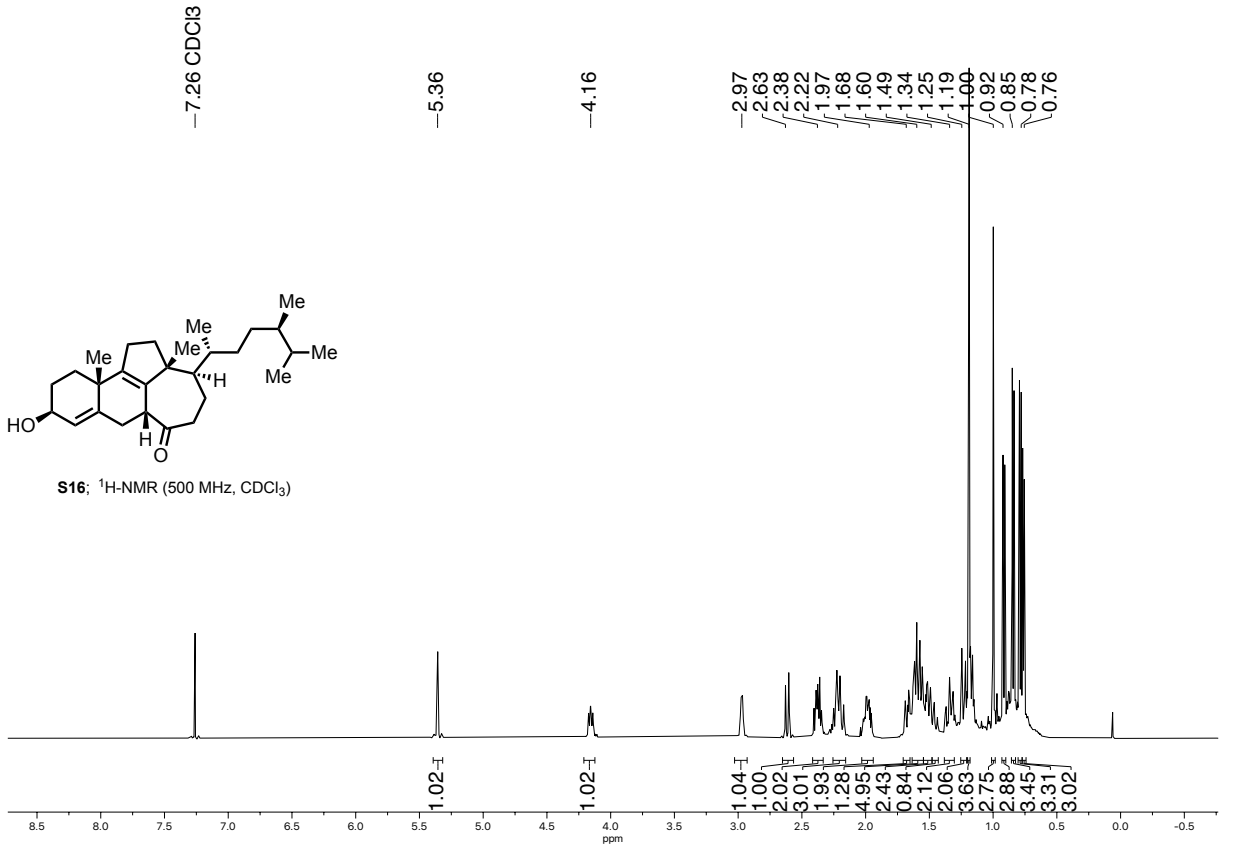
S15; ^{1}H-NMR (500 MHz, $CDCl_3$)



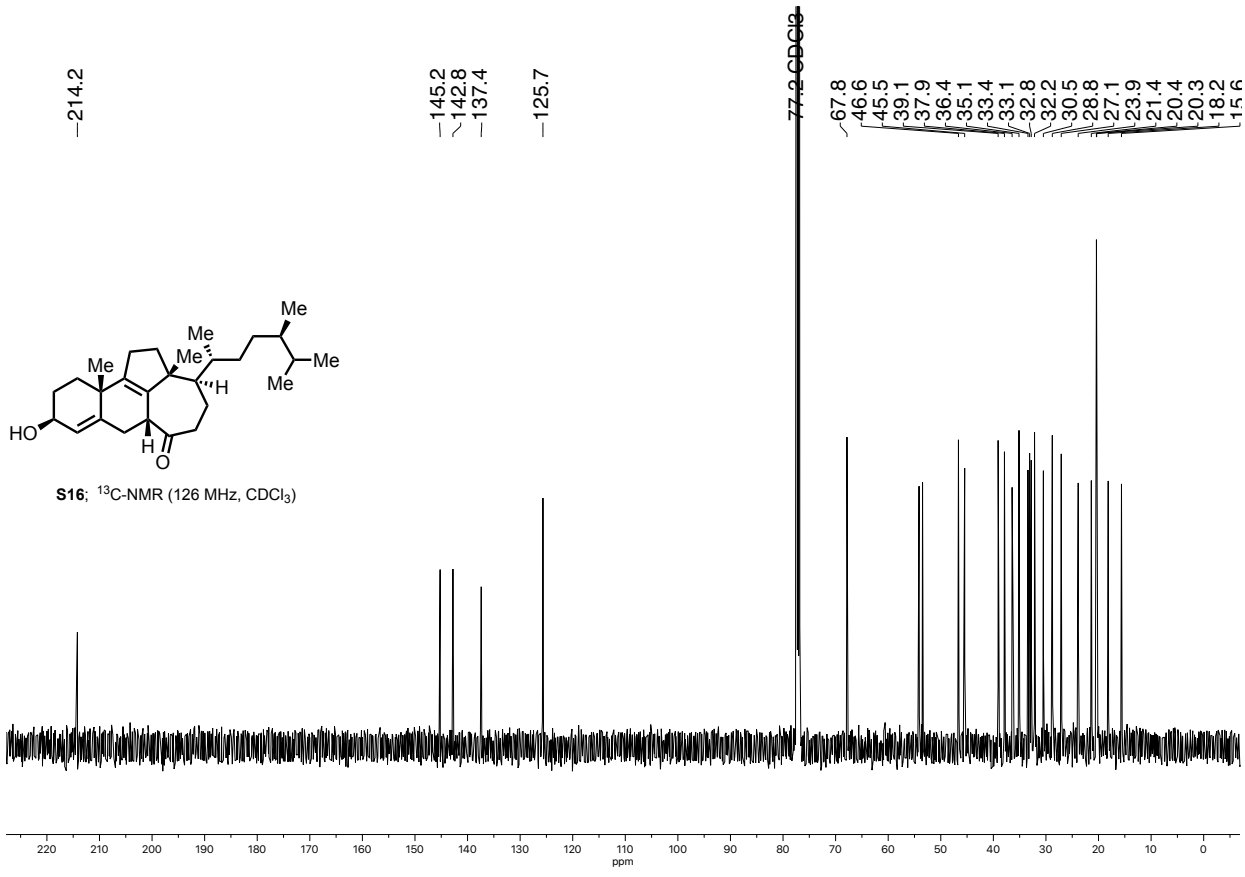
16; ^{1}H-NMR (500 MHz, $CDCl_3$)



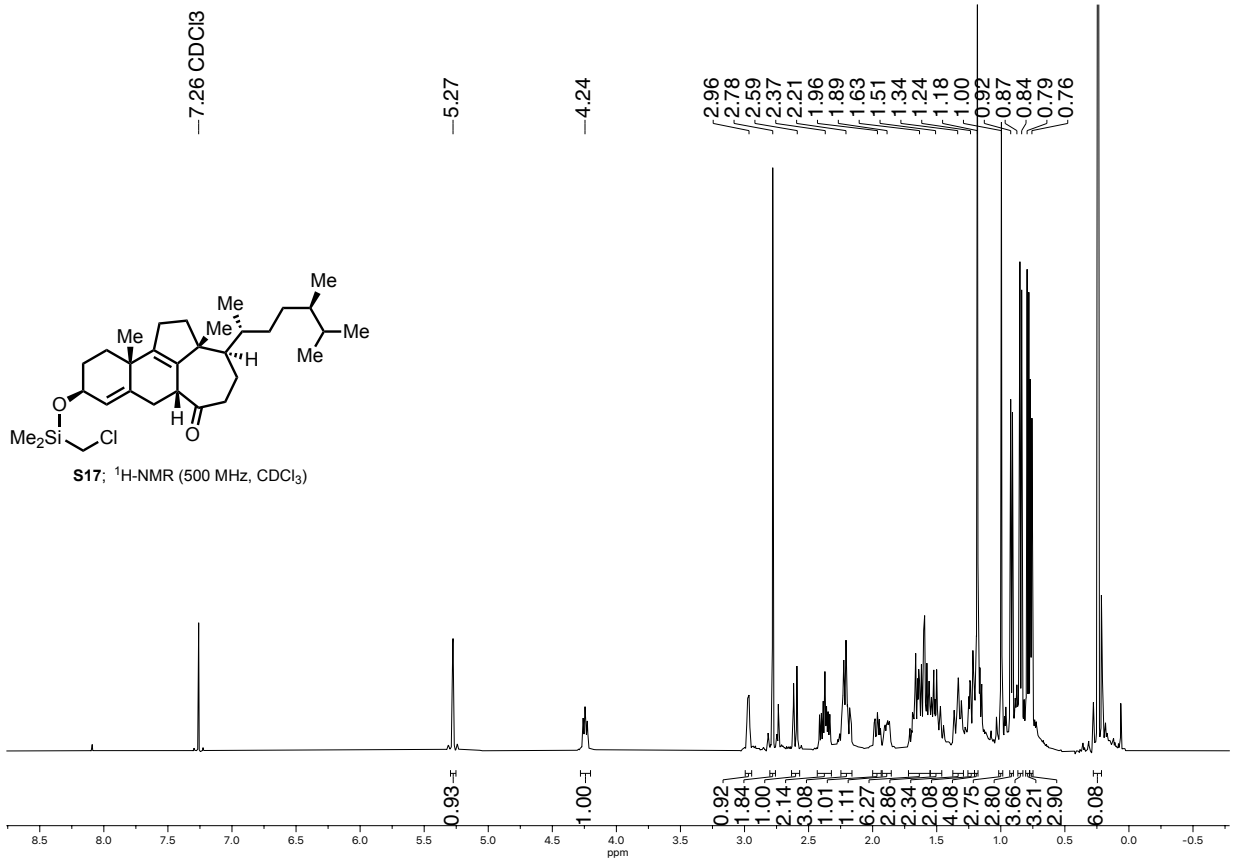
16; ^{13}C-NMR (126 MHz, $CDCl_3$)



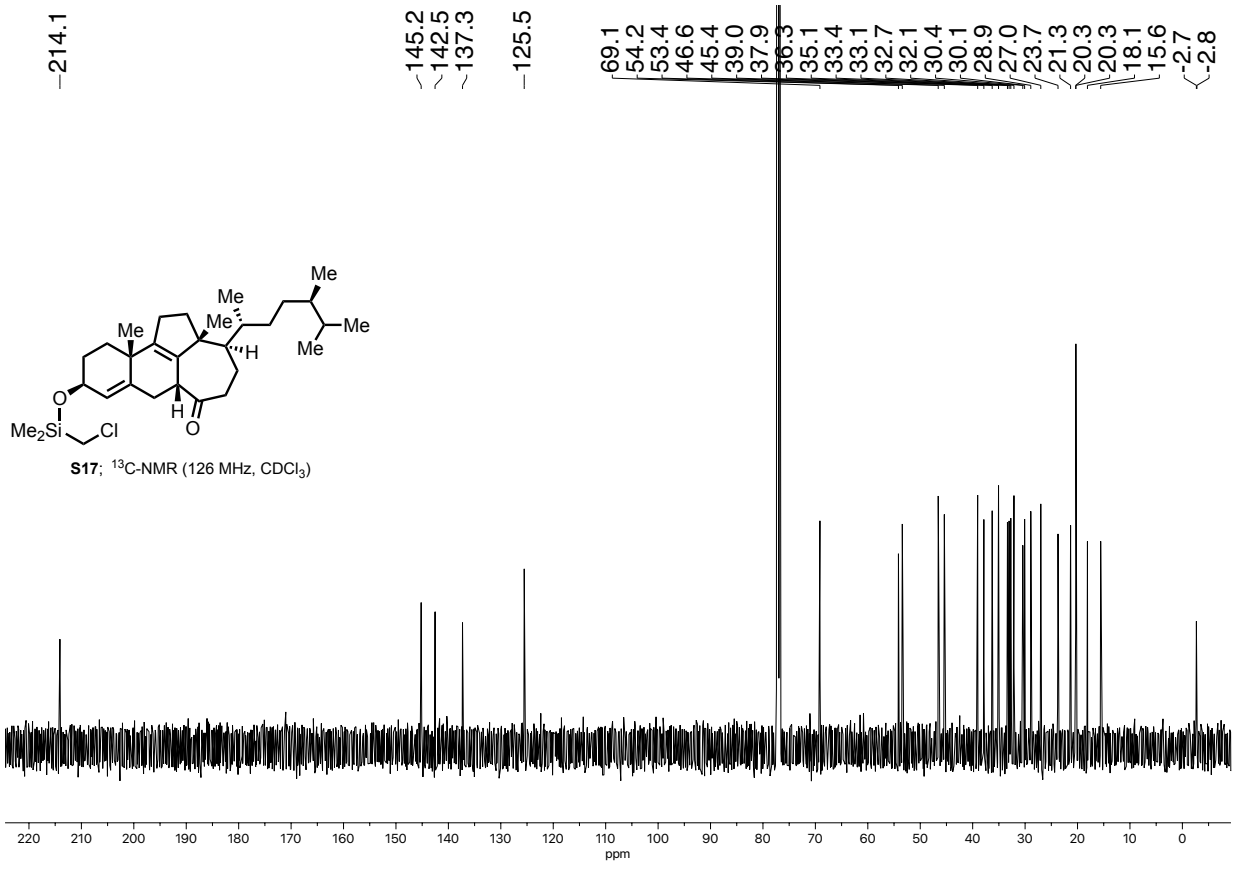
S16; ^{1}H-NMR (500 MHz, $CDCl_3$)



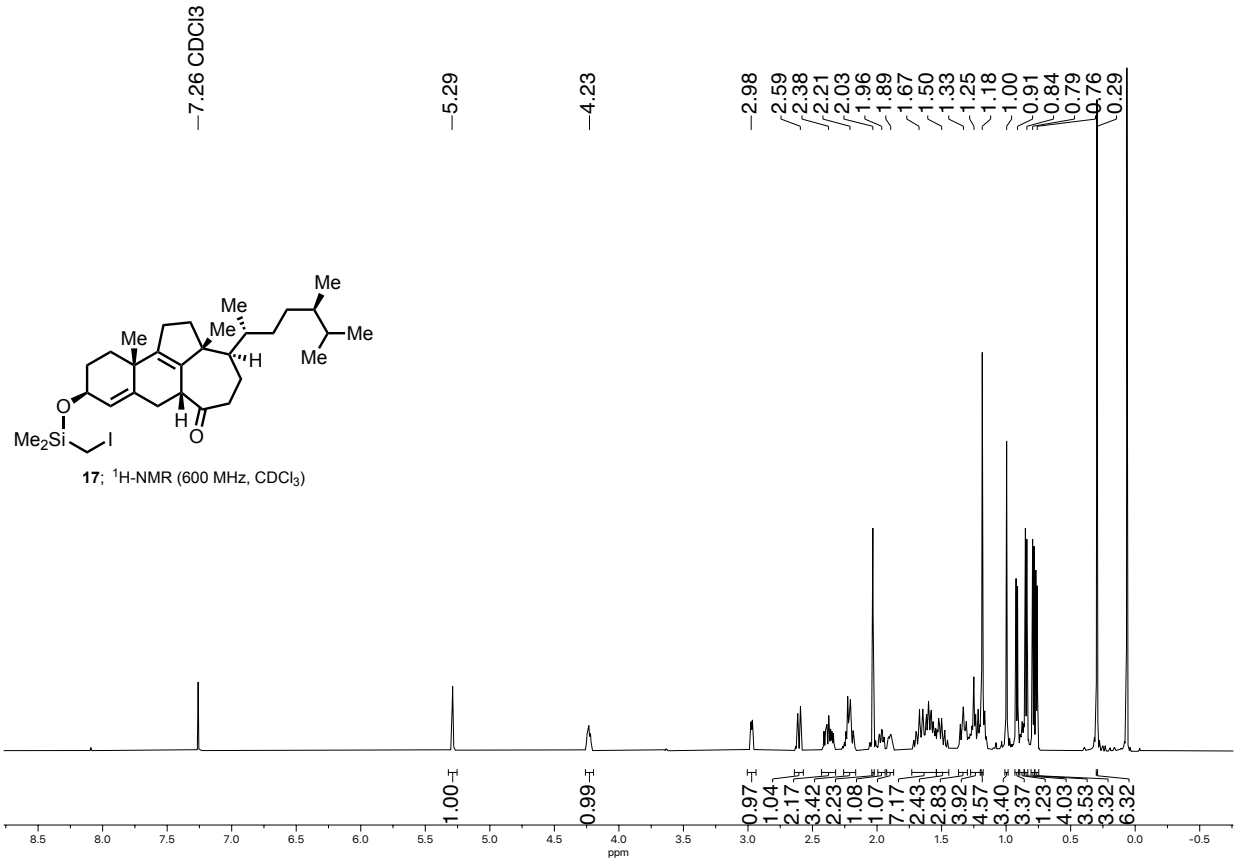
S16; ^{13}C-NMR (126 MHz, $CDCl_3$)



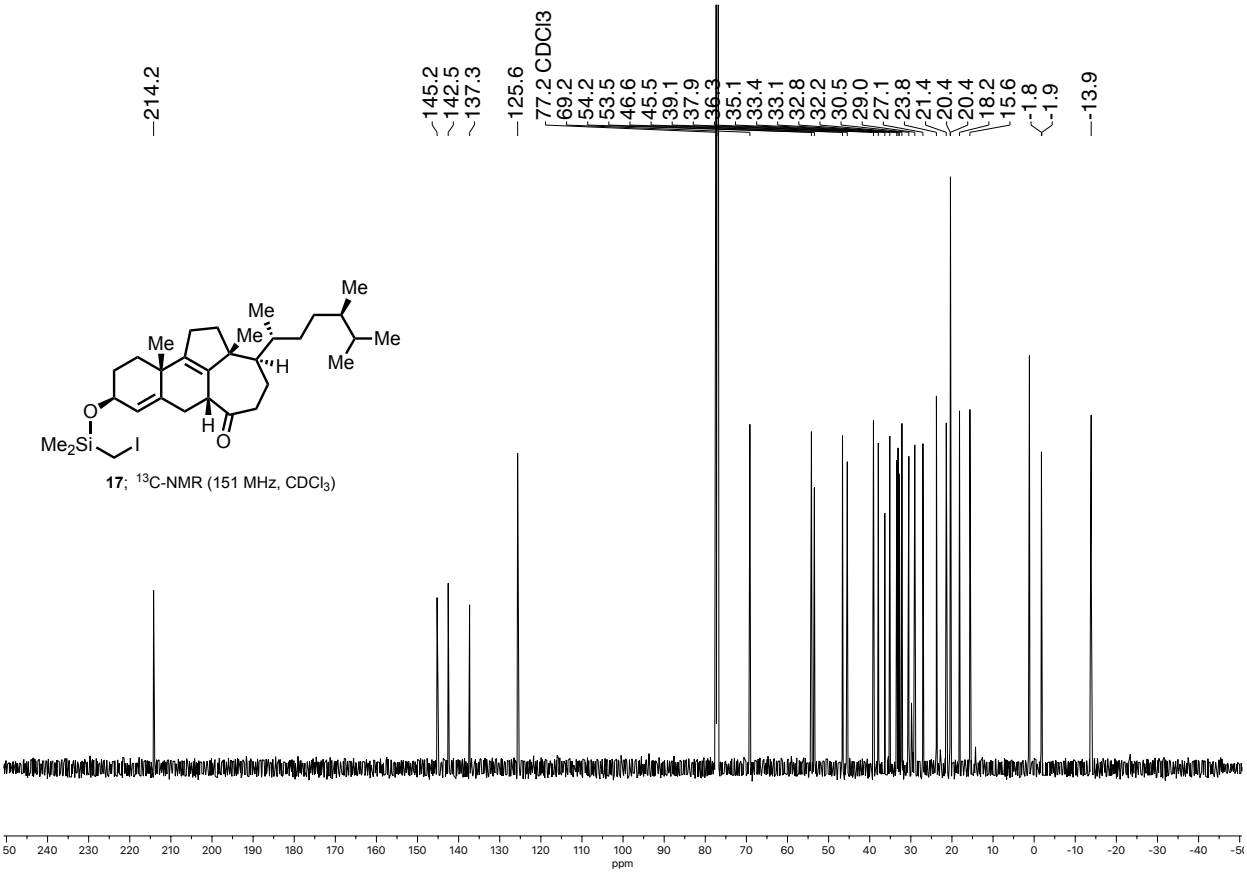
S17; ^{1}H-NMR (500 MHz, $CDCl_3$)



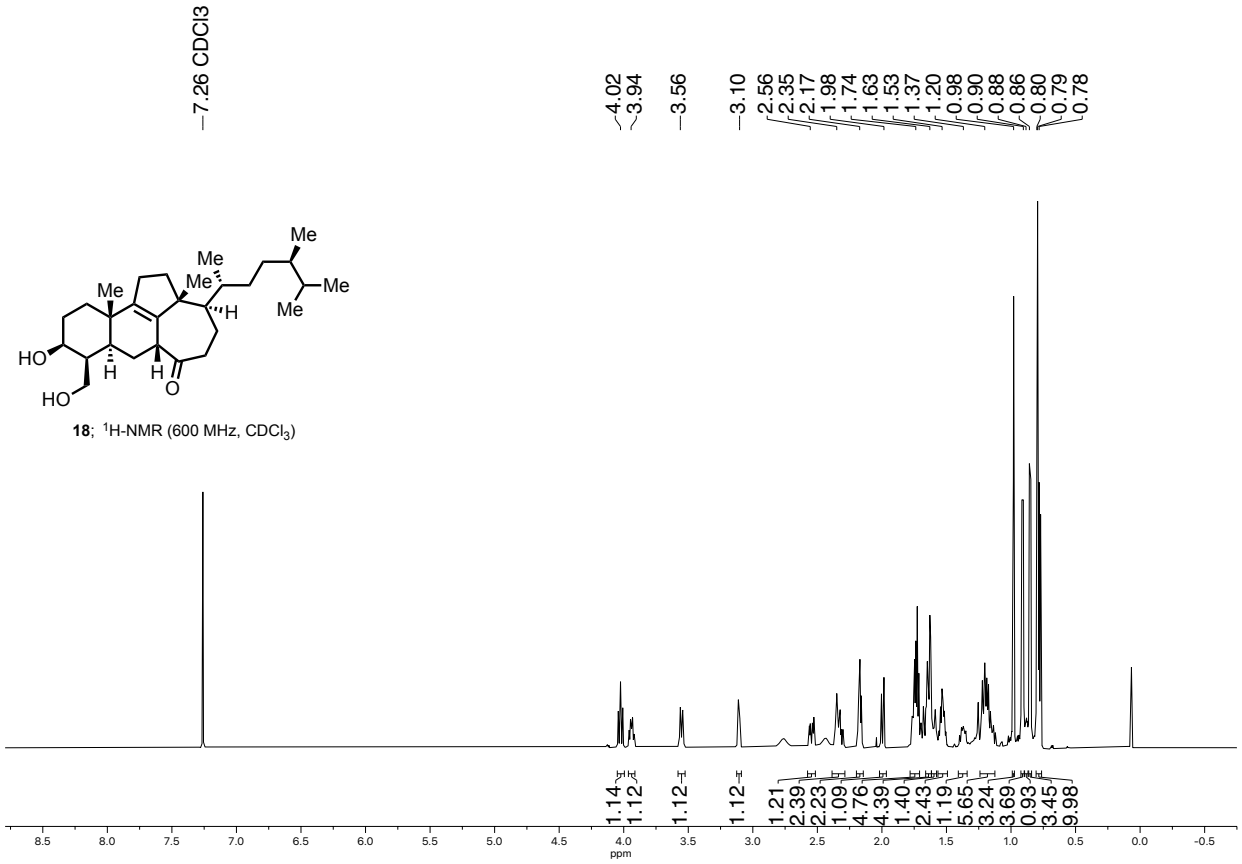
S17; ^{13}C-NMR (126 MHz, $CDCl_3$)



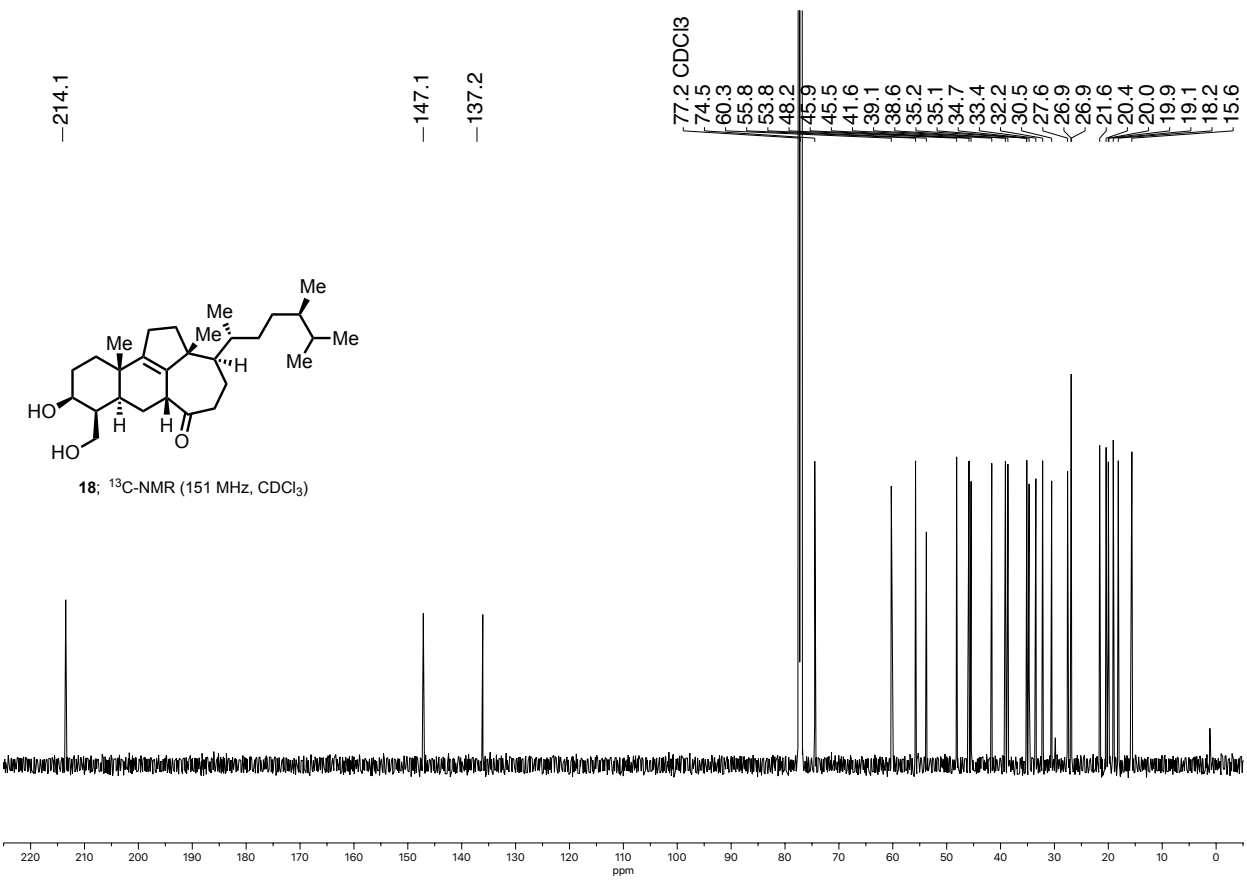
17; ^{1}H-NMR (600 MHz, $CDCl_3$)



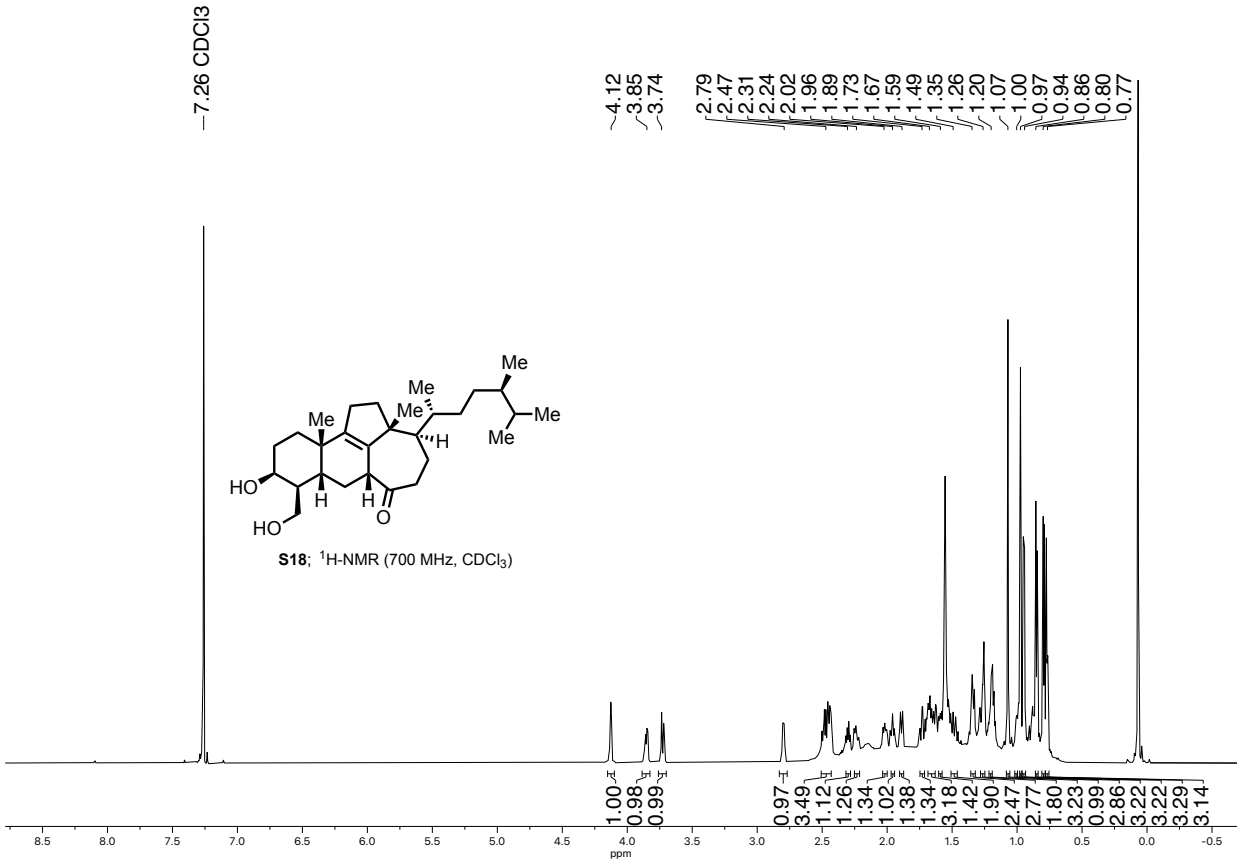
17; ^{13}C-NMR (151 MHz, $CDCl_3$)

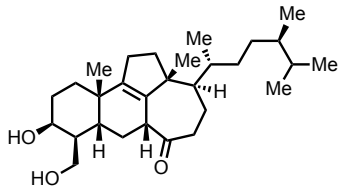


18; ^{1}H-NMR (600 MHz, $CDCl_3$)



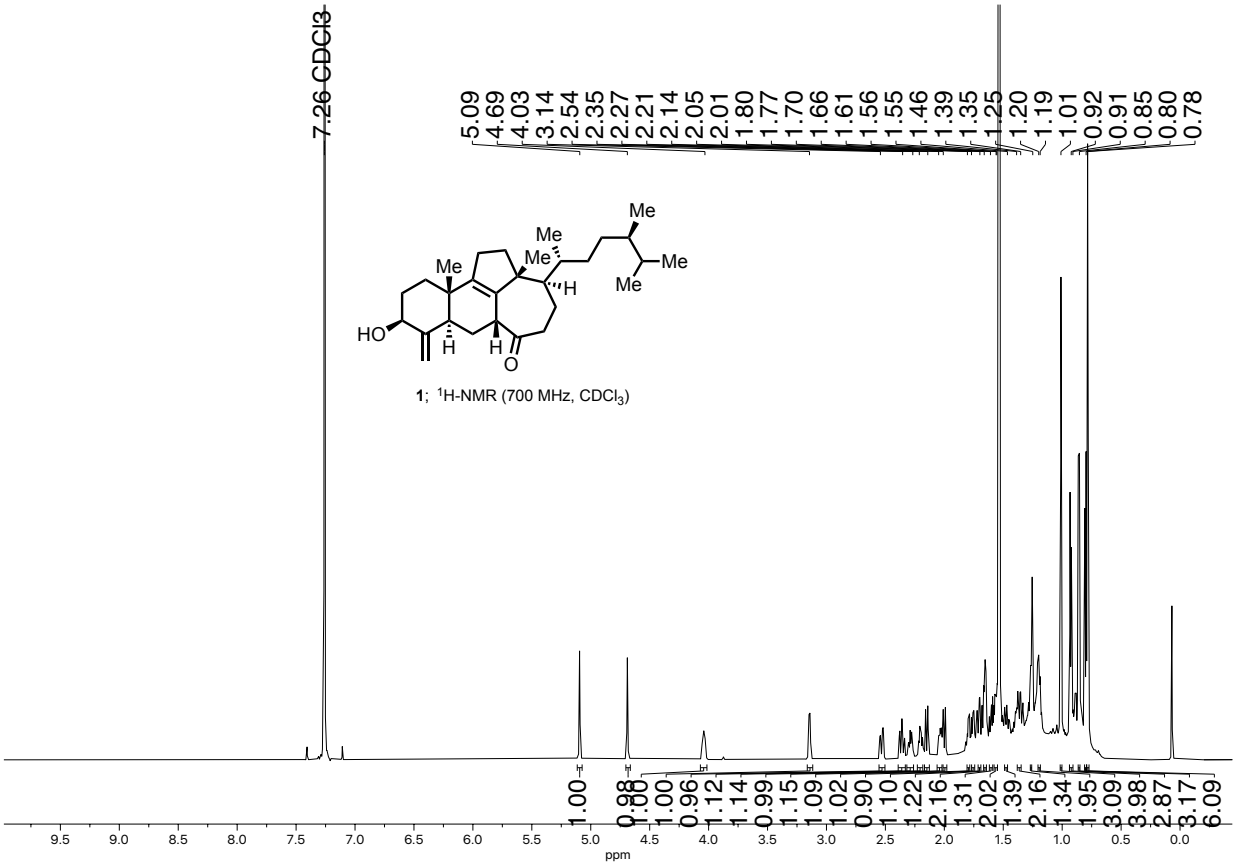
18; ^{13}C-NMR (151 MHz, $CDCl_3$)



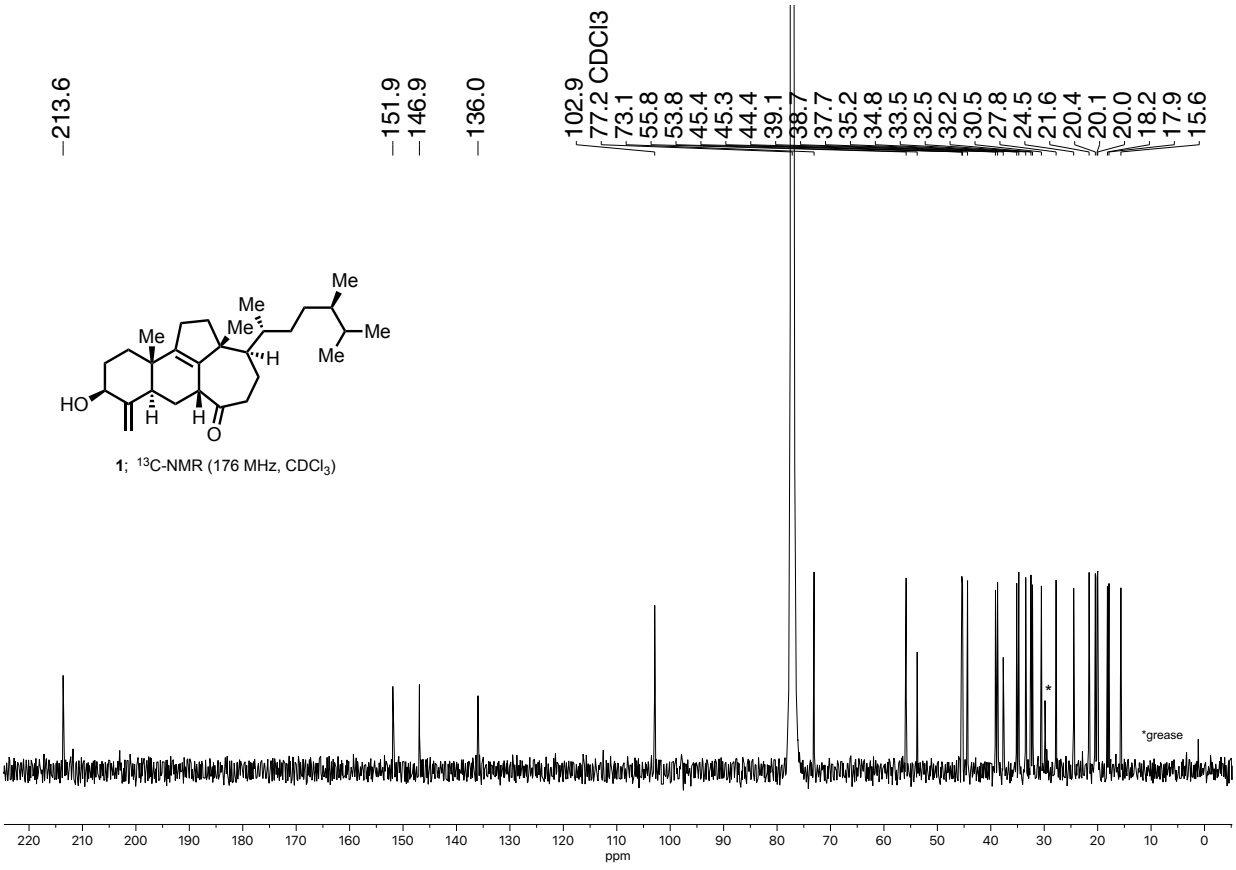


S18; ^{1}H-NMR (700 MHz, $CDCl_3$)

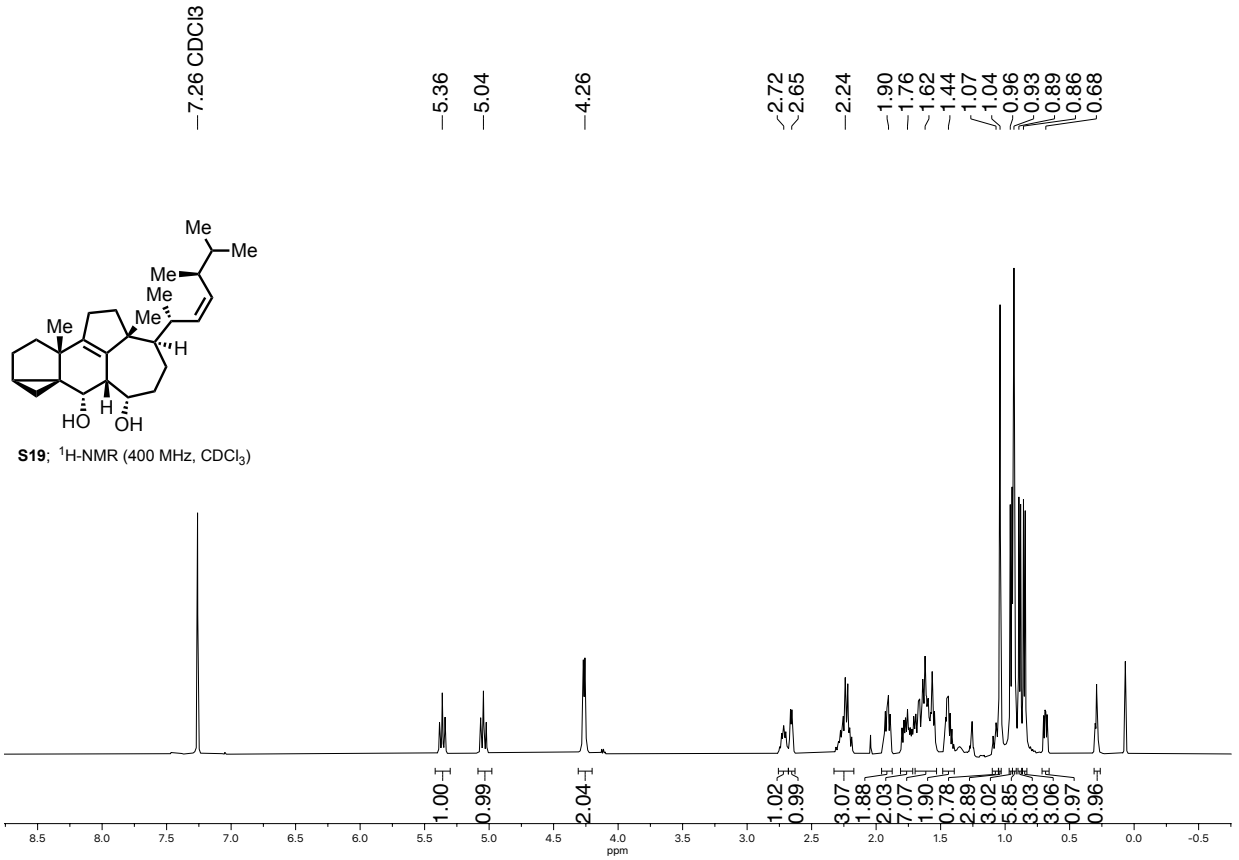
S18; ^{13}C-NMR (176 MHz, $CDCl_3$)



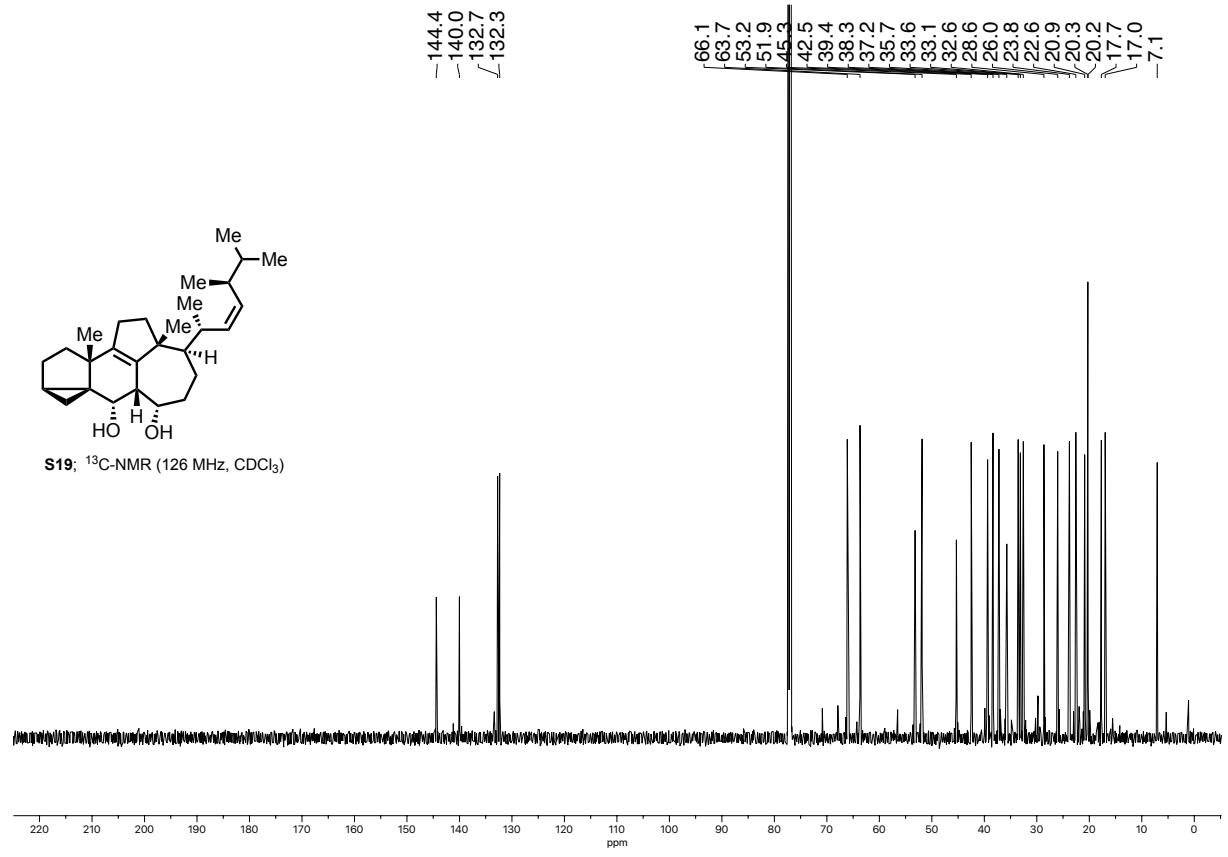
1; ^{1}H-NMR (700 MHz, $CDCl_3$)



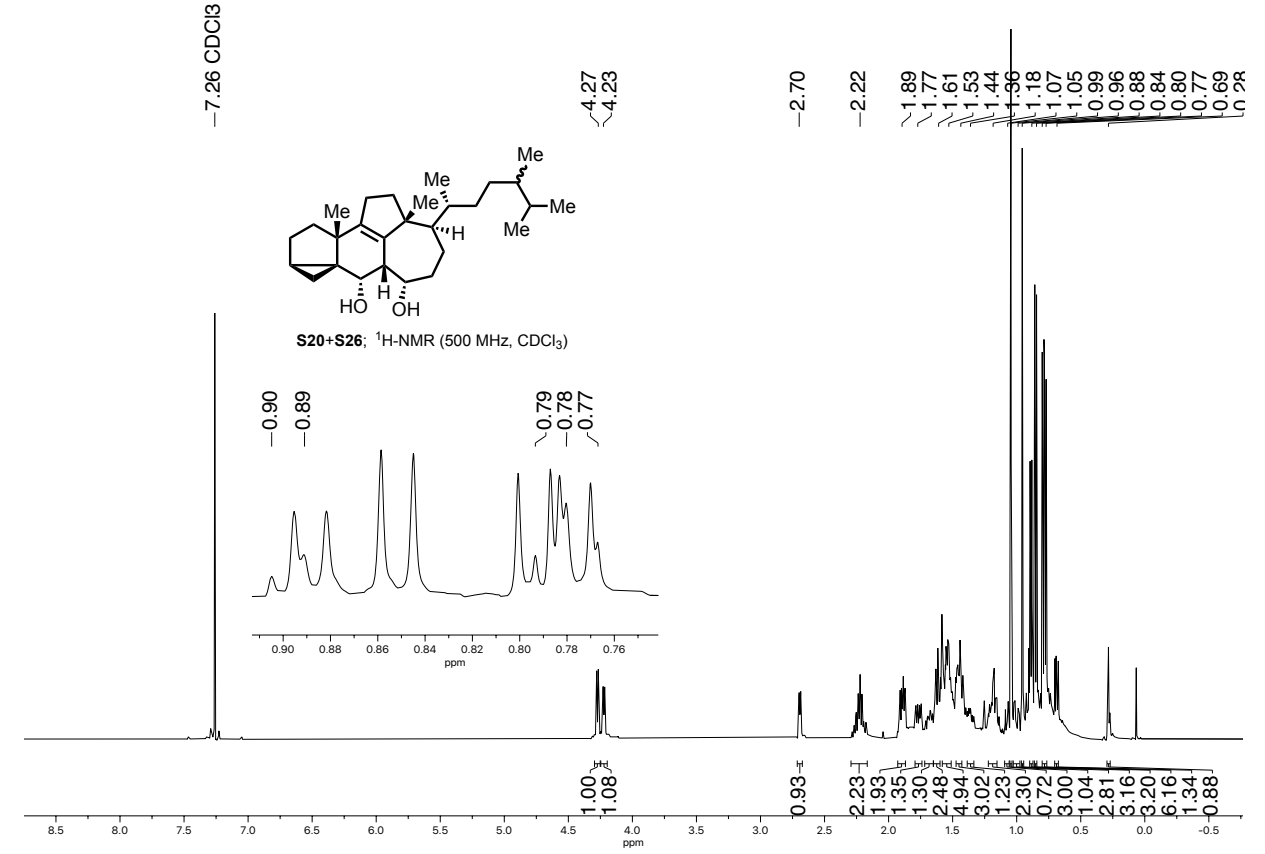
1; ^{13}C-NMR (176 MHz, $CDCl_3$)



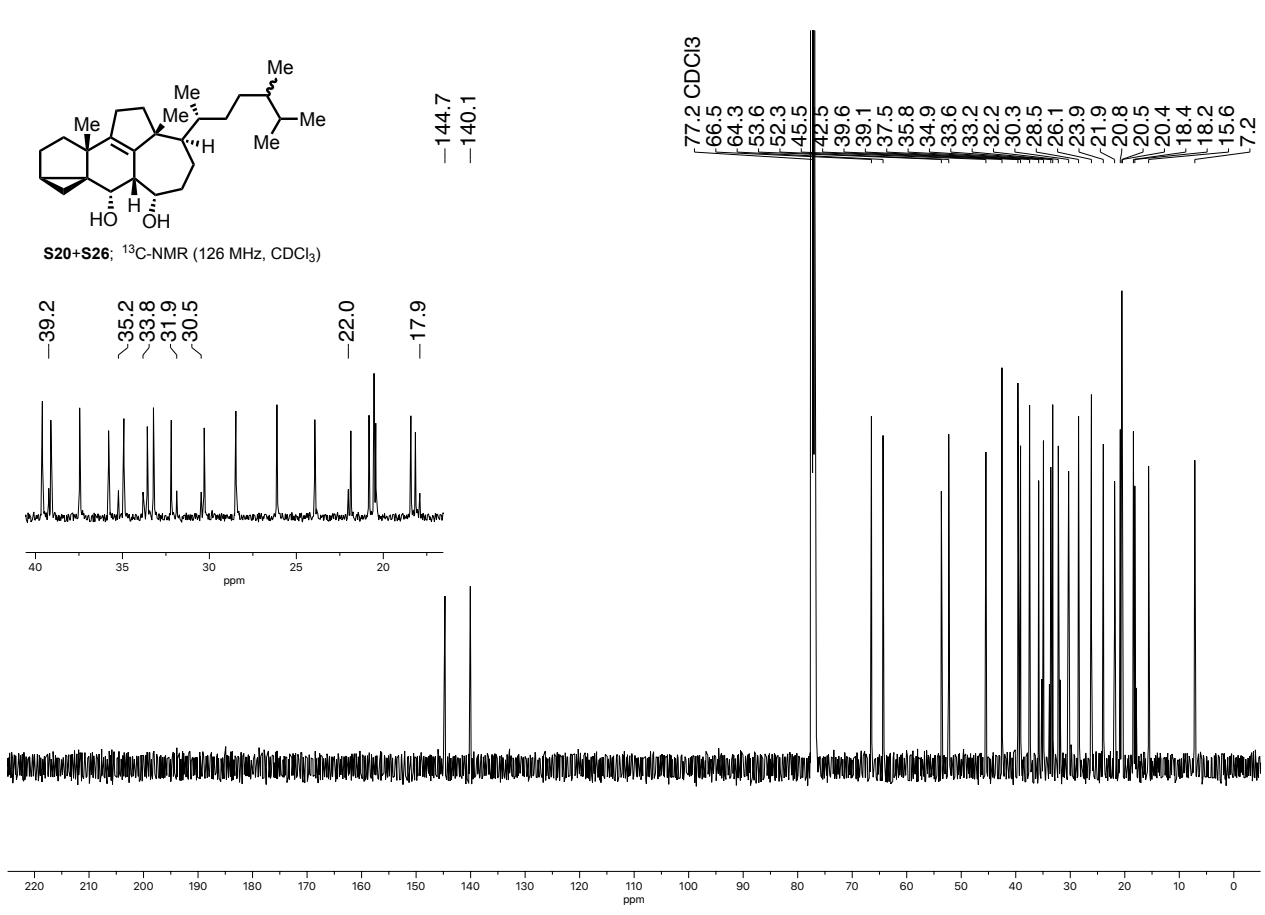
S19; ^{1}H-NMR (400 MHz, $CDCl_3$)



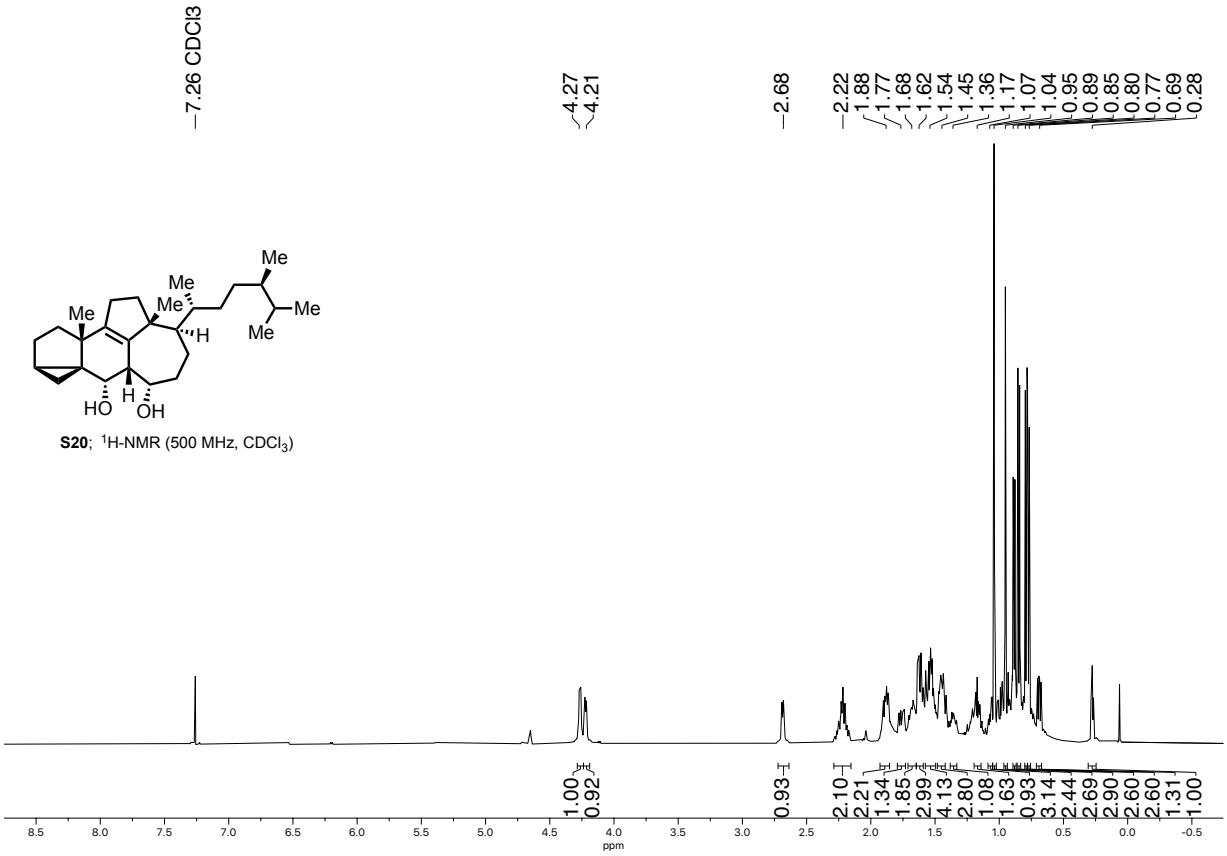
S19; ^{13}C-NMR (126 MHz, $CDCl_3$)



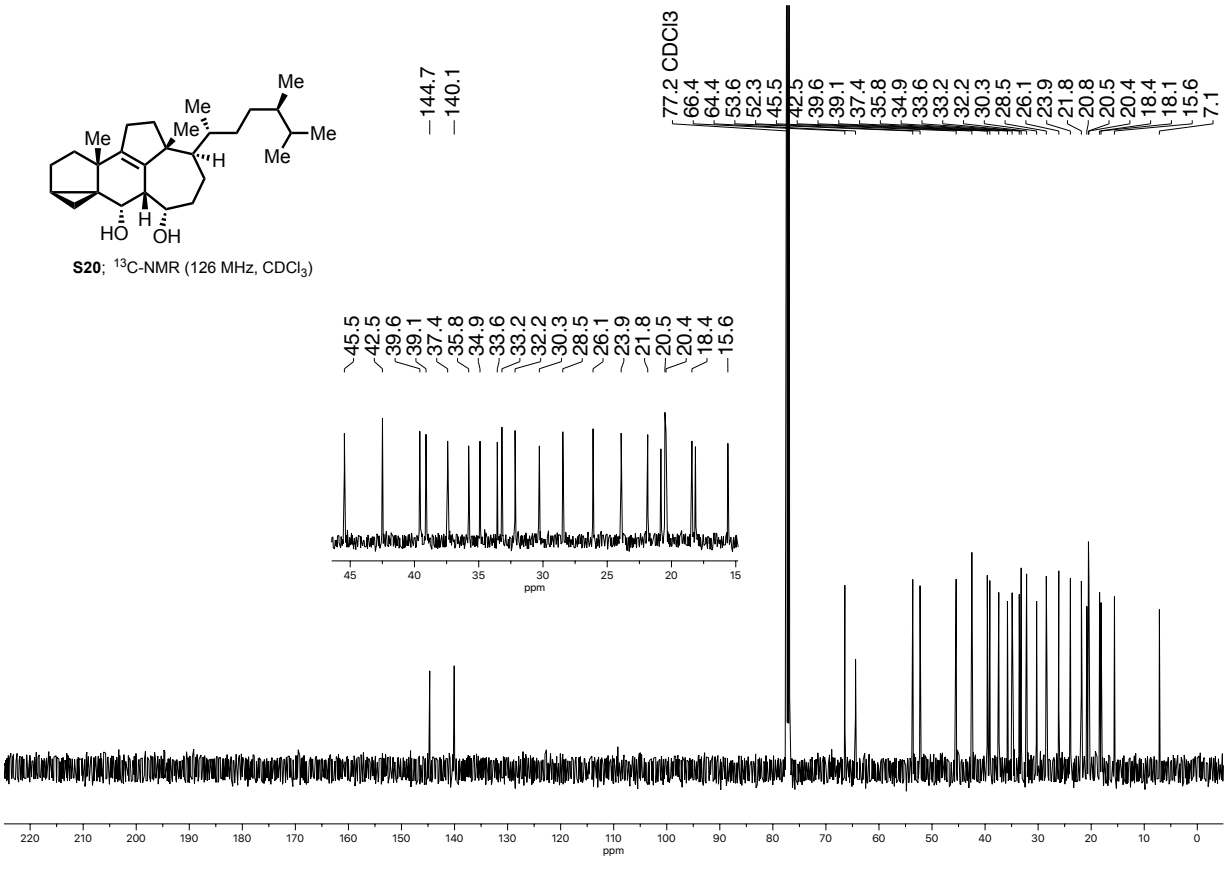
S20+**S26**; ^{1}H-NMR (500 MHz, $CDCl_3$)



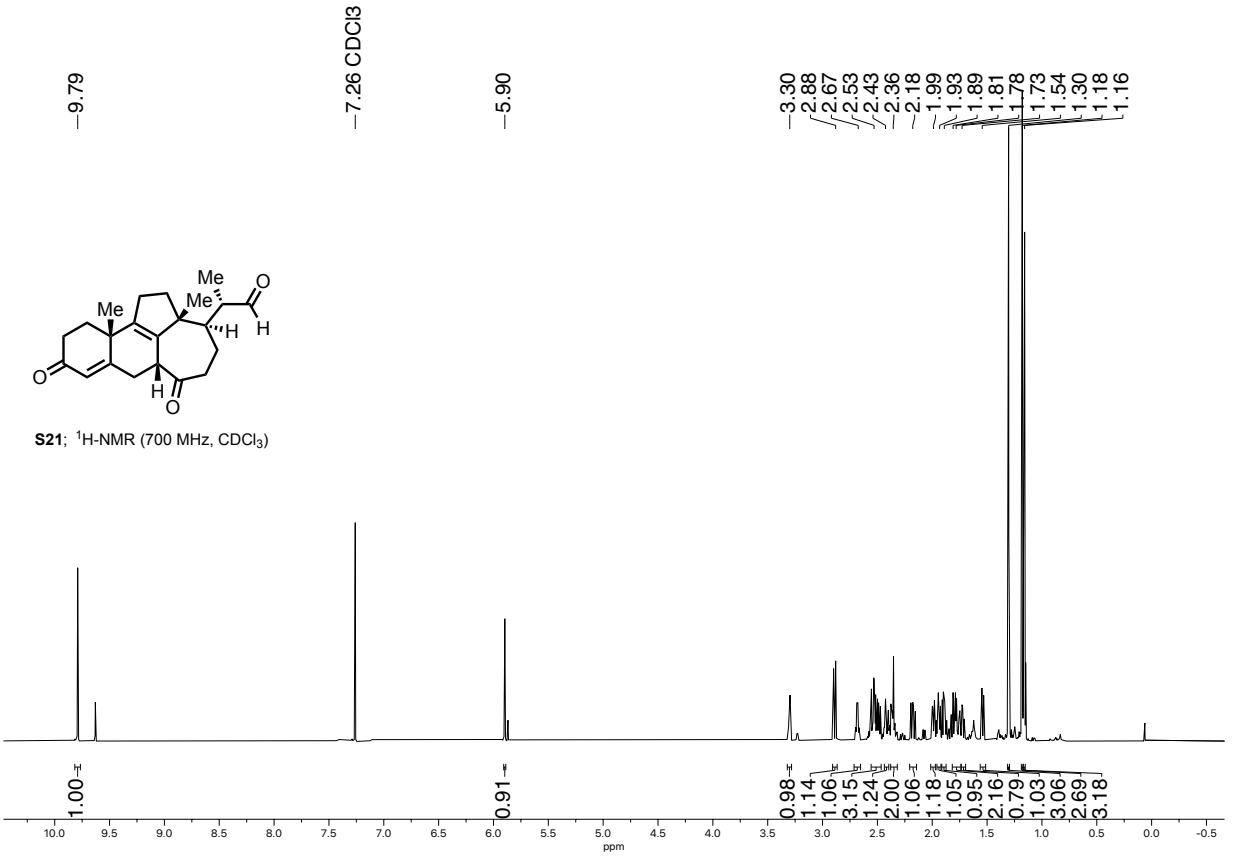
S20+**S26**; ^{13}C-NMR (126 MHz, $CDCl_3$)



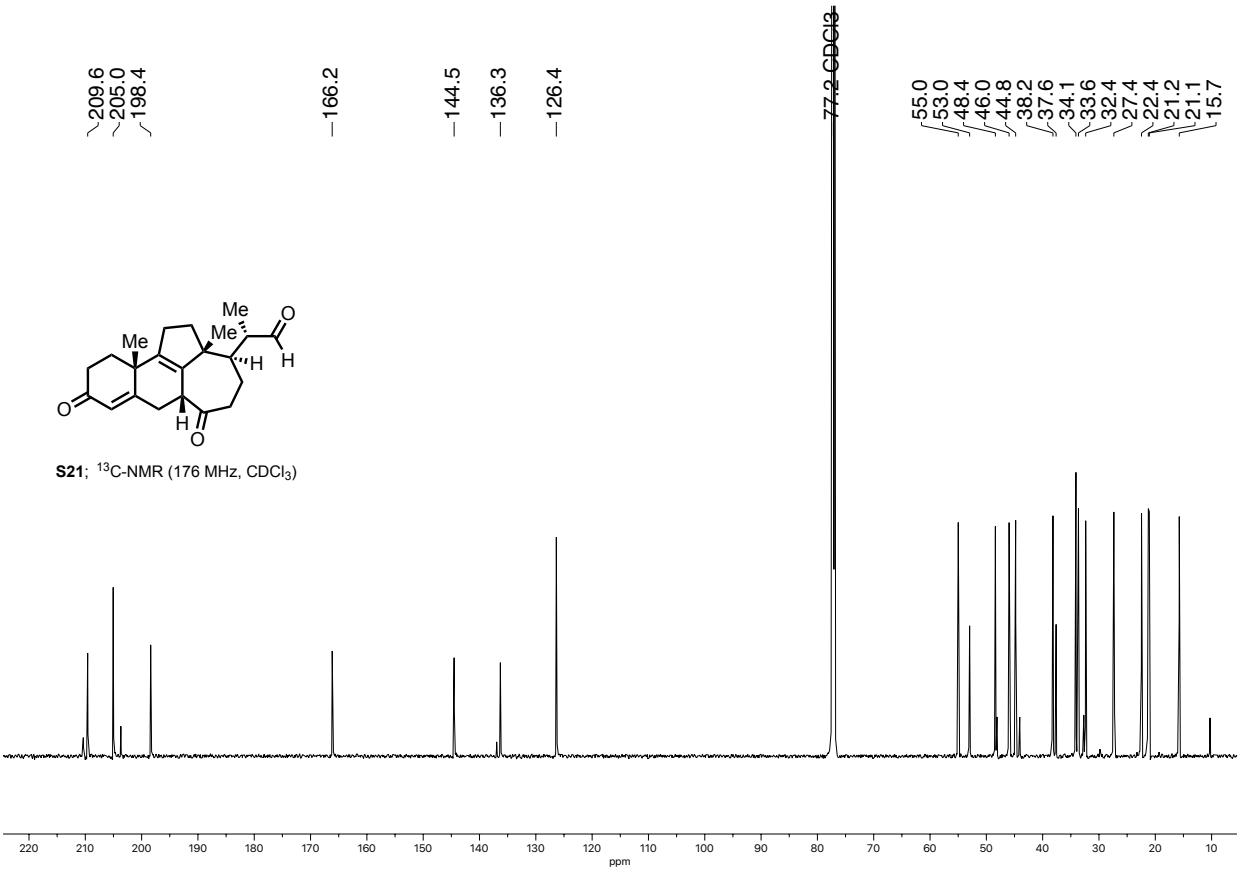
S20; ^{1}H-NMR (500 MHz, $CDCl_3$)



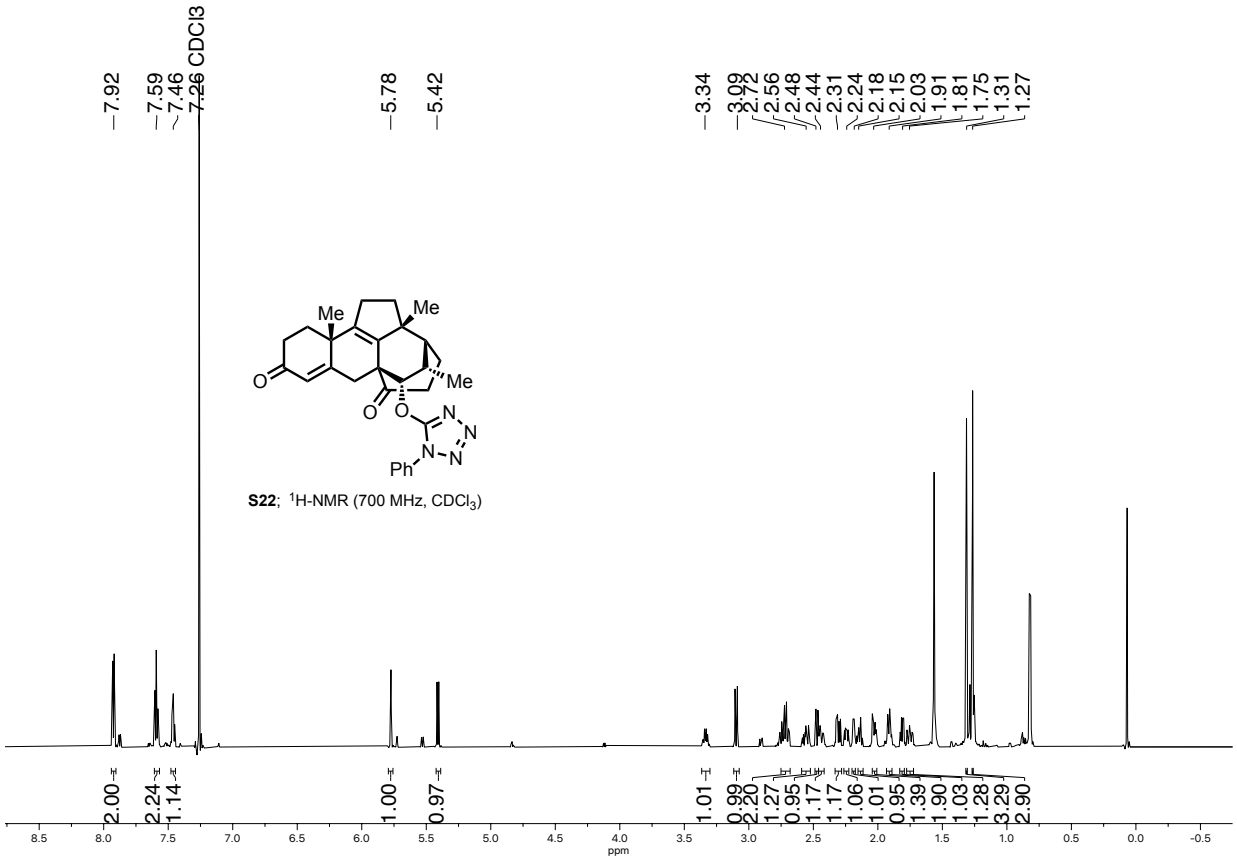
S20; ^{13}C-NMR (126 MHz, $CDCl_3$)



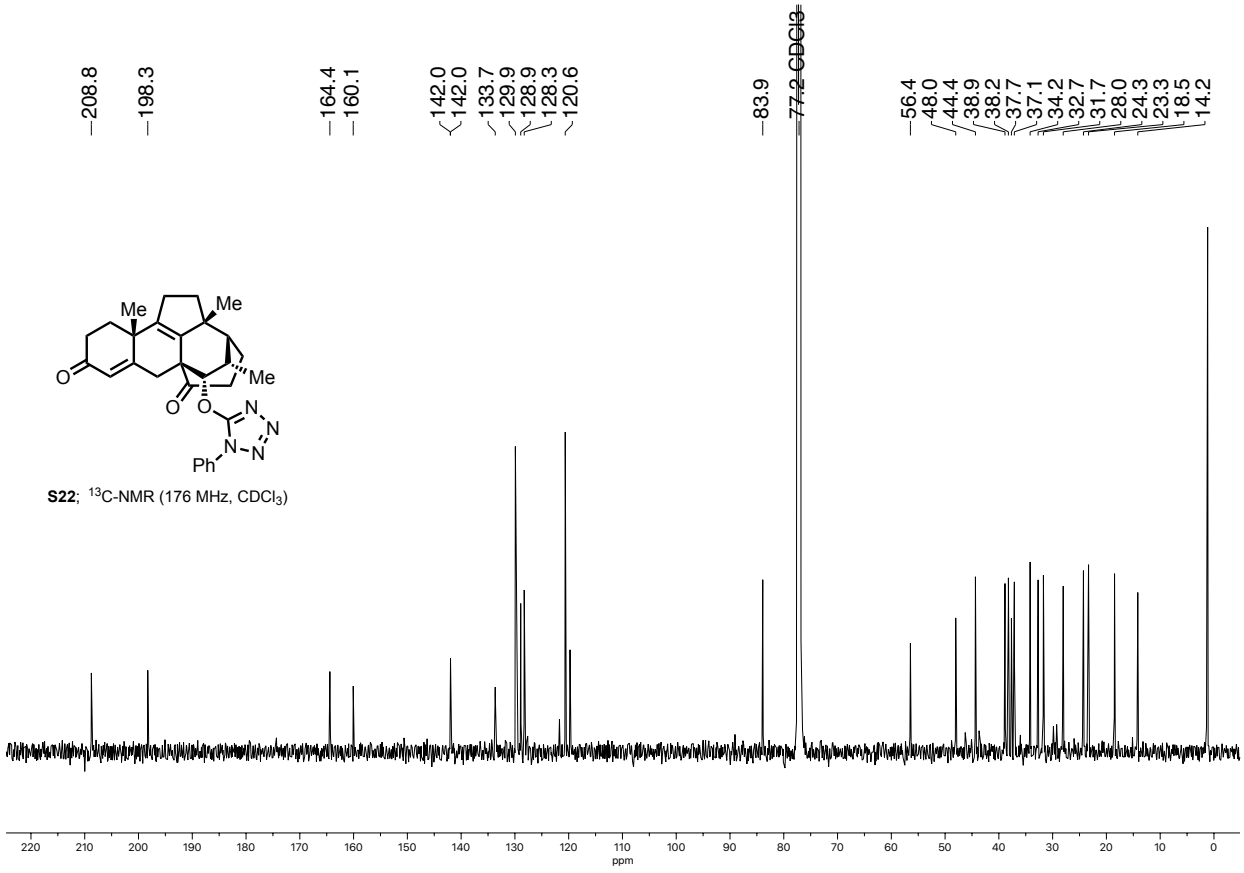
S21; ^{1}H-NMR (700 MHz, $CDCl_3$)



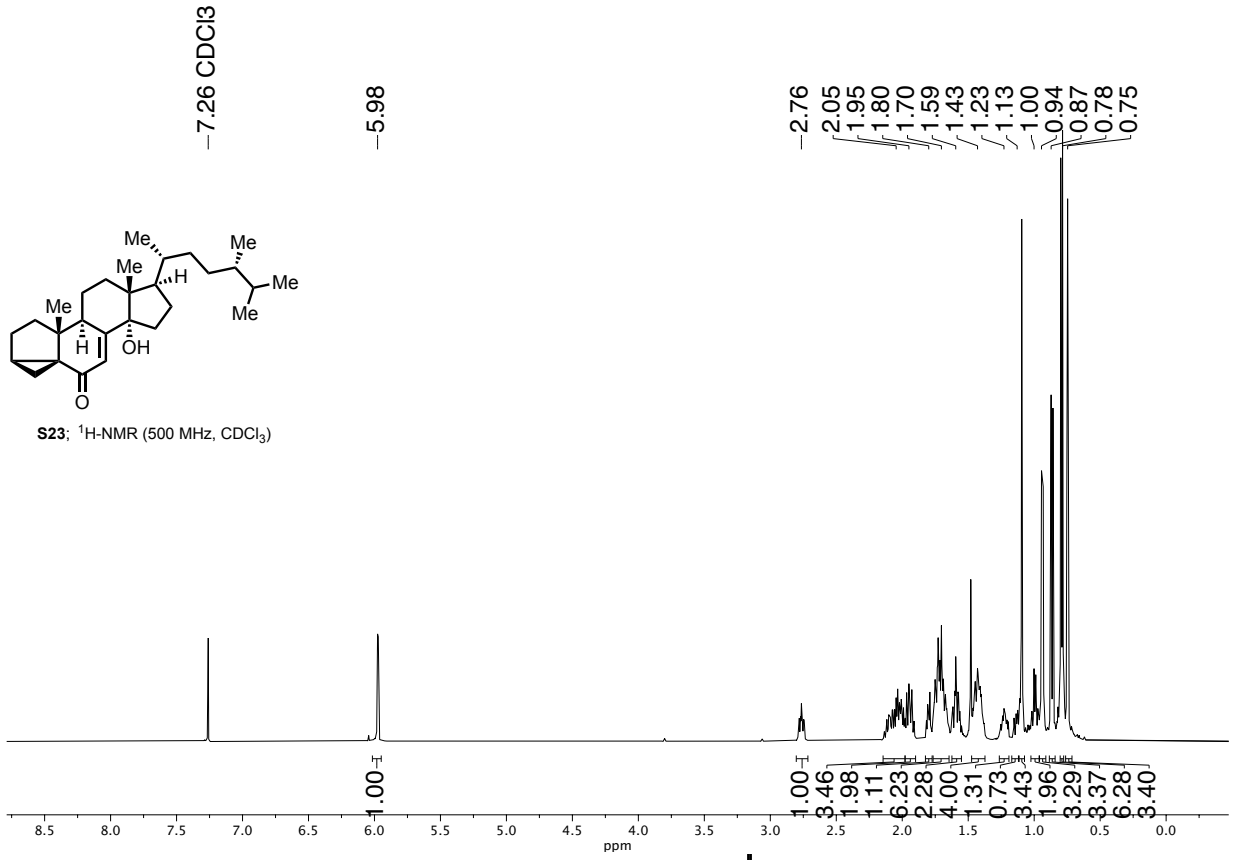
S21; ^{13}C-NMR (176 MHz, $CDCl_3$)



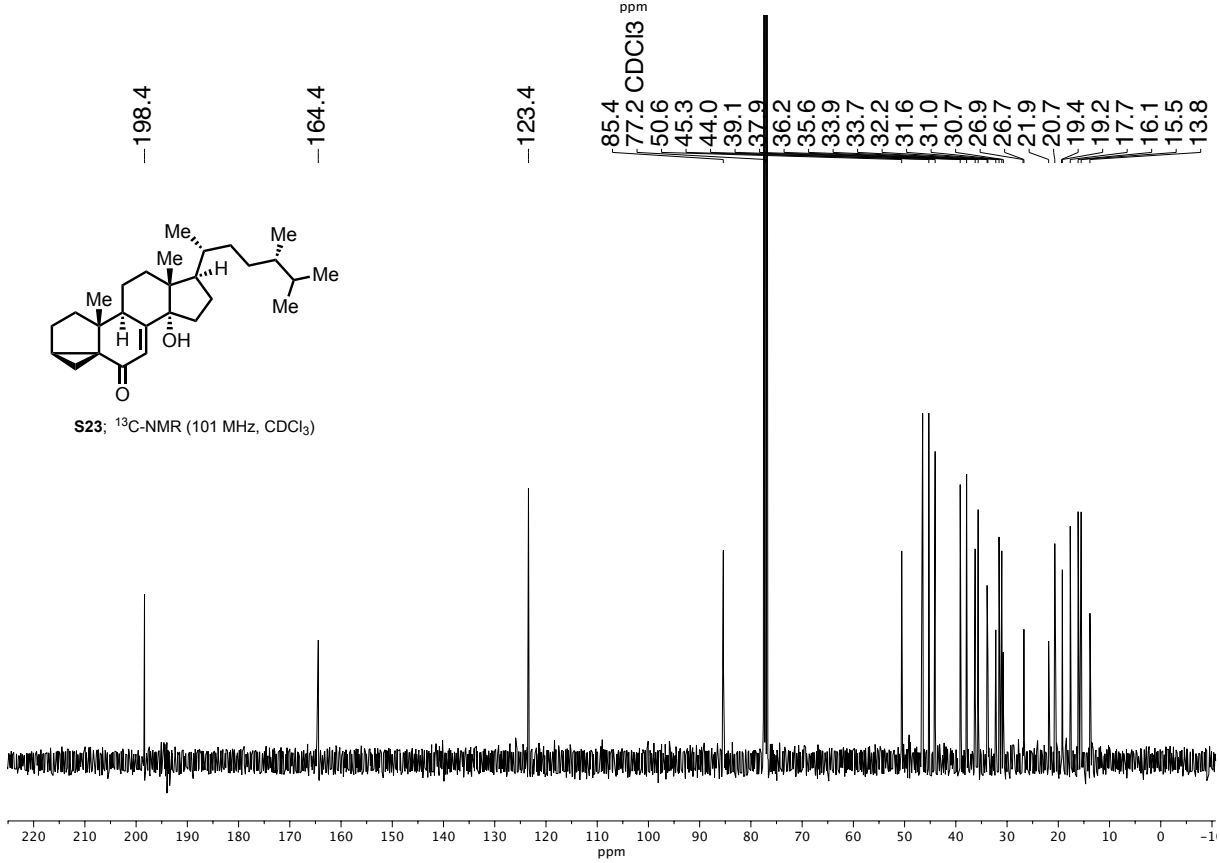
S22; ^{1}H-NMR (700 MHz, $CDCl_3$)



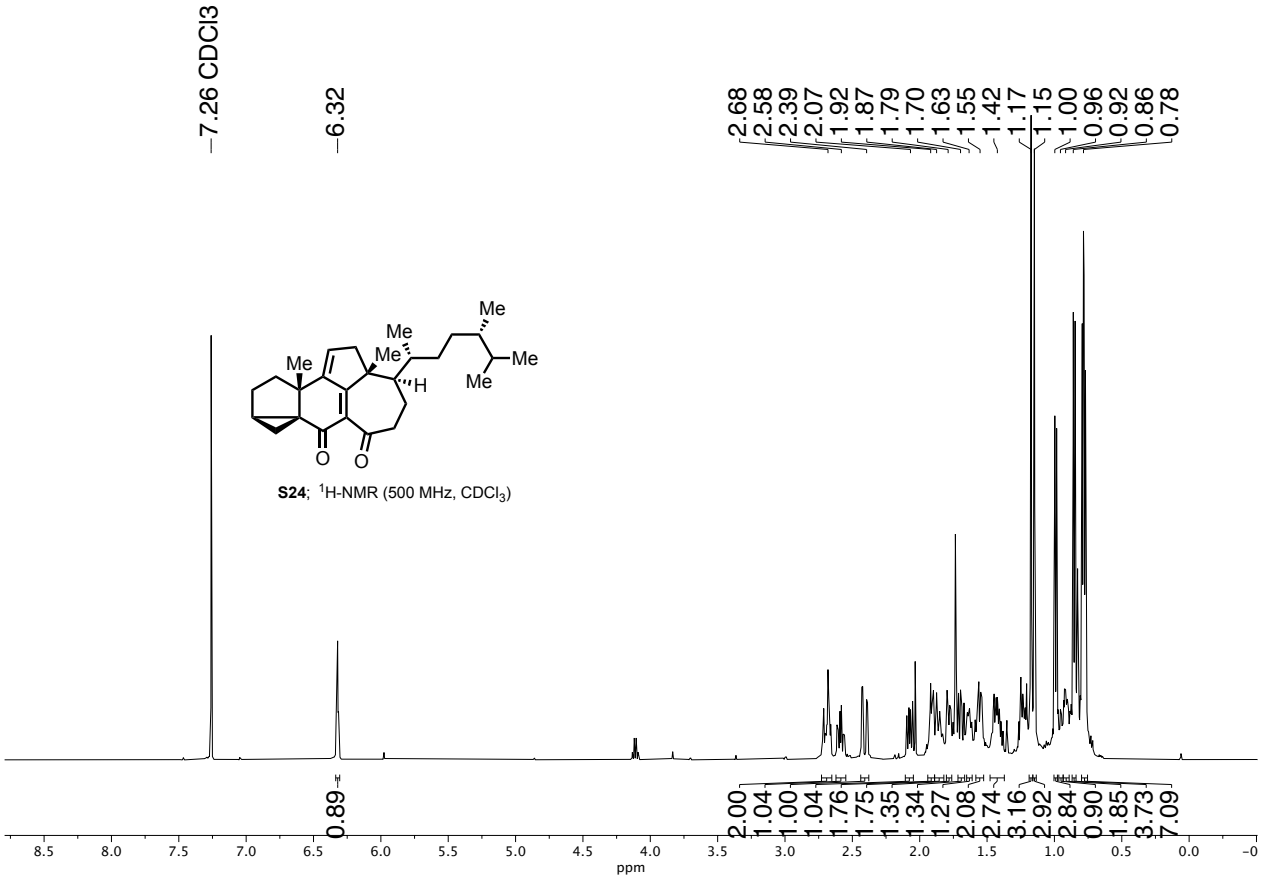
S22; ^{13}C-NMR (176 MHz, $CDCl_3$)



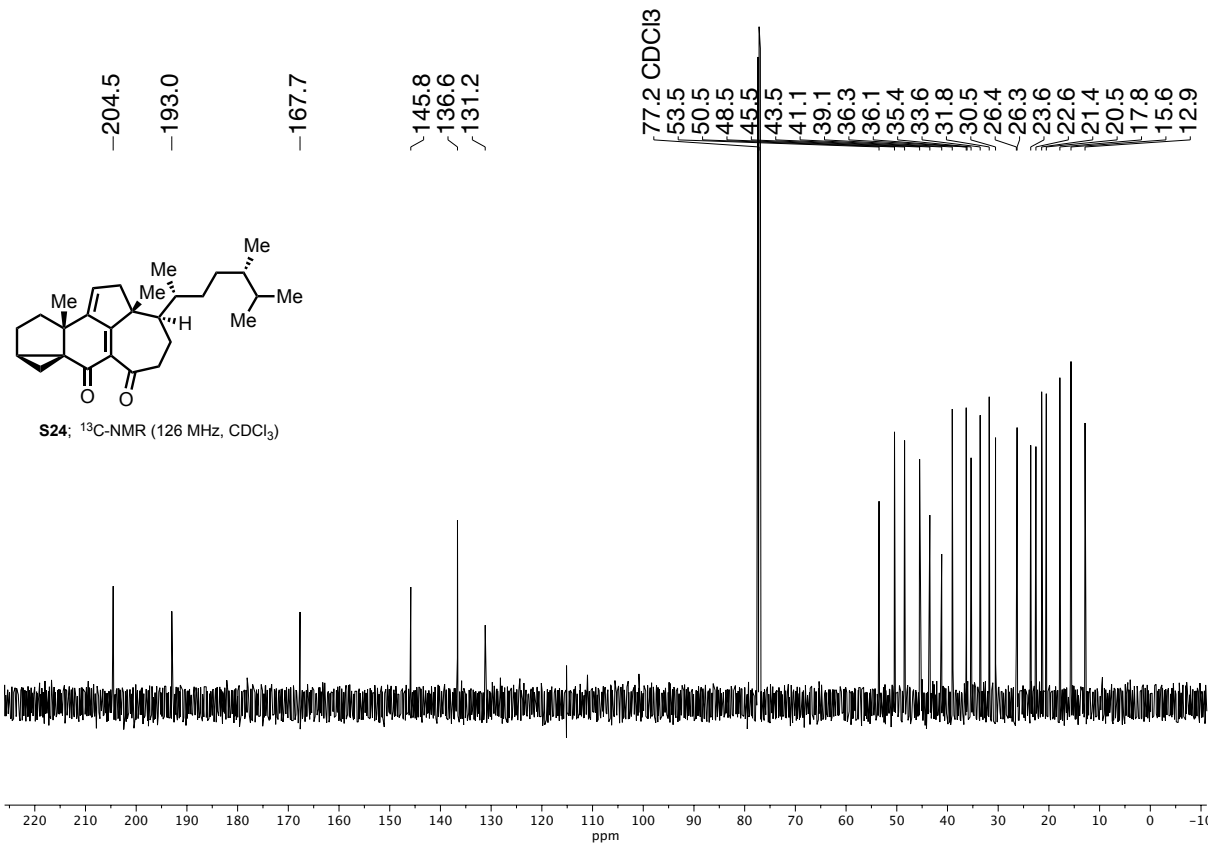
S23; ^{1}H-NMR (500 MHz, $CDCl_3$)



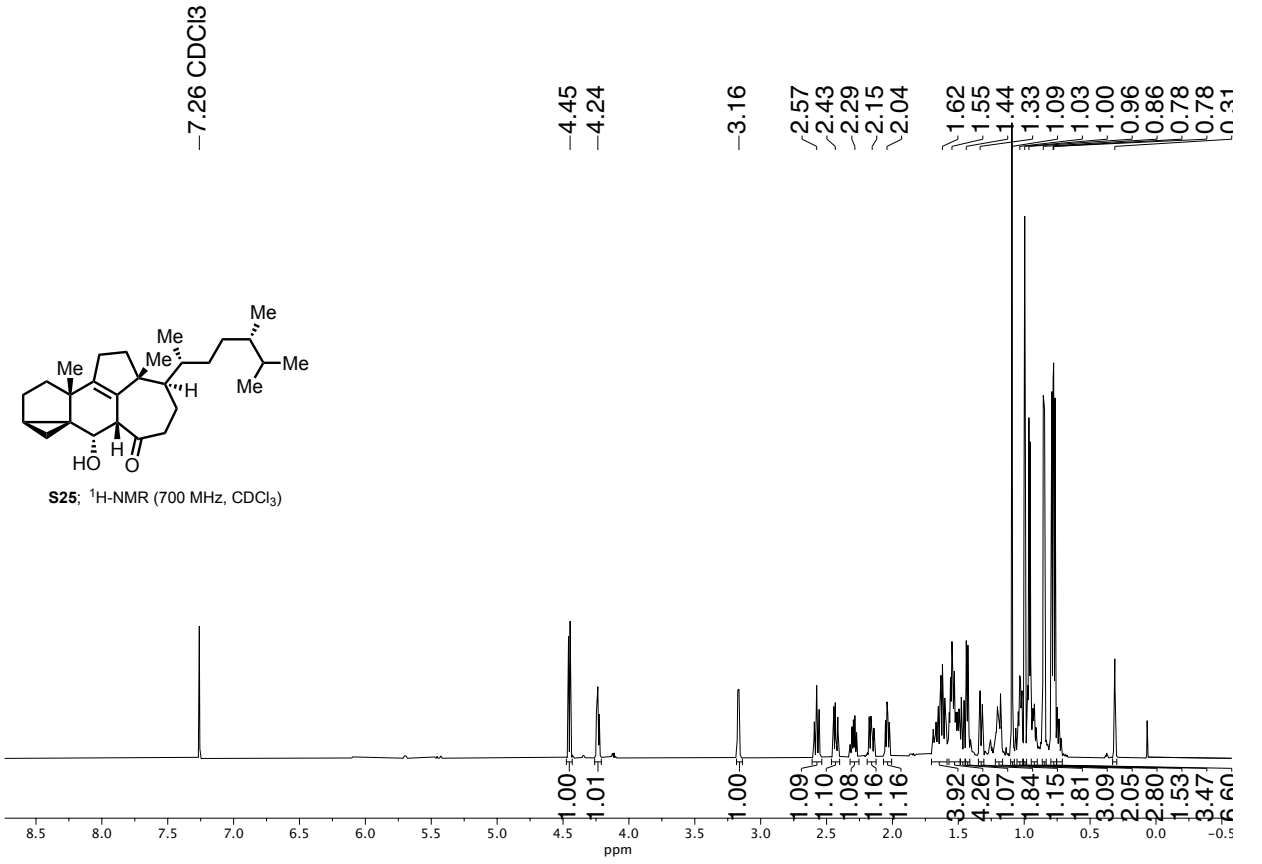
S23; ^{13}C-NMR (101 MHz, $CDCl_3$)



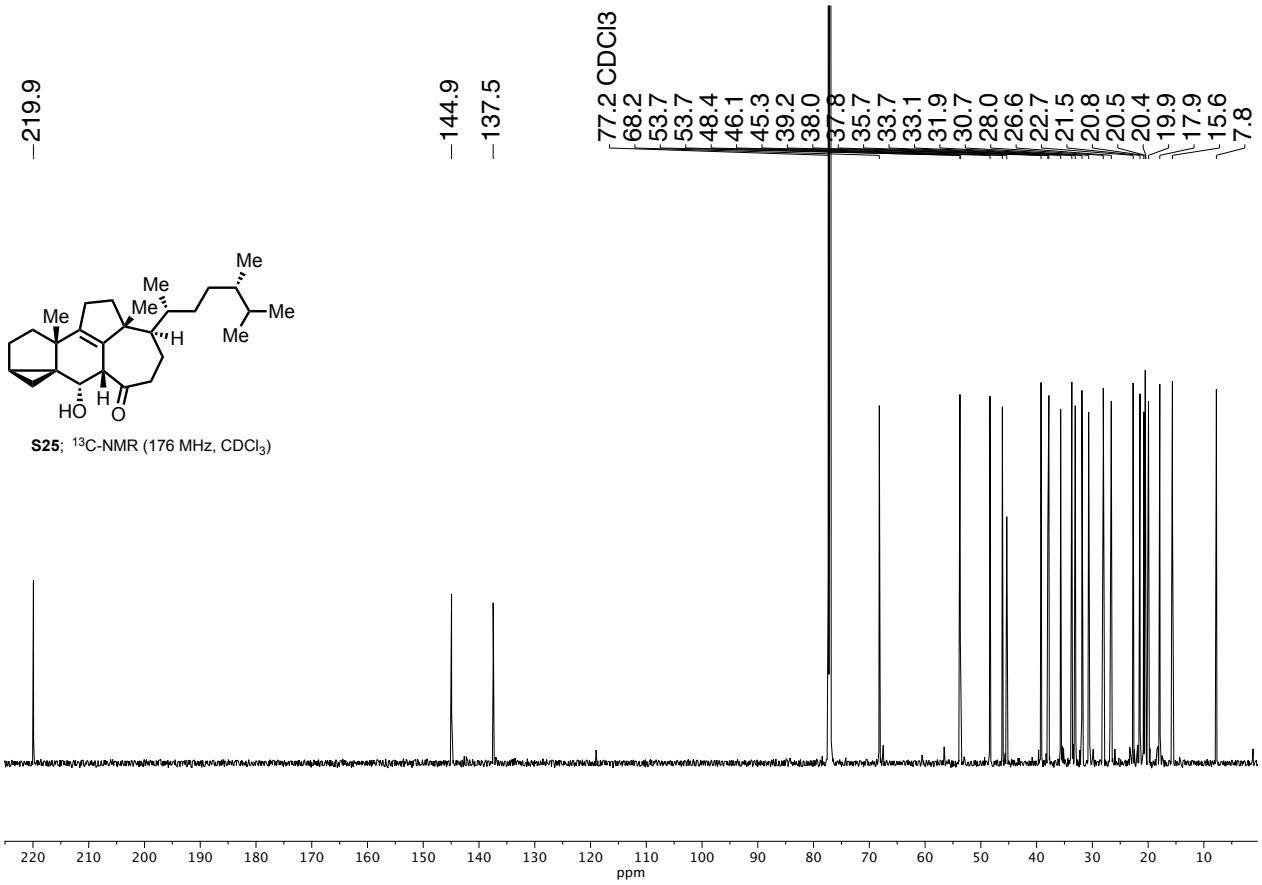
S24; ^{1}H-NMR (500 MHz, $CDCl_3$)



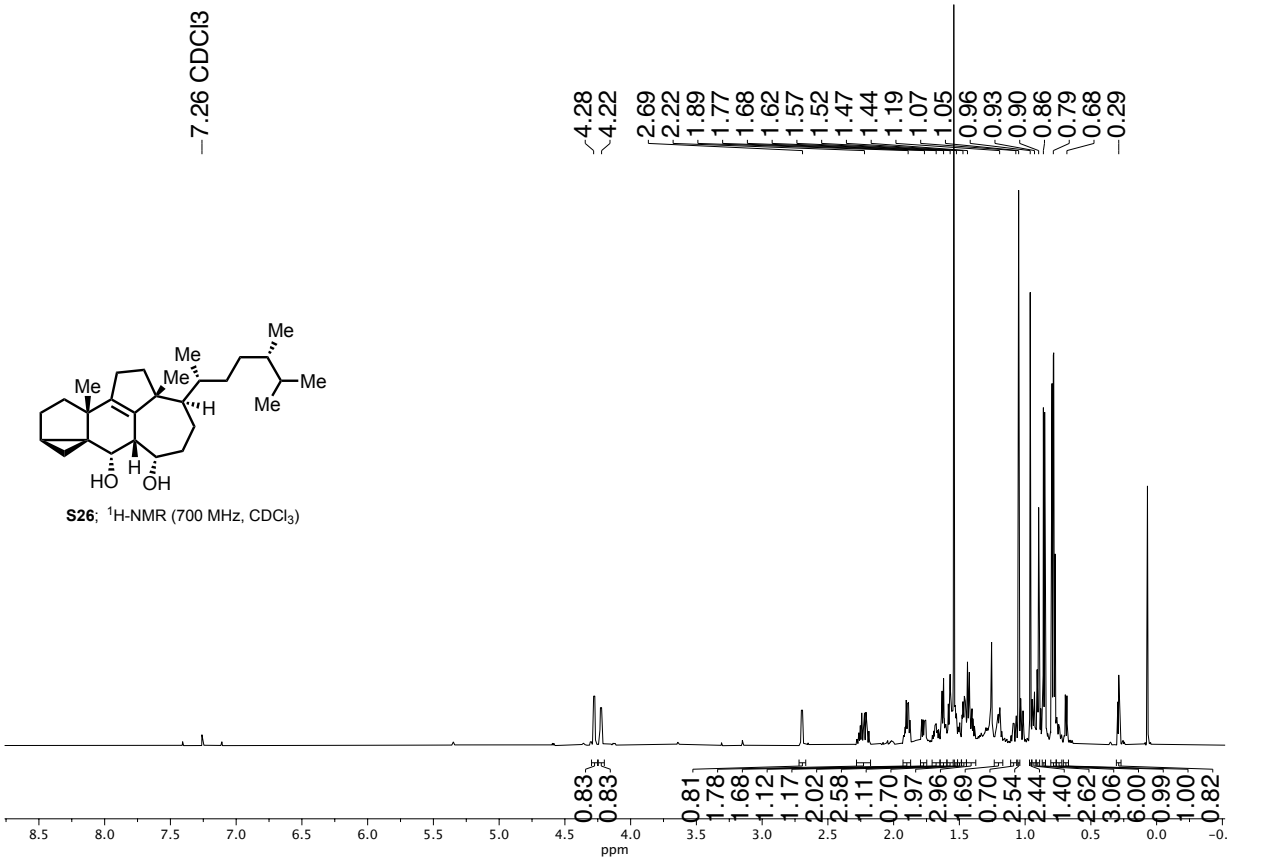
S24; ^{13}C-NMR (126 MHz, $CDCl_3$)



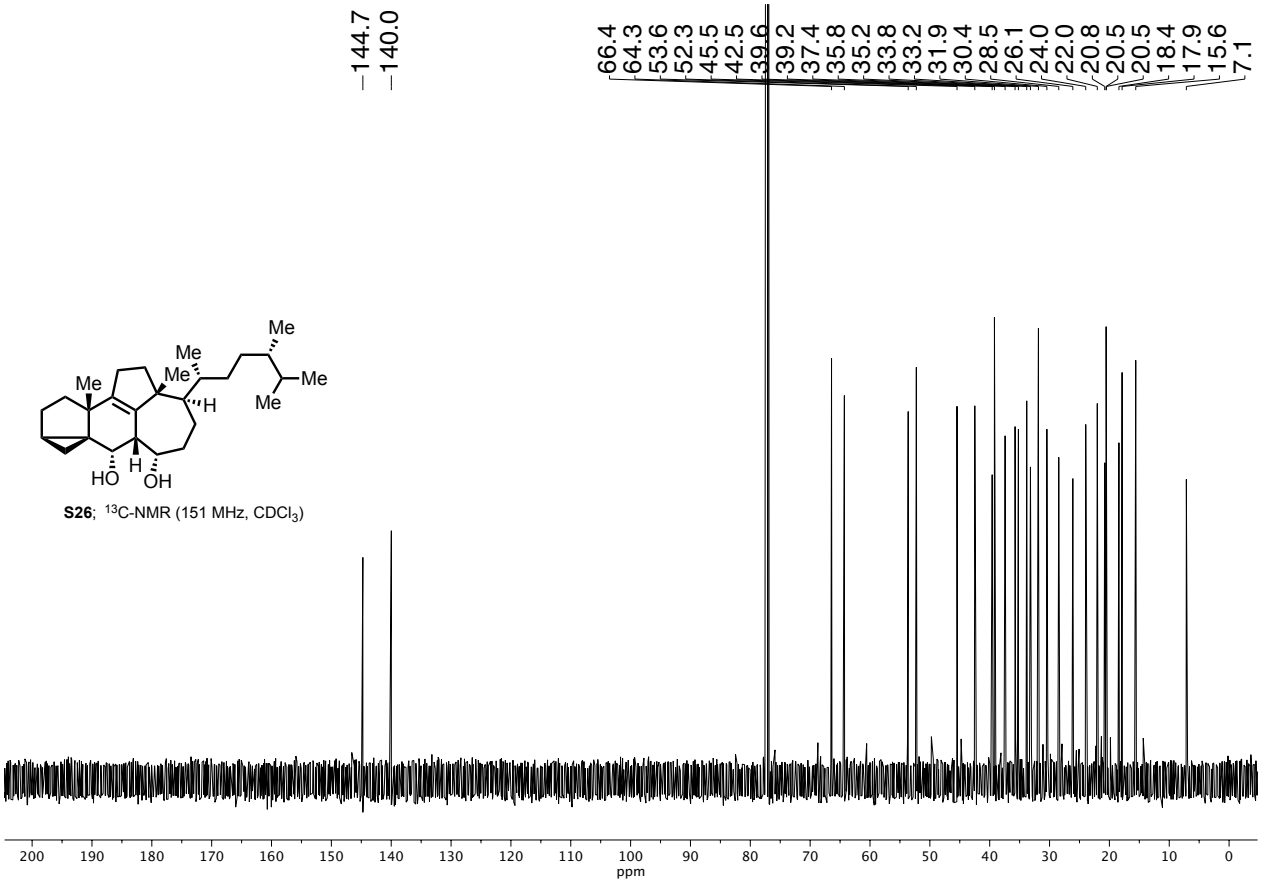
S25; ^{1}H-NMR (700 MHz, $CDCl_3$)



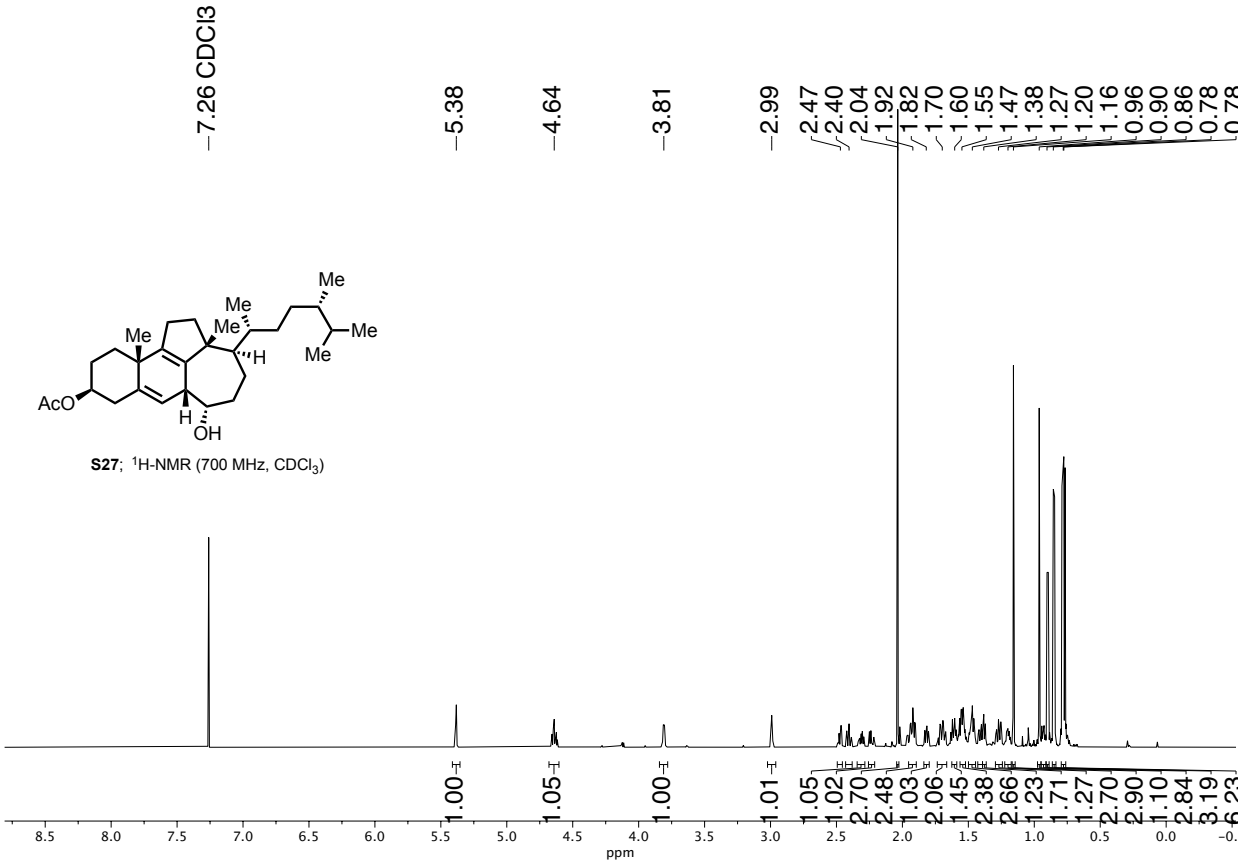
S25; ^{13}C-NMR (176 MHz, $CDCl_3$)



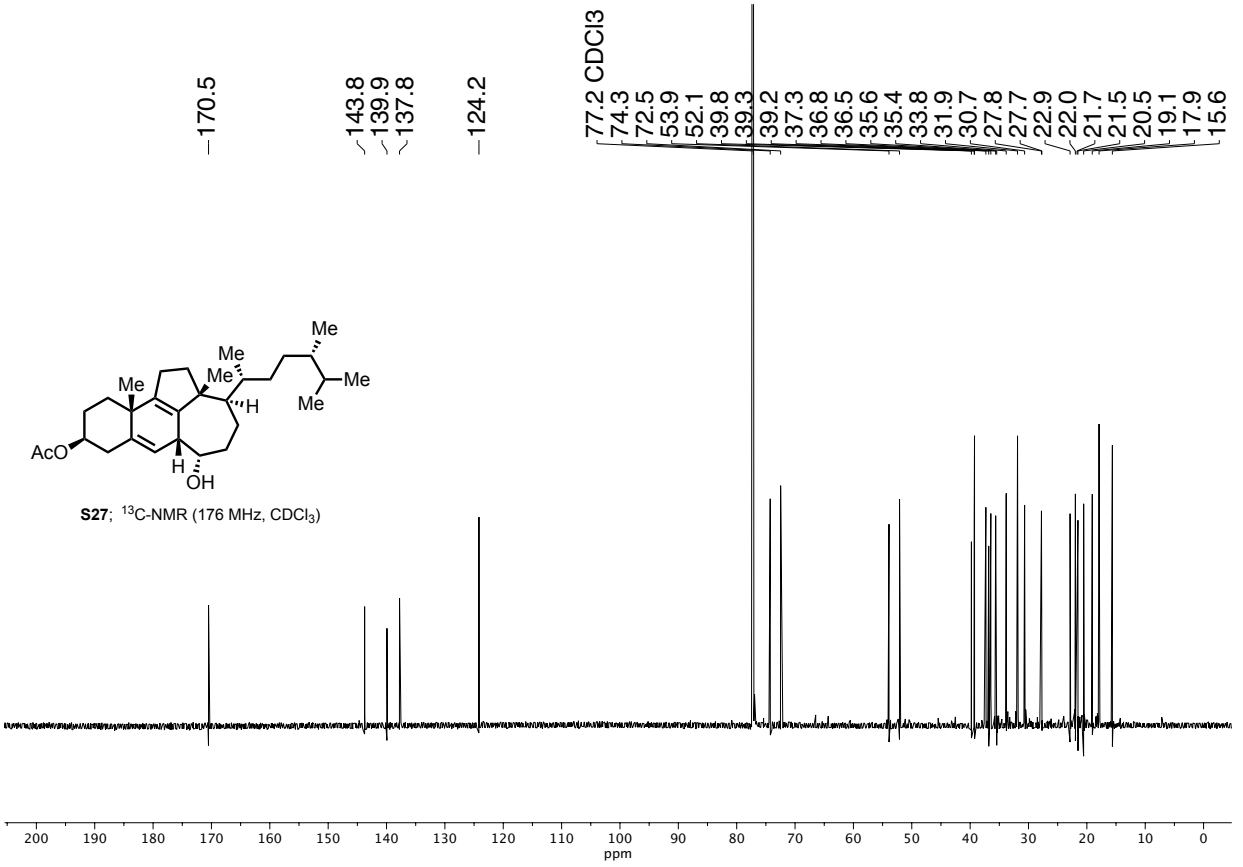
S26; ^{1}H-NMR (700 MHz, $CDCl_3$)



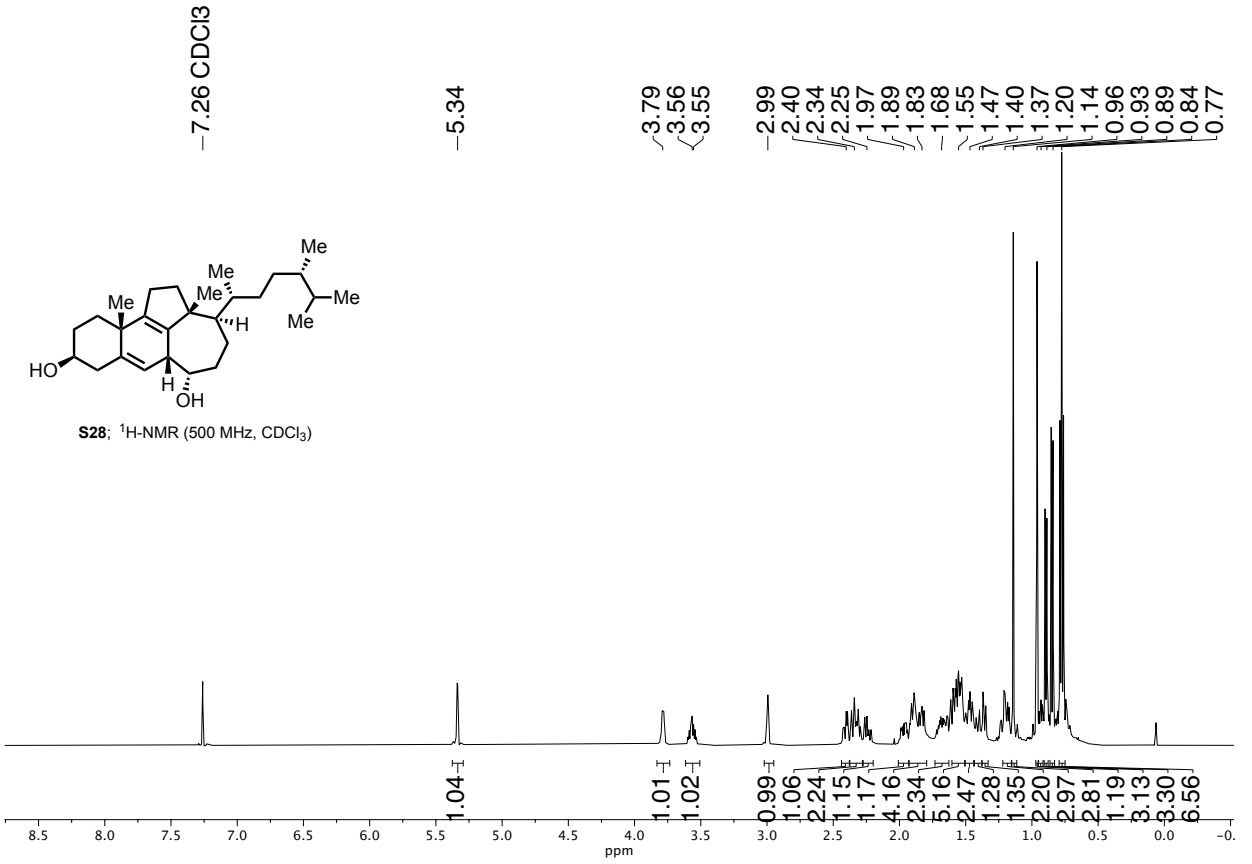
S26; ^{13}C-NMR (151 MHz, $CDCl_3$)



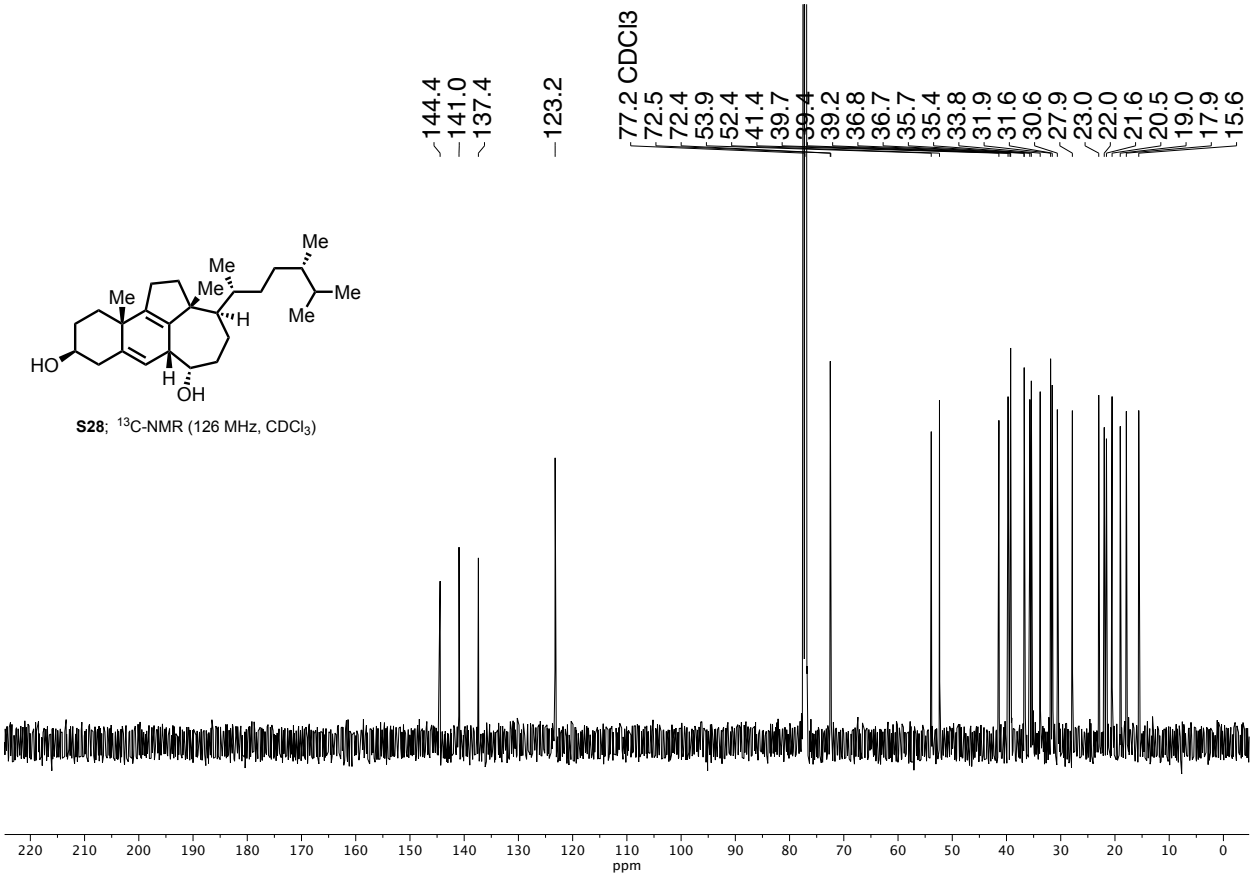
S27; ^{1}H-NMR (700 MHz, $CDCl_3$)



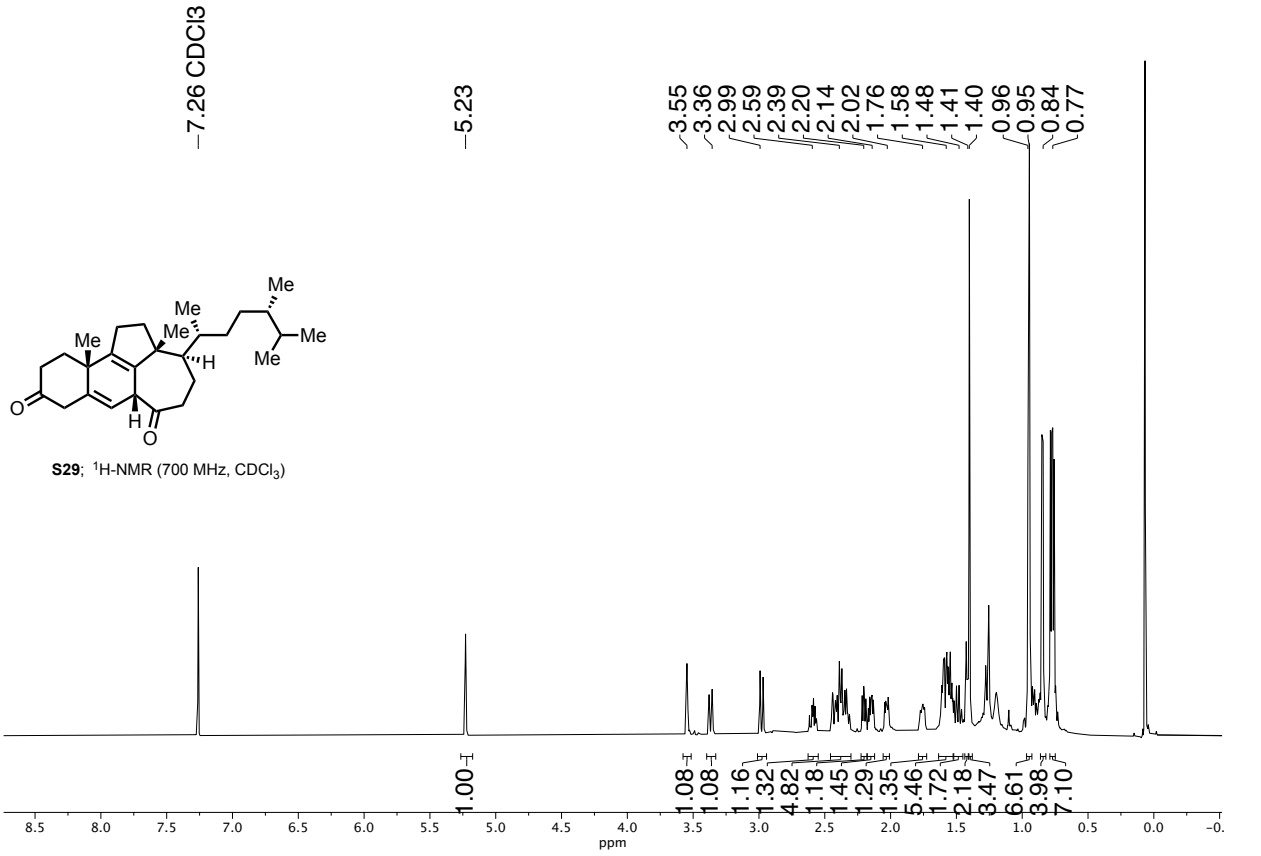
S27; ^{13}C-NMR (176 MHz, $CDCl_3$)



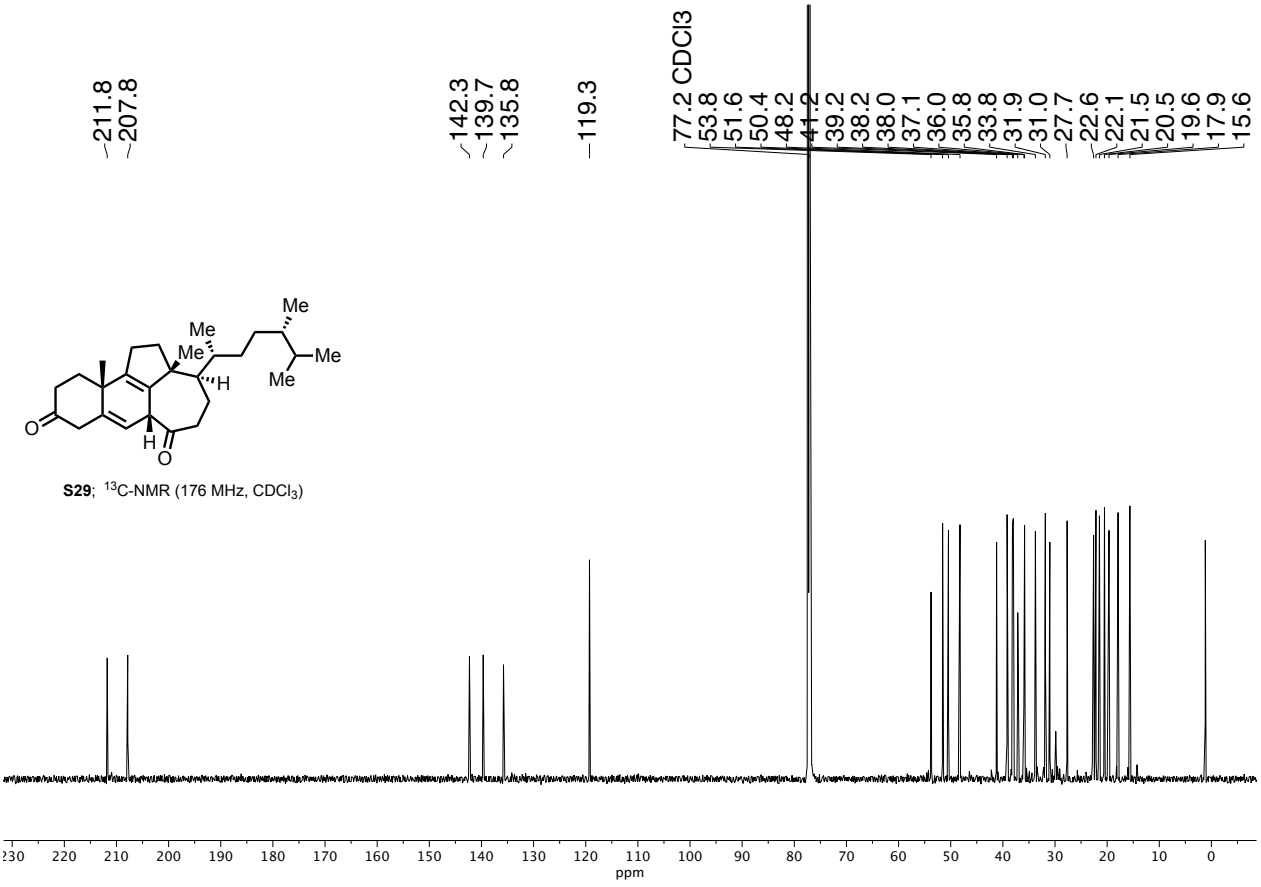
S28; ^{1}H-NMR (500 MHz, $CDCl_3$)



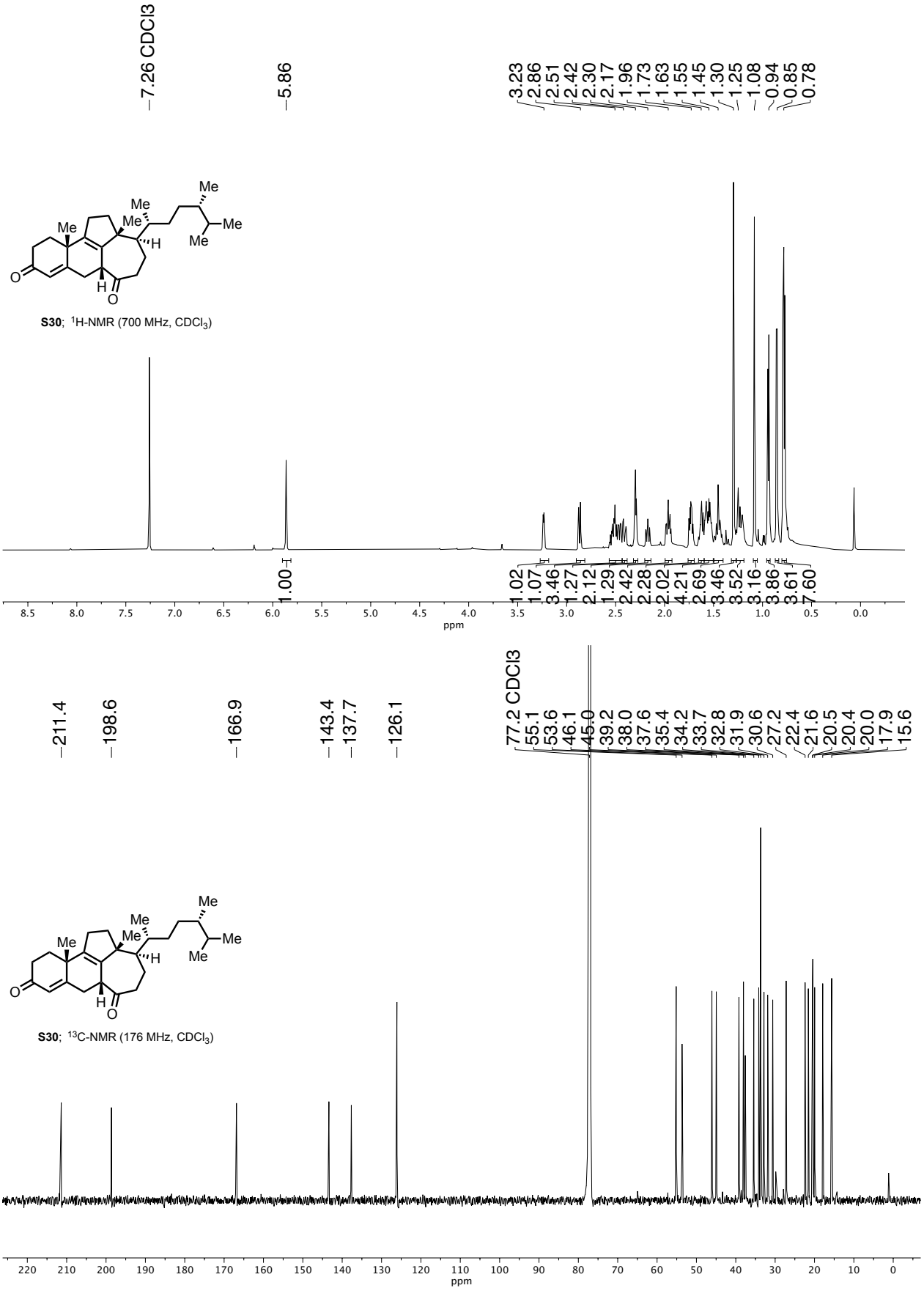
S28; ^{13}C-NMR (126 MHz, $CDCl_3$)



S29; ^{1}H-NMR (700 MHz, $CDCl_3$)

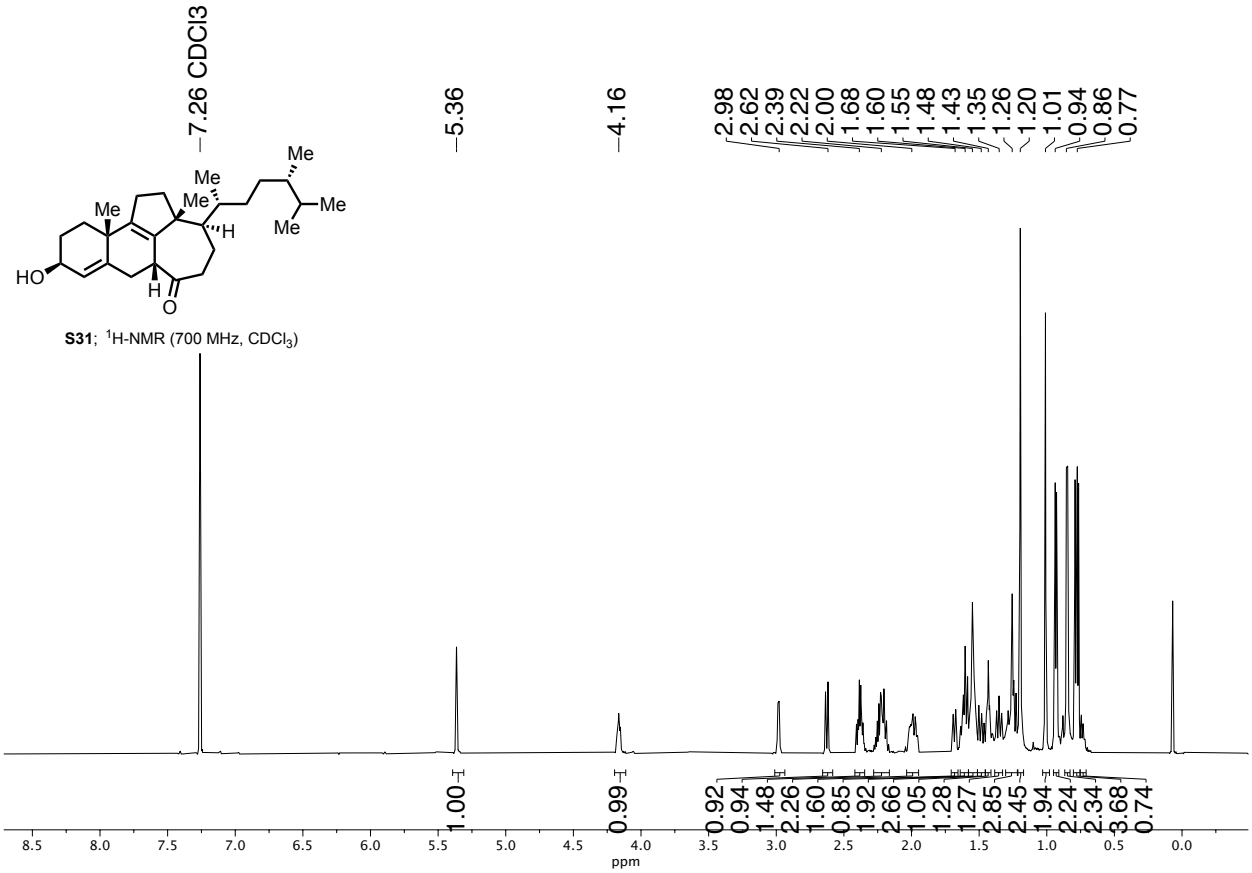


S29; ^{13}C-NMR (176 MHz, $CDCl_3$)

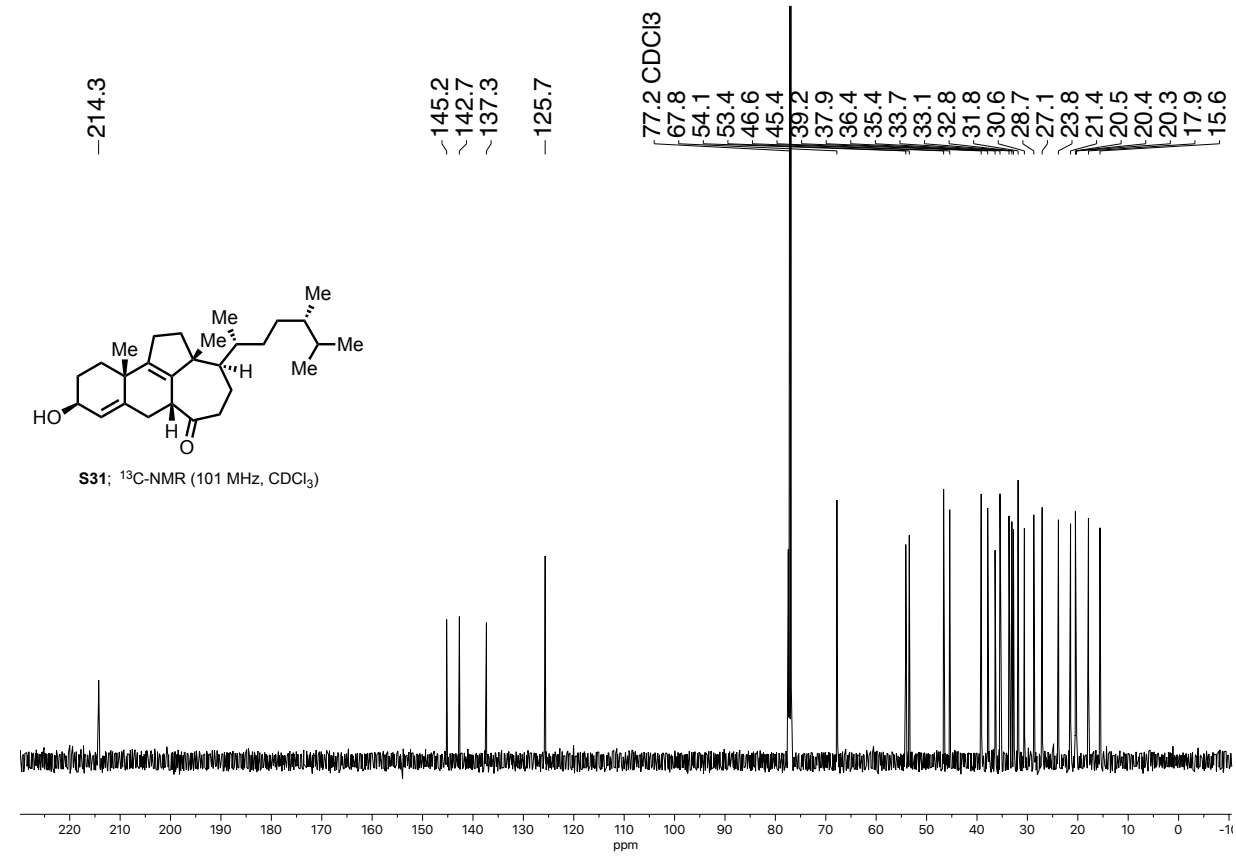


S30; ^{1}H-NMR (700 MHz, $CDCl_3$)

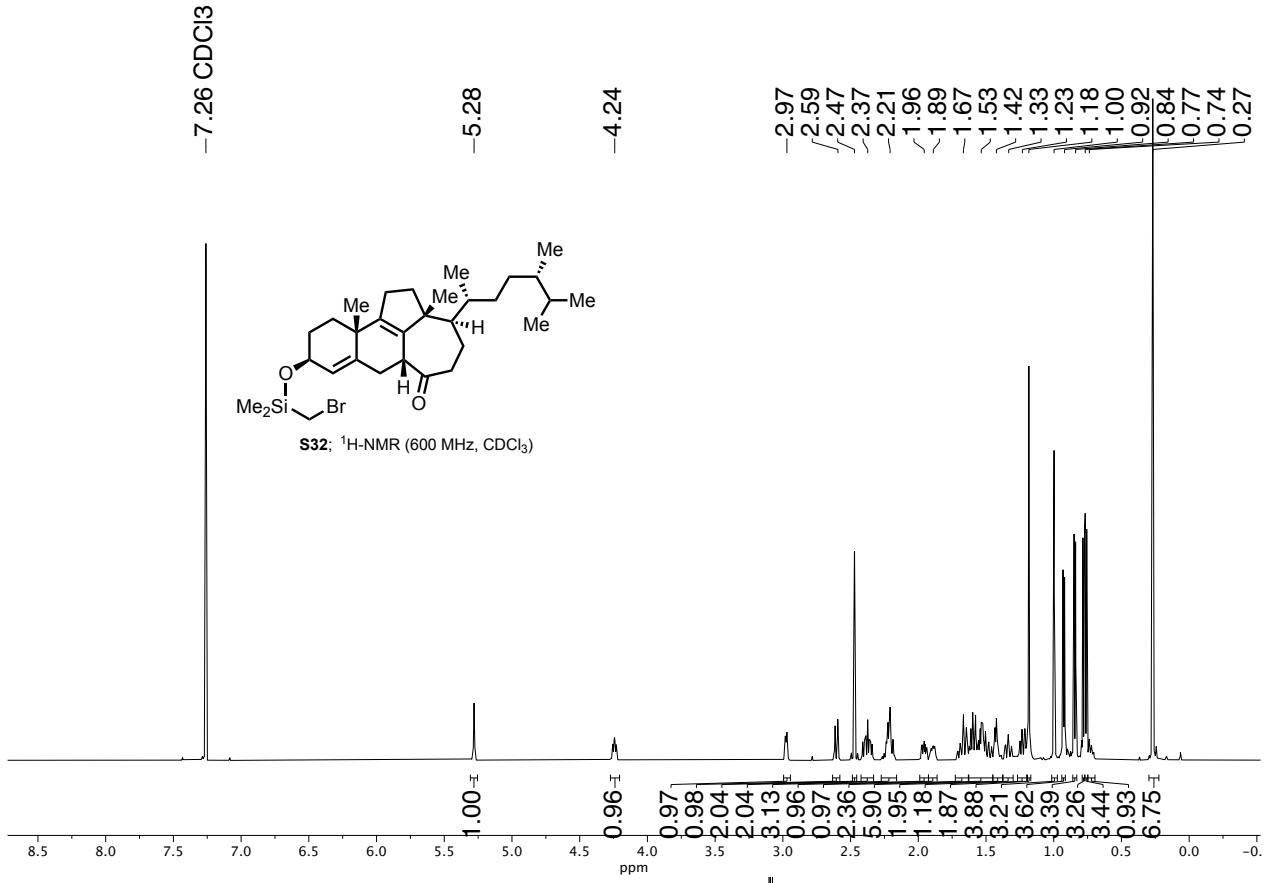
S30; ^{13}C-NMR (176 MHz, $CDCl_3$)



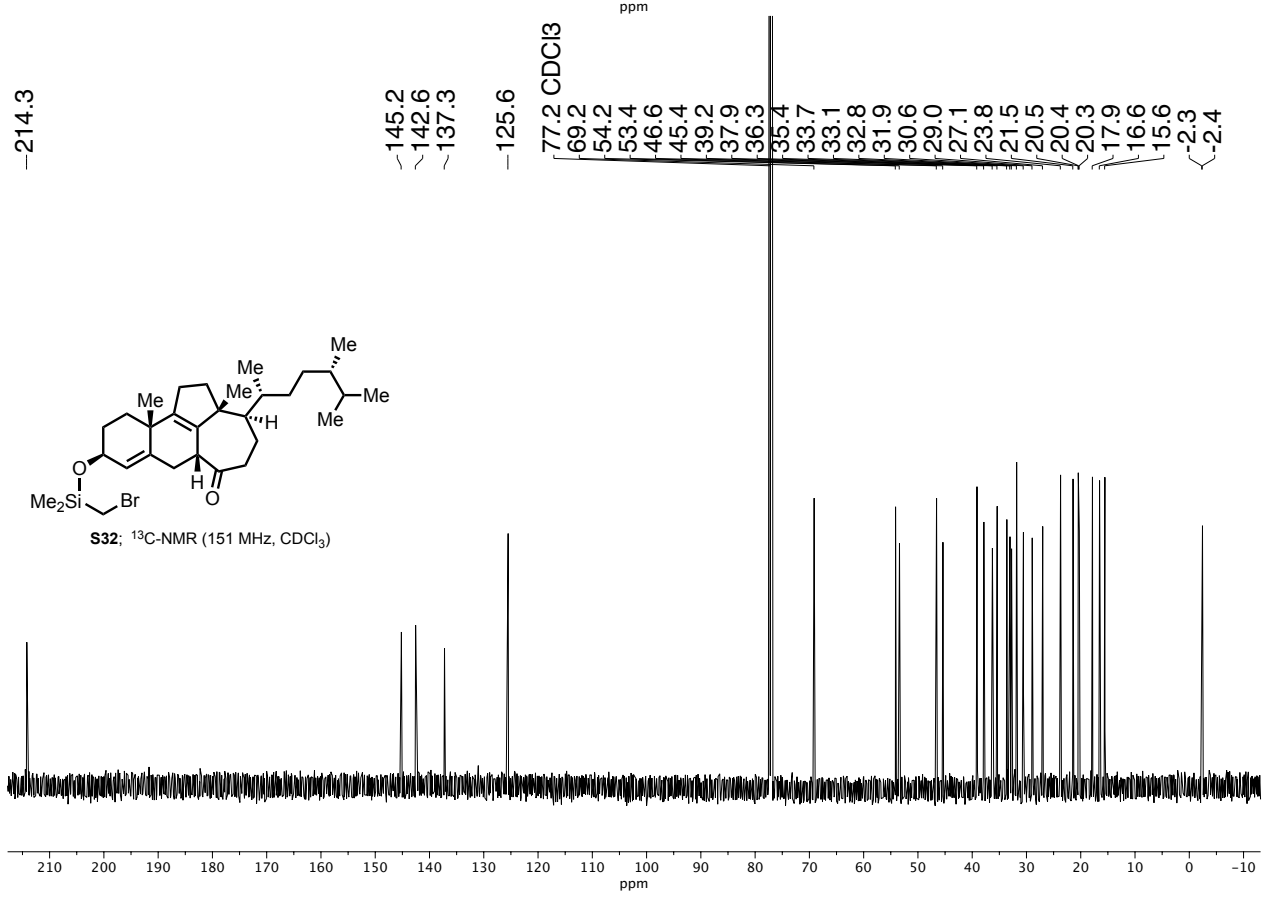
S31; ^{1}H-NMR (700 MHz, $CDCl_3$)



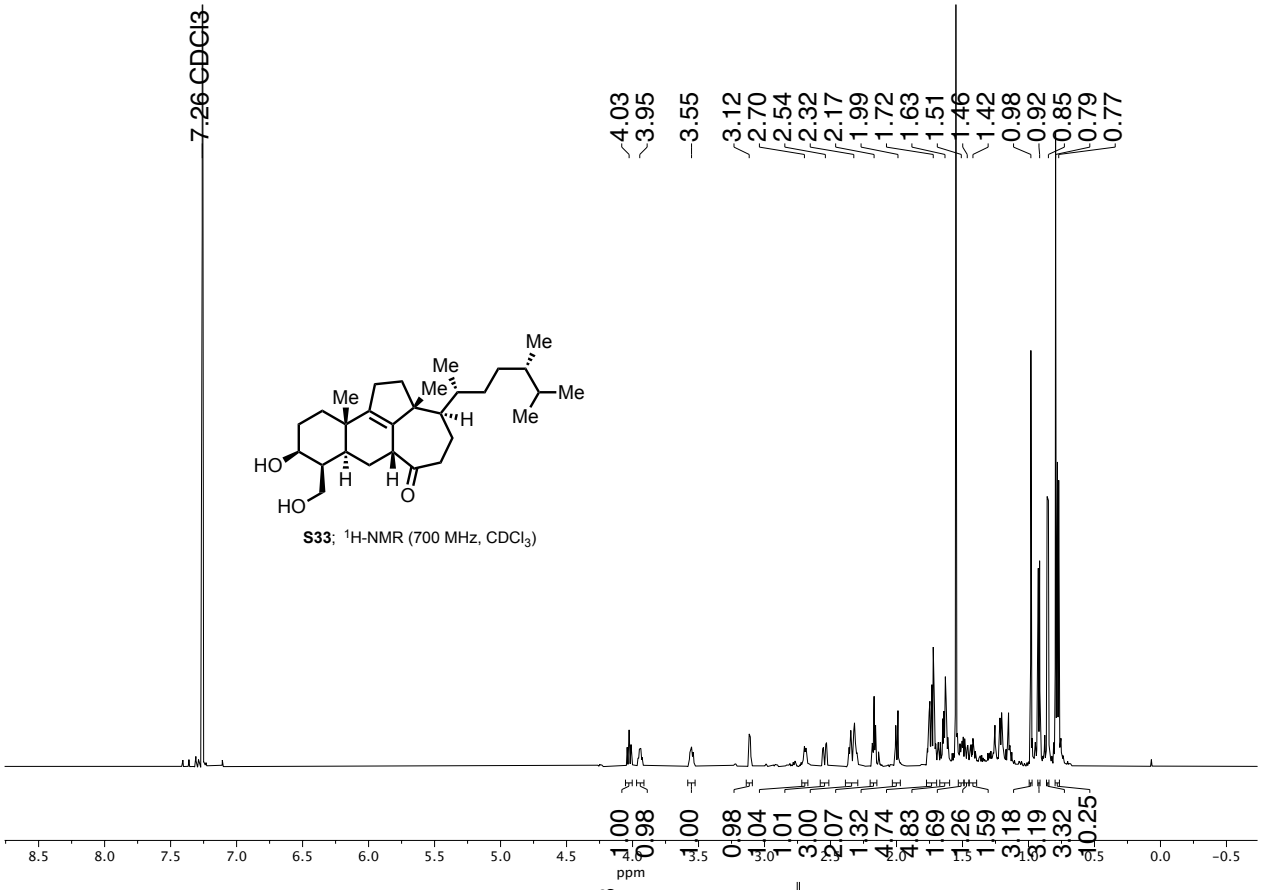
S31; ^{13}C-NMR (101 MHz, $CDCl_3$)



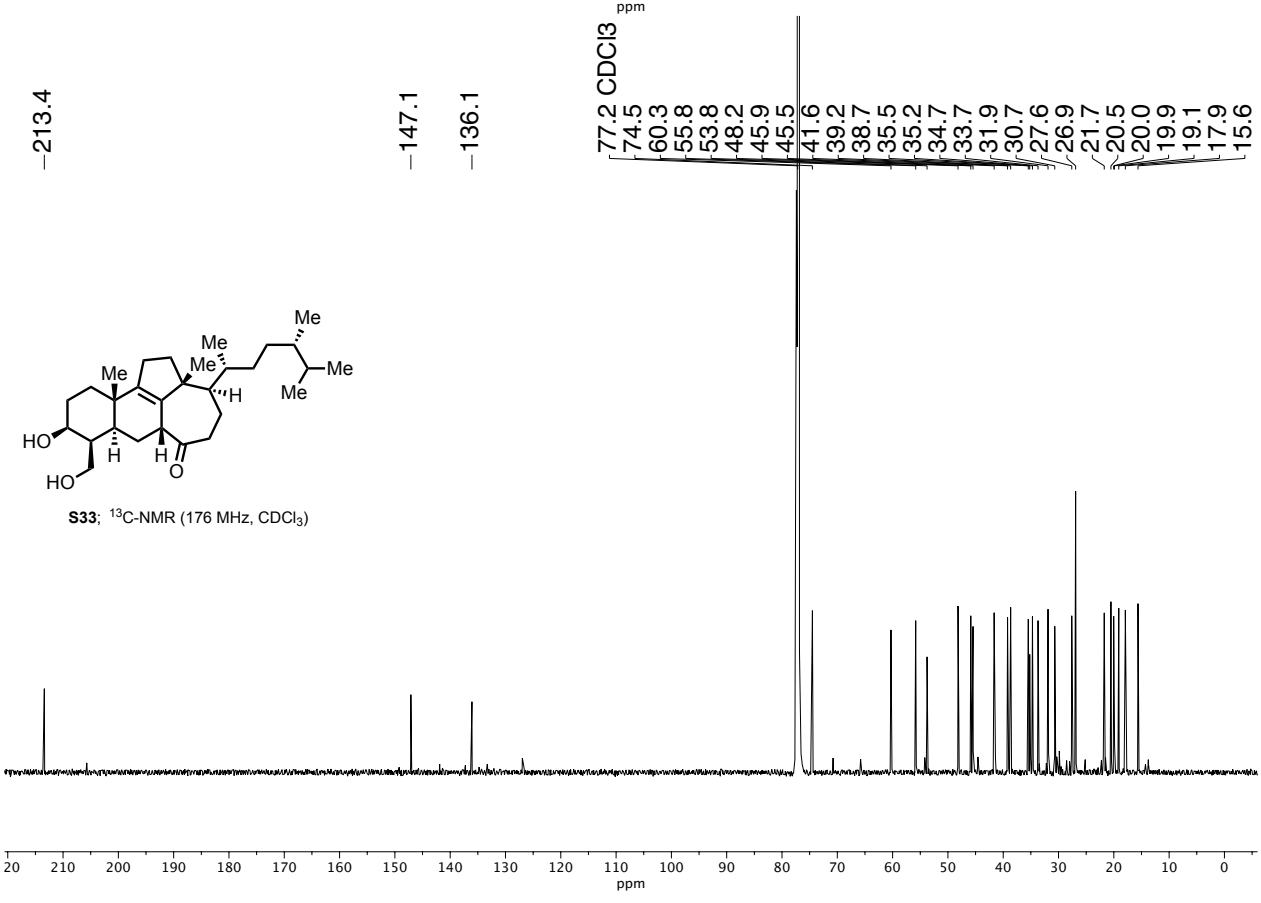
S32; ^{1}H-NMR (600 MHz, $CDCl_3$)



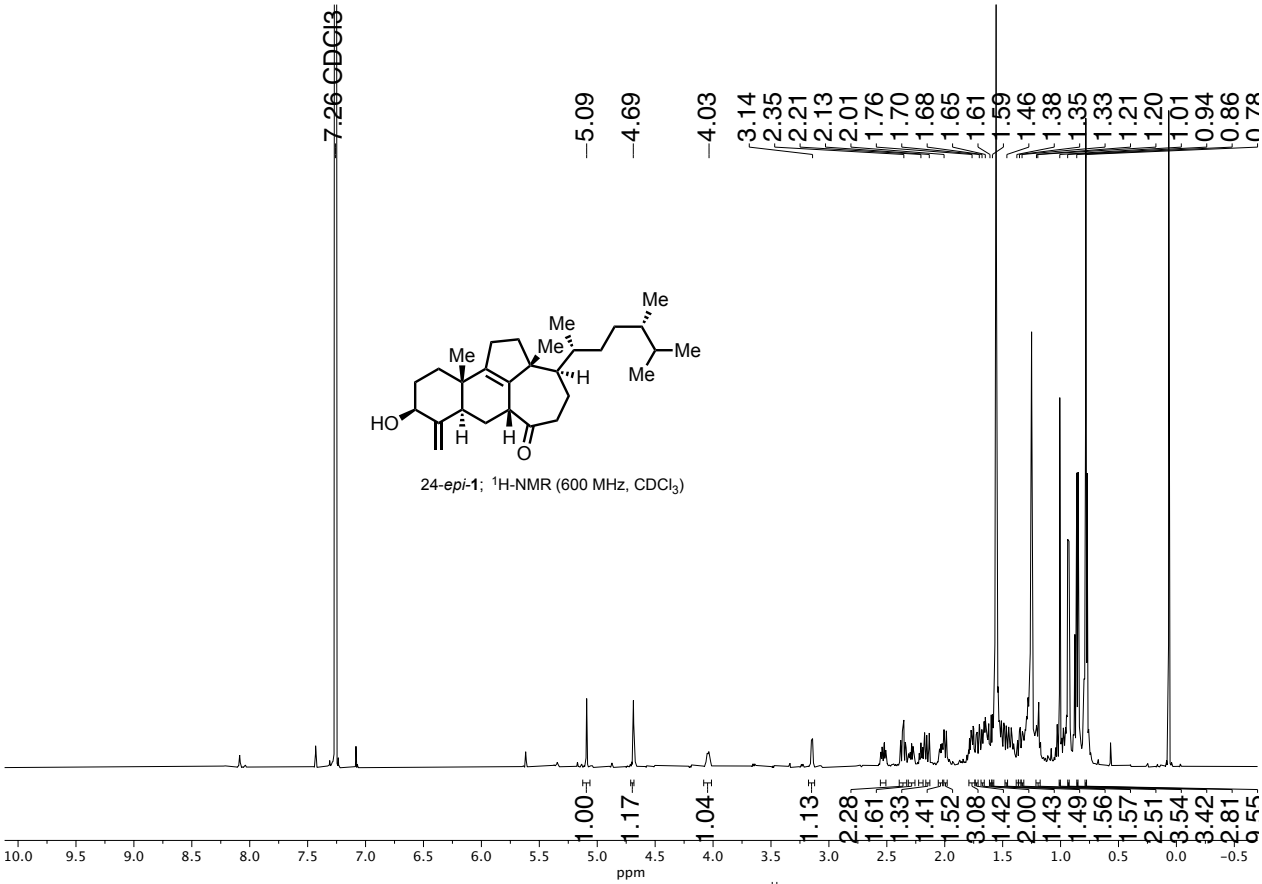
S32; ^{13}C-NMR (151 MHz, $CDCl_3$)



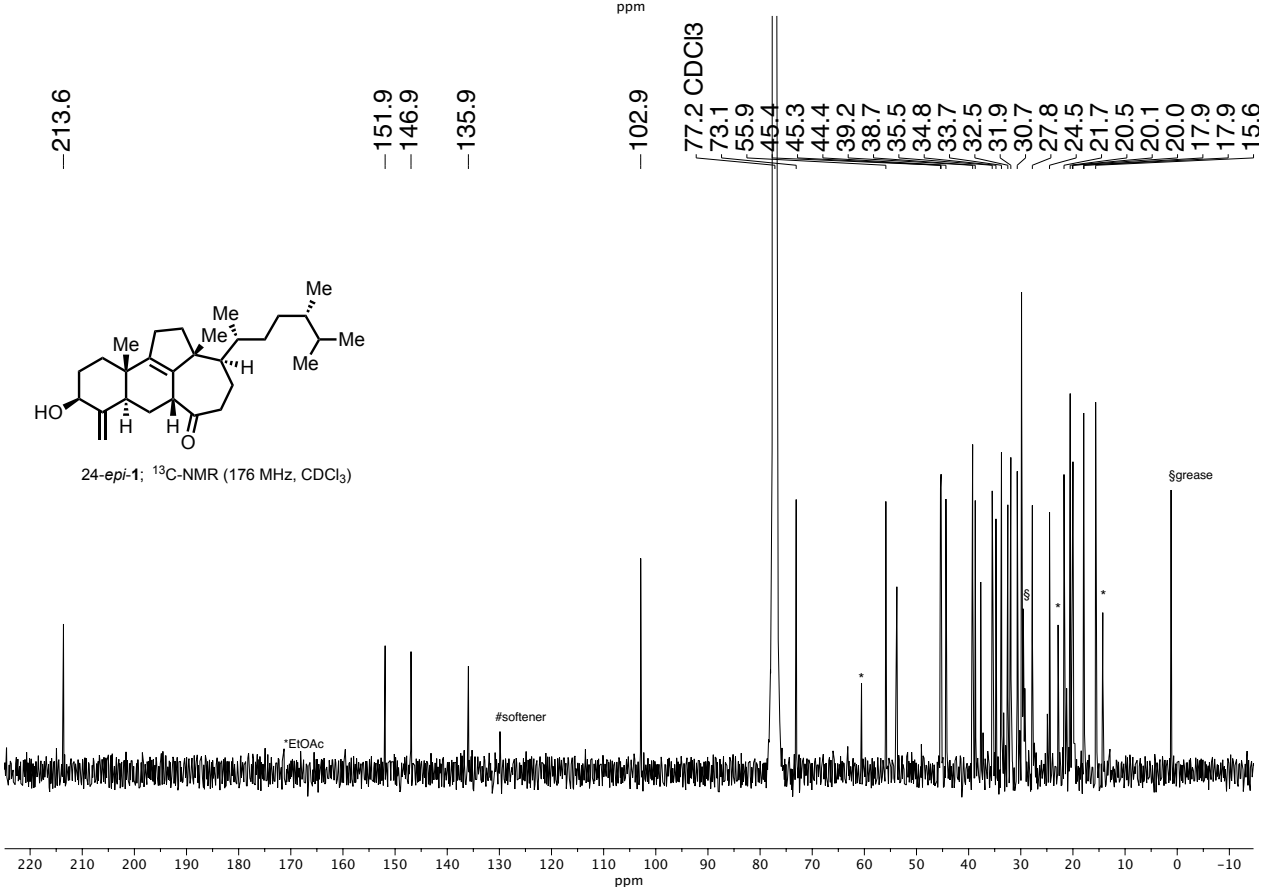
S33; ^{1}H-NMR (700 MHz, $CDCl_3$)



S33; ^{13}C-NMR (176 MHz, $CDCl_3$)



24-*epi*-**1**; ^{1}H-NMR (600 MHz, $CDCl_3$)



24-*epi*-**1**; ^{13}C-NMR (176 MHz, $CDCl_3$)

5 X-Ray Crystallographic Data

(22*E*)-3α,5-Cyclo-7α-iodo-13(14→8)*abeo*-5α-ergosta-22-en-6,14-dione (**8**)

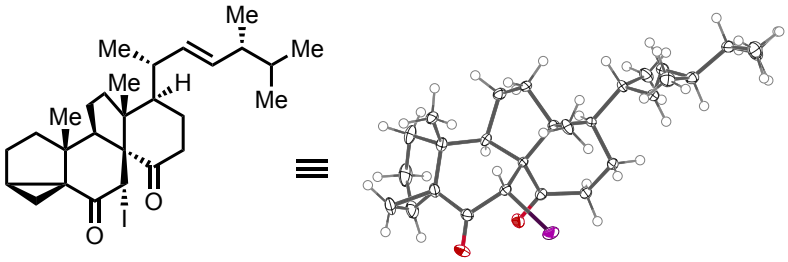


Table S6. Crystal data and structure refinement for **8**.

Identification code	1900562
Empirical formula	$C_{28}H_{41}IO_2$
Formula weight	536.54
Temperature/K	99.96
Crystal system	monoclinic
Space group	$P2_1$
a/Å	9.8801(14)
b/Å	11.6963(17)
c/Å	11.5219(17)
α/°	90
β/°	104.747(5)
γ/°	90
Volume/Å^3	1287.6(3)
Z	2
ρ_{calc} g/cm^3	1.3838
μ/mm^{-1}	1.265
F(000)	555.4
Crystal size/mm^3	0.8 × 0.18 × 0.03
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.86 to 55.16
Index ranges	–12 ≤ h ≤ 12, –15 ≤ k ≤ 15, –14 ≤ l ≤ 14
Reflections collected	33879
Independent reflections	5901 [R_{int} = 0.0440, R_{sigma} = 0.0322]
Data/restraints/parameters	5901/1/286
Goodness-of-fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.0226, wR_2 = 0.0463
Final R indexes [all data]	R_1 = 0.0277, wR_2 = 0.0485
Largest diff. peak/hole / e Å^{-3}	0.71/–0.45
Flack parameter	0.026(15)

Dankasterone B (**2**)

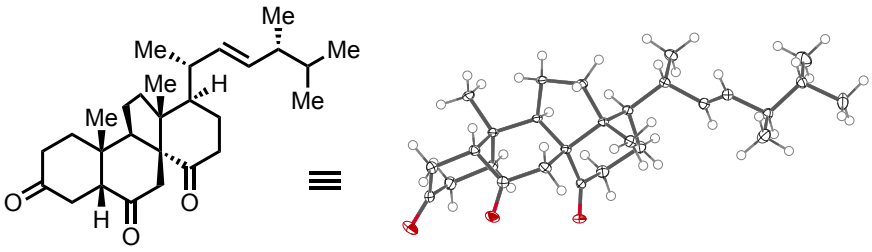


Table S7. Crystal Data and Structure Refinement for **2**.

Identification code	1900563
Empirical formula	$C_{28}H_{42}O_3$
Formula weight	426.61
Temperature/K	100.04
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	11.238
b/Å	11.741
c/Å	18.649
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2460.8
Z	4
ρ_{calc} g/cm^3	1.152
μ/mm^{-1}	0.072
F(000)	936.0
Crystal size/mm^3	0.35 × 0.18 × 0.06
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.018 to 61.236
Index ranges	–16 ≤ h ≤ 16, –16 ≤ k ≤ 16, –26 ≤ l ≤ 26
Reflections collected	56666
Independent reflections	7551 [R_{int} = 0.0458, R_{sigma} = 0.0302]
Data/restraints/parameters	7551/0/286
Goodness-of-fit on F^2	1.140
Final R indexes [I>=2σ (I)]	R_1 = 0.0537, wR_2 = 0.1233
Final R indexes [all data]	R_1 = 0.0563, wR_2 = 0.1244
Largest diff. peak/hole / e Å^{-3}	0.73/–0.33
Flack parameter	–0.1(3)

References

(1) R. C. Heinze, P. Heretsch, Translation of a Polar Biogenesis Proposal into a Radical Synthetic Approach: Synthesis of Pleurocin A/Matsutakone and Pleurocin B, *J. Am. Chem. Soc.* **2019**, *141*, 1222–1226.

(2) R. C. Heinze, D. Lentz, P. Heretsch, Synthesis of Strophasterol A Guided by a Proposed Biosynthesis and Innate Reactivity, *Angew. Chem., Int. Ed.* **2016**, *55*, 11656–11659.

(3) T. Amagata, M. Tanaka, T. Yamada, M. Doi, K. Minoura, H. Ohishi, T. Yamori, A. Numata, Variation in Cytostatic Constituents of a Sponge-Derived *Gymnascella dankaliensis* by Manipulating the Carbon Source, *J. Nat. Prod.* **2007**, *70*, 1731–1740.

(4) T. Amagata, M. Doi, M. Tohgo, K. Minoura, A. Numata, Dankasterone, a new class of cytotoxic steroid produced by a *Gymnascella* species from a marine sponge, *Chem. Commun.* **1999**, *14*, 1321–1322.

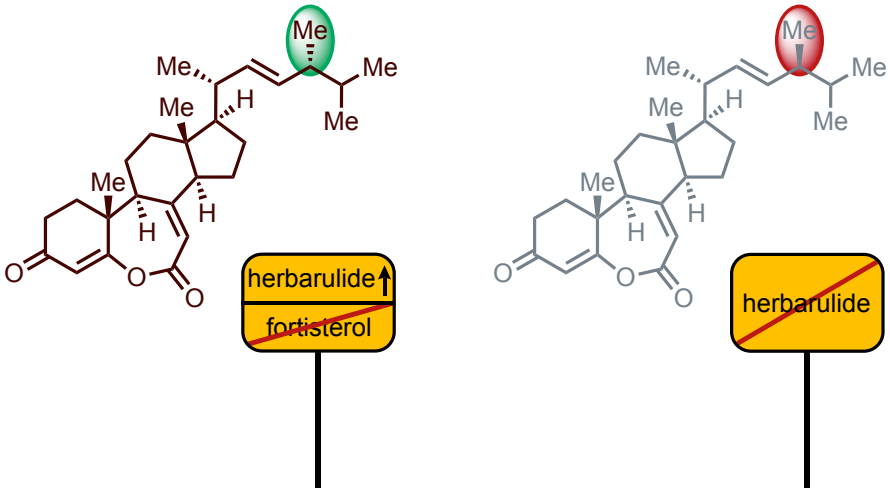
(5) W. Gao, C. Chai, Y. He, F. Li, X. Hao, F. Cao, L. Gu, J. Liu, Z. Hu, Y. Zhang, Periconiastone A, an Antibacterial Ergosterol with a Pentacyclo[8.7.0.$0^{1,5}$.$0^{2,14}$.$0^{10,15}$]-heptadecane System from *Periconia* sp. TJ403-rc01, *Org. Lett.* **2019**, *21*, 8469–8472.

(6) J. Gong, P. Sun, N. Jiang, R. Riccio, G. Lauro, G. Bifulco, T.-J- Li, W. H. Gerwick, W. Zhang, New Steroids with a Rearranged Skeleton as (h)P300 Inhibitors from the Sponge *Theonella swinhoei, Org. Lett.* **2014**, *16*, 2224–2227.

Appendix C

Synthesis of the Alleged Structures of Fortisterol and Herbarulide and Structural Revision of Herbarulide

Fenja L. Duecker, Robert C. Heinze, Mira Mueller, Sudong Zhang, Philipp Heretsch[a]



a Institut für Chemie und Biochemie
Freie Universität Berlin
Takustraße 3, 14195 Berlin, Germany

This article is reproduced with permission from:
F. L. Duecker, R. C. Heinze, M. Mueller, S. Zhang, P. Heretsch, *Org. Lett.* **2020**, 22, 1585–1588.
DOI: 10.1021/acs.orglett.0c00180

Author contribution: This project was designed by Fenja L. Dücker, Robert C. Heinze and Philipp Heretsch. The experimental and synthetic work was carried out by Fenja L. Dücker, Robert C. Heinze, Mira Müller (during her Bachelor thesis, supervised by Fenja L. Dücker) and Sudong Zhang (during his Master thesis). The analytical characterizations were conducted by Fenja L. Dücker and Mira Müller. The manuscript was prepared by Fenja L. Dücker and Philipp Heretsch.

OL | Organic Letters

pubs.acs.org/OrgLett Letter

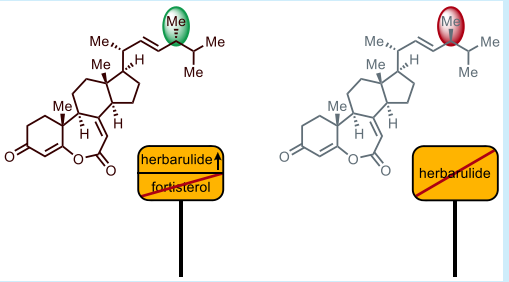
Synthesis of the Alleged Structures of Fortisterol and Herbarulide and Structural Revision of Herbarulide

Fenja L. Duecker, Robert C. Heinze, Mira Mueller, Sudong Zhang, and Philipp Heretsch*

Cite This: *Org. Lett.* 2020, 22, 1585−1588 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The alleged structures of 5,6-epoxy-5,6-secosteroids fortisterol and herbarulide differ only in the stereoconfiguration of C24. Applying insights into the hypothetical biosynthesis of this class of natural products, we devised a short synthetic access (four and eight steps, respectively) starting from commercial ergosterol and featuring an alkoxy radical rearrangement. The comparison of nuclear magnetic resonance spectroscopic data revealed herbarulide having the proposed structure of fortisterol, whereas synthesis of another two diastereomers could not conclusively prove the true structure of fortisterol. Along the way, a high-yielding and scalable access to the infamous Burawoy's ketone not requiring chromium(VI) reagents was developed.



Secosteroids constitute a growing compound class with new examples being continuously reported.[1] Their common structural feature, one or several cleaved C−C bonds in the tetracyclic steroid framework, provides means for their formal classification. Unusual C−C scissions, typically accompanied by oxidative modifications, contribute to the complexity of these natural products and attract the attention of the (bio)synthetic community, frequently leading to speculation on possible biosynthesis and viable chemical access.[2] On several occasions, however, unusual structures have been proposed, based mainly on spectroscopic evidence. In the absence of an X-ray crystallographic analysis, these bear an inherent structural ambiguity.[3] In these cases, either biosynthetic insights or chemical synthesis can corroborate a proposed structure.

The comparably small collection of 5,6-epoxy-5,6-secosteroids, with herbarulide (**1**),[4] fortisterol (**2**),[5] astersterol A (**3**),[6] and eringiacetal A (**4**)[7] as members (Figure 1), shares additional degrees of oxidation at C5 and C6. Among them, **1** and **2** differ only with respect to their stereoconfiguration at C24. Herbarulide (**1**) has been isolated by Krohn and coworkers from cultures of the ascomycete *Pleospora herbarum* in 1999, with its structural elucidation mainly based on 2D NMR analysis as well as a comparison with (22*E*)-campesta-4,6,8(14),22-tetraen-3-one (**5**).[4] This appears especially problematic in light of the side chain stereocenter C24 because spectral differences for the respective ergostane and campestane series are known to be minuscule.[8] In 2006, Guo reported a very similar structure for a secosteroid isolated from the marine sponge *Biemna fortis*, accordingly named fortisterol (**2**), without referencing Krohn's preceding work and, once more, basing the stereoconfiguration of the side chain on a comparison, this time to (22*E*)-ergosta-4,7,22-triene-3,6-dione (**6**).[5] Interestingly, material with the alleged structure of **1** was

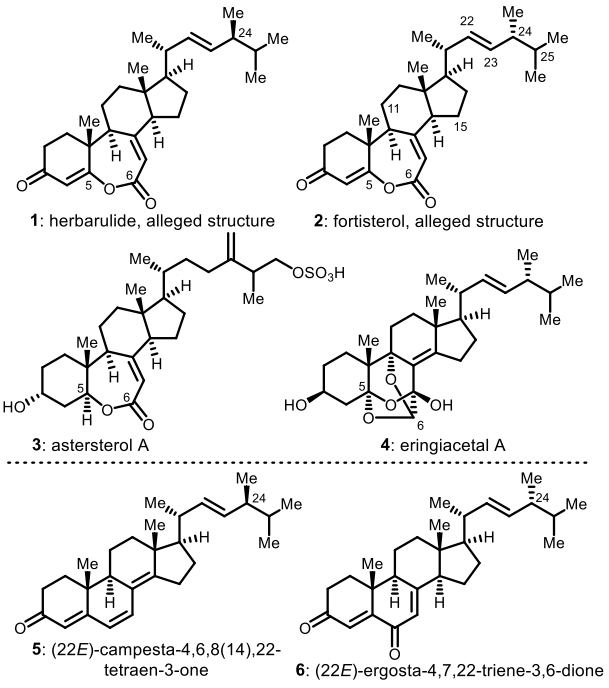
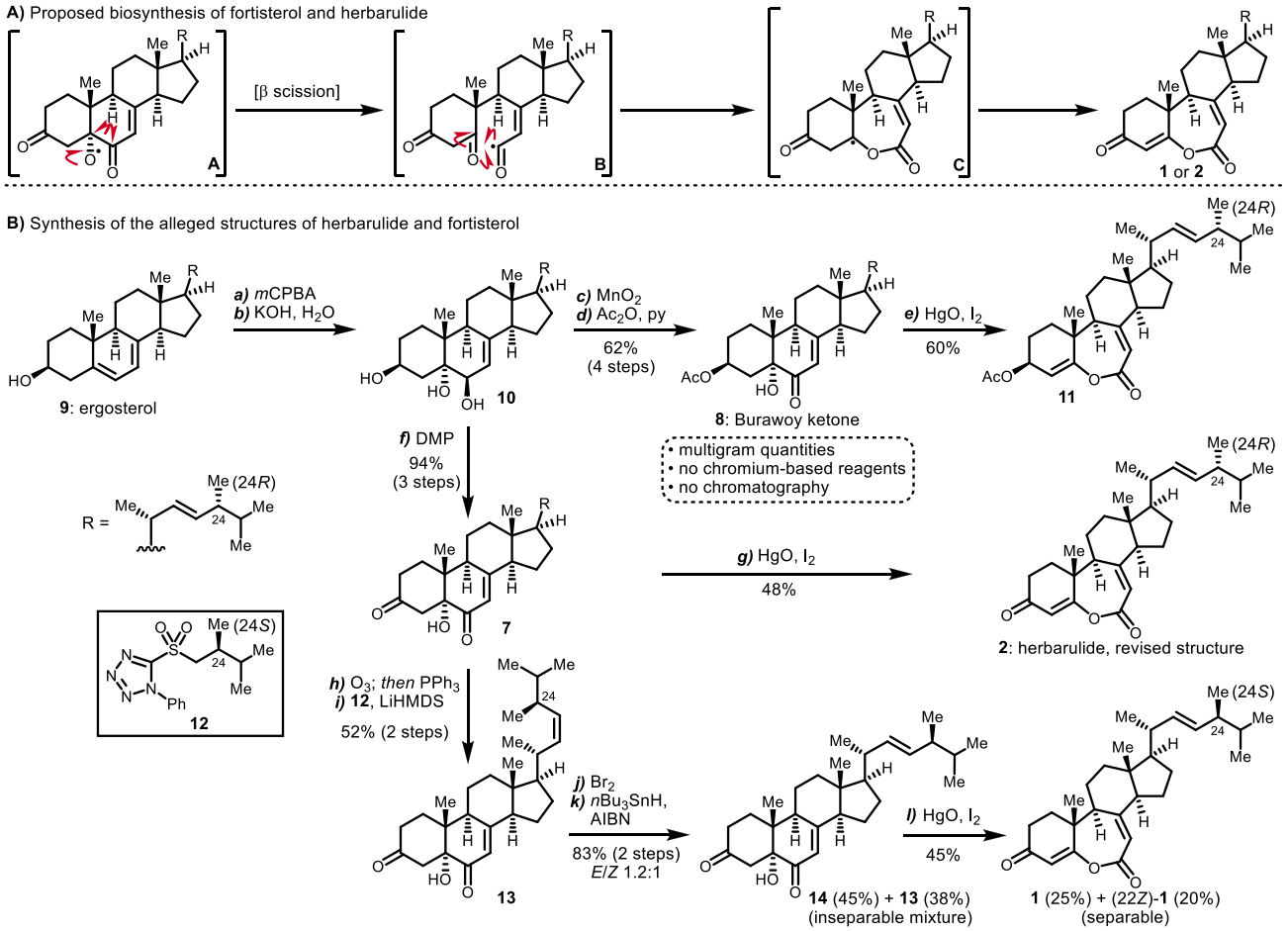


Figure 1. Alleged molecular structures of 5,6-epoxy-5,6-secosteroids herbarulide (**1**) and fortisterol (**2**). Molecular structures of astersterol A (**3**), eringiacetal A (**4**), campestane **5**, and ergostane **6**.

Received: January 13, 2020
Published: January 30, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00180
Org. Lett. 2020, 22, 1585−1588

Scheme 1. (A) Proposed Biosynthesis of Fortisterol and Herbarulide Following a Radical Pathway and (B) Synthesis of the Alleged Structures of Fortisterol and Herbarulide and Structural Revision[a]



[a]See the Supporting Information for reagents and conditions. AIBN = 2,2′-azobis(2-methylpropionitrile), DMP = Dess−Martin periodinane, HMDS = *bis*(trimethylsilyl)amide, *m*CPBA = *meta*-chloroperoxybenzoic acid, py = pyridine.

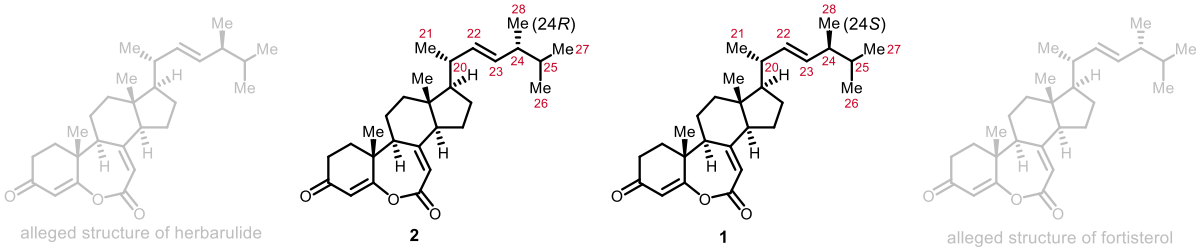
reisolated at least twice, once by Ren in 2017 from the Taiwanese fungus *Antrodia camphorata*, neither citing Krohn's work nor providing spectral data,[9] and another time by Chen and Liu in 2019 from the fungus *Stereum hirsutum*, this time citing the work of Krohn but displaying the alleged structure of fortisterol (**2**) and naming the compound herbarulide without further explanation or structural corroboration (with the NMR data being in agreement with Krohn's report).[10] Since tabulated NMR-shifts in Guo's seminal paper on fortisterol show several inconsistencies with regard to the assignment of H- as well as C-atoms 2, 11, 15, 22, 23, and 25 (see the Supporting Information), we suspected the structures of fortisterol and herbarulide to be ambiguous and engaged in their elucidation by chemical synthesis.

Our synthetic rationale was based on biosynthetic considerations and entailed an oxidative radical cascade, as depicted in Scheme 1A.[11] In line with our radical-based approach to seco- and *abeo*-steroids,[12] we have recently shown a 14-alkoxy radical to initiate a cascade and give rise to swinhoeisterol A, periconiastone A, and dankasterones A and B, where seemingly remote and subtle structural changes bore a large influence on the reaction outcome.[12c]

A 5-alkoxy radical such as **A** (Scheme 1A) was expected to undergo β scission of the C5−C6 bond (intermediate **B**), followed by recombination of the 5-oxo moiety with the thus-generated acyl radical to form lactone radical **C**, which then gives the enol ester motifs of **1** and **2**. As a viable synthetic precursor for this plan, we envisioned dione **7**, which, by deacetylation and oxidation, was traced back to well-known Burawoy ketone (**8**, Scheme 1B).[13] Whereas Burawoy prepared ketone **8** as early as 1937, his approach from ergosterol acetate (not shown) was afflicted by a low yield (25%), difficult-to-remove byproducts, and the excessive use of chromium(VI) oxide. While employing **8** in their syntheses of brassinolides, Barton revisited its preparation but reported an even lower yield of 20%.[14] Later, Segal published a modified procedure and reported on small-scale (2 mmol) yields of up to 72%,[15] whereas Fernández in 1996 again could not reproduce these results and settled for a 33% isolated yield.[16] In our hands, and especially on a multigram scale, a reproduction of Segal's results could not be achieved either, and only yields in the range of Burawoy's and Fernández' reports were reached. Desiring a high-yielding, reproducible access to Burawoy's ketone (**8**) that is amenable to scale-up and does not require any toxic chromium reagents or tedious purification, we aimed for a mild, stepwise oxidation of ergosterol (**9**). Chemo- and diastereoselective epoxidation was achieved using *m*CPBA.[17] After careful optimization, we determined the system KOH/*i*PrOH/H_2O to be ideally suited for epoxide opening. Burawoy's ketone (**8**) was now easily

https://dx.doi.org/10.1021/acs.orglett.0c00180
Org. Lett. 2020, 22, 1585−1588

Table 1. Comparison of ^{1}H and ^{13}C NMR Spectroscopic Data of the Side Chain of Synthetic Material with Reported Data for Fortisterol and Herbarulide



no.	^{1}H shifts herbarulide[a]	^{1}H shifts synthetic **2**[b]	^{1}H shifts synthetic **1**[b]	^{1}H shifts fortisterol[c]	^{13}C shifts herbarulide[a]	^{13}C shifts synthetic **2**[b]	^{13}C shifts synthetic **1**[b]	^{13}C shifts fortisterol[c]
20	2.03 m	2.04 m	2.04 m	2.04 m	40.2	40.2	40.3	40.2
21	1.02 d 6.6	1.02 d 6.6	1.02 d 6.6	1.01 s	21.1	21.0	21.0	21.0
22	5.15 dd 15.2, 8.5	5.15 dd 15.2, 8.6	5.14 dd 15.2, 8.6	5.25 dd 15.2, 7.7*	134.7	134.7	134.9	134.7
23	5.25 dd 15.2, 7.8	5.25 dd 15.2, 7.9	5.23 dd 15.2, 8.1	5.15 dd 15.2, 8.4*	132.9	132.8	132.9	132.8
24	1.86 m	1.86 m	1.84 m	1.84 m	42.9	42.8	43.1	42.8
25	1.48 m	1.48 m	1.47 m	2.44 m*	33.1	33.0	33.1	33.0*
26	0.84 d 6.8	0.84 d 6.8	0.84 d 6.8	0.82 d 6.8	20.0	19.9	20.1	19.9
27	0.82 d 6.8	0.82 d 6.8	0.82 d 6.7	0.82 d 6.8	19.7	19.6	19.6	19.6
28	0.91 d 6.8	0.91 d 6.8	0.92 d 6.8	0.87 d 6.8	17.6	17.6	18.0	17.5

[a]Data collected in $CDCl_3$ at 600 MHz for ^{1}H and 151 MHz for ^{13}C; see ref 4. [b]Data collected in $CDCl_3$ at 600 MHz for ^{1}H, referenced to the residual solvent peak at δ_H 7.26, and 151 MHz for ^{13}C, referenced to the solvent peak at δ_C 77.00. [c]Data collected in $CDCl_3$ at 400 MHz for ^{1}H and 100 MHz for ^{13}C; see ref 5a. Misassigned signals are marked with *.

accessed from triol **10**[18] by the chemoselective oxidation of the 6-hydroxyl moiety (MnO_2), followed by the selective acetylation of the equatorial 3-hydroxy group. Recrystallization of the crude material furnished **8** with high purity and in an overall yield of 62% on a 5 g scale.

In a first try, Burawoy's ketone (**8**) was treated with HgO and I_2 to indeed provide the 5,6-epoxy-5,6-secosteroid **11** in a yield of 60%. To gain access to the desired structure **2**, we found intermediary triol **10** even better suited for directly reaching the alkoxy radical precursor **7** through oxidation with Dess–Martin's periodinane. When applying the conditions for radical rearrangement to dione **7**, 5,6-epoxy-5,6-secosteroid **2** could be directly obtained in 48% yield (four steps, 45% overall yield from ergosterol).

Whereas the ^{13}C NMR shifts of synthetic **2** were in close agreement with the reported data, the ^{1}H NMR data revealed three small deviations (Table 1): 24-H, 26-H, and 28-H were detected 0.02 to 0.04 ppm more downfield compared with the reported values. Comparing our synthetic material with the data for herbarulide instead revealed a much closer agreement (for both ^{1}H and ^{13}C shifts). This result led us to reassign the structure of herbarulide to that of compound **2** in Scheme 1B but left us with uncertainty regarding the true structure of fortisterol. In the absence of any copies of the spectra in the original publication, we can only suspect that there were several mistakes in the original assignment of fortisterol, that is, confusing 2-H with 25-H, as well as 2-C with 25-C, furthermore 11-H with 15-H, as well as 11-C with 15-C, and eventually 22-H with 23-H. We tentatively assumed fortisterol to rather be campestane **1** which was originally assigned as herbarulide. To provide unequivocal structural proof, we decided to engage in the synthesis of structure **1**. Thus, dione **7** was ozonolytically cleaved to an aldehyde (structure not shown), which was reacted with sulfone **12** in a Julia–Kocienski olefination under conditions previously employed by us.[12c] As a result, only (*Z*)-configurated material was obtained, but partial isomerization was achieved through a dibromination/radical debromination sequence to give the (*E*)-diastereomer **14** together with its (*Z*)-diastereomer **13** (d.r. 1.2:1) in excellent yield. Radical rearrangement was performed on the (*E*)-/(*Z*)-mixture and gave, after HPLC separation, **1** and (22*Z*)-**1**. The NMR spectral data of **1** were strikingly similar to our synthetic **2**. (See Table 1 and the Supporting Information.) The ^{13}C NMR data did not match the reported data for fortisterol, however, with the indicative signals C22, C24, C26, and C28 being 0.2 to 0.5 ppm more downfield than the reported values. Additionally, comparing diastereomer (22*Z*)-**1** with the reported data showed even greater deviation, especially for C20 and C24. A comparison of the optical activity values to the reported ones also did not provide any hint: Whereas for herbarulide, $[\alpha]_D^{25}$ = +55.0 (*c* 0.185 in CH_2Cl_2) was reported, and for fortisterol, $[\alpha]_D^{20}$ = +1.8 (*c* 0.2 in $CHCl_3$) was reported, our synthetic material showed absolutely no agreement with either of the two, independently of the concentration and the solvent employed (see the Supporting Information): synthetic **1**: $[\alpha]_D^{22}$ = +176.4 (*c* 0.18 in CH_2Cl_2); synthetic **2**: $[\alpha]_D^{22}$ = +177.2 (*c* 0.22 in $CHCl_3$). As a result, the true structure of fortisterol remains elusive, although the original report raises questions regarding the correct assignment of the originally obtained NMR data.[19]

In conclusion, we have achieved a potentially biomimetic synthesis of the alleged structures of 5,6-epoxy-5,6-secosteroids herbarulide and fortisterol through an alkoxy radical-mediated process. A careful comparison of the obtained NMR spectral data with the reported data led us to correct the originally proposed structure of herbarulide, whereas the true structure of fortisterol remains ambiguous. Toward this goal, we revisited the preparation of Burawoy's ketone (**8**) and developed it into a scalable and sustainable process.

https://dx.doi.org/10.1021/acs.orglett.0c00180
Org. Lett. 2020, 22, 1585–1588

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00180.

General methods; detailed experimental studies; experimental procedures and spectral data; comparison of synthetic and natural herbarulide and of synthetic and natural alleged fortisterol; ^{1}H and ^{13}C NMR spectra; and references (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Philipp Heretsch − *Institut für Chemie und Biochemie, Freie Universität Berlin 14195 Berlin, Germany;* orcid.org/0000-0002-9967-3541; Email: philipp.heretsch@fu-berlin.de

Authors

Fenja L. Duecker − *Institut für Chemie und Biochemie, Freie Universität Berlin 14195 Berlin, Germany;* orcid.org/0000-0002-1060-9309

Robert C. Heinze − *Institut für Chemie und Biochemie, Freie Universität Berlin 14195 Berlin, Germany;* orcid.org/0000-0002-3431-816X

Mira Mueller − *Institut für Chemie und Biochemie, Freie Universität Berlin 14195 Berlin, Germany*

Sudong Zhang − *Institut für Chemie und Biochemie, Freie Universität Berlin 14195 Berlin, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00180

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by Deutsche Forschungsgemeinschaft (grant no. HE 7133/7-1) and the Boehringer Ingelheim Stiftung (exploration grant to P.H.). We acknowledge Dr. Carlo Fasting (FU Berlin) for HPLC separation and the assistance of the Core Facility BioSupraMol supported by the DFG.

■ REFERENCES

(1) (a) D'Auria, M. V.; Minale, L.; Riccio, R. Polyoxygenated Steroids of Marine Origin. *Chem. Rev.* **1993**, *93*, 1839−1895. (b) Gasi, K.; Sakac, M.; Jovanovic-Santa, S.; Djurendic, E. An Overview of Partial Synthesis and Transformations of Secosteroids. *Curr. Org. Chem.* **2014**, *18*, 216−259. (c) Khripach, V. Synthesis of 5,10- and 13,14-Secosteroids. *Curr. Top. Steroid Res.* **2010**, *7*, 61−72. (d) Sica, D.; Musumeci, D. Secosteroids of marine origin. *Steroids* **2004**, *69*, 743−756.

(2) (a) Heinze, R. C.; Heretsch, P. Synthesis of Secosterols as an Arena for C−H Functionalization and C−C Manipulation Tactics. *Synlett* **2017**, *28*, 1127−1133. (b) Duecker, F. L.; Reuß, F.; Heretsch, P. Rearranged ergostane-type natural products: chemistry, biology, and medicinal aspects. *Org. Biomol. Chem.* **2019**, *17*, 1624−1633. (c) Noack, F.; Heinze, R. C.; Heretsch, P. Contemporary Synthetic Strategies towards Secosteroids, *abeo*-Steroids, and Related Triterpenes. *Synthesis* **2019**, *51*, 2039−2057.

(3) Chhetri, B. K.; Lavoie, S.; Sweeney-Jones, A. M.; Kubanek, J. Recent trends in the structural revision of natural products. *Nat. Prod. Rep.* **2018**, *35*, 514−531.

(4) Krohn, K.; Biele, C.; Aust, H.-J.; Draeger, S.; Schulz, B. Herbarulide, a Ketodivinyllactone Steroid with an Unprecedented Homo-6-oxaergostane Skeleton from the Endophytic Fungus Pleospora herbarum. *J. Nat. Prod.* **1999**, *62*, 629−630.

(5) (a) Huang, X.-C.; Guo, Y.-W.; Song, G.-Q. Fortisterol, a novel steroid with an unusual seven-membered lactone ring B from the Chinese marine sponge *Biemna fortis* Topsent. *J. Asian Nat. Prod. Res.* **2006**, *8*, 485−489. (b) Chen, D., Fan, M. Sterol Lactol Compound and Its Application As Complement Inhibitor. Faming Zhuanli Shenqing CN 105985403 A, October 5, 2016. (c) Kitchawalit, S.; Kanokmedhakul, K.; Kanokmedhakul, S.; Soytong, K. A new benzyl ester and ergosterol derivatives from the fungus *Gymnoascus reesii*. *Nat. Prod. Res.* **2014**, *28*, 1045−1051.

(6) De Marino, S.; Palagiano, E.; Zollo, F.; Minale, L.; Iorizzi, M. A novel sulphated steroid with a 7-membered 5-oxalactone B-ring from an Antarctic starfish of the family *Asteriidae*. *Tetrahedron* **1997**, *53*, 8625−8628.

(7) Kikuchi, T.; Masumoto, Y.; In, Y.; Tomoo, K.; Yamada, T.; Tanaka, R. Eringiacetal A, 5,6-*seco*-(5*S*,6*R*,7*R*,9*S*)-5,6:5,7:6,9-Triepoxyergosta-8(14),22-diene-3β,7β-diol, an Unusual Ergostane Sterol from the Fruiting Bodies of *Pleurotus eryngii*. *Eur. J. Org. Chem.* **2015**, *2015*, 4645−4649.

(8) Mulheirn, L. J. Identification of C-24 alkylated steranes by P.M.R. spectroscopy. *Tetrahedron Lett.* **1973**, *14*, 3175−3178.

(9) Tong, Z.-B.; Cui, X.-H.; Wang, J.; Zhang, C.-L.; Zhang, Y.-Y.; Ren, Z.-J. Constituents from solid-cultured Antrodia camphorata. *Nat. Prod. Res.* **2017**, *31*, 2564−2567.

(10) Zhao, Z.-Z.; Han, K.-Y.; Li, Z.-H.; Feng, T.; Chen, H.-P.; Liu, J.-K. Cytotoxic ergosteroids from the fungus *Stereum hirsutum*. *Phytochem. Lett.* **2019**, *30*, 143−149.

(11) (a) Stiver, S.; Yates, P. Photochemistry of cyclic α-hydroxy ketones. I. The nature and genesis of the photoproducts from steroidal 5-hydroxy 6-keto steroids and related compounds. *Can. J. Chem.* **1988**, *66*, 214−226. (b) Suginome, H.; Wang, J. B.; Satoh, G. Regioselective β-Scission of α-Oxoalkoxyl Radicals: a Novel Formation of α-Hydroxy ε-Lactones by Photolysis of Steroidal α-Oxo Alcohol Hypoiodites in the Presence of Mercury(II) Oxide and Iodine. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1553−1555.

(12) (a) Heinze, R. C.; Lentz, D.; Heretsch, P. Synthesis of Strophasterol A Guided by a Proposed Biosynthesis and Innate Reactivity. *Angew. Chem., Int. Ed.* **2016**, *55*, 11656−11659. (b) Heinze, R. C.; Heretsch, P. Translation of a Polar Biogenesis Proposal into a Radical Synthetic Approach: Synthesis of Pleurocin A/Matsutakone and Pleurocin B. *J. Am. Chem. Soc.* **2019**, *141*, 1222−1226. (c) Duecker, F. L.; Heinze, R. C.; Heretsch, P. Synthesis of Swinhoeisterol A, Dankasterone A and B, and Periconiastone A by Radical Framework Reconstruction. *J. Am. Chem. Soc.* **2020**, *142*, 104−108.

(13) Burawoy, A. Studies in the sterol group. Part XXX. The oxidation of ergosterol, ergosteryl acetate, and lumisteryl acetate with chromic anhydride. *J. Chem. Soc.* **1937**, 409−411.

(14) Barton, D. H. R.; Robinson, C. H. The stereospecificity of carbanion reduction processes. *J. Chem. Soc.* **1954**, 3045−3051.

(15) Yablonskaya, E. V.; Segal, G. M. Oxidation of ergosterol acetate with chromic anhydride. *Chem. Nat. Compd.* **1971**, *7*, 476−480.

(16) Brosa, C.; Puig, R.; Comas, X.; Fernández, C. New synthetic strategy for the synthesis of 24-epibrassinolide. *Steroids* **1996**, *61*, 540−543.

(17) Xu, S.; Liao, X.; Du, B.; Zhou, X.; Huang, Q.; Wu, C. A series of new 5,6-epoxysterols from a Chinese sponge Ircinia aruensis. *Steroids* **2008**, *73*, 568−573.

(18) Notaro, G.; Piccialli, V.; Sica, D.; Corriero, G. 3β,5α,6β-Trihydroxylated Sterols with a Saturated Nucleus from Two Populations of the Marine Sponge *Cliona copiosa*. *J. Nat. Prod.* **1991**, *54*, 1570−1575.

(19) We cannot conclusively confirm the existence of fortisterol. References 5a−c may also have (re)isolated herbarulide.

Synthesis of the Alleged Structures of Fortisterol and Herbarulide and Structural Revision of Herbarulide

Fenja L. Duecker, Robert C. Heinze, Mira Mueller, Sudong Zhang, Philipp Heretsch*

Institute of Chemistry and Biochemistry, Freie Universität Berlin, Takustraße 3, 14195 Berlin, Germany

*Correspondence to: philipp.heretsch@fu-berlin.de

Supporting Information

Table of Contents

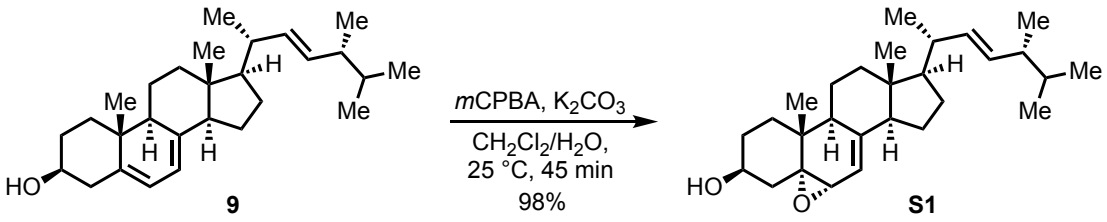
1 General Methods

All reactions sensitive to moisture and/or air were carried out using heat gun-dried glassware, an argon atmosphere, and anhydrous solvents. Anhydrous dichloromethane, toluene, and Et_2O were taken from a M. Braun GmbH MB SPS-800 solvent purification system. THF was distilled from sodium and stored over 4 Å molecular sieves. Ethyl acetate and *n*hexane were purified by distillation on a rotary evaporator. All other solvents and commercially available reagents were used without further purification unless otherwise stated. In case reactions required heating, this was carried out using silicone oil baths. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck Silica Gel 50 F245-plates and visualized by fluorescence quenching under UV-light or an aqueous solution of cerium sulfate and phosphomolybdic acid and heat as developing agent. Column chromatographic purification was performed on Macherey-Nagel Silica Gel 60 M (40–60 μm). HPLC separation was performed on a high-pressure gradient system (stainless steel), equipped with a Shimadzu LC-8A pump, Shimadzu CBM-20A controller, variable wavelength UV detector from Knauer and a Rheodyne injector with 10 mL sample loop. Concentration under reduced pressure was performed by rotary evaporation at 45 °C and appropriate pressure, followed by exposure to high vacuum (10^{-3} mbar) at 25 °C. NMR spectra were recorded on either a Jeol ECP500 (500 MHz), a Bruker AVANCE III 500 (500 MHz) or a Varian INOVA600 (600 MHz). Chemical shifts δ are reported in parts per million (ppm) and are referenced using residual undeuterated solvent ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; DMSO-d_6: δ_H = 2.50 ppm, δ_C = 39.52 ppm; pyridine-d_5: δ_H = 8.74 ppm, δ_C = 150.35 ppm; unless otherwise stated) as an internal reference at 298 K. The given multiplicities are phenomenological; thus, the actual appearance of the signals is stated and not the theoretically expected one. The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, and combinations thereof. In case no multiplicity could be identified, the chemical shift range of the signal is given (m = multiplet). Overlaid signals (typically by solvent) are marked as ov. Infrared (IR) spectra were measured on a Jasco FT/IR-4100 Type A spectrometer with a TGS detector. Wavenumbers $\tilde{\nu}$ are given in cm^{-1} and intensities are as follows: s = strong, m = medium, w = weak. High-resolution mass spectra (HRMS) were recorded using an Agilent 6210 ESI-TOF or an Ionspec QFT-7 ESI-TOF spectrometer. Optical rotations were measured on a JASCO P-2000 polarimeter at 589 nm using 100 mm cells and the solvent and concentration (g/100 mL) indicated. Melting points were measured on a Stuart SMP30.

2 Experimental Procedures and Characterization Data

2.1 Synthesis of Burawoy Ketone (**8**) and Initial Radical Rearrangement

(22*E*)-5α,6α-Epoxyergosta-7,22-dien-3β-ol (**S1**)



To a suspension of (–)-ergosterol (**9**) (5.00 g, 12.6 mmol, 1.0 eq.) in CH_2Cl_2 (125 mL) was added a solution of K_2CO_3 (3.48 g, 25.3 mmol, 2.0 eq.) in H_2O (125 mL). In a separate flask, *m*CPBA (70% *w/w*, 3.10 g, 12.6 mmol, 1.0 eq.) was suspended in CH_2Cl_2 (50 mL) by sonication to give a turbid solution, which was then added dropwise to the reaction mixture over a period of 5 min. After vigorous stirring for 45 min at 25 °C the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic phases were sequentially washed with $NaHCO_3$ (sat. aq., 250 mL) and brine (sat., 250 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure to give epoxide **S1** (5.10 g, 12.4 mmol, 98%) as a white solid, which was used in the next step without further purification.

M.p.: 233–235 °C ($CHCl_3$).

TLC: R_f = 0.40 (*n*hexane/EtOAc 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.45 – 5.41 (m, 1H), 5.24 – 5.12 (m, 2H), 4.01 – 3.91 (m, 1H), 3.00 (d, *J* = 4.1 Hz, 1H), 2.26 (dd, *J* = 13.0, 11.5 Hz, 1H), 2.06 – 1.99 (m, 3H), 1.99 – 1.92 (m, 2H), 1.87 – 1.80 (m, 2H), 1.75 – 1.66 (m, 2H), 1.57 – 1.50 (m, 3H), 1.51 – 1.38 (m, 3H), 1.35 – 1.20 (m, 4H), 1.02 (s, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.55 (s, 3H).

^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 148.1, 135.5, 132.2, 114.9, 68.5, 67.0, 55.8, 55.0, 54.7, 42.9, 42.3, 41.5, 40.5, 39.9, 38.8, 35.1, 33.6, 33.2, 31.3, 28.0, 23.3, 21.2, 21.1, 20.1, 19.8, 17.7, 16.5, 12.2.

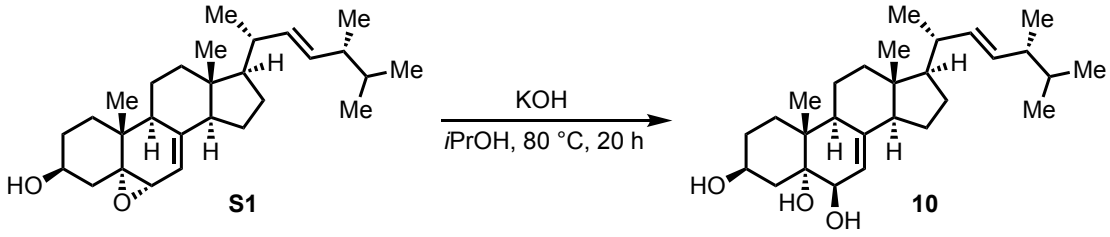
IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3441 (br w), 2953 (s), 2871 (m), 1457 (w), 1370 (w), 1052 (w), 969 (w), 902 (w), 870 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{44}O_2Na^+$ $[M+Na]^+$: 435.3234, found: 435.3252.

Opt. Act.: $[\alpha]_D^{22}$ = –66.5 (*c* = 1.00, $CHCl_3$).

All characterization data were consistent with those reported in the literature (^{1}H- and ^{13}C-NMR, IR).[1]

(22*E*)-Ergosta-7,22-diene-3β,5α,6β-triol/cerevisterol (**10**)



To epoxide **S1** (5.10 g, 12.4 mmol, 1.0 eq.) were added KOH (1 M in H_2O, 50 mL) and *i*PrOH (50 mL). The suspension was heated to 80 °C and stirred at this temperature for 18 h. The reaction mixture was allowed to cool to 25 °C and neutralized with HCl (1 M in H_2O). The layers were separated, and the aqueous phase was extracted with $CHCl_3$/*i*PrOH (4:1, 3 × 75 mL). The combined organic phases were washed with brine (sat., 250 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure to give crude triol **10** (5.33 g, 12.4 mmol, quant.) as a light yellow solid, which was used in the next step without further purification.

Analytically pure triol **10** could be obtained by column chromatography (silica gel, EtOAc) as a colorless solid.

M.p.: 231–233 °C ($CHCl_3$).

TLC: R_f = 0.25 (EtOAc).

^{1}H-NMR: (500 MHz, DMSO-d_6); δ [ppm] = 5.23 (dd, *J* = 15.3, 7.2 Hz, 1H), 5.17 (dd, *J* = 15.3, 8.0 Hz, 1H), 5.10 – 5.06 (m, 1H), 4.49 (d, *J* = 5.5 Hz, 1H), 4.22 (d, *J* = 5.7 Hz, 1H), 3.81 – 3.72 (m, 1H), 3.58 (s, 1H), 3.39 – 3.35 (m, 1H), 2.04 – 1.91 (m, 3H), 1.90 – 1.77 (m, 3H), 1.70 – 1.57 (m, 2H), 1.52 – 1.43 (m, 5H), 1.42 – 1.34 (m, 2H), 1.31 – 1.21 (m, 5H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.54 (s, 3H).

^{13}C-NMR: (126 MHz, DMSO-d_6); δ [ppm] = 139.6, 135.4, 131.4, 119.5, 74.5, 72.1, 66.5, 55.3, 54.2, 43.0, 42.3, 42.0, 40.2, 40.1, 39.0, 36.6, 32.5 (2C), 31.2, 27.7, 22.1, 21.3, 21.0, 19.7, 19.4, 17.7, 17.3, 12.0.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3364 (br w), 2956 (s), 2928 (s), 2871 (m), 1722 (m), 1457 (m), 1372 (w), 1269 (m), 1050 (w), 973 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{46}O_3Na^+$ [M+Na]$^+$: 453.3339, found: 453.3359.

Opt. act. $[\alpha]_D^{20}$ = –56.3 (*c* = 1.00, $(CH_3)_2SO$).

All characterization data were consistent with those reported in the literature (m.p., ^{1}H- and ^{13}C-NMR,[2] α[3]).

(22*E*)-3β,5α-Dihydroxyergosta-7,22-dien-6-one (**S2**)

To a stirred suspension of triol **10** (5.33 g, 12.4 mmol, 1.0 eq.) in $CHCl_3$ (125 mL) were added $MgSO_4$ (1.25 g) and MnO_2 (8.58 g, 98.8 mmol, 8.0 eq.). The resulting mixture was heated to 50 °C and stirred at this temperature for 16 h. The reaction mixture was allowed to cool to 25 °C and $CHCl_3$/*i*PrOH (4:1, 65 mL) and silica gel were added. The solvent was removed under reduced pressure and the residue was added onto a short plug of silica gel (10 cm) to remove manganese solids. It was rinsed with $CHCl_3$/*i*PrOH (4:1) until all product was recovered from the column to give a mix of crude α-ketol **S2** along with over oxidized side product **7** as a yellow solid (5.3 g).

Analytically pure α-ketol **S2** could be obtained by column chromatography (silica gel, *n*hexane/EtOAc 1:2) as a colorless solid.

M.p.: 248–250 °C (EtOAc).

TLC: R_f = 0.50 (EtOAc).

^{1}H-NMR: (500 MHz, pyridine-d_5); δ [ppm] = 7.23 (s, 1H), 6.24 – 6.11 (m, 1H), 5.94 (t, *J* = 2.3 Hz, 1H), 5.29 (dd, *J* = 15.2, 7.7 Hz, 1H), 5.21 (dd, *J* = 15.3, 8.5 Hz, 1H), 4.76 – 4.66 (m, 1H), 3.02 – 2.91 (m, 2H), 2.33 (dd, *J* = 13.8, 11.4 Hz, 1H), 2.27 – 2.18 (m, 2H), 2.09 – 2.00 (m, 3H), 1.95 – 1.87 (m, 1H), 1.87 – 1.81 (m, 1H), 1.79 – 1.74 (m, 1H), 1.74 – 1.68 (m, 2H), 1.62 (qd, *J* = 13.4, 4.3 Hz, 1H), 1.54 – 1.45 (m, 3H), 1.41 – 1.34 (m, 1H), 1.33 – 1.23 (m, 2H), 1.12 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 4.3 Hz, 3H), 0.89 (d, *J* = 4.4 Hz, 3H), 0.63 (s, 3H).

^{13}C-NMR: (126 MHz, pyridine-d_5); δ [ppm] = 200.4, 164.4, 136.3, 132.9, 121.1, 77.8, 67.5, 56.5, 56.3, 45.1, 44.8, 43.6, 41.7, 41.1, 39.7, 38.2, 33.8, 32.2, 31.7, 28.7, 23.3, 22.6, 21.8, 20.6, 20.3, 18.3, 16.9, 13.2.

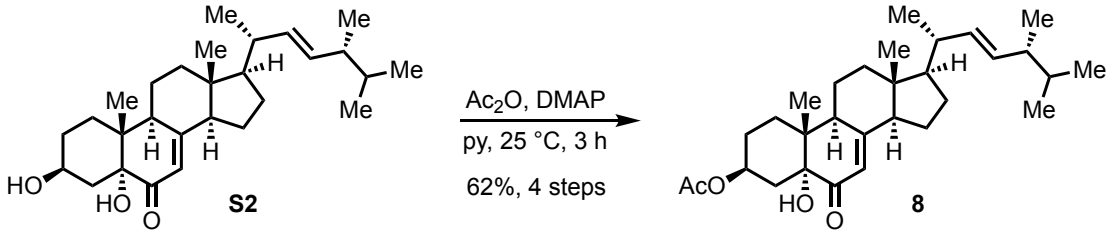
IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3485 (br w), 3320 (br w), 2954 (s), 2871 (m), 1738 (w), 1673 (s), 1623 (w), 1458 (m), 1371 (m), 1250 (m), 1155 (m), 1081 (m), 970 (m), 870 (m), 827 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{44}O_3Na^+$ $[M+Na]^+$: 451.3183, found: 451.3177.

Opt. act. $[\alpha]_D^{20}$ = +8.8 (*c* = 1.00, $CHCl_3$).

All characterization data were consistent with those reported in the literature (IR, ^{1}H-NMR, α and m.p,[4] ^{13}C-NMR[5]).

(22*E*)-5α-Hydroxyergosta-7,22-dien-6-on-3β-yl acetate/Burawoy ketone (**8**)



To a stirred solution of crude α-ketol **S2** (5.3 g, 12.4 mmol, 1.0 eq.) in pyridine (50 mL) were added 4-dimethylaminopyridine (150 mg, 1.23 mmol, 0.1 eq.) and acetic anhydride (3.3 mL, 34 mmol, 2.75 eq.) at 25 °C and stirring was continued at this temperature for 3 h. The reaction mixture was poured into H_2O (50 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL) and the combined organic phases were washed with HCl (1 M in H_2O, 3 × 200 mL) and brine (sat., 400 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a yellow residue (5.7 g). Recrystallization of the crude product from EtOAc gave Burawoy ketone (**8**) (3.68 g, 7.80 mmol, 62% over 4 steps) as colorless needles.

M.p.: 261–264 °C (EtOAc).

TLC: R_f = 0.35 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.63 (t, *J* = 2.3 Hz, 1H), 5.23 (dd, *J* = 15.2, 7.7 Hz, 1H), 5.14 (dd, *J* = 15.3, 8.2 Hz, 1H), 5.11 – 5.04 (m, 1H), 2.77 (s, 1H), 2.54 (ddd, *J* = 12.2, 6.9, 2.5 Hz, 1H), 2.17 (ddd, *J* = 16.1, 6.0, 2.8 Hz, 1H), 2.14 – 2.07 (m, 2H), 2.01 (s, 3H), 1.89 – 1.82 (m, 3H), 1.78 – 1.68 (m, 2H), 1.77 (dd, *J* = 14.0, 11.8 Hz, 1H), 1.64 – 1.56 (m, 3H), 1.52 – 1.43 (m, 4H), 1.41 (dd, *J* = 13.1, 4.4 Hz, 1H), 1.36 – 1.31 (m, 2H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.94 (s, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.59 (s, 3H).

^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 198.4, 171.0, 165.4, 135.2, 132.6, 119.8, ,77.4 (ov), 70.8, 56.2, 55.9, 44.8, 43.8, 43.0, 40.6, 40.5, 39.0, 33.2, 32.7, 30.2, 28.0, 26.5, 22.6, 22.0, 21.5, 21.3, 20.1, 19.8, 17.7, 16.3, 12.8.

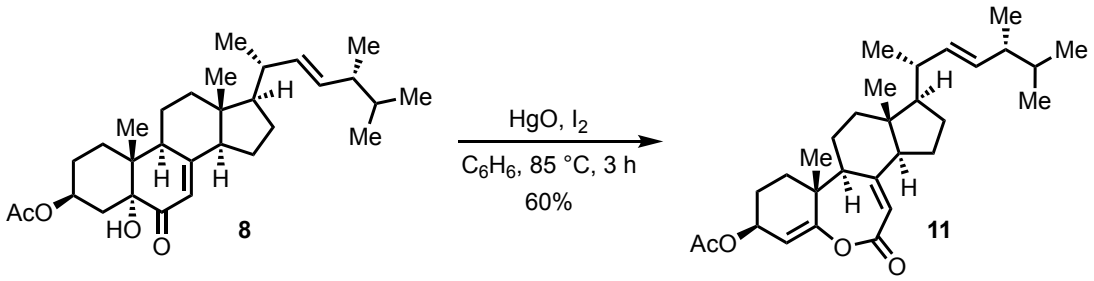
IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3414 (br w), 2955 (s), 2871 (m), 1718 (m), 1679 (s), 1457 (w), 1382 (m), 1365 (m), 1267 (s), 1245 (s), 11259 (w), 1118 (w), 1103 (w), 1045 (w), 1019 (w), 974 (w), 871 (w), 756 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{30}H_{46}O_4Na^+$ [M+Na]$^+$: 493.3288, found: 493.3279.

Opt. act. $[\alpha]_D^{25}$ = +2.1 (*c* = 1.00, $CHCl_3$).

All characterization data were consistent with those reported in the literature (IR and ^{1}H-NMR,[4] ^{13}C-NMR,[6] α and m.p[7]).

(22*E*)-5,6-Epoxy-6-oxo-5,6-secoergosta-4,7,22-trien-3β-yl acetate (**11**)



Through a solution of Burawoy ketone (**8**) (50.0 mg, 106 *µ*mol, 1.0 eq.) in benzene (5 mL) was bubbled argon *via* cannula for 10 min. Iodine (65.0 mg, 255 *µ*mol, 2.4 eq.) and HgO (yellow, 62.0 mg, 287 *µ*mol, 2.7 eq.) were added and the resulting mixture was heated to 85 °C for 3 h. The reaction mixture was cooled to 25 °C, filtered through a plug of Celite®, and rinsed with EtOAc (15 mL). The organic phase was washed sequentially with $Na_2S_2O_3$ (sat. aq., 25 mL) and brine (sat., 25 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1) gave enol ester **11** (29.9 mg, 63.8 *µ*mol, 60%) as a colorless oil.

TLC: R_f = 0.37 (*n*hexane/EtOAc 5:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.64 (s, 1H), 5.47 (d, *J* = 4.5 Hz, 1H), 5.30 (dt, *J* = 4.7, 2.3 Hz, 1H), 5.24 (dd, *J* = 15.3, 7.8 Hz, 1H), 5.14 (dd, *J* = 15.3, 7.7 Hz, 1H), 2.30 (ddd, *J* = 12.6, 4.7, 2.1 Hz, 1H), 2.12 (dd, *J* = 12.0, 6.5 Hz, 1H), 2.06 – 2.01 (m, 5H), 1.98 – 1.90 (m, 1H), 1.88 – 1.83 (m, 1H), 1.82 – 1.73 (m, 4H), 1.72 – 1.66 (m, 1H), 1.61 – 1.54 (m, 2H), 1.50 – 1.43 (m, 2H), 1.42 – 1.35 (m, 3H), 1.12 (s, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.61 (s, 3H).

^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 170.6, 165.1, 159.2, 158.3, 135.0, 132.8, 113.2, 110.0, 66.6, 58.4, 56.5, 48.5, 47.2, 43.0, 40.4, 39.6, 38.9, 33.2, 30.9, 27.9, 25.4, 24.5, 22.7, 21.4, 21.2, 20.3, 20.1, 19.8, 17.7, 12.6.

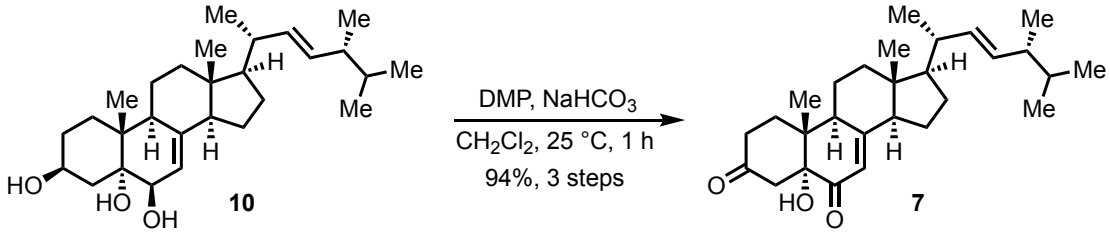
IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (m), 2925 (m), 2871 (w), 1722 (s), 1668 (m), 1456 (w), 1371 (w), 1233 (s), 1138 (m), 1012 (w), 996 (w), 960 (m), 891 (w), 865 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{30}H_{44}O_4Na^+$ $[M+Na]^+$: 491.3132, found: 491.3124.

Opt. act. $[\alpha]_D^{22}$ = +42.4 (*c* = 1.00, $CHCl_3$).

2.2 Synthesis of Herbarulide (**2**)

(22*E*)-5α-Hydroxyergosta-7,22-diene-3,6-dione (**7**)



To a stirred solution of triol **10** (71 mg, 0.16 mmol, 1.0 eq.) in CH_2Cl_2 (1.6 mL) at 25 °C were added $NaHCO_3$ (81 mg, 0.96 mmol, 6.0 eq.) and Dess–Martin periodinane (136 mg, 320 μmol, 2.0 eq.), and the reaction mixture was stirred at this temperature for 1 h. After diluting with CH_2Cl_2 (5 mL), $Na_2S_2O_3$ (sat. aq., 5 mL) was added and the mixture was vigorously stirred for 30 min. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were sequentially washed with $NaHCO_3$ (sat. aq., 25 mL) and brine (sat., 25 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was adsorbed on silica gel and column chromatography (silica gel, *n*hexane/EtOAc, 3:1) gave dione **7** (65 mg, 0.15 mmol, 94%, 3 steps from ergosterol) as a colorless solid.

M.p.: 230–232 °C (EtOAc).

TLC: R_f = 0.31 (*n*hexane/EtOAc 2:1).

^{1}H-NMR: (500 MHz, pyridine-d_5); δ [ppm] = 8.12 (s, 1H), 5.98 (t, *J* = 2.3 Hz, 1H), 5.29 (dd, *J* = 15.3, 7.7 Hz, 1H), 5.20 (dd, *J* = 15.3, 8.2 Hz, 1H), 3.25 – 3.16 (m, 2H), 2.98 (ddd, *J* = 12.2, 7.0, 2.5 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.52 – 2.41 (m, 2H), 2.10 – 2.00 (m, 3H), 1.94 – 1.85 (m, 2H), 1.77 – 1.69 (m, 2H), 1.69 – 1.62 (m, 1H), 1.57 – 1.45 (m, 3H), 1.40 – 1.32 (m, 1H), 1.32 – 1.25 (m, 2H), 1.24 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 4.3 Hz, 3H), 0.89 (d, *J* = 4.2 Hz, 3H), 0.64 (s, 3H).

^{13}C-NMR: (126 MHz, pyridine-d_5); δ [ppm] = 210.5, 198.9, 165.2, 135 (ov), 132.9, 120.7, 80.2, 56.5, 56.3, 45.7, 45.1, 44.6, 43.5, 42.0, 41.1, 39.5, 38.4, 33.8, 32.9, 28.7, 23.2, 22.7, 21.8, 20.6, 20.3, 18.3, 16.0, 13.2.

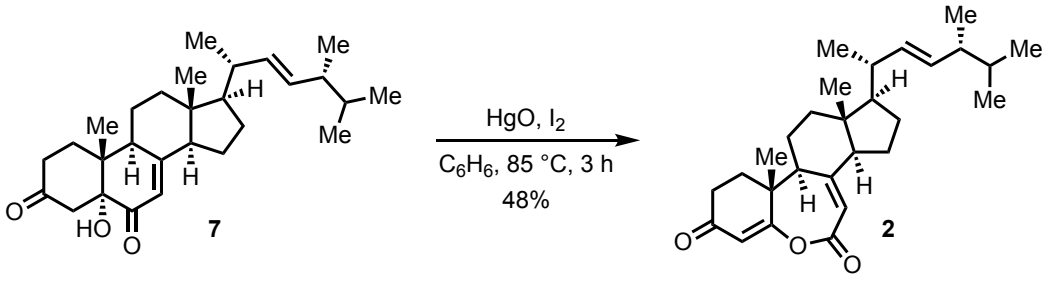
IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2922 (s), 2853 (m), 1740 (w), 1460 (w), 1377 (w), 1217 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_3Na^+$ $[M+Na]^+$: 449.3026, found: 449.3031.

Opt. act. $[\alpha]_D^{22}$ = +34.8 (*c* = 1.00, $CHCl_3$).

All characterization data were consistent with those reported in the literature (m.p., IR and ^{1}H-NMR).[8]

(22*E*)-5,6-Epoxy-5,6-secoergosta-4,7,22-triene-3,6-dione / Herbarulide (**2**)



Through a solution of dione **7** (9.8 mg, 23 μmol, 1.0 eq.) in benzene (2.5 mL) was bubbled argon *via* cannula for 10 min. Iodine (14 mg, 55 μmol, 2.4 eq.) and HgO (yellow, 13 mg, 62 μmol, 2.7 eq.) were added and the resulting mixture was heated to 85 °C for 3 h. The reaction mixture was cooled to 25 °C, filtered through a plug of Celite®, and rinsed with EtOAc (10 mL). The organic phase was washed sequentially with $Na_2S_2O_3$ (sat. aq., 20 mL) and brine (sat., 20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1 → 3:1) gave herbarulide (**2**) (4.7 mg, 11 μmol, 48%) as a colorless solid.

M.p.: Decomposition at 200 °C (EtOAc).

TLC: R_f = 0.24 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.75 (s, 1H), 5.72 (t, *J* = 1.8 Hz, 1H), 5.25 (dd, *J* = 15.3, 7.8 Hz, 1H), 5.15 (dd, *J* = 15.3, 8.5 Hz, 1H), 2.53 (ddd, *J* = 12.5, 4.8, 2.1 Hz, 1H), 2.48 (dd, *J* = 14.0, 4.8 Hz, 1H), 2.46 – 2.40 (m, 1H), 2.19 (ddd, *J* = 14.1, 4.9, 2.2 Hz, 1H), 2.14 (ddd, *J* = 11.8, 6.7, 1.3 Hz, 1H), 2.11 (ddd, *J* = 13.1, 4.1, 2.8 Hz, 1H), 2.07 – 2.02 (m, 1H), 1.98 (td, *J* = 14.2, 5.4 Hz, 1H), 1.88 – 1.82 (m, 2H), 1.81 – 1.75 (m, 1H), 1.69 (qd, *J* = 13.3, 4.1 Hz, 1H), 1.61 – 1.56 (m, 1H), 1.52 – 1.45 (m, 3H), 1.42 – 1.35 (m, 2H), 1.24 (s, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.64 (s, 3H).

^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 198.6, 174.0, 162.6, 159.6, 134.9, 133.0, 114.8, 113.5, 58.3, 56.5, 47.4, 47.1, 43.0, 40.5, 40.4, 39.3, 34.1, 33.3, 33.2, 27.8, 25.5, 22.7, 21.2, 20.1 (2C), 19.8, 17.7, 12.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (s), 2871 (m), 1733 (s), 1673 (s), 1622 (s), 1457 (m), 1340 (m), 1186 (m), 1138 (s), 864 (w), 764 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{40}O_3Na^+$ $[M+Na]^+$: 447.2870, found: 447.2854.

Opt. act. $[\alpha]_D^{22}$ = +176.4 (*c* = 0.18, CH_2Cl_2), lit.: $[\alpha]_D^{22}$ = +55 (*c* = 0.185, CH_2Cl_2).[9]

$[\alpha]_D^{22}$ = +162.9 (*c* = 0.50, CH_2Cl_2).

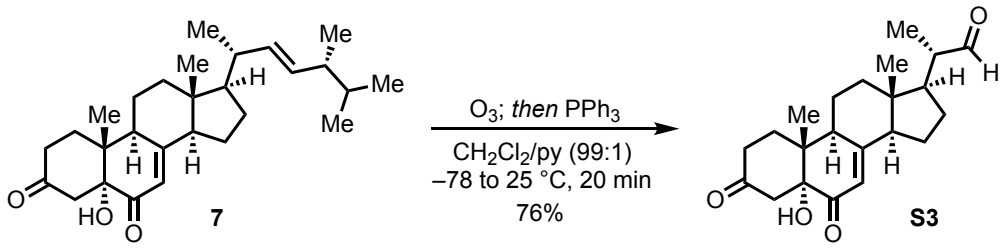
$[\alpha]_D^{22}$ = +186.4 (*c* = 0.18, $CHCl_3$).

$[\alpha]_D^{22}$ = +172.3 (*c* = 0.50, $CHCl_3$).

All characterization data except for the optical rotation were consistent with those reported in the literature.[9]

2.3 Synthesis of (22*E*)-5,6-Epoxy-5,6-secocampesta-4,7,22-triene-3,6-dione (**1**)

5α-Hydroxy-3,6-dioxopregn-7-ene-20α-carboxaldehyde (**S3**)



A stream of ozone-rich oxygen was passed through a solution of dione **7** (100 mg, 234 μmol, 1.0 eq.) in CH_2Cl_2/pyridine (99:1, 10 mL) at –78 °C for 20 min. PPh_3 (122 mg, 468 μmol, 2.0 eq.) was added and the reaction mixture was allowed to warm to 25 °C over 16 h. The solvent was removed, the residue was adsorbed on silica gel and column chromatography (silica gel, *n*hexane/EtOAc 2:1 → 1:2) gave aldehyde **S3** (63.9 mg, 178 μmol, 76%) as a crystalline solid.

M.p.: 225–227 °C ($CHCl_3$).

TLC: R_f = 0.35 (*n*hexane/EtOAc 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 9.59 (d, *J* = 3.0 Hz, 1H), 5.70 (t, *J* = 2.3 Hz, 1H), 2.93 (s, 1H), 2.77 (d, *J* = 16.1 Hz, 1H), 2.69 (ddd, *J* = 12.2, 6.9, 2.6 Hz, 1H), 2.54 (dd, *J* = 16.1, 1.9 Hz, 1H), 2.44 – 2.35 (m, 3H), 2.24 – 2.17 (m, 2H), 2.11 (ddd, *J* = 12.7, 4.5, 2.7 Hz, 1H), 2.07 – 1.98 (m, 1H), 1.90 (ddd, *J* = 13.1, 6.0, 2.7 Hz, 1H), 1.85 – 1.78 (m, 1H), 1.79 – 1.73 (m, 2H), 1.72 – 1.67 (m, 1H), 1.63 – 1.57 (m, 1H), 1.54 (dd, *J* = 13.0, 4.5 Hz, 1H), 1.52 – 1.44 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.13 (s, 3H), 0.66 (s, 3H).

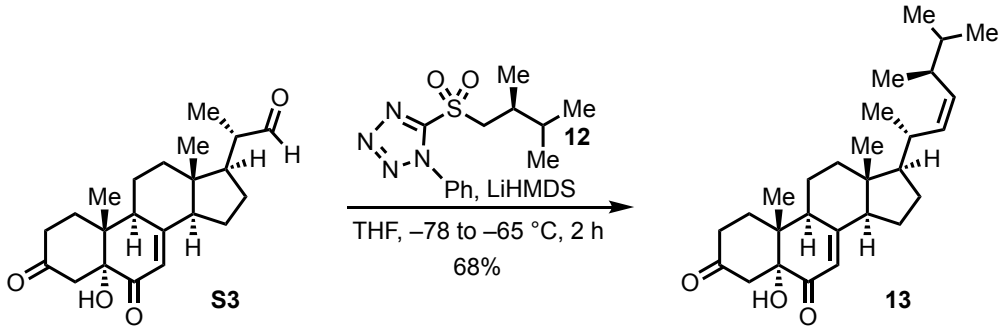
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 210.3, 204.4, 197.3, 164.8, 120.0, 79.8, 55.1, 51.1, 49.6, 45.2, 44.6, 43.8, 41.0, 38.7, 37.4, 32.0, 26.7, 23.0, 22.0, 15.9, 13.7, 13.0.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3349 (br w), 2954 (w), 2922 (m), 2874 (w), 2850 (w), 1712 (m), 1671 (s), 1620 (w), 1458 (w), 1374 (w), 1232 (w), 1158 (w), 1124 (w), 873 (w) 758 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{22}H_{30}O_4Na^+$ $[M+Na]^+$: 381.2036, found: 381.2031.

Opt. act. $[\alpha]_D^{22}$ = +48.5 (*c* = 1.00, $CHCl_3$).

(22*Z*)-5α-Hydroxycampesta-7,22-diene-3,6-dione (**13**)



To a solution of hexamethyldisilazane (119 μL, 578 μmol, 3.26 eq.) in THF (0.2 mL) at 0 °C was added *n*BuLi (1.6 M in *n*hexane, 343 μL, 549 μmol, 3.1 eq.) and it was stirred for 15 min at this temperature before the solution was added to sulfone **12** (261 mg, 885 μmol, 5.0 eq.) in THF (2.5 mL) at –78 °C. The resulting bright yellow solution was stirred at –65 °C for 1 h when a solution of aldehyde **S3** (63.5 mg, 177 μmol, 1.0 eq.) in THF (2 mL) was added to the reaction mixture over 30 min. The reaction was stirred at –65 °C for further 30 min before EtOAc (3 mL) and HCl (1 M in H_2O, 5 mL) were added to the reaction mixture. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 20 mL) and brine (sat., 20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 12:1 → 5:1 → 2:1) gave (22*Z*)-olefin **13** (51 mg, 0.12 mmol, 68%, 52% over two steps) as a crystalline solid and reisolated sulfone **12** (193 mg, 655 μmol) as a colorless oil.

The synthesis of sulfone **12** was carried out starting from (*R*)-Roche ester as previously described by us.[10]

M.p.: 245–248 °C (EtOAc).

TLC: R_f = 0.31 (*n*hexane/EtOAc 2:1).

^{1}H-NMR: (600 MHz, pyridine-d_5); δ [ppm] = 8.10 (s, 1H), 5.98 (t, *J* = 2.3 Hz, 1H), 5.16 (t, *J* = 10.5 Hz, 1H), 5.10 (t, *J* = 10.5 Hz, 1H), 3.27 – 3.14 (m, 2H), 3.03 – 2.93 (m, 1H), 2.60 – 2.42 (m, 4H), 2.34 – 2.25 (m, 1H), 2.13 – 2.01 (m, 2H), 1.93 – 1.86 (m, 1H), 1.81 – 1.73 (m, 2H), 1.68 (qd, *J* = 13.1, 4.4 Hz, 1H), 1.56 – 1.48 (m, 2H), 1.46 – 1.35 (m, 2H), 1.35 – 1.26 (m, 2H), 1.23 (s, 3H), 1.08 (d, *J* = 5.8 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.92 – 0.86 (m, 6H), 0.72 (d, *J* = 3.7 Hz, 3H).

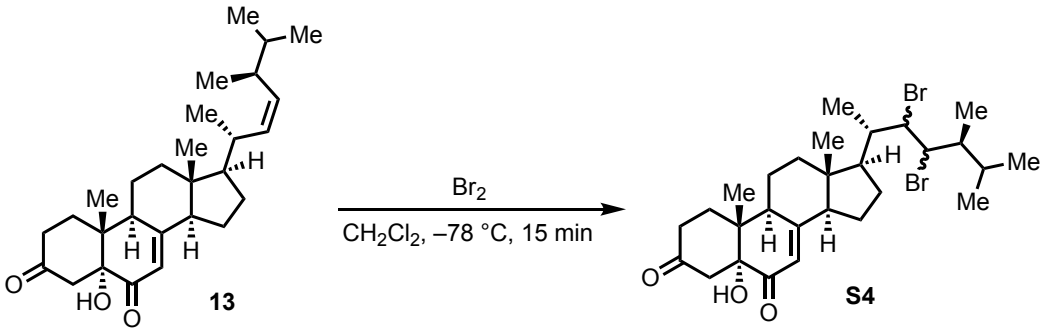
^{13}C-NMR: (151 MHz, pyridine-d_5); δ [ppm] = 210.5, 198.9, 165.2, 135.6, 132.2, 120.7, 80.2, 56.7, 56.3, 45.7, 45.1, 44.7, 42.0, 39.5, 39.0, 38.3, 35.4, 34.0, 32.9, 28.6, 23.1, 22.7, 21.3, 21.0, 20.4, 19.3, 16.0, 13.2.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (m), 2023 (s), 2853 (m), 1739 (m), 1459 (w), 1376 (w), 1217 (w), 757 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_3Na^+$ [M+Na]$^+$: 449.3026, found: 449.3024.

Opt. act. $[\alpha]_D^{20}$ = +27.5 (*c* = 1.00, $CHCl_3$).

22,23-Dibromo-5α-hydroxycampesta-7-ene-3,6-dione (**S4**)



A stock solution of bromine (92 μL, 0.18 mmol, 100 eq.) in CH_2Cl_2 (5 mL) was prepared by dissolution at 0 °C. In a separate flask, a portion of this stock solution (50 μL, equals 1.1 eq. bromine) was added to a solution of (22*Z*)-olefin **13** (7.8 mg, 18 μmol, 1.0 eq.) in CH_2Cl_2 (0.75 mL) at –78 °C and the reaction mixture was stirred at this temperature for 15 min. The reaction was then diluted with CH_2Cl_2 (5 mL) and quenched with $Na_2S_2O_3$ (sat. aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine (sat., 25 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The yellow residue was used in the next step without further purification.

An analytically pure sample of dibromide diastereomers **S4** (d.r. 2:1, determined by integration of 22-H and 23-H signals δ [ppm] = 4.55 (minor), 4.50 (major), 4.35 (major) and 3.97 (minor) in ^{1}H-NMR) could be obtained by column chromatography (silica gel, *n*hexane/EtOAc 3:1 → 2:1) as a light-yellow solid.

M.p.: 170–173°C (CH_2Cl_2).

TLC: R_f = 0.24 (*n*hexane/EtOAc 2:1).

Significant signals of the minor diastereomer are marked with *.

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.74 – 5.68 (m, 1H), 4.55 (dd, *J* = 6.2, 1.5 Hz, 1H)*, 4.50 (dd, *J* = 9.8, 2.1 Hz, 1H), 4.35 (dd, *J* = 9.8, 1.9 Hz, 1H), 3.97 (dd, *J* = 9.8, 1.4 Hz, 1H)*, 2.82 – 2.77 (m, 1H), 2.70 – 2.64 (m, 1H), 2.56 (dd, *J* = 16.2, 1.8 Hz, 1H), 2.49 (s, 1H), 2.41 – 2.36 (m, 2H), 2.27 – 2.22 (m, 1H), 2.22 – 2.10 (m, 2H), 2.09 – 2.02 (m, 1H), 1.97 (ddd, *J* = 9.8, 6.9, 2.6 Hz, 1H)*, 1.94 – 1.88 (m, 1H), 1.86 – 1.78 (m, 3H), 1.78 – 1.73 (m, 1H), 1.71 – 1.65 (m, 2H), 1.62 – 1.54 (m, 2H), 1.32 (d, *J* = 7.1 Hz, 3H)*, 1.31 – 1.27 (m, 1H), 1.23 – 1.17 (m, 1H), 1.14 (s, 3H), 1.14 (s, 3H)*, 1.01 (d, *J* = 6.3 Hz, 3H), 0.99

– 0.96 (m, 6H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H)*, 0.75 (d, *J* = 6.8 Hz, 3H)*, 0.67 (s, 3H), 0.66 (s, 3H)*.

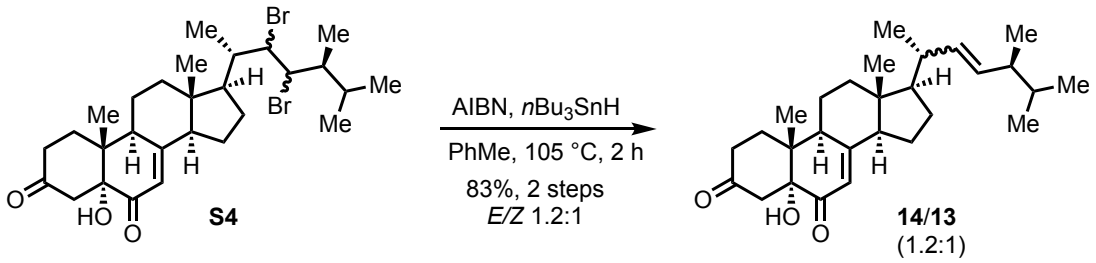
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 210.1, 197.2, 165.0, 120.0*, 119.9, 79.9, 68.9, 66.9, 62.1*, 60.4*, 55.5, 55.5*, 55.1, 53.1*, 45.6*, 45.1*, 44.7, 44.7*, 43.8, 43.8, 42.8, 41.0, 38.9, 38.7*, 38.7, 37.5, 32.8, 32.1*, 32.0, 28.4*, 26.9*, 26.7, 22.6*, 22.3, 22.1, 22.1*, 21.9*, 21.0, 20.6, 16.6*, 16.0, 15.9*, 15.3*, 14.0, 13.3, 13.3*, 12.7, 10.6*.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3342 (br w), 2925 (m), 2873 (w), 2857 (w), 1714 (m), 1675 (s), 1622 (w), 1459 (w), 1380 (w), 1232 (w), 1159 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}Br_2O_3Na^+$ $[M+Na]^+$: 607.1393, found: 607.1377.

Opt. act. $[\alpha]_D^{22}$ = +16.6 (*c* = 1.00, $CHCl_3$).

(22*E*)-5α-Hydroxycampesta-7,22-diene-3,6-dione (**14**) and (22*Z*)-5α-Hydroxycampesta-7,22-diene-3,6-dione (**13**)



A solution of azobisisobutyronitrile (0.6 mg, 3.6 μmol, 0.2 eq.), nBu$_3$SnH (24 μL, 90 μmol, 5.0 eq.) and crude dibromide **S4** (18 μmol, 1.0 eq.) in toluene (0.75 mL) was degassed by applying three freeze-pump-thaw cycles before the reaction mixture was heated to 105 °C for 2 h. It was cooled to 25 °C and the solvent was removed under reduced pressure. The residue was adsorbed on silica and column chromatography (silica gel, *n*hexane/EtOAc 3:1 → 2:1) gave a mixture of (*E*)-isomer **14** and (*Z*)-isomer **13** (E/Z 1.2:1, determined by integration of 22-H and 23-H signals δ [ppm] = 5.22 (major), 5.16 (major), 5.08 (minor) and 5.03 (minor) in ^{1}H-NMR, 6.4 mg, 15 μmol, 83% over two steps) as a colorless solid.

M.p.: Decomposition at 238–240°C (EtOAc).

TLC: R_f = 0.28 (*n*hexane/EtOAc 2:1).

Significant signals of the minor diastereomer are marked with *.

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.71 (t, *J* = 2.3 Hz, 1H), 5.22 (dd, *J* = 15.2, 7.9 Hz, 1H), 5.16 (dd, *J* = 15.2, 8.3 Hz, 1H), 5.10 – 5.06 (m, 1H)*, 5.03 (t, *J* = 10.5, 1H)*, 2.81 (dd, *J* = 16.2, 1.6 Hz, 1H), 2.68 – 2.62 (m, 1H), 2.57 (dd, *J* = 16.1, 2.1 Hz, 1H), 2.45 – 2.36 (m, 2H), 2.26 (s, 1H), 2.22 – 2.13 (m, 3H), 2.08 – 2.00 (m, 1H), 1.95 – 1.89 (m, 1H),

1.87 – 1.77 (m, 2H), 1.72 (tt, *J* = 12.6, 4.3 Hz, 1H), 1.68 – 1.63 (m, 1H), 1.56 – 1.44 (m, 3H), 1.44 – 1.35 (m, 2H), 1.33 – 1.28 (m, 1H), 1.16 (s, 3H)*, 1.15 (s, 3H), 1.04 (t, *J* = 5.7 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H)*, 0.92 (d, *J* = 6.8 Hz, 3H)*, 0.92 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H)*, 0.67 (s, 3H)*, 0.64 (s, 3H).

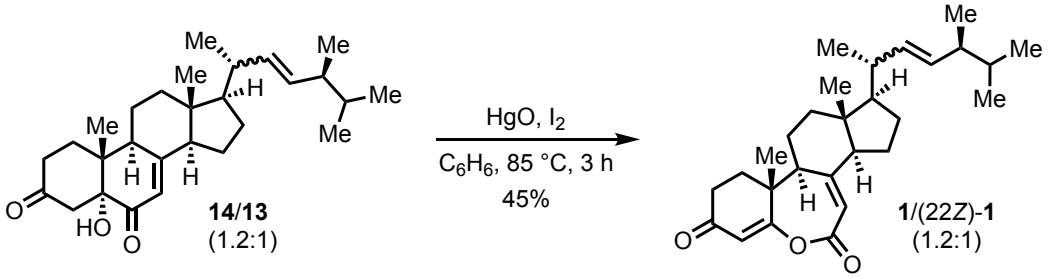
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 210.1, 197.1, 166.0, 135.3, 134.5*, 132.8, 132.0*, 119.7, 80.0, 56.3*, 56.1*, 56.0, 44.9, 44.8, 43.9*, 43.9, 43.2, 41.0, 41.0*, 40.5, 39.0*, 38.9, 38.5*, 37.5, 34.7, 33.5*, 33.3, 32.1, 28.3, 27.9*, 22.7, 22.6*, 22.2, 21.3, 20.8*, 20.5*, 20.3, 20.0*, 19.8, 18.8*, 18.1, 16.0*, 16.0, 12.9*, 12.8.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3334 (br w), 2954 (m), 2922 (s), 2852 (m), 1716 (w), 1674 (m), 1622 (w), 1457 (w), 1378 (w), 1233 (w), 874 (w), 721 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_3Na^+$ [M+Na]$^+$: 449.3026, found: 449.3032.

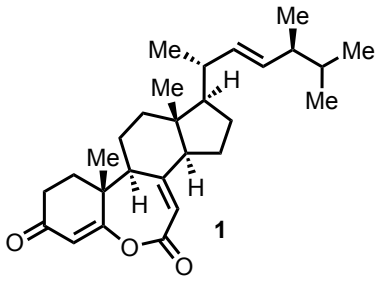
Opt. act. $[\alpha]_D^{22}$ = +34.1 (*c* = 1.00, $CHCl_3$).

(22*E*)-5,6-Epoxy-5,6-secocampesta-4,7,22-triene-3,6-dione (**1**) and
(22*Z*)-5,6-Epoxy-5,6-secocampesta-4,7,22-triene-3,6-dione (22*Z*)-**1**



Through a mixture of *E* and *Z* dione **14** and **13** (9.9 mg, 23 μmol, 1.0 eq.) in benzene (2 mL) was bubbled argon *via* cannula for 10 min. Iodine (14.0, 55.2 μmol, 2.4 eq.) and HgO (yellow, 13.5 mg, 62.1 μmol, 2.7 eq.) were added and the resulting mixture was heated to 85 °C for 3 h. The reaction mixture was cooled to 25 °C, filtered through a plug of Celite®, and rinsed with EtOAc (10 mL). The organic phase was washed sequentially with $Na_2S_2O_3$ (sat. aq., 250 mL) and brine (sat., 250 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1 → 3:1) gave a mixture of enol esters **1** and 22*Z*-**1** (4.40 mg, 10.4 μmol, 45%) as a colorless oil.

Separation of the diastereomers was performed using a pre-packed RP 18 column (Kinetex EVO, 5 μm, 250 × 21 mm), λ = 254 nm, acetonitrile/H_2O 85:15, flow rate = 15 mL/min; t_R = 20.40 min (major, **1**), 18.25 min (minor, (22*Z*)-**1**) and gave **1** (2.4 mg, 5.6 μmol, 20% over 3 steps) as a colorless oil and (22*Z*)-**1** (2.0 mg, 4.7 μmol, 17% over 3 steps) as a colorless solid.



1

TLC: R_f = 0.28 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.75 (s, 1H), 5.72 (s, 1H), 5.23 (dd, *J* = 15.2, 8.1 Hz, 1H), 5.14 (dd, *J* = 15.2, 8.6 Hz, 1H), 2.56 – 2.51 (m, 1H), 2.49 (dd, *J* = 14.0, 4.8 Hz, 1H), 2.43 (ddd, *J* = 18.4, 5.5, 2.1 Hz, 1H), 2.19 (ddd, *J* = 14.1, 5.0, 2.2 Hz, 1H), 2.15 (dd, *J* = 11.9, 6.6 Hz, 1H), 2.13 – 2.08 (m, 1H), 2.07 – 2.01 (m, 1H), 1.98 (td, *J* = 14.3, 5.6 Hz, 1H), 1.88 – 1.82 (m, 2H), 1.82 – 1.76 (m, 1H), 1.69 (qd, *J* = 13.3, 4.1 Hz, 1H), 1.60 – 1.55 (m, 1H), 1.52 – 1.45 (m, 3H), 1.42 – 1.35 (m, 2H), 1.24 (s, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.64 (s, 3H).

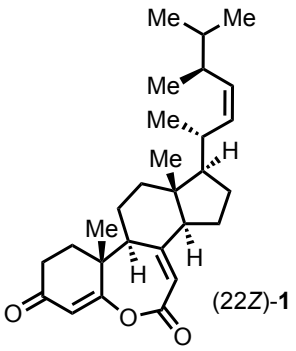
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 198.6, 174.0, 162.6, 159.6, 135.1, 133.1, 114.8, 113.5, 58.3, 56.4, 47.4, 47.1, 43.2, 40.5, 40.5, 39.3, 34.1, 33.3, 33.3, 28.1, 25.5, 22.8, 21.2, 20.3, 20.1, 19.8, 18.1, 12.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (s), 2923 (s), 2854 (m), 1735 (s), 1673 (m), 1622 (m), 1457 (m), 1377 (w), 1340 (w), 1280 (w), 1232 (m), 1186 (m), 1138 (s), 970 (w), 864 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{40}O_3Na^+$ $[M+Na]^+$: 447.2870, found: 447.2871.

Opt. act. $[\alpha]_D^{22}$ = +160.1 (*c* = 0.22, CH_2Cl_2).

$[\alpha]_D^{22}$ = +177.2 (*c* = 0.22, $CHCl_3$).



(22*Z*)-**1**

M.p.: 210–213 °C ($CHCl_3$).

TLC: R_f = 0.28 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.75 (s, 1H), 5.73 (t, *J* = 1.7 Hz, 1H), 5.09 – 5.01 (m, 2H), 2.54 (ddd, *J* = 12.6, 4.9, 2.4 Hz, 1H), 2.49 (dd, *J* = 14.1, 4.8 Hz, 1H), 2.45 (dd, *J* = 5.3, 2.1 Hz, 1H), 2.44 – 2.38 (m, 1H), 2.22 – 2.20 (m, 1H), 2.20 – 2.17 (m, 1H), 2.16 (dd, *J* = 11.8, 6.7 Hz, 1H), 2.11 (dt, *J* = 13.2, 3.2 Hz, 1H), 1.98 (td, *J* = 14.1, 5.4 Hz, 1H), 1.88 – 1.78 (m, 2H), 1.70 (qd, *J* = 13.3, 4.0 Hz, 1H), 1.62 – 1.56 (m, 1H), 1.52 – 1.49 (m, 1H), 1.49 – 1.47 (m, 1H), 1.44 – 1.37 (m, 2H), 1.30 – 1.26 (m, 1H), 1.24 (s, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.66 (s, 3H).

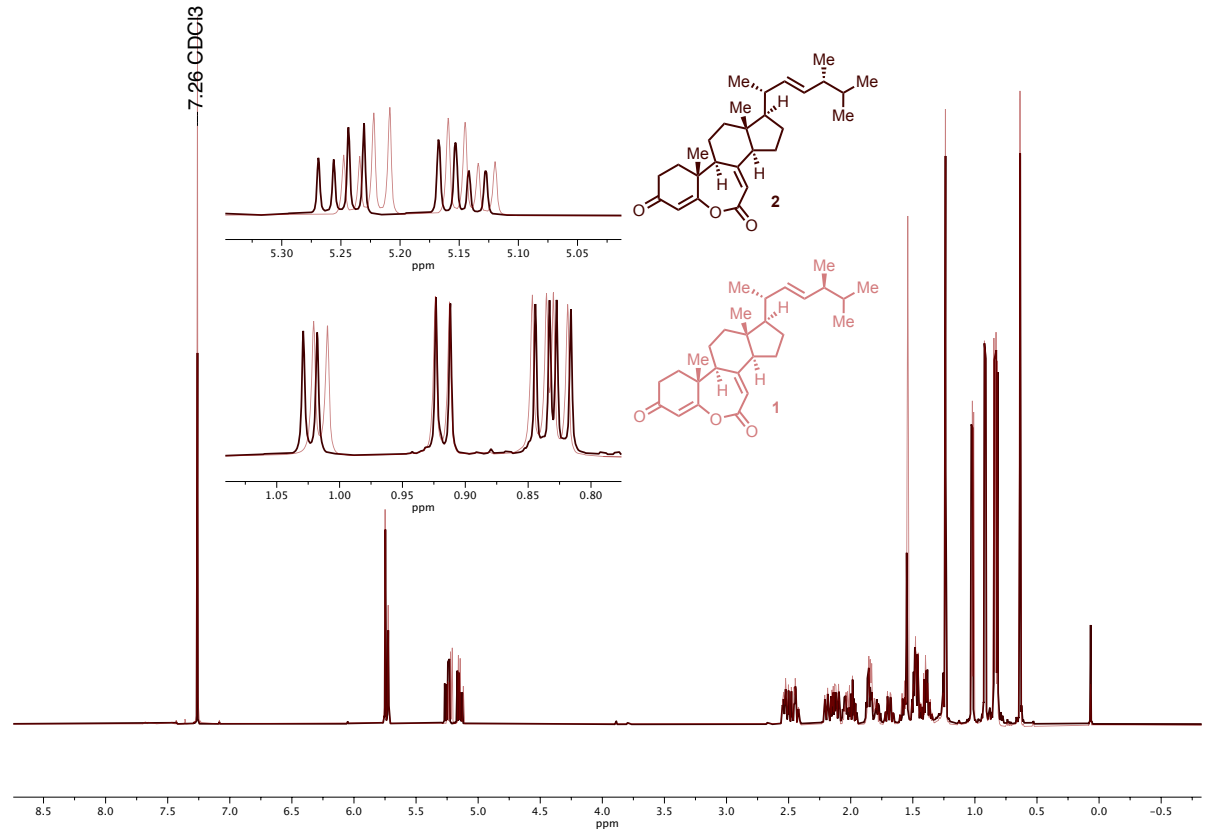
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 198.6, 174.0, 162.6, 159.5, 134.2, 132.3, 114.8, 113.5, 58.3, 56.5, 47.4, 47.1, 40.5, 39.4, 38.6, 34.7, 34.1, 33.5, 33.3, 27.7, 25.5, 22.7, 20.7, 20.5, 20.1, 20.1, 18.8, 12.6.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (m), 2924 (s), 2853 (m), 1721 (m),1681 (w), 1623 (w), 1458 (w), 1377 (w), 1339 (w), 1141 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{40}O_3Na^+$ $[M+Na]^+$: 447.2870, found: 447.2870.

Opt. act. $[\alpha]_D^{20}$ = +132.5 (*c* = 0.16, $CHCl_3$).

3 NMR Comparisons of synthetic **2** and **1**



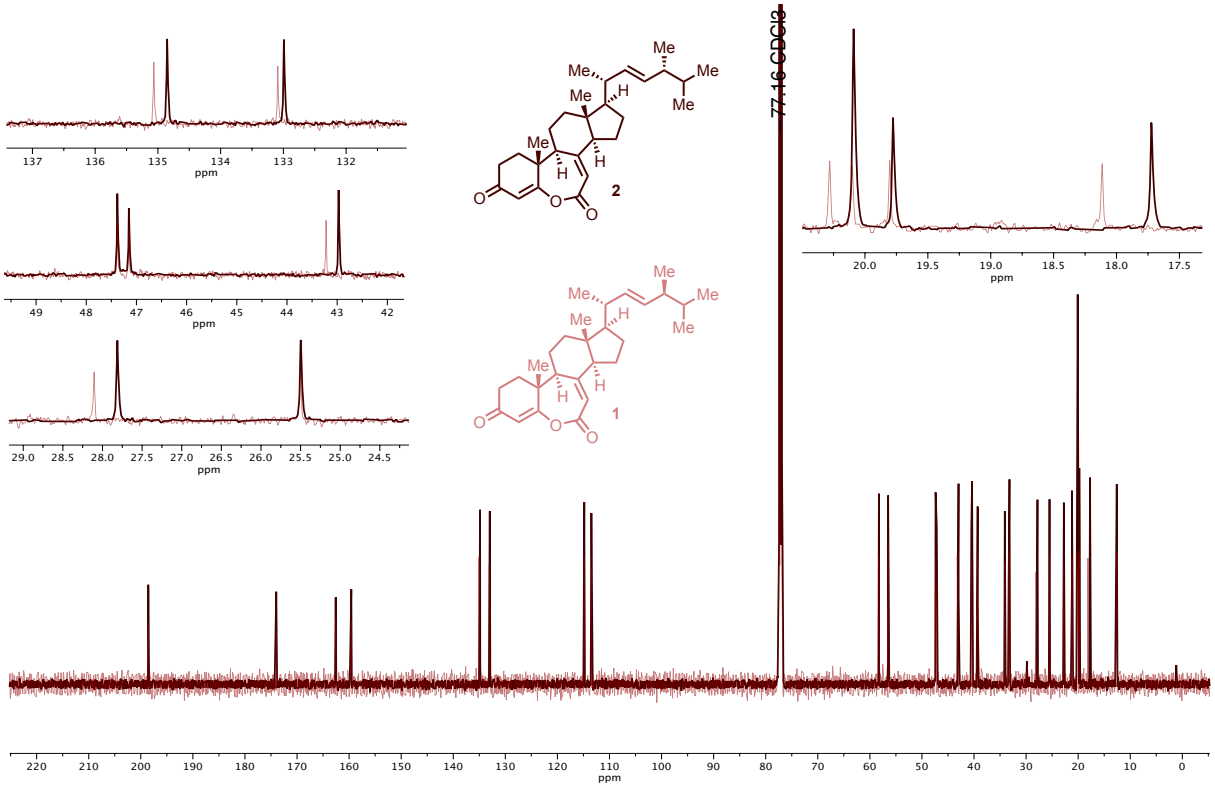


Table S1. ^{1}H-NMR comparison of natural materials[11],[9],[12] and synthetic **2** and **1**.

#	Patent[11],a,b	Herbarulide[9],c	$\Delta\delta_{(\text{Herb. vs. } \mathbf{2})}$	Synthetic **2**c	Synthetic **1**c	Fortisterol[12],a
1		2.19 m; 1.95 m	0.00; 0.03	2.19 ddd (14.3, 5.0, 2.1); 1.98 td (14.2, 5.3)	2.20 ddd (14.1, 5.0, 2.2); 1.98 td (14.3, 5.6)	2.21 m; 1.96 m
2		2.46 m; 2.46 m	0.03; 0.03	2.49 dd (14.1, 4.8); 2.43 ddd (18.4, 5.2, 1.7)	2.49 dd (14.0, 4.8); 2.43 ddd (18.4, 5.5, 2.0)	2.50 m; 1.47 m*
3	-	-	-	-	-	-
4	5.75 s	5.75 s	0.00	5.75 s	5.75 s	5.74 m
5	-	-	-	-	-	-
6	-	-	-	-	-	-
7	5.73 s	5.72 s	0.00	5.72 t (1.8)	5.72 t (1.8)	5.71 m
8	-	-	-	-	-	-
9		2.52 m	0.01	2.53 ddd (12.4, 4.9, 2.2)	2.53 m	2.51 m
10	-	-	-	-	-	-
11		1.84 m; 1.68 m	0.02; 0.01	1.86 m, 1.69 dd (13.0 4.1)	1.85 m, 1.69 qd (13.1, 4.1)	1.55 m*; 1.52 m*
12		2.09 m; 1.45 m	0.01	2.10 ddd (13.0, 4.1, 2.8); 1.48 m	2.11 dt (13.1, 3.6); 1.47 m	2.12 m; 1.45 m
13	-	-	-	-	-	-
14		2.14	0.00	2.14 m	2.14 dd (12.0, 7.5)	2.13 m
15		1.50 m; 1.50 m	0.06; 0.02	1.56 m; 1.48 m	1.59 m, 1.48 m	1.84 m*; 1.82 m*
16		1.78 m; 1.78 m*	0.01; 0.39	1.79 m; 1.39 m	1.80 m, 1.38 m	1.73 m; 1.35 m
17		1.38 m	0.01	1.39 m	1.41 m	1.37 m
18		0.64 s	0.01	0.63 s	0.64 s	0.63 s
19	1.24 s	1.24 s	0.00	1.24 s	1.24 s	1.23 s
20		2.03 m	0.01	2.04 m	2.04 m	2.04 m
21	1.02 d (6.5)	1.02 d (6.6)	0.00	1.02 d (6.6)	1.02 d (6.6)	1.01 s
22	5.14 m	5.15 dd (15.2, 8.5)	0.00	5.15 dd (15.2, 8.6)	5.14 dd (15.2, 8.6)	5.25 dd (15.2, 7.7)*
23	5.25 m	5.25 dd (15.2, 7.8)	0.00	5.25 dd (15.2, 7.9)	5.23 dd (15.2, 8.1)	5.15 dd (15.2, 8.4)*
24		1.86 m	0.00	1.86 m	1.84 m	1.84 m
25		1.48 m	0.00	1.48 m	1.47 m	2.44 m*
26	0.84 d (8.4)	0.84 d (6.8)	0.00	0.84 d (6.8)	0.84 d (6.8)	0.82 d (6.8)
27	0.82 d (8.4)	0.82 d (6.8)	0.00	0.82 d (6.8)	0.82 d (6.7)	0.82 d (6.8)
28	0.92 d (6.8)	0.91 d (6.8)	0.00	0.91 d (6.8)	0.92 d (6.8)	0.87 d (6.8)

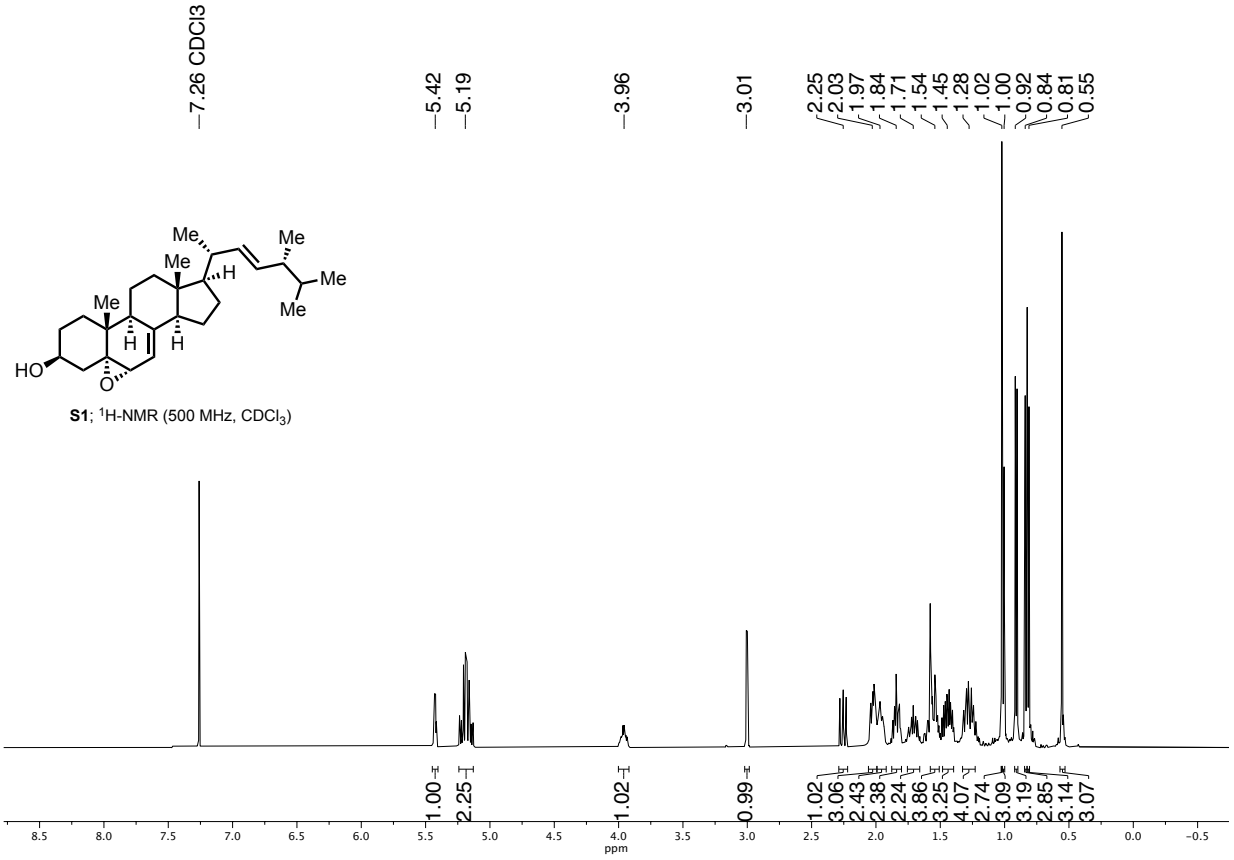
All chemical shifts are reported in ppm. Coupling constants are in parentheses and are reported in Hz. m = centered multiplet. All spectra were measured in $CDCl_3$ and are referenced to the residual solvent peak at δ_H = 7.26 ppm. [a] Recorded at 400 MHz; [b] signals were not assigned; [c] recorded at 600 MHz, misassigned signals are marked with*.

Table S2. ^{13}C-NMR comparison of natural materials[11],[9],[12] and synthetic **2** and **1**.

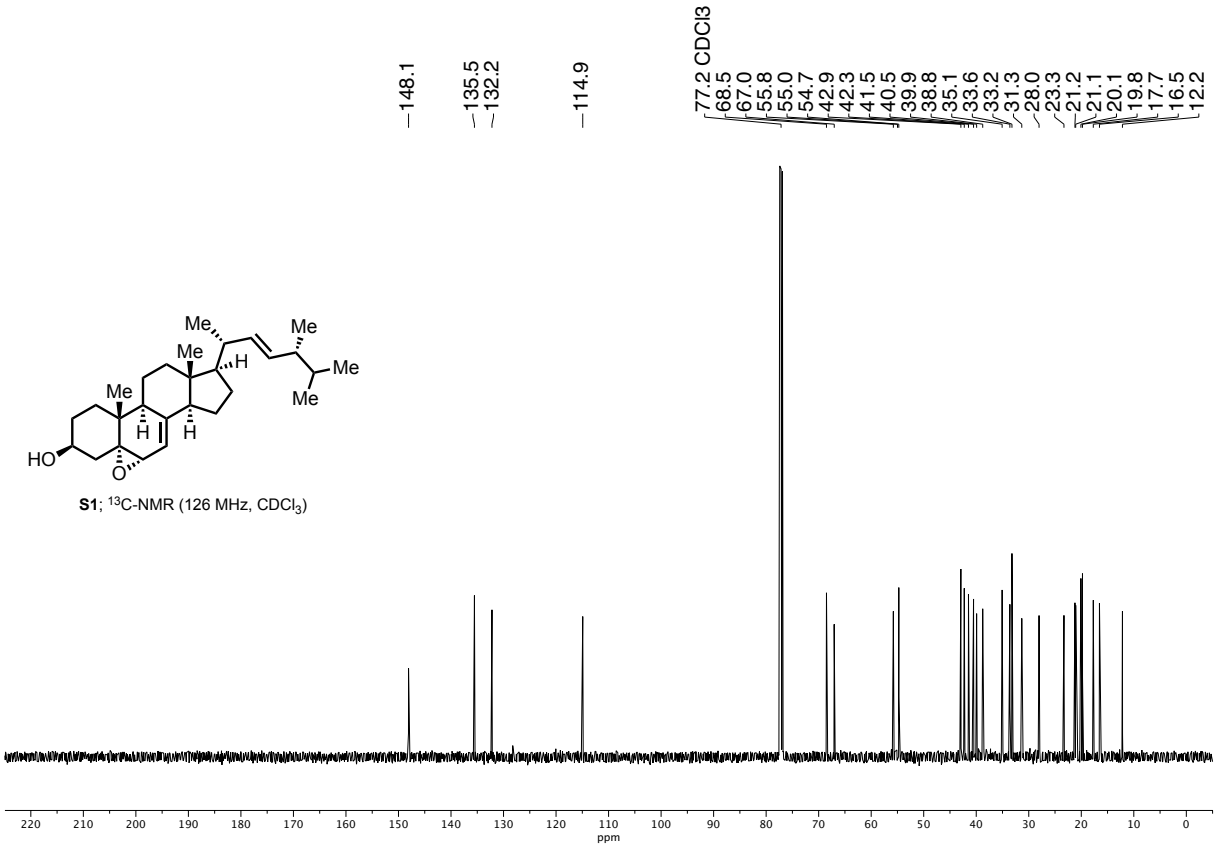
#	Patent[11],a	Herbarulide[9],b	$\Delta\delta_{(\text{Herb. vs. } \mathbf{2})}$	Synthetic **2**b,c	Synthetic **1**b,c	Fortisterol[12],a
1	33.9	34.0	0.1	33.9	33.9	33.8
2	33.2*	33.2	0.0	33.2	33.2	33.1*
3	198.5	198.4	0.0	198.4	198.4	198.5
4	114.7	114.7	0.0	114.7	114.7	114.6
5	173.8	173.9	0.1	173.8	173.8	173.9
6	162.4	162.4	0.0	162.4	162.4	162.4
7	113.3	113.4	0.1	113.3	113.3	113.2
8	159.5	159.4	0.0	159.4	159.4	159.5
9	47.2	47.3	0.1	47.2	47.2	47.2
10	40.3	40.4	0.0	40.4	40.4	40.3
11	22.6*	25.4	0.1	25.3	25.3	22.6*
12	39.2	39.2	0.1	39.1	39.2	39.1
13	45.9	47.0	0.0	47.0	47.0	47.0
14	58.1	58.2	0.1	58.1	58.1	58.0
15	25.3*	22.6	0.0	22.6	22.6	25.3*
16	27.7	27.7	0.0	27.7	27.9	27.6
17	56.3	56.4	0.1	56.3	56.3	56.3
18	12.4	12.5	0.1	12.4	12.4	12.4
19	19.9	20.0	0.1	19.9	19.9	19.9
20	40.3	40.2	0.0	40.2	40.3	40.2
21	21.0	21.1	0.1	21.0	21.0	21.0
22	134.7	134.7	0.0	134.7	134.9	134.7
23	132.8	132.9	0.1	132.8	132.9	132.8
24	42.8	42.9	0.1	42.8	43.1	42.8
25	33.0*	33.1	0.1	33.0	33.1	33.0*
26	19.6	20.0	0.1	19.9	20.1	19.9
27	19.9	19.7	0.1	19.6	19.6	19.6
28	17.6	17.6	0.0	17.6	18.0	17.5

All chemical shifts are reported in ppm. [a] Recorded at 100 MHz; [b] recorded at 151 MHz; [c] spectra referenced to the solvent peak at δ_C = 77.00 ppm, misassigned signals are marked with *. Signals that are shifted due to different configuration at C24 are marked in light grey.

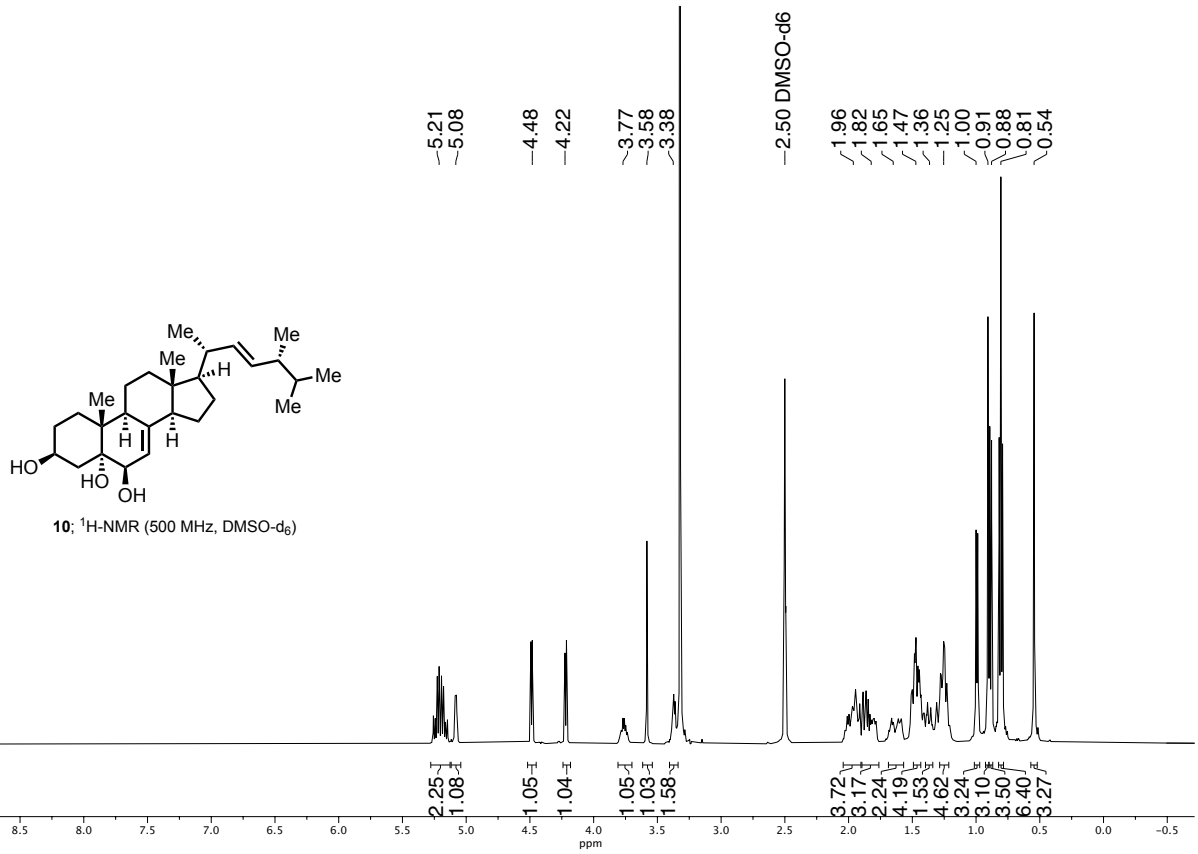
4 NMR Spectra

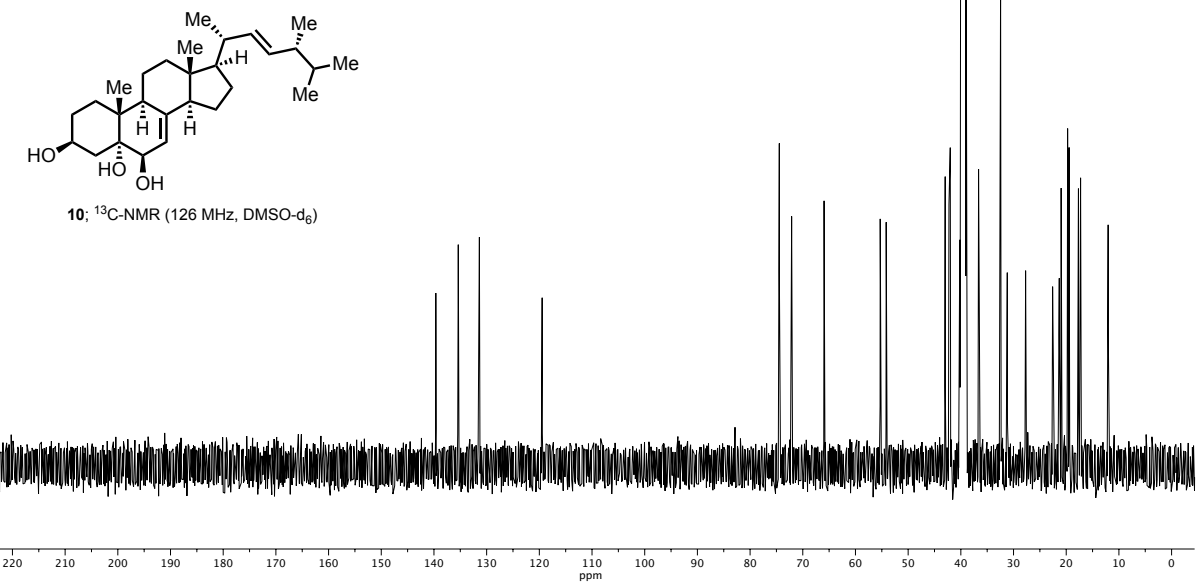


S1; ^{1}H-NMR (500 MHz, $CDCl_3$)



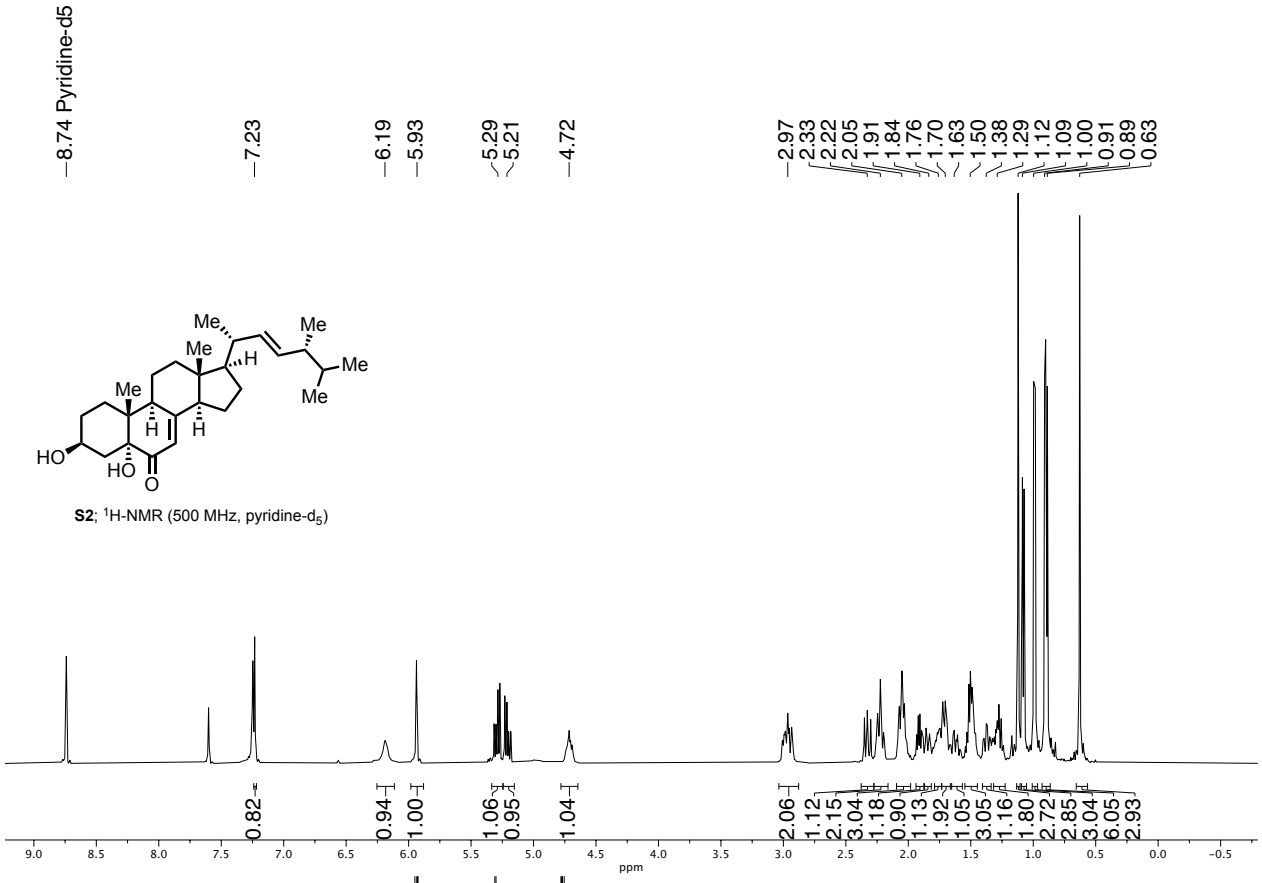
S1; ^{13}C-NMR (126 MHz, $CDCl_3$)



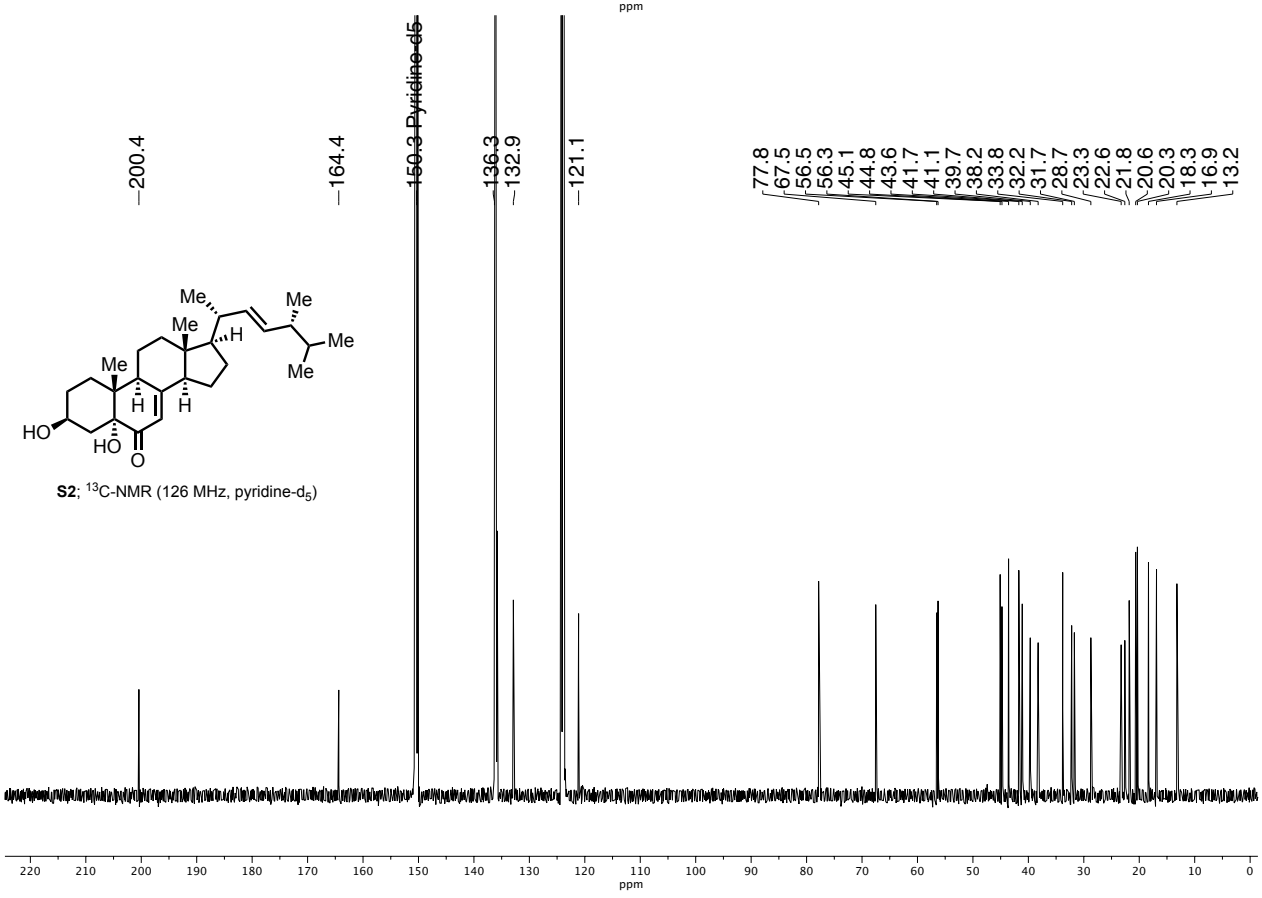


10; ^{1}H-NMR (500 MHz, DMSO-d_6)

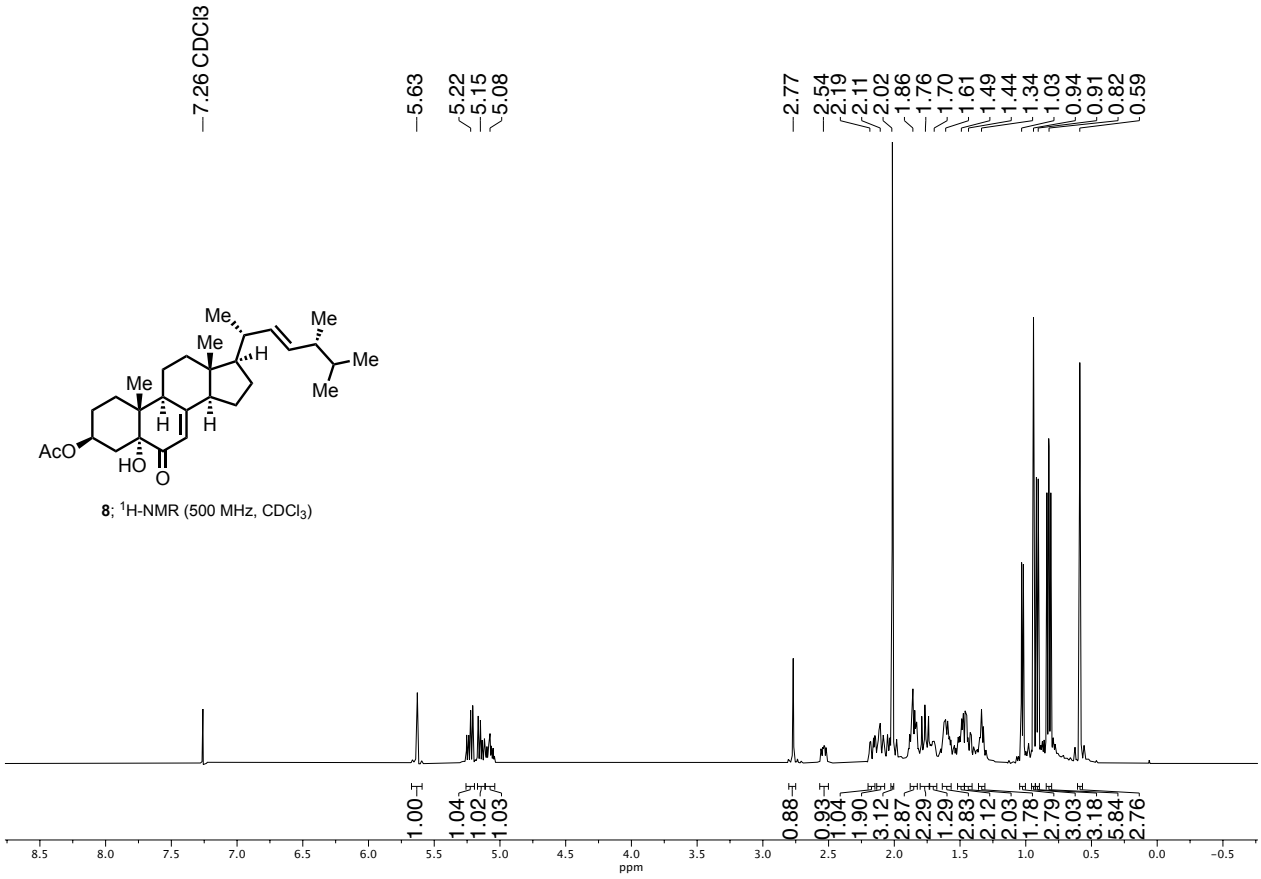
10; ^{13}C-NMR (126 MHz, DMSO-d_6)



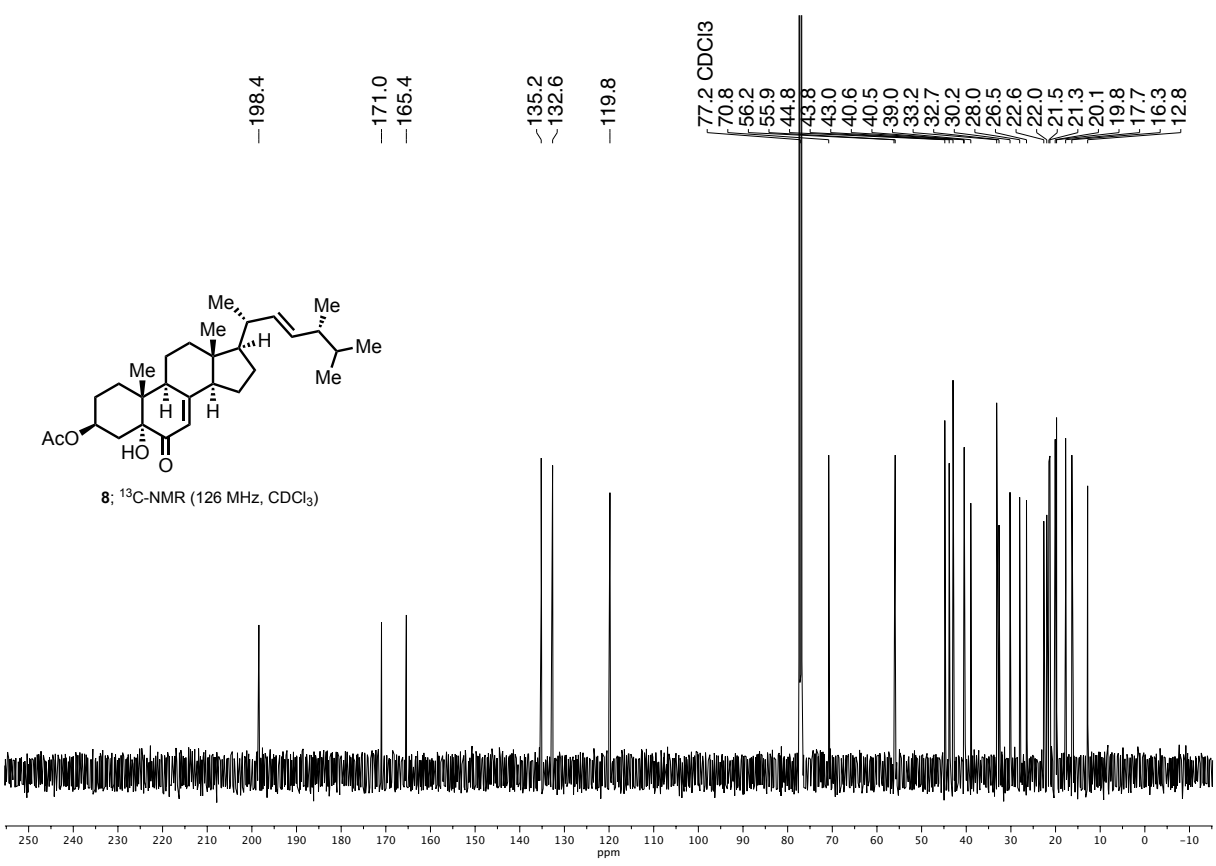
S2; ^{1}H-NMR (500 MHz, pyridine-d_5)



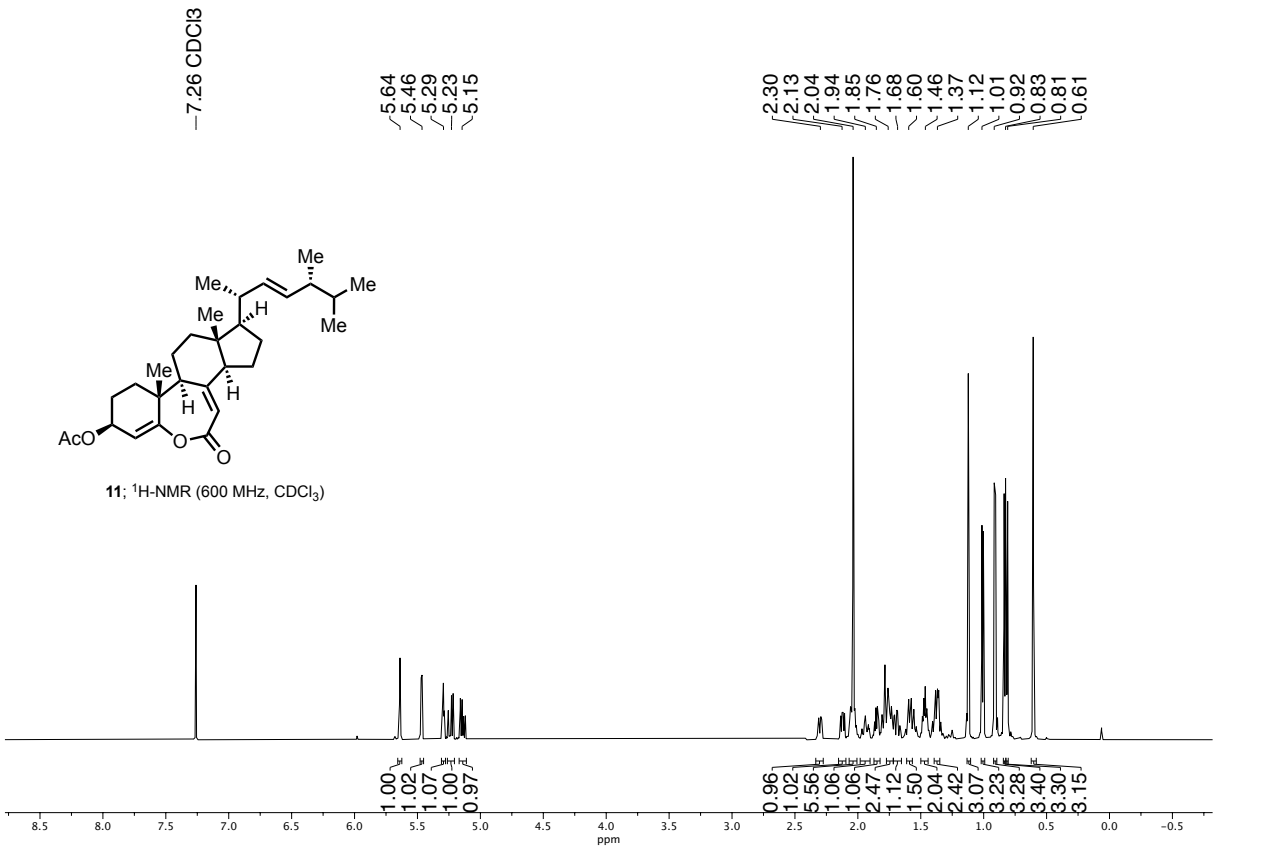
S2; ^{13}C-NMR (126 MHz, pyridine-d_5)



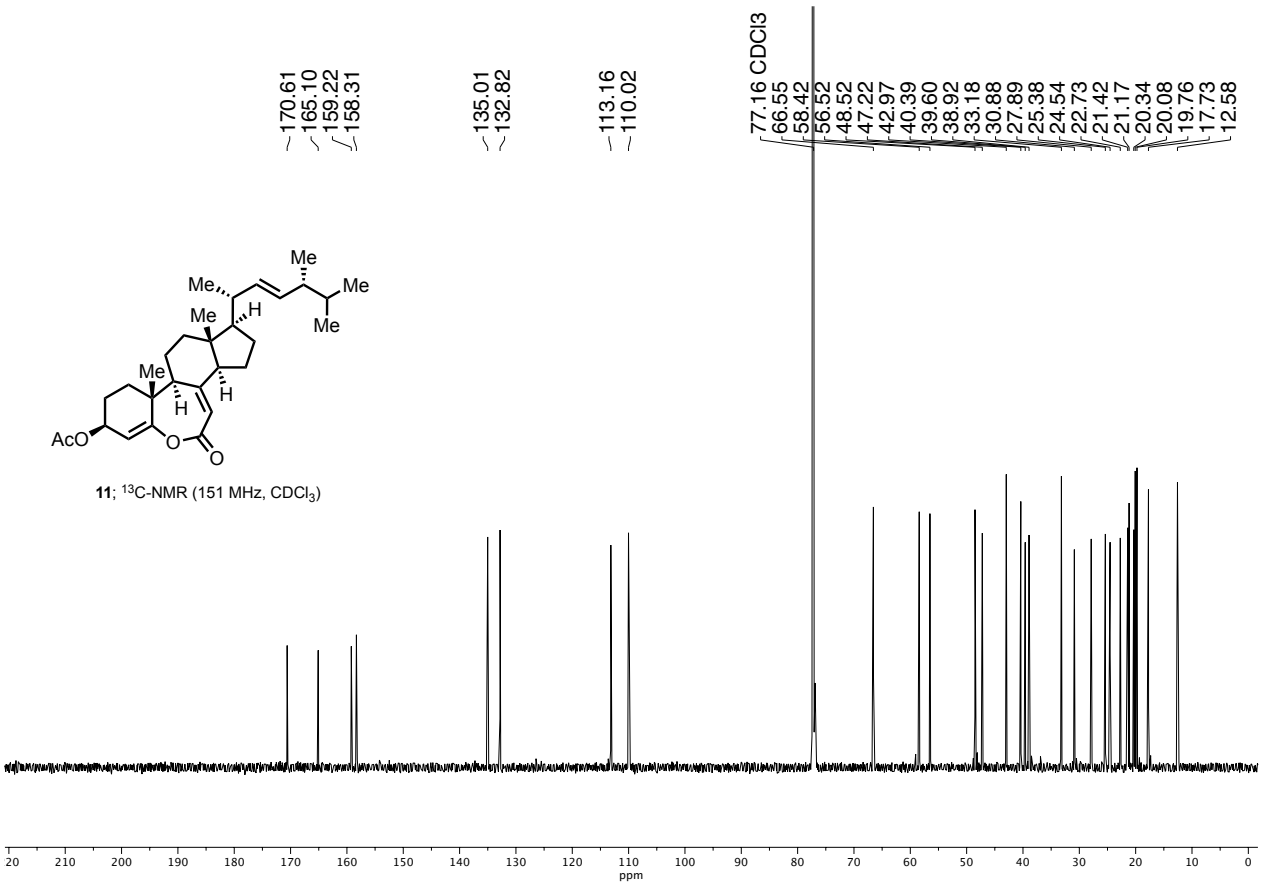
8; ^{1}H-NMR (500 MHz, $CDCl_3$)



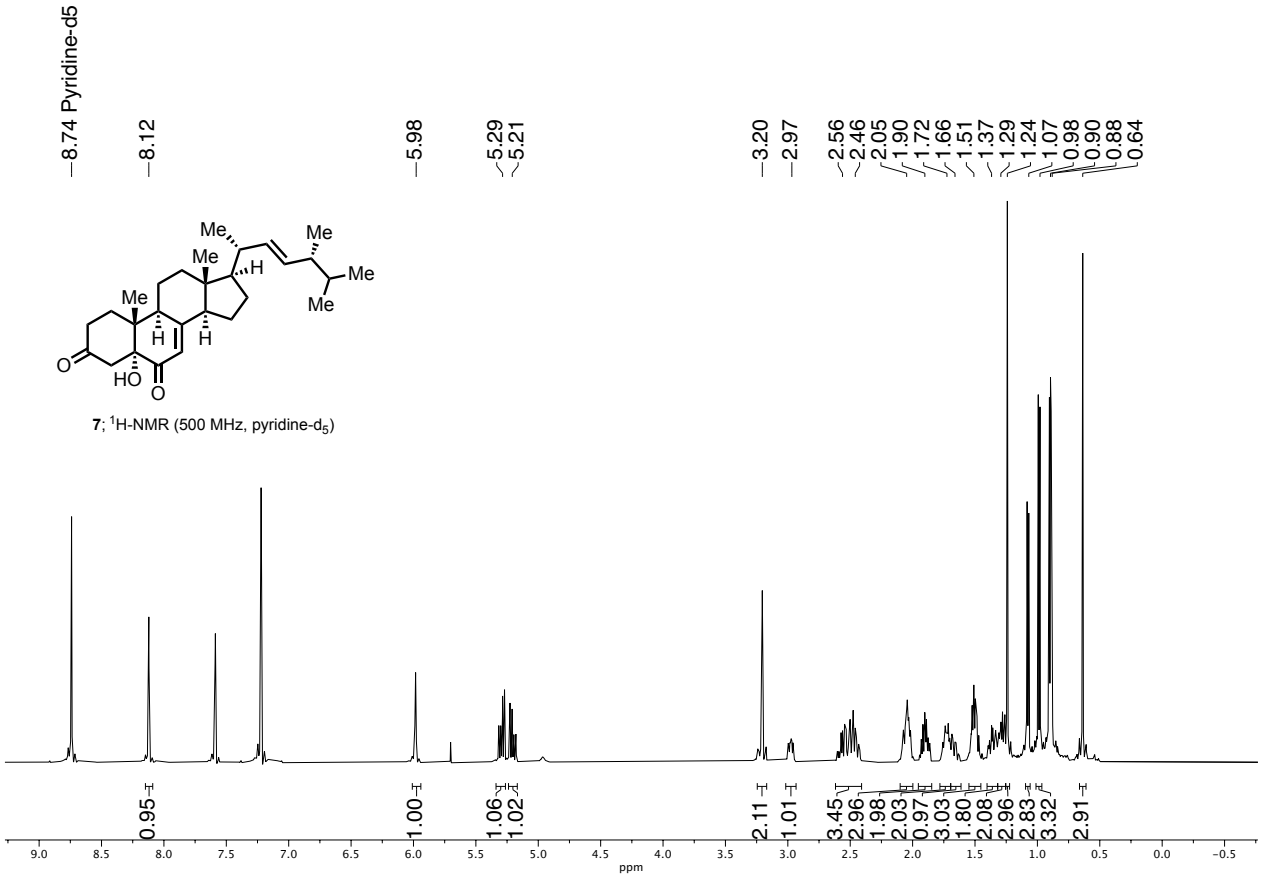
8; ^{13}C-NMR (126 MHz, $CDCl_3$)



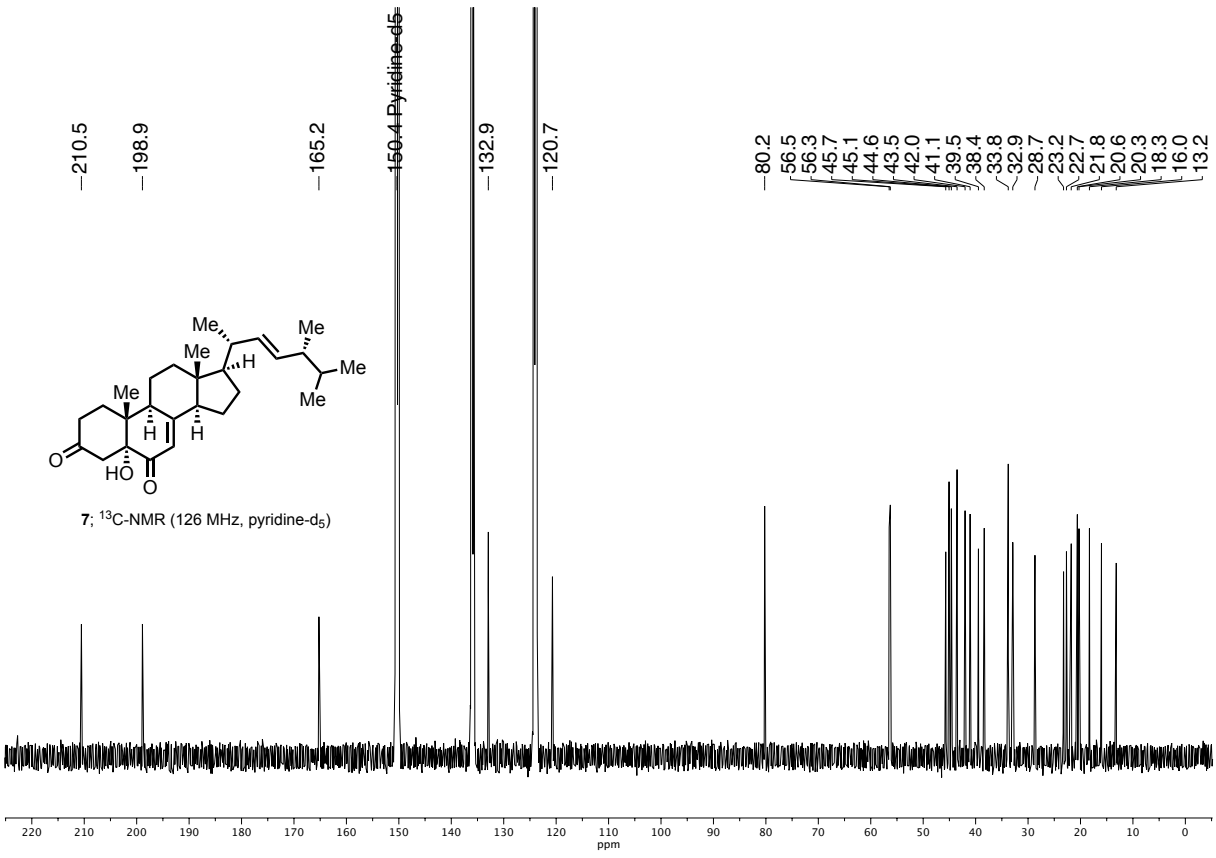
11; ^{1}H-NMR (600 MHz, $CDCl_3$)



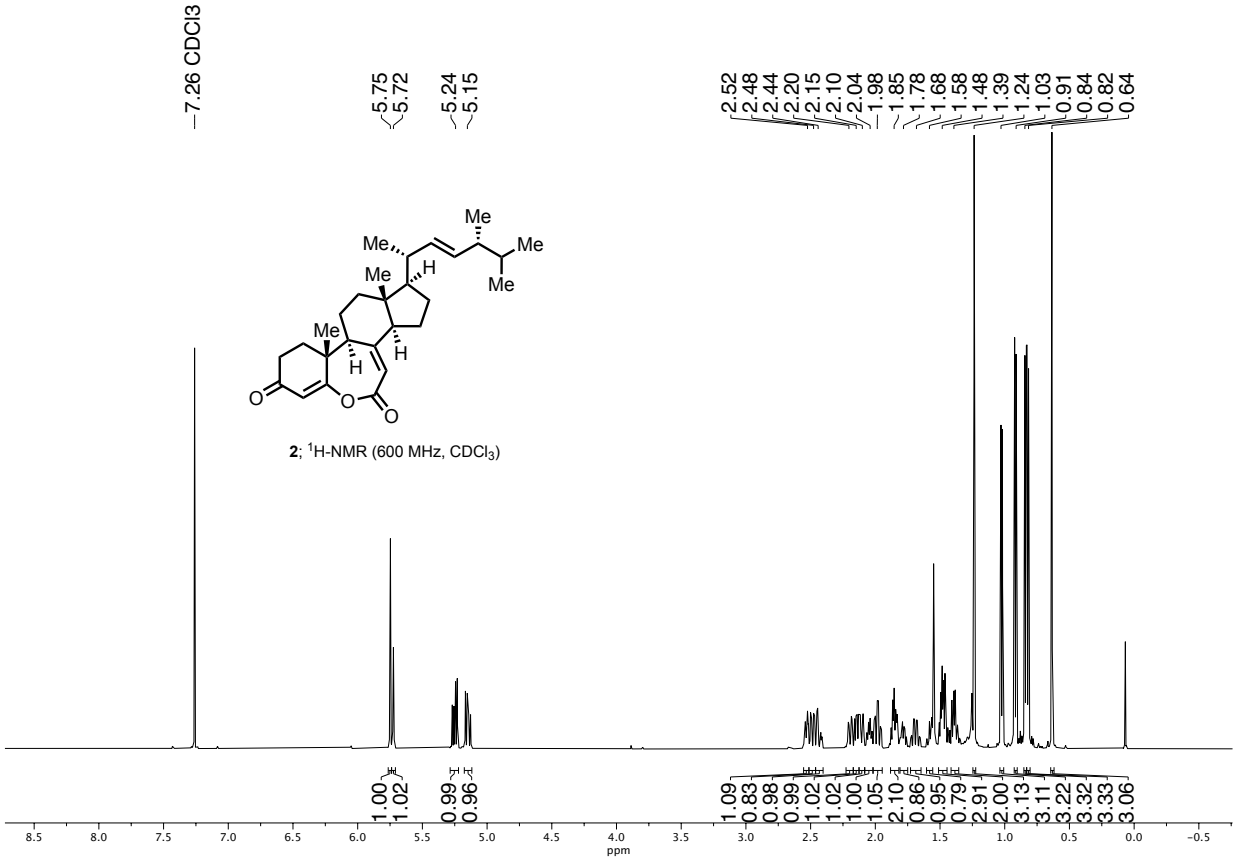
11; ^{13}C-NMR (151 MHz, $CDCl_3$)



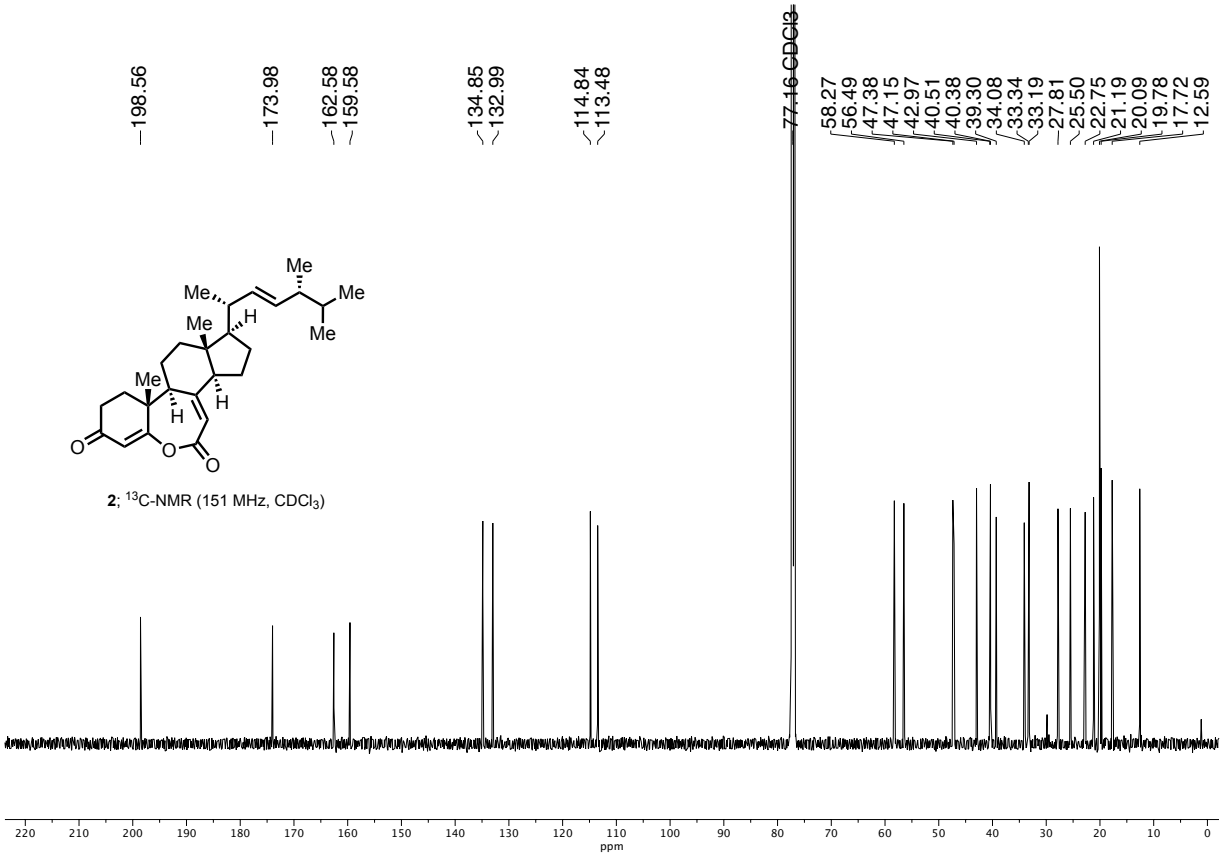
7; ^{1}H-NMR (500 MHz, pyridine-d_5)



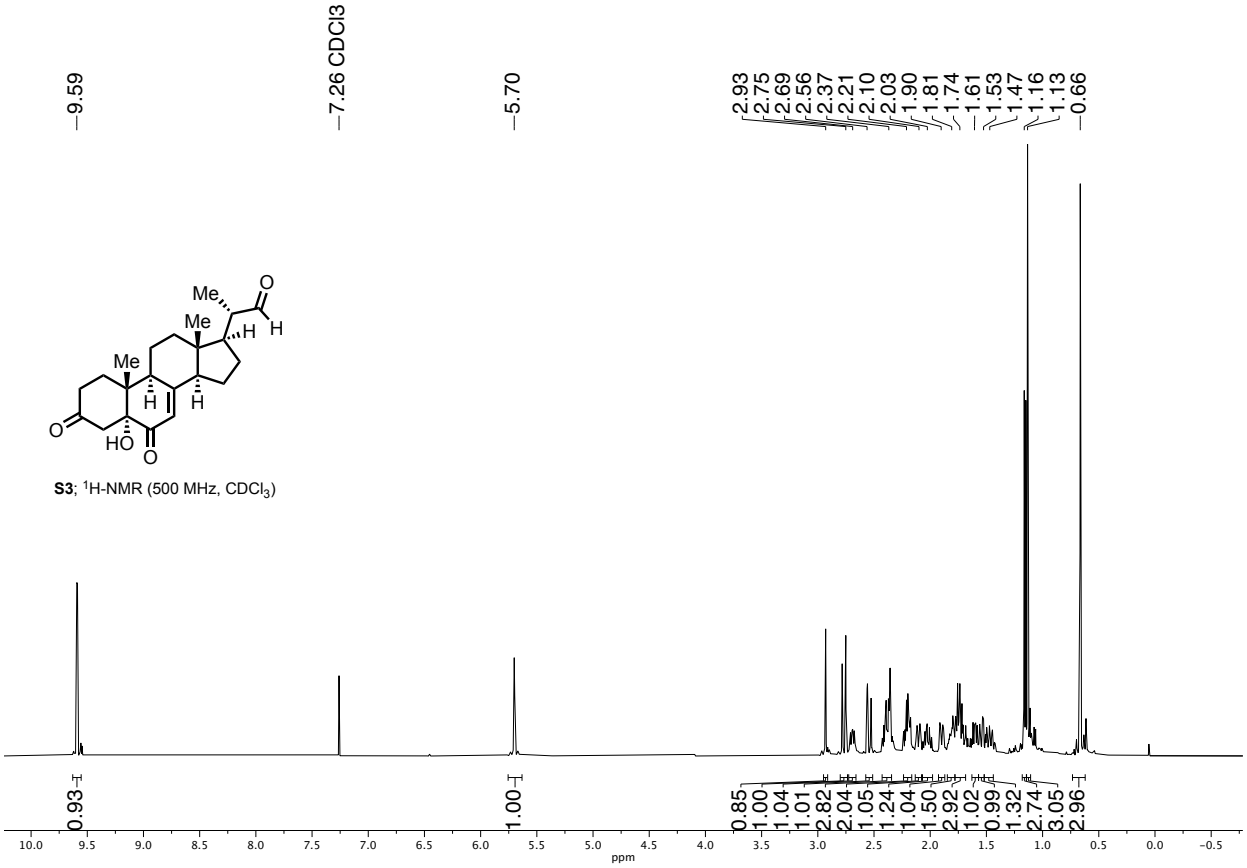
7; ^{13}C-NMR (126 MHz, pyridine-d_5)



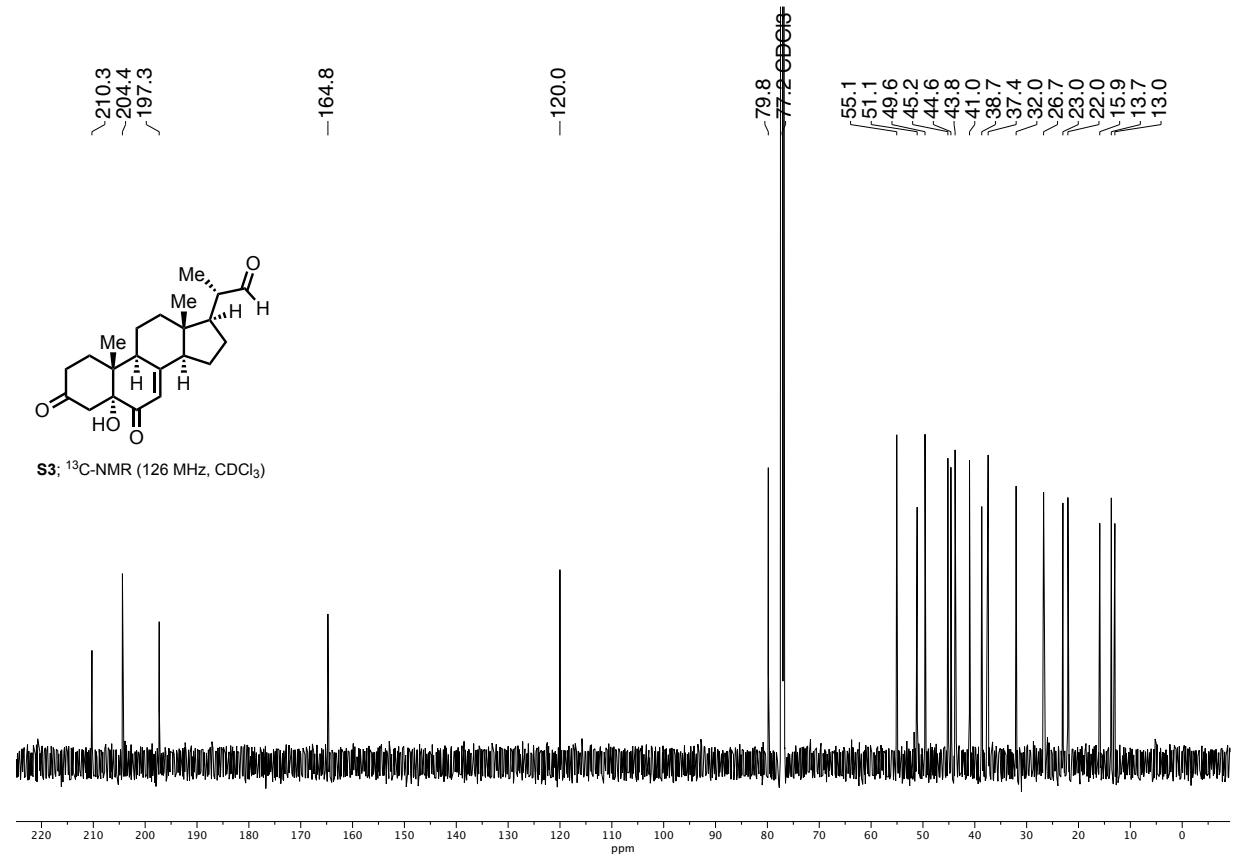
2; ^{1}H-NMR (600 MHz, $CDCl_3$)



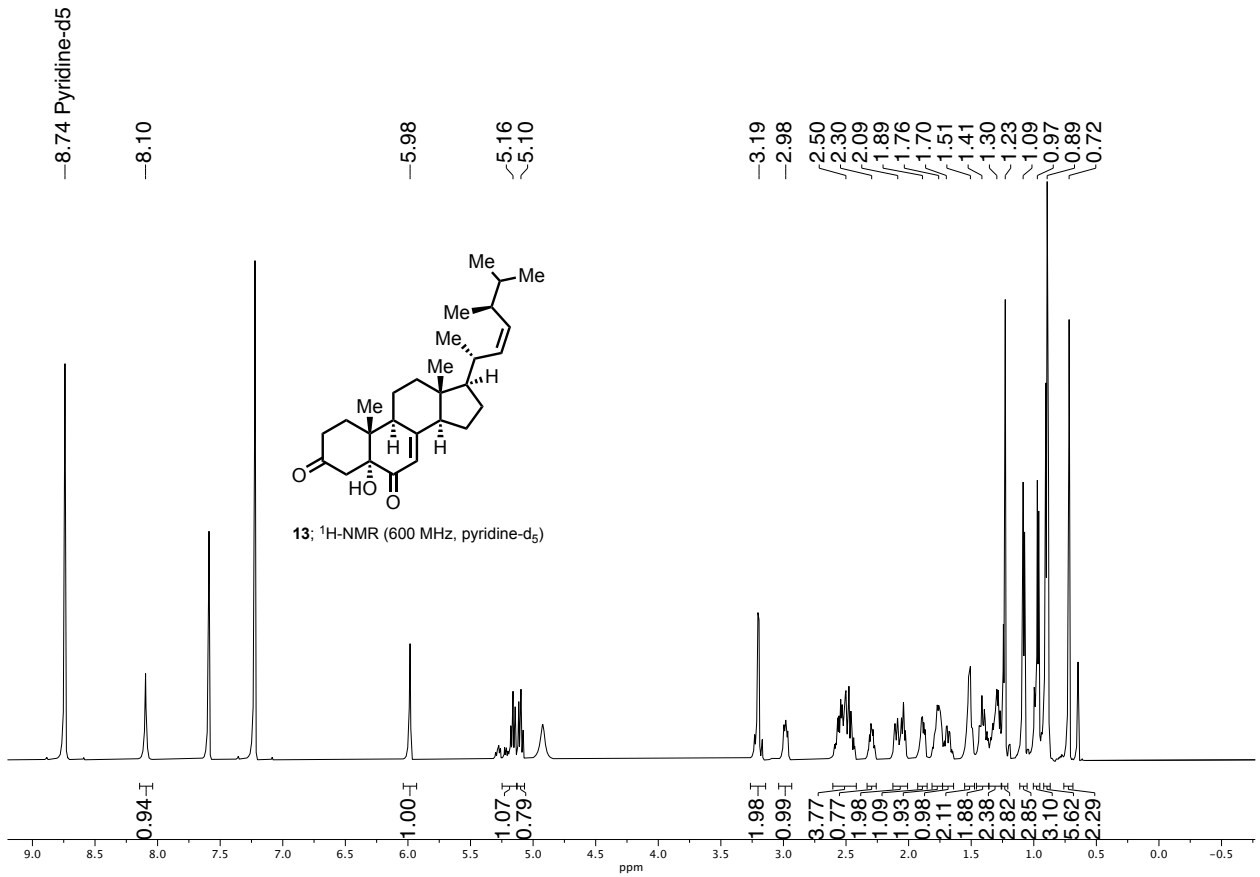
2; ^{13}C-NMR (151 MHz, $CDCl_3$)



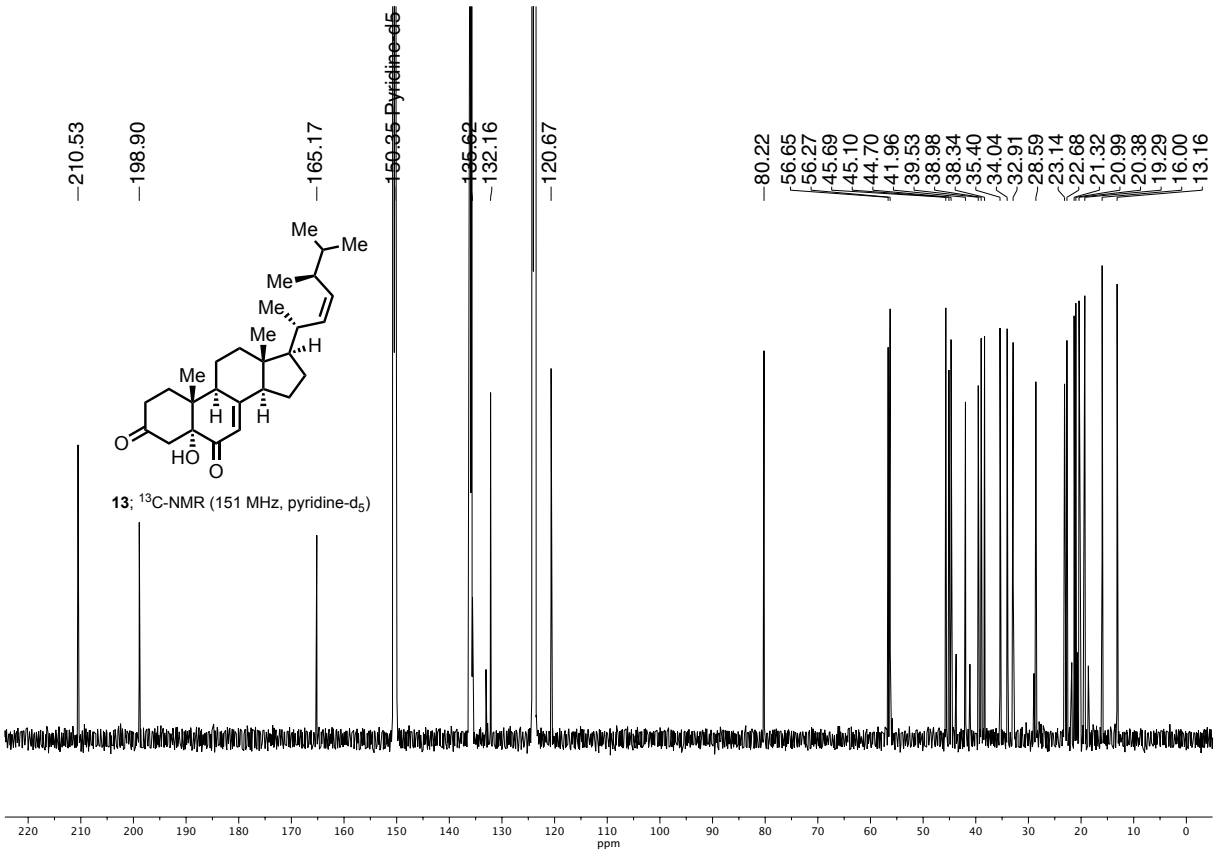
S3; ^{1}H-NMR (500 MHz, $CDCl_3$)



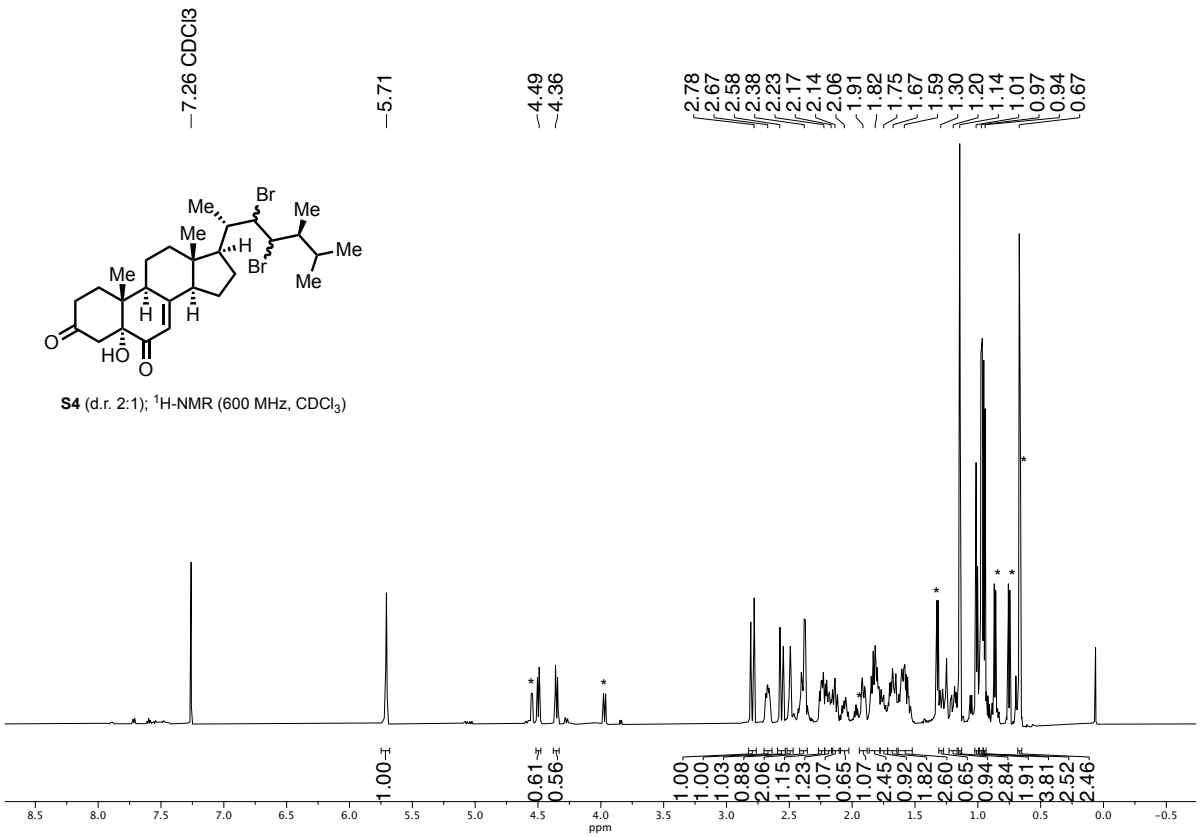
S3; ^{13}C-NMR (126 MHz, $CDCl_3$)



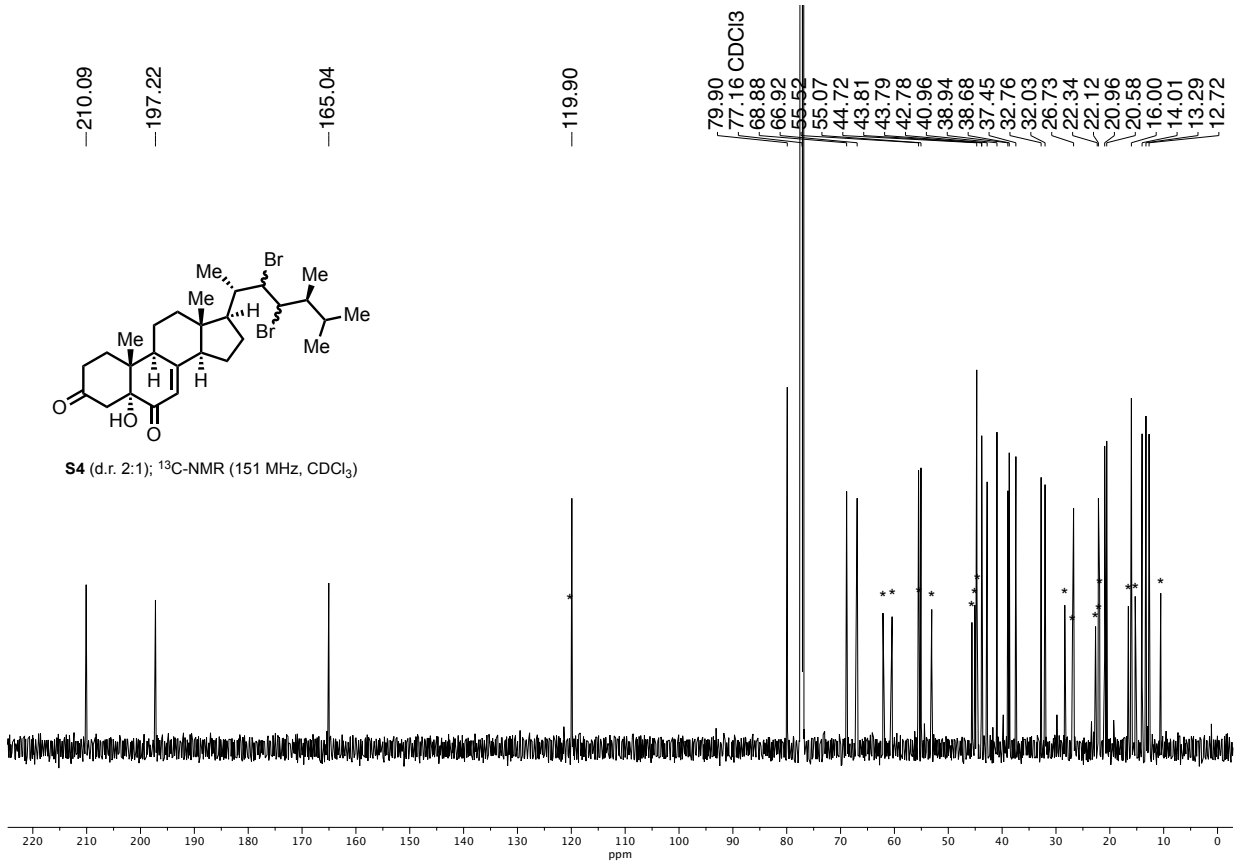
13; ^{1}H-NMR (600 MHz, pyridine-d_5)



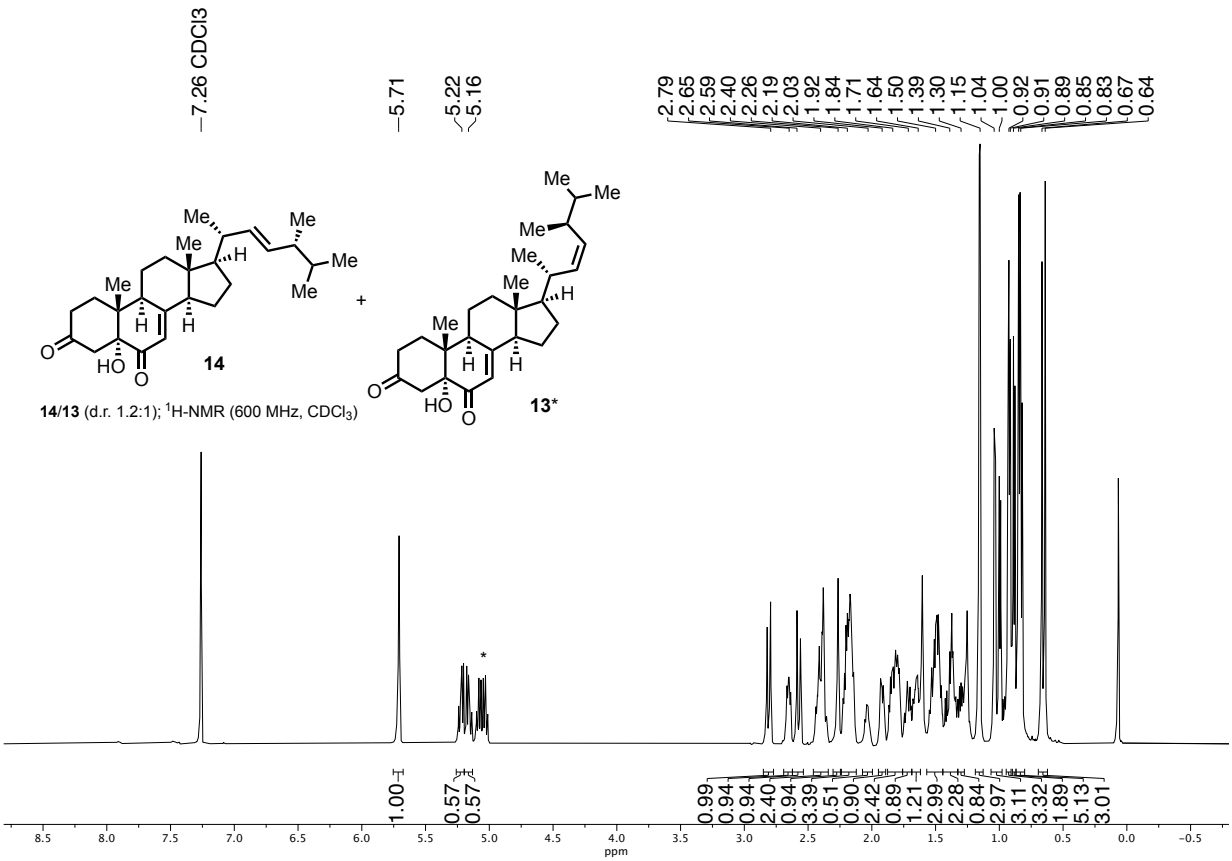
13; ^{13}C-NMR (151 MHz, pyridine-d_5)

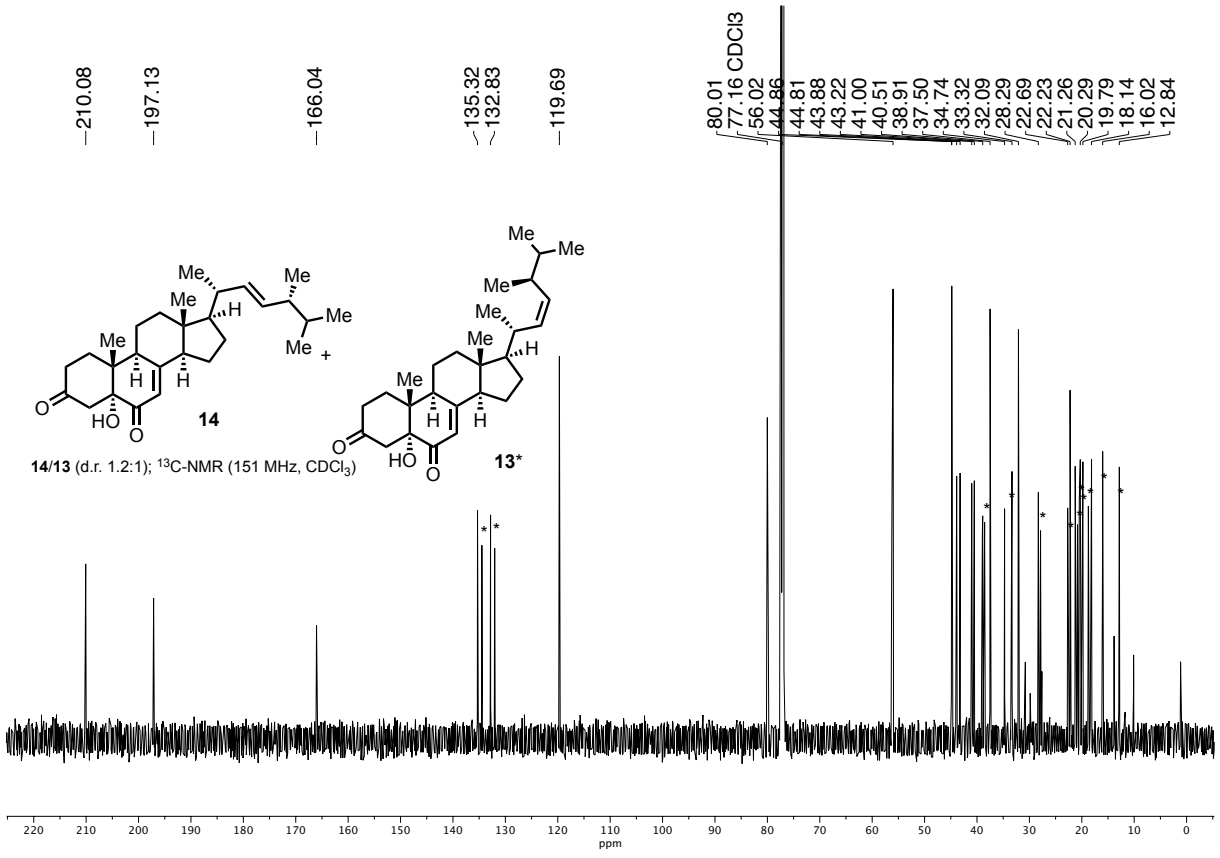


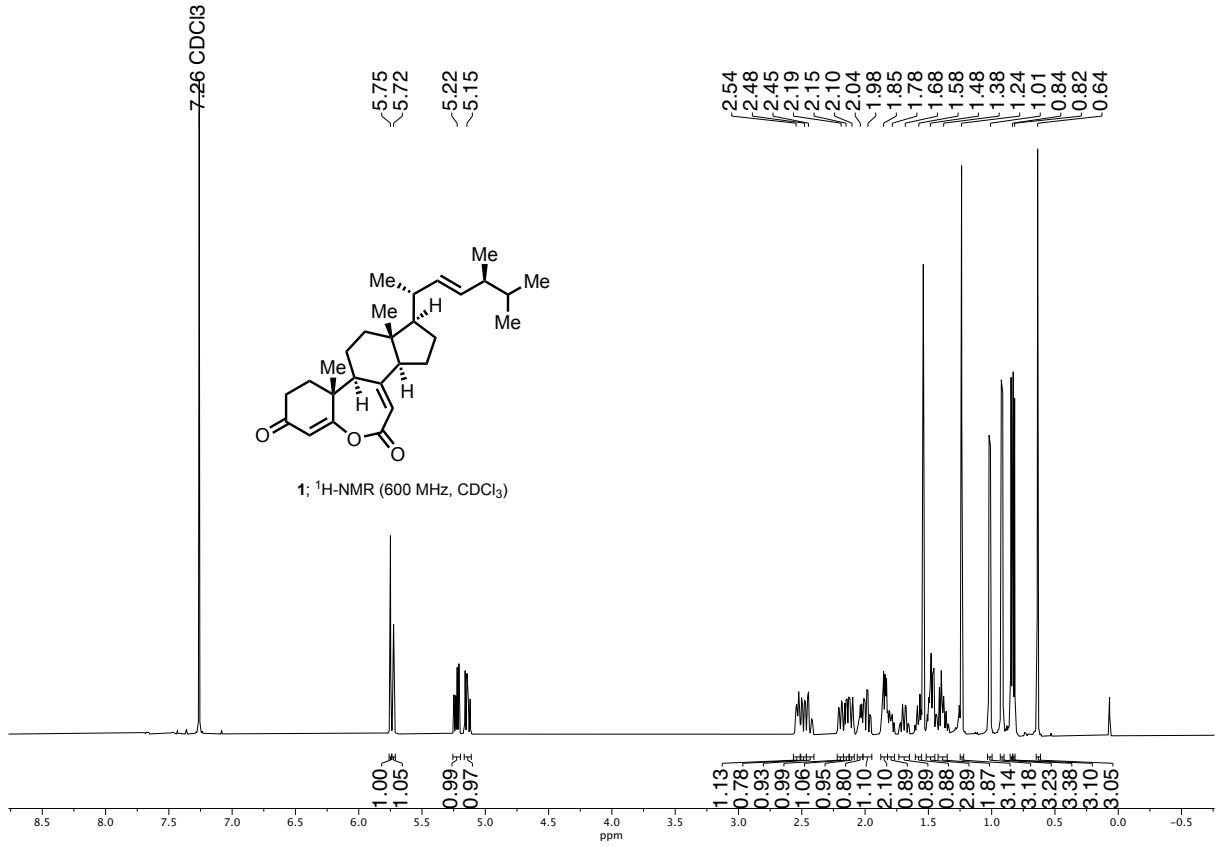
S4 (d.r. 2:1); ^{1}H-NMR (600 MHz, $CDCl_3$)



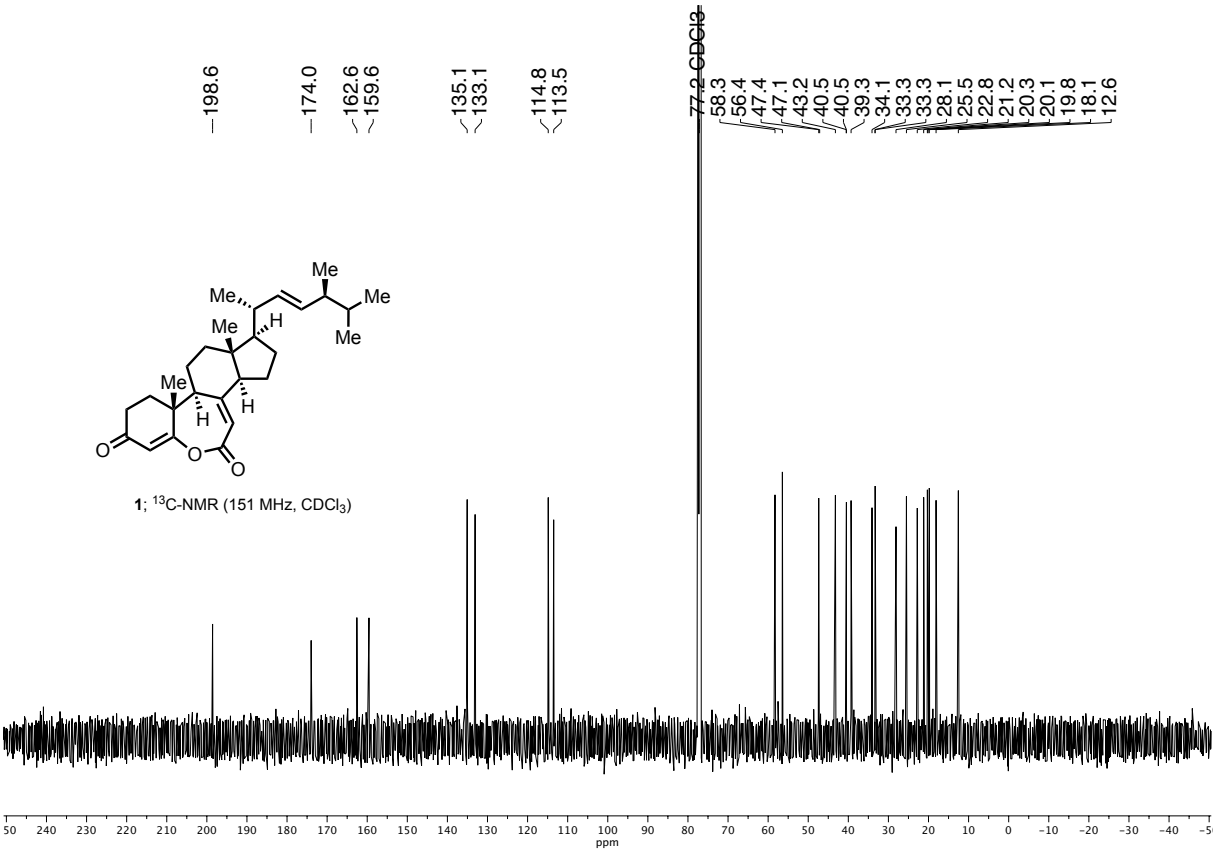
S4 (d.r. 2:1); ^{13}C-NMR (151 MHz, $CDCl_3$)


7.26 CDCl3
5.71
5.22
5.16
2.79
2.65
2.59
2.40
2.26
2.19
2.03
1.92
1.84
1.71
1.64
1.50
1.39
1.30
1.15
1.04
1.00
0.92
0.91
0.89
0.85
0.83
0.67
0.64
14
13*
14/13 (d.r. 1.2:1); 1H-NMR (600 MHz, CDCl3)
1.00
0.57
0.57
0.99
0.94
0.94
2.40
0.94
3.39
0.51
0.90
2.42
0.89
1.21
2.99
2.28
0.84
2.97
3.11
3.32
1.89
5.13
3.01
ppm

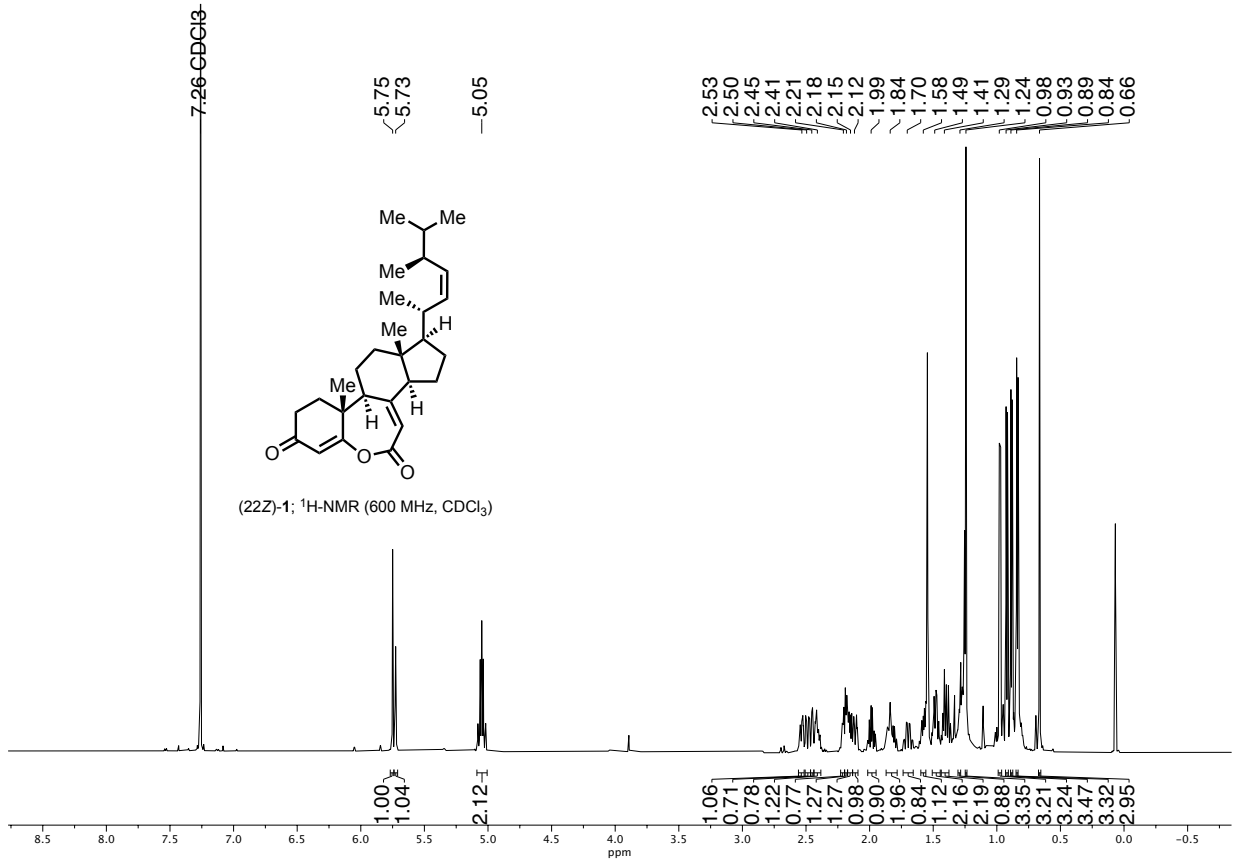

210.08
197.13
166.04
135.32
132.83
119.69
80.01
77.16 CDCl3
56.02
44.86
44.81
43.88
43.22
41.00
40.51
38.91
37.50
34.74
33.32
32.09
28.29
22.69
22.23
21.26
20.29
19.79
18.14
16.02
12.84
14
13*
14/13 (d.r. 1.2:1); 13C-NMR (151 MHz, CDCl3)
ppm



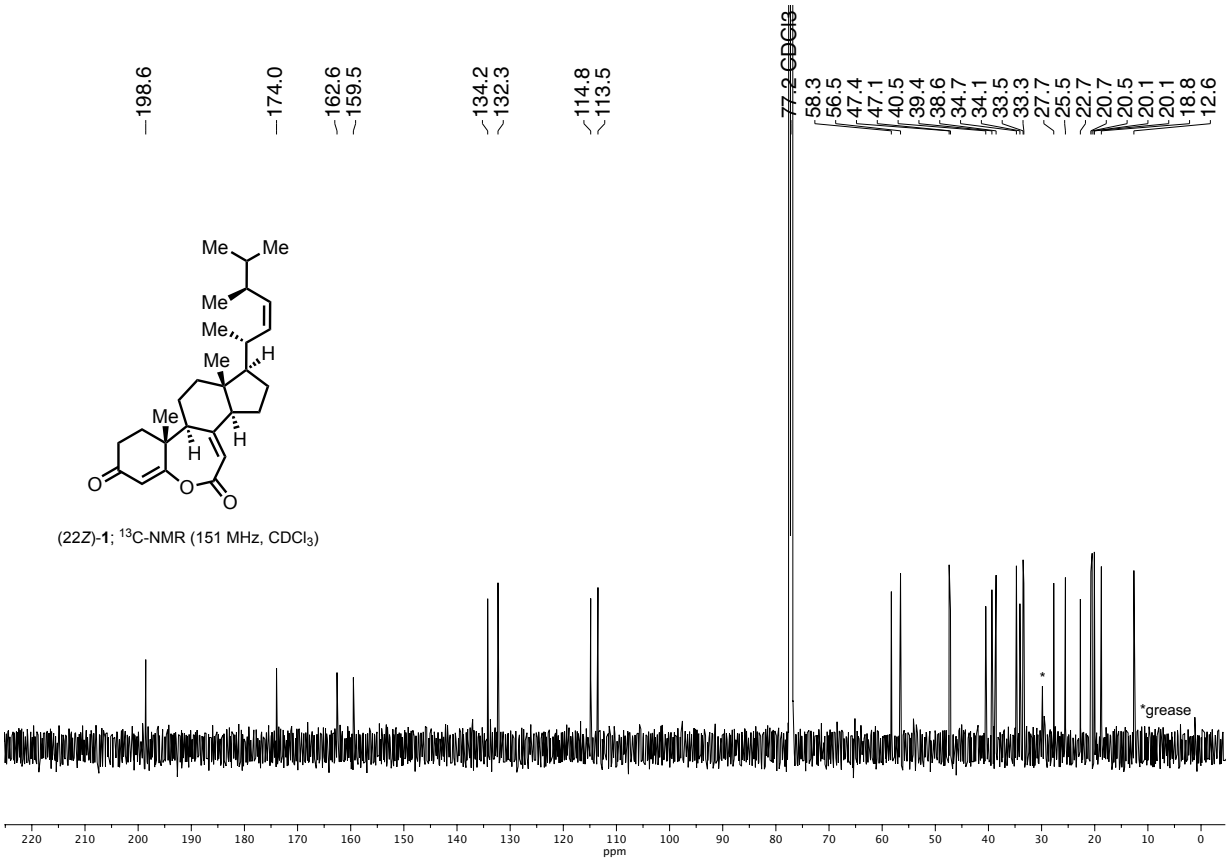
1; ^{1}H-NMR (600 MHz, $CDCl_3$)



1; ^{13}C-NMR (151 MHz, $CDCl_3$)



(22*Z*)-**1**; ^{1}H-NMR (600 MHz, $CDCl_3$)



(22*Z*)-**1**; ^{13}C-NMR (151 MHz, $CDCl_3$)

References

[1] J. W. Bok, L. Lermer, J. Chilton, H. G. Klingeman, G. H. N. Towers, Antitumor sterols from the mycelia of *Cordyceps sinensis*. *Phytochemistry* **1999**, *51*, 891–898.

[2] S. H. Lee, S. H. Shim, J. S. Kim, S. S. Kang, Constituents from the Fruiting Bodies of *Ganoderma applanatum* and Their Aldose Reductase Inhibitory Activity. *Arch. Pharm. Res.* **2006**, *29*, 479–483.

[3] E. M. Honeywell, C. E. Bills, Cerevisterol, a sterol accompanying ergosterol in yeast. *J. Biolog. Chem.* **1932**, *99*, 71–78.

[4] J. Valisolalao, B. Luu, G. Ourisson, STEROIDES CYTOTOXIQUES DE POLYPORUS VERSICOLOR.*Tetrahedron* **1983**, *39*, 2779–2785.

[5] S.-P. Yang, J. Xu, J.-M. Yue, Sterols from the Fungus *Catathelasma imperiale*.*Chinese J. Chem.* **2003**, *21*, 1390–1394.

[6] C. Brosa, R. Puig, X. Comas, C. Fernández, New synthetic strategy for the synthesis of 24-epibrassinolide. *Steroids* **1996**, *61*, 540–543.

[7] M. Fieser, A. Quilico, A. Nickon, W. E. Rosen, E. J. Tarlton, L. F. Fieser, Permanganate Oxidation of Ergosterol. *J. Am. Chem. Soc.* **1953**, *75*, 4066–4071.

[8] G. Kusano, Y. Koike, H. Inoue, S. Nozoe, The Constituents of *Gymnopilus spectabilis*. *Chem. Pharm. Bull.* **1986**, *34*, 3465–3470.

[9] K. Krohn, C. Biele, H.-J. Aust, S. Draeger, B. Schulz, Herbarulide, a Ketodivinyllactone Steroid with an Unprecedented Homo-6-oxaergostane Skeleton form the Endophytic Fungus *Pleospora herbarum*. *J. Nat. Prod.* **1999**, *62*, 629–630.

[10] F. L. Duecker, R. C. Heinze, P. Heretsch, Synthesis of Swinhoeisterol A, Dankasterone A and B, and Periconiastone A by Radical Framework Reconstruction. *J. Am. Chem. Soc.* **2020**, *142*, 104–108.

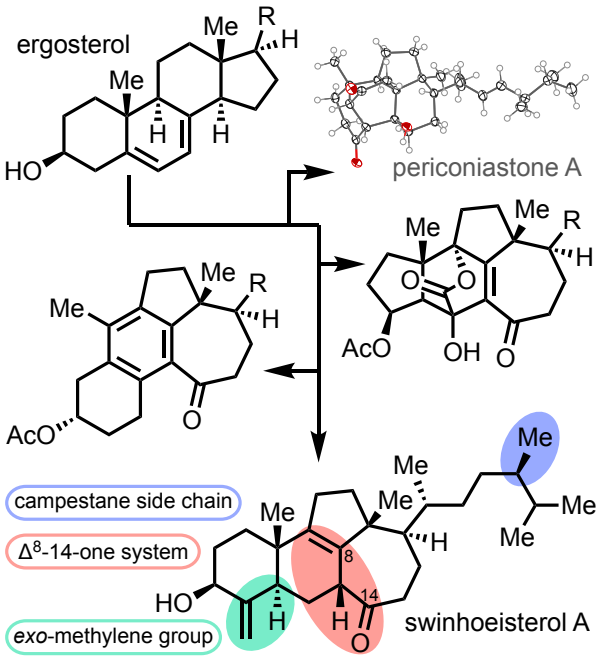
[11] D. Chen, M. Fan, Sterol Lactol Compound and its application as complement inhibitor. Faming Zhuanli Shenqing CN 105985403 A, October 5, 2016.

[12] X.-C. Huang, Y.-W. Guo, G.-Q. Song, Fortisterol, a novel steroid with an unusual seven-membered lactone ring B from the Chinese marine sponge *Biemna fortis* Topsent. *J. Asian Nat. Prod. Res.* **2006**, *8*, 485–489.

Appendix D

Discoveries and Challenges *en route* to Swinhoeisterol A

Fenja L. Duecker,[a] Robert C. Heinze,[a] Simon Steinhauer,[b] Philipp Heretsch[a]



a Institut für Chemie und Biochemie
Freie Universität Berlin
Takustraße 3, 14195 Berlin, Germany

b Institut für Chemie und Biochemie
Freie Universität Berlin
Fabeckstraße 34–36, 14195 Berlin, Germany

This is the accepted version of the following article:
F. L. Duecker, R. C. Heinze, S. Steinhauer, P. Heretsch, *Chem. Eur. J* **2020**, *26*, 9971–9981.
DOI: 10.1002/chem.202001405

Author contribution: This project was designed by Fenja L. Dücker, Robert C. Heinze and Philipp Heretsch. The synthetic work and analytical characterizations were carried out by Fenja L. Dücker. X-ray diffraction analysis was performed by Simon Steinhauer. The manuscript was prepared by Fenja L. Dücker, Robert C. Heinze and Philipp Heretsch.

Chemistry
A European
Journal

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

Title: Discoveries and Challenges en route to Swinhoeisterol A

Authors: Fenja L. Duecker, Robert C. Heinze, Simon Steinhauer, and Philipp Heretsch

To be cited as: *Chem. Eur. J.* 10.1002/chem.202001405

Link to VoR: https://doi.org/10.1002/chem.202001405

WILEY-VCH

10.1002/chem.202001405

WILEY-VCH

FULL PAPER

Discoveries and Challenges *en route* to Swinhoeisterol A

Fenja L. Duecker[a], Robert C. Heinze[a], Simon Steinhauer[b], and Philipp Heretsch*[a]

[a] M.Sc. F. L. Duecker, Dr. R. C. Heinze, Prof. Dr. P. Heretsch
Institut für Chemie und Biochemie, Organische Chemie, Freie Universität Berlin
Takustrasse 3, 14195 Berlin, Germany
E-mail: philipp.heretsch@fu-berlin.de
[b] Dr. S. Steinhauer
Institut für Chemie und Biochemie, Anorganische Chemie, Freie Universität Berlin
Fabeckstrasse 34–36, 14195 Berlin, Germany

Supporting information for this article is given via a link at the end of the document.

Abstract: We here give a full account of our synthetic studies that culminated in the first synthesis of 13(14→8),14(8→7) di*abeo*-steroid swinhoeisterol A as well as the related dankasterones A and B, 13(14→8)*abeo*-steroids, and periconiastone A, a 13(14→8)*abeo*-4,14-cyclo-steroid. We describe in detail experiments that provided further insight into the mechanism of our switchable radical framework reconstruction approach. By discussing failed strategies and tactics towards swinhoeisterol A, we eventually present the successful route that also allowed an access to structurally closely related analogues as Δ^{22}-24-*epi*-swinhoeisterol A.

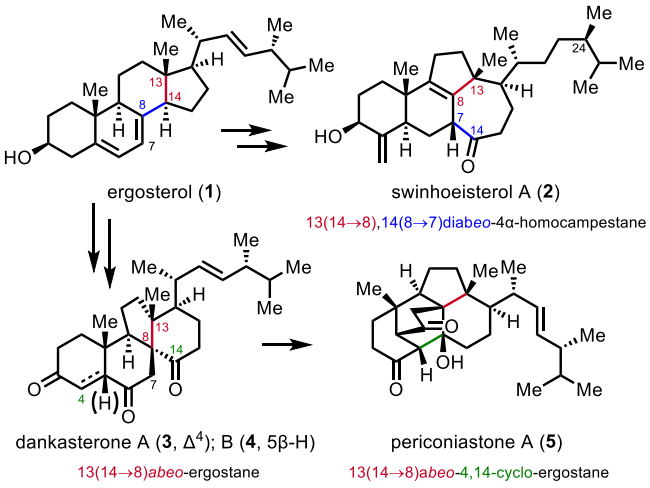
Introduction

Traditionally, the majority of bioactive compounds has been isolated from terrestrial plants and fungi, whereas the marine biosphere was more difficult to access. Undersea organisms often produce structurally highly complex, rearranged secondary metabolites with unique bioactivities.[1]

An increasing number of chemical syntheses relies on biogenetic information, gaining access to natural products *via* biomimetic approaches.[2] Still, many of the proposed pathways are established without the support of co-isolated biosynthetic precursors from the producing organism. Commonly, biogenetic proposals anticipate polar pathways to account for skeletal rearrangements and radical routes are rarely considered.[3] One class of steroidal natural products with such rearranged skeletons are the so-called *abeo*-steroids, which display one or several C–C bond migrations with respect to the classic, tetracyclic steroid backbone.[4]

In recent years, our group as well as others have demonstrated that key synthetic transformations (possibly biomimetic in nature) can indeed be carried out using radical reactivity, giving the desired skeletal modifications with high selectivity as shown in the syntheses of rearranged steroids cortistatin A,[5] aplysiasecosterol A,[6] strophasterol A,[7] pleurocin A/matsutakone,[8] and herbarulide.[9] It was also a cascade of rearrangements initiated by an alkoxy radical that cleared the way to the dankasterone [13(14→8)*abeo*-steroids][10] and the swinhoeisterol class of natural products [13(14→8),14(8→7)di*abeo*-steroids].[11] Only recently, we achieved the synthesis of swinhoeisterol A (**2**), its 24-*epi*-counterpart (24-*epi*-**2**), dankasterone A (**3**) and B (**4**), and periconiastone A (**5**),[12] the 4,14-cyclo aldol product of the latter, starting from commercial ergosterol (**1**) by exploiting a radical cascade (Scheme 1).[13] Regarding the biological activities of these natural products, dankasterone A (**3**) and B (**4**) show significant cytotoxicity against the P388 lymphocytic leukemia test system (ED_{50} 2.2 and 2.8 µg/mL, respectively)[10] whereas di*abeo*-steroid swinhoeisterol A (**2**) exhibits a remarkable inhibition of the histone acetyltransferase (h)p300 with an IC_{50} of 2.9µM.[11a] The most recently isolated secondary metabolite, periconiastone A (**5**), is reported to display intriguing antibacterial activity against two Gram-positive microbial pathogens, namely *S. aureus* (MIC 4 µg/mL) and *E. faecalis* (MIC 32 µg/mL).[12]

Herein, we want to report on the evolution of our synthetic studies towards swinhoeisterol A (**2**) and its 24-*epi*-isomer (24-*epi*-**2**) as well as present experimental support for our mechanistic proposal for our radical framework reconstruction approach.



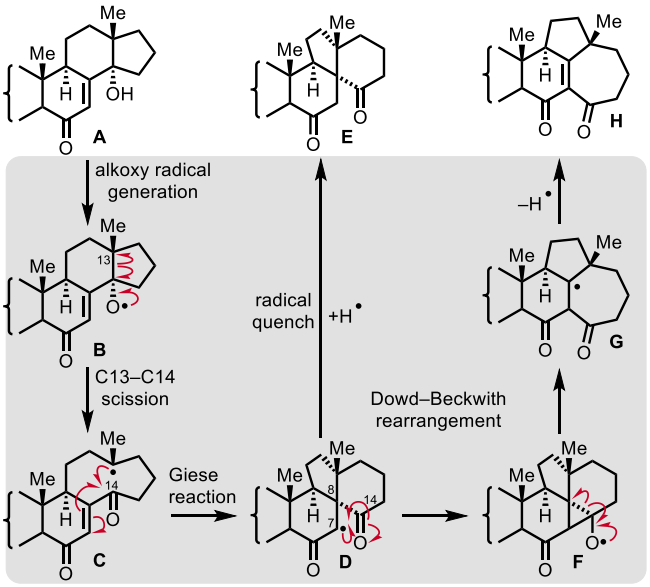
Scheme 1. Structures of the *abeo*-steroids swinhoeisterol A (**2**), dankasterone A (**3**) and B (**4**), and periconiastone A (**5**), their common synthetic starting material, ergosterol (**1**), as well as their generic classes.

Results and Discussion

Our rationale to gain synthetic access to the rearranged skeletons of *abeo*-steroids relied on the initial generation of an alkoxy radical. The following radical rearrangement (Scheme 2) enabled the synthesis of the above-mentioned natural products and selective access to either the mono- or di*abeo*-skeleton was gained by adapting the reaction conditions ($PhI(OAc)_2/I_2$ for the former; HgO/I_2 for the latter) to generate **B** – starting from a γ-hydroxy enone **A**. Subsequent β scission of the C13–C14 bond in **B** would

10.1002/chem.202001405

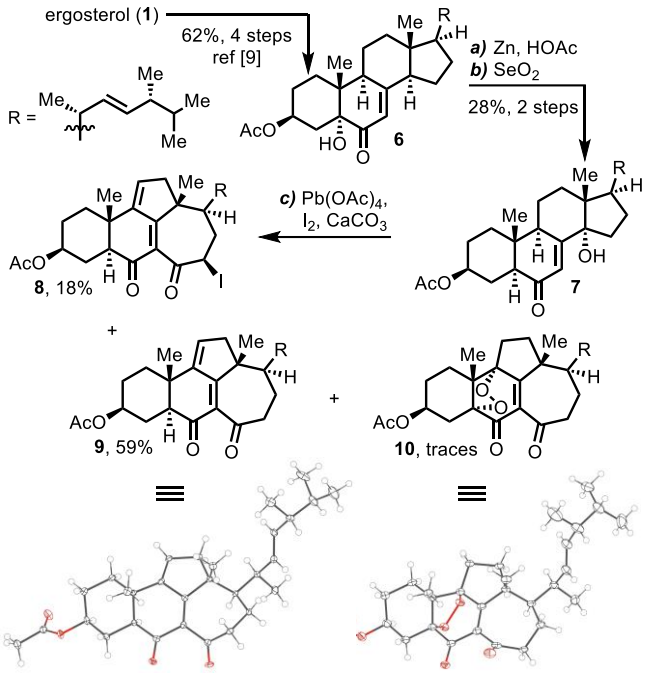
form an intermediary 14-oxo functionality along with a stabilized tertiary radical at C13 (**C**). An attack onto the Δ^7-bond generates α-keto radical **D**, which is either quenched reductively to give the 13(14→8)*abeo* skeleton (**E**)[14] as present in the dankasterone class of natural products, or further reacts in a Dowd–Beckwith rearrangement.[15] This comprises of an attack of the C7-centered radical to the 14-oxo functionality to give alkoxy radical **F**. Another β scission, this time of C8–C14, yields the 13(14⟶8),14(8⟶7)di*abeo* core (**G**) of the swinhoeisterols after abstraction of an H atom (**G**→**H**).



Scheme 2. Mechanistic proposal for the alkoxy radical initiated framework reconstruction leading to the structural precursors of the dankasterones **E** and swinhoeisterols **G**.

Initially, 5α-hydroxy enone **7** was chosen as a substrate for the envisioned radical rearrangement (Scheme 3). As we described in our synthesis of herbarulide,[9] the preparation of Burawoy's ketone (**6**) following reported procedures has proven to lack reproducibility.[16] Aiming for a stepwise oxidation of ergosterol (**1**), **6** was available in 62% yield over 4 steps.[9] Reduction with zinc in acetic acid provided 5α-enone (not shown) in 47% along with 20% of its 5β-epimer (not shown). While Riley oxidation employing 1,4-dioxane as solvent gave the desired product in only low and irreproducible yields, the solvent system pyridine/*t*BuOH[17] allowed for the formation of alcohol **7** in an acceptable yield of 59%. To generate the alkoxy radical at C14 from alcohol **7**, the literature-known combination of $Pb(OAc)_4$, I_2 and $CaCO_3$ in benzene[18] was used and, indeed, all isolated products showed the desired 13(14→8),14(8→7)di*abeo*-skeleton, though in higher oxidation states than expected. Diene dione **9** was obtained as the major product (40%) along with endoperoxide **10** (20%). When the reaction mixture was carefully degassed prior to addition of $Pb(OAc)_4$, 59% of **9**, only traces of **10**, and 18% of 15β-iodo diene dione **8** were obtained.

To prevent formation of the oxygen adduct and to keep options for later A-ring functionalization, elimination of the tertiary alcohol in Burawoy's ketone (**6**) was carried out using thionyl chloride and basic conditions to give Δ^4-enone **11** (75% yield). In this case, standard Riley conditions gave Δ^4-hydroxy enone **12** as another substrate for the radical cascade. Again, the $Pb(OAc)_4/I_2$-system

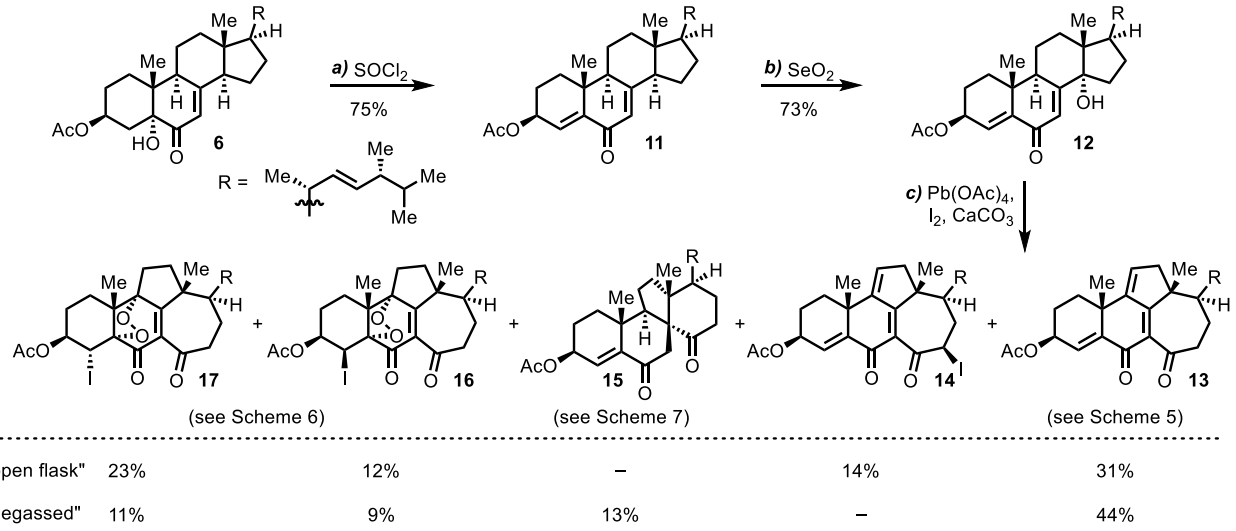


Scheme 3. Radical rearrangement of **7** leading to the 13(14→8),14(8→7)di*abeo* structures **8**, **9**, and **10**. ORTEP plots of **9** and **10**. Thermal ellipsoids are drawn at 50% probability. Reagents and conditions: a) Zn (29 eq.), HOAc, 90 °C, 3 h, 47%; b) SeO_2 (4.75 eq.), *t*BuOH/pyridine (4:1), 80 °C, 4 h, 59%; c) $Pb(OAc)_4$ (2.0 eq.), I_2 (2.0 eq.), $CaCO_3$ (2.0 eq.), C_6H_6, 85 °C, 2 h, **8**: 18%, **9**: 59%, **10**: traces. CCDC 1991055 (compound **9**) and 1991054 (compound **10**) contain the supplementary crystallographic data.

was used leading to a different product distribution for "open flask" and "degassed" conditions (see Scheme 4). Tetraene dione **13** was isolated as the major product (31% yield) and its yield could be improved to 44% when carefully degassing the reaction mixture. Under "open flask" conditions, 4-iodo substituted endoperoxides **16** and **17** were obtained in 12 and 23% yield, respectively, or in 9 and 11% for the "degassed" experiment. The formation of **16** and **17** presumably results from remaining traces of oxygen in the reaction mixture. Interestingly, aerobic conditions led to the isolation of 15β-iodo tetraene dione **14** (14%) whereas oxygen-free conditions delivered the 13(14→8)*abeo* species **15** (13%), instead, providing first conformation of our mechanistic proposal (Scheme 2).

Gaining synthetic access to the swinhoeisterols by further processing one or several of the obtained products was tested on tetraene dione **13** (Scheme 5) as well as epimeric 4-iodo endoperoxides **16** and **17** (Scheme 6). For **13**, we envisioned to reduce the oxo-functionality at C6 to the corresponding allylic alcohol, which could then be used to perform a sigmatropic rearrangement, either directly (Johnson–Claisen), after acetylation (Ireland–Claisen), or after methyl stannylation ([2,3]-Wittig–Still), thereby installing a precursor for the *exo*-methylene function at C4. However, no conversion of starting material was observed when applying Johnson–Claisen conditions to the allylic alcohol and in case of the [2,3]-Wittig–Still rearrangement, addition of *n*BuLi to the methyl stannylated alcohol only resulted in the formation of the 1,2-rearranged product. In case of the Ireland–Claisen reaction, the allylic acetate was successfully converted to the corresponding silyl ketene acetal as judged by

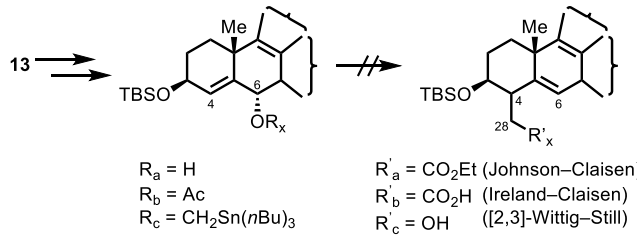
10.1002/chem.202001405



Scheme 4. Radical rearrangement of **12** and product distributions depending on the reaction conditions. Reagents and conditions: a) $SOCl_2$ (4.5 eq.), pyridine, –10 °C, 45 min, 75%; b) SeO_2 (4.75 eq.), dioxane/H_2O (50:1), 65 °C, 5 h, 73%; c) $Pb(OAc)_4$ (2.0 eq.), I_2 (1.5 eq.), $CaCO_3$ (2.0 eq.), C_6H_6, 85 °C, 2 h, R as in Scheme 3.

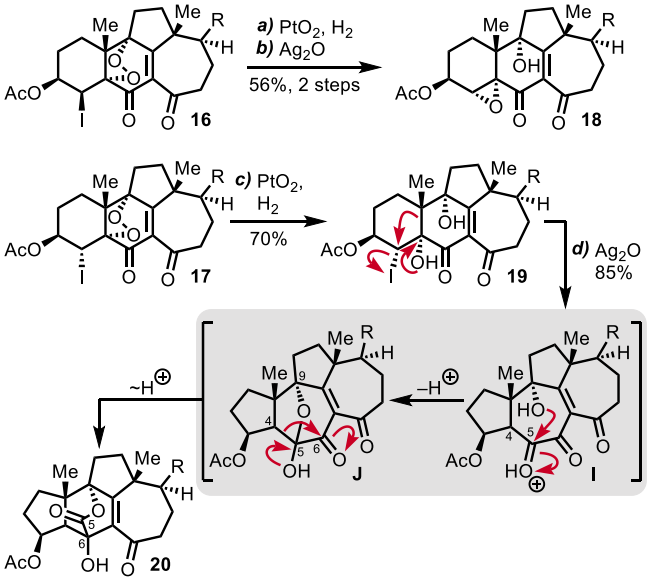
^{1}H-NMR, but further reaction to the desired carboxylic acid was not successful.

Since the diastereomeric endoperoxides **16** and **17** contained the structural motif of a Δ^7-9α-hydroxy ketone, which is also present in other members of the swinhoeisterols, they were also assumed valuable intermediates *en route* to **2** (Scheme 6). Thus, reduction of the peroxide functionality to the corresponding 5,9-diol (as in **19**) was carried out on both 4-iodo epimers using PtO_2/H_2. In case of 4β-iodo endoperoxide **16**, a mixture of the diol (not shown) and epoxide **18** resulting from concomitant S_N2 reaction was obtained. Full conversion was possible by treatment with Ag_2O and gave **18** in 56% over 2 steps. As **18** was deemed a suitable precursor for further transformations (e.g. Wharton transposition), diol **19** was to be transformed to **18** as well through a S_N1 reaction. Treatment with Ag_2O showed no conversion at room temperature but after 16 h at 60 °C selective formation of a new product was observed. Careful analysis of the NMR data obtained led us to propose the structure of lactone **20**, which was confirmed by X-ray single crystal structure analysis. Presumably, formation of the expected cation at C4 did indeed take place but was immediately or concertedly followed by bond migration to give 10(5→4)*abeo* intermediate **I**.



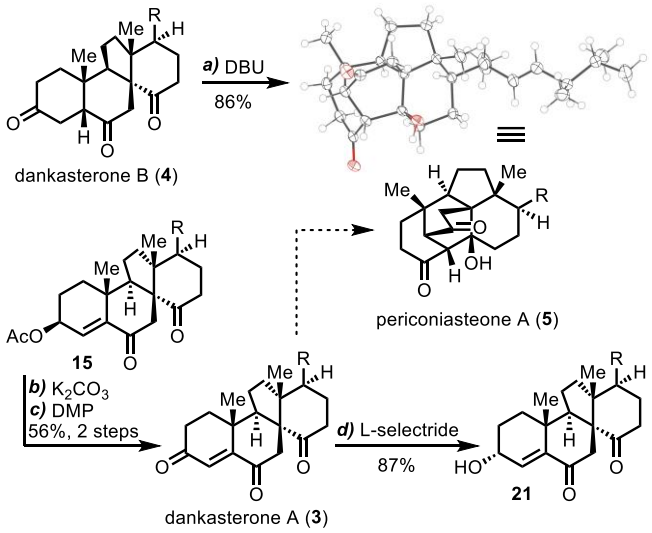
Scheme 5. Attempted sigmatropic rearrangements to introduce a synthetic precursor for the desired *exo*-methylene unit.

Assumedly, this oxocarbenium facilitated an attack of the C9 hydroxyl and thereby set the stage for a benzilic acid-type rearrangement ring contraction/expansion[19] (see structure **J**) yielding lactone **20**, which features immense connectivity changes in the A and B ring. To the best of our knowledge, this structural motif has not been observed in any steroidal context, before. Afore mentioned Wharton transposition was envisioned to convert epoxide **18** to C4 allylic alcohol, but as the initial conversion to the corresponding hydrazone was unsuccessful, further studies employing iodo-endoperoxides **16** and **17** were discarded.

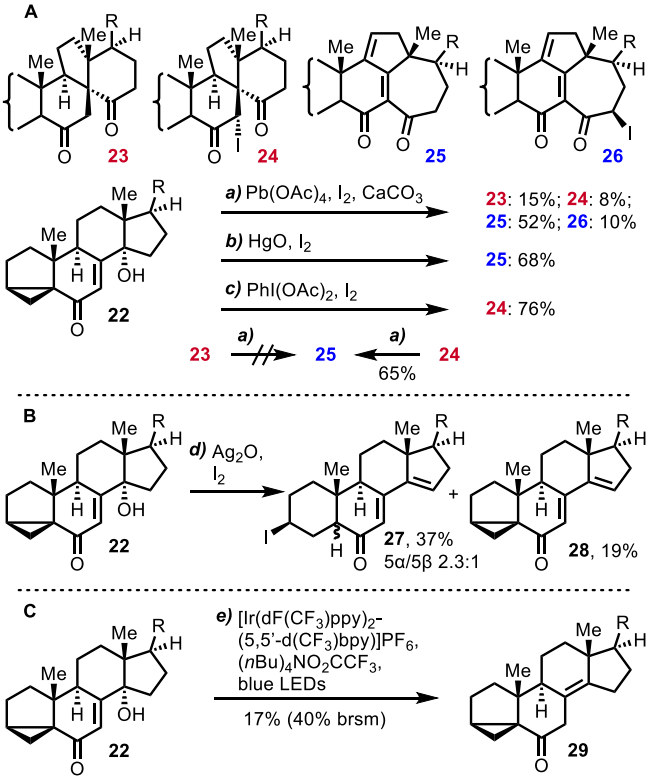


Scheme 6. Synthetic transformations of endoperoxides **16** and **17** and mechanistic proposal for the rearrangement to **20**. Reagents and conditions: a) PtO_2 (0.2 eq.), H_2 (balloon), EtOAc, 25 °C, 4 h; b) Ag_2O, THF, 25 °C, 1 h, 56% (2 steps); c) PtO_2 (0.2 eq.), H_2 (balloon), EtOAc, 25 °C, 4 h, 70%; d) Ag_2O, THF, 60 °C, 16 h, 85%, R as in Scheme 3.

10.1002/chem.202001405

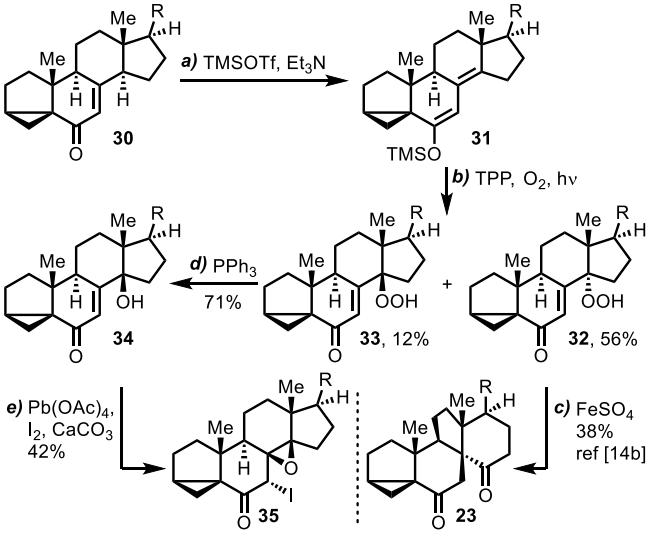


Scheme 7. Synthesis of periconiastone A (**5**) (ORTEP plot of **5**. Thermal ellipsoids are drawn at 50% probability) and alternative synthetic access to dankasterone A (**3**) and its reduction. Reagents and conditions: a) DBU (10 eq.), PhMe, 25 °C, 12 h; b) K_2CO_3 (5.0 eq.), MeOH, 25 °C, 1 h; c) DMP (2.0 eq.), CH_2Cl_2, 25 °C, 1 h, 56% (2 steps); d) L-selectride (2.0 eq.), THF, –78 °C, 1 h, 87%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene DMP = Dess–Martin periodinane, R as in Scheme 3. CCDC 1989984 contains the supplementary crystallographic data for compound **5**.



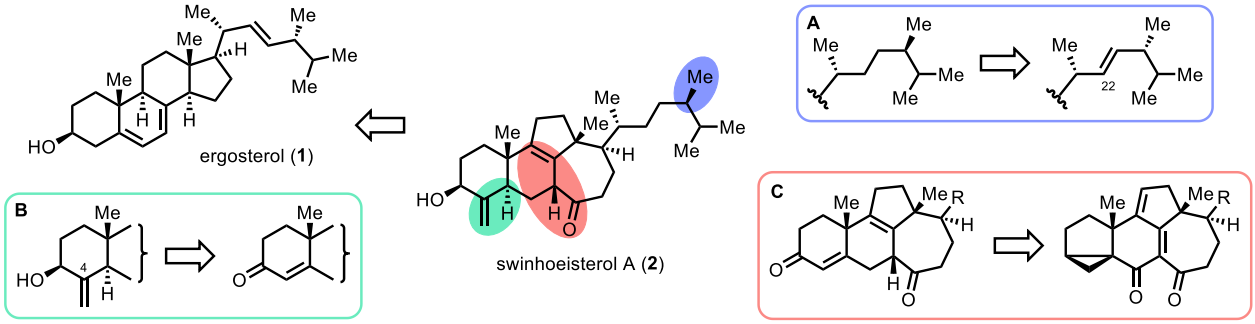
Scheme 8. A: Radical rearrangement of **22** leading to mono- and di*abeo* structures **23**, **24**, **25** and **26**. **B** and **C**: Attempted rearrangements using alternative conditions. Reagents and conditions a) $Pb(OAc)_4$ (2.0 eq.), I_2 (2.0 eq.), $CaCO_3$ (2.0 eq.), C_6H_6, 85 °C, 2 h; b) HgO (2.7 eq.), I_2 (2.4 eq.), C_6H_6, 105 °C (sealed tube), 2 h, 68%; c) $PhI(OAc)_2$ (2.0 eq.), I_2 (1.0 eq.), C_6H_6, 25 °C, 30 min, 76%; d) Ag_2O (2.0 eq.), I_2 (1.5 eq.), C_6H_6, 85 °C, 2 h, **27**: 37% (5α/5β 2.3:1), **28**: 19%; e) $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}d(CF_3)bpy)]PF_6$ (3 mol%), $(n\text{Bu}_4)NO_2CCF_3$ (0.4 eq.), blue LEDs, PhMe, 35 °C, 3 d, 17% (40% brsm). brsm = based on recovered starting material, R as is Scheme 3.

Another compound isolated from the reaction of **12** with $Pb(OAc)_4/I_2$ was Δ^4-13(14→8)*abeo*-steroid **15**. Although not further employed in the synthesis of the swinhoeisterols, its isolation supported our mechanistic proposal and transformation to dankasterone A (**3**) in 56% yield over two steps (Scheme 7) was successful. In the meantime, we were able to provide proof of the cage-like 13(14→8)*abeo*-4,14-cyclo structure of periconiastone A (**5**)[12] by X-ray single crystal analysis. Previously, we had synthesized **5** from dankasterone B (**4**)[13] and now set out to explore the possibility to generate an enolate by 1,4-reduction of dankasterone A (**3**), which would then undergo aldol addition and give the desired 4,14-cyclo skeleton. Interestingly, reaction with L-selectride only gave 3α-alcohol **21**, the product of 1,2-reduction, presumably due to steric inaccessibility of C5.



Scheme 9. Synthetic access to 14β-OH **34** and attempted rerarrangement. Reagents and conditions: a) TMSOTf (1.5 eq.), Et_3N (2.0 eq.), CH_2Cl_2, 0 °C, 1 h; b) TPP (0.2 mol%), O_2, hv, CH_2Cl_2, –78 °C, 15 min, **32**: 56%, **33**: 12%; c) $FeSO_4$•7 H_2O (1.05 eq.), acetic buffer (pH 3), THF/H_2O (1.5:1), 25 °C, 1 h, 38%; d) PPh_3 (1.0 eq.), CH_2Cl_2, 25 °C, 1 h, 71%; e) $Pb(OAc)_4$ (2.0 eq.), I_2 (2.0 eq.), $CaCO_3$ (2.0 eq.), C_6H_6, 85 °C, 1 h, 42%. TMSOTf = trimethylsilyl trifluoromethanesulfonate, TPP = *meso*-tetraphenylporphyrin, R as in Scheme 3.

As so far, all our efforts to process any rearranged material obtained towards swinhoeisterol, and for a further generalization of the radical cascade, next γ-hydroxy enone **22** which was accessible in 4 steps and 42% from ergosterol (**1**)[7] was to be investigated. When treating **22** with $Pb(OAc)_4/I_2$, four main products were obtained after careful separation (Scheme 8**A**). Once more, two of those contained the di*abeo*-structure (triene dione **25** and its 15β-iodo analogue **26**); the other two being 13(14→8)*abeo* dione **23** and its 7α-iodo analogue **24**. To further substantiate our mechanistic proposal, **23** as well as **24** were both separately treated with $Pb(OAc)_4/I_2$. As expected, no conversion of the starting material was observed in case of dione **23**, but the reaction of iodide **24** gave rise to 65% of di*abeo*-compound **25**. As we reported earlier, it was possible to selectively access either the di*abeo*-framework (**25**, HgO/I_2, 68% yield) or the mono*abeo*-skeleton (**24**, $PhI(OAc)_2$, 76% yield), depending on the conditions to generate the initial alkoxy radical.[13] To test if the rearrangement to the di*abeo*-structures could be initiated without employing toxic Hg or Pb reagents, **22** was treated with Ag_2O and I_2.[20] However, only elimination of the 14-hydroxyl was observed (to give **28**) along with partial *i*-steroid opening to give iodide **27**



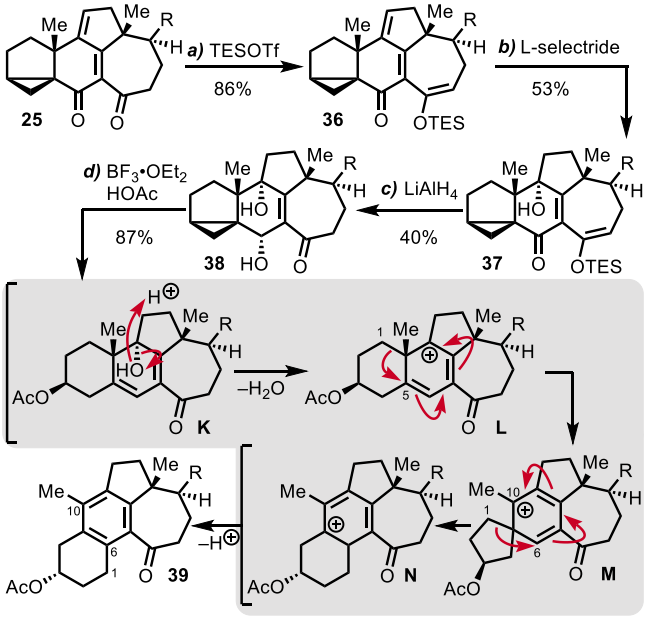
Scheme 10. Analysis of synthetic challenges in swinhoeisterol A (**2**).

as a mixture of epimers (5α/5β 2.3:1).[21] Knowles' photocatalytic ring expansion conditions[22] either did not yield any rearranged product but resulted in the isolation of $\Delta^{8,14}$-steroid **29**.[14a] Any other attempts to initiate a radical-promoted cascade employing other metal salts, did not lead to any conversion of the starting material.

To further study the influence of the stereoconfiguration at C14 on the radical cascade, we prepared14β-hydroxy enone **34** (Scheme 9). Since all Riley oxidations carried out resulted in 14α-hydroxylation, a Schenck ene reaction followed by reduction of the hydroperoxide was envisioned, instead. *i*-Steroid enone **30** was converted into TMS dienol ether **31**, which was then treated with oxygen and TPP as photosensitizer under irradiation with white light to give 14α-hydroperoxide **32** and 14β-hydroperoxide **33** (56 and 12% yield, respectively). While 14α-OOH **32** could be converted to 13(14→8)*abeo*-dione **23** in a yield of 38% using Danieli's conditions ($FeSO_4$),[14b] 14β-OOH **33** was reduced to the corresponding alcohol **34**, which was then exposed to $Pb(OAc)_4/I_2$. This time, no rearrangement of the steroid skeleton was observed. The alkoxy radical generated at C14 rather added to the double bond at C8, giving rise to an epoxide and the C7 centered radical was then quenched by iodine leading to 7α-iodo epoxide **35**. This difference in reactivity can be explained with an unfavorable orbital overlap of the radical's SOMO and the σ-orbital of the C13–C14 bond so that no β scission could occur.

As the radical rearrangement was most selective on the *i*-steroid system, it was chosen as starting material for our synthetic efforts towards swinhoeisterol A (**2**) and analogues. In the following, we want to discuss the major synthetic challenges that had to be overcome *en route* to swinhoeisterol A (Scheme 10). Starting from ergosterol (**1**), our synthetic approach consisted of an oxidative cleavage/olefination/hydrogenation sequence of Δ^{22} to introduce the desired (saturated) campestane side chain (Scheme 10, **A**). We envisioned to introduce the *exo*-methylene moiety *via* elimination of a hydroxymethyl group at C4 at a late stage of the synthesis making use of an enone functionality in the A-ring (Scheme 10, **B**). This key intermediate was traced back to a diene dione system from our radical cascade (Scheme 10, **C**).

Following these studies, we attempted a synthetic approach towards swinhoeisterol A (**2**) making use of **25** (Scheme 11), which was obtained in a good yield from **22** when applying HgO/I_2 (68%). It was possible to differentiate the C6- and C14-oxo functionalities of diene dione **25** by selective formation of C14 silyl enol ether **36**. We planned to adjust the oxidation state by 1,6-reduction with L-selectride, which along with the expected reduction involved the incorporation of an oxygen at C9 to give 9α-hydroxy dione **37** presumably through attack of O_2 by the intermediary dienolate. Even though this was not the expected product, the synthetic route was continued, since the obtained 9α-hydroxy enone pattern is present in swinhoeisterol B (not shown). Reduction with $LiAlH_4$ gave de-silylated 6α-OH **38**, which seemed to be a suitable precursor for an *i*-steroid opening. However, when treating **38** with acetic acid and $BF_3{\bullet}OEt_2$,[23] unexpected anthrasteroid[24a,b] **39** was isolated in 87%. Presumably, the initial *i*-steroid opening took place as expected (**K**) but was followed by generation of cation **L** through loss of the hydroxy group. Stabilization of the cation by bond migration could then lead to spiro-compound **M**,[24c,d] which, after formation of the C1–C6 bond, gives Wheland complex **N**. Loss of a proton would generate aromatic **39**, whose 1(10→6)*abeo*-structure can be found in a number of natural products.[24d–g]

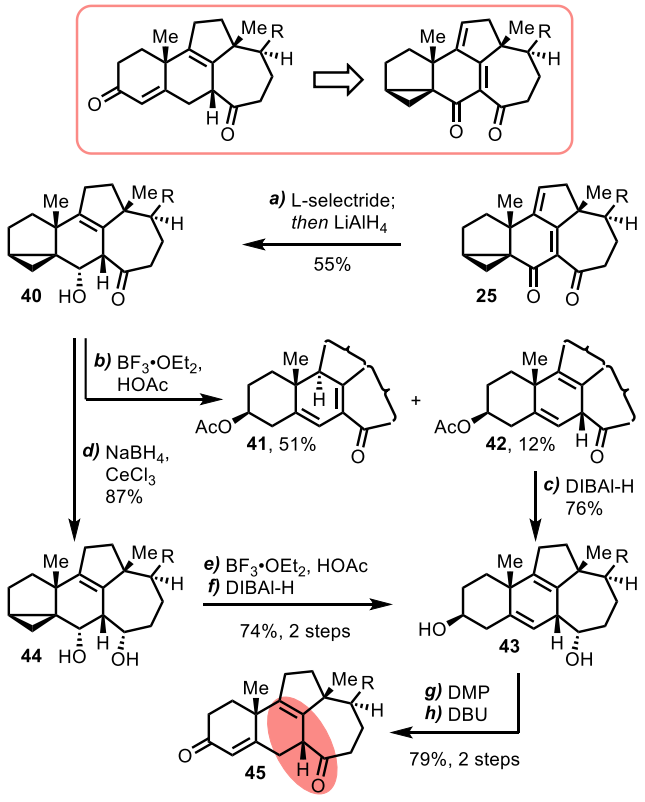


Scheme 11. Transformations on *i*-steroid diene dione **25** and mechanistic proposal for the formation of anthrasteroid **39**. Reagents and conditions: a) TESOTf (5.0 eq.), 2,6-lutidine (10 eq.), CH_2Cl_2, 0 °C, 1 h, 86%; b) L-selectride (3.0 eq.), THF, –78 °C, 1 h, 53%; c) $LiAlH_4$ (5.0 eq.). THF, 0 °C, 1 h, 40%; d) $BF_3{\bullet}OEt_2$/HOAc/Et_2O (1:1:2), 0 °C, 1 h, 87%. TESOTf = triethylsilyl trifluoromethanesulfonate, R as in Scheme 3.

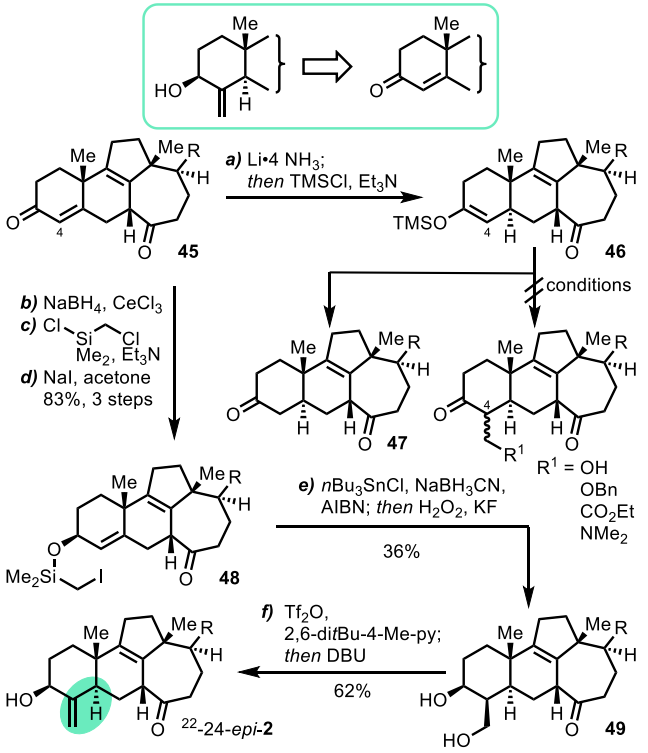
Through these experiments, the tertiary alcohol at C9 had been identified to be problematic in the cyclopropane opening reaction of **38** and, thus, its formation was tried to be avoided by vigorous exclusion of oxygen prior to reduction with L-selectride

10.1002/chem.202001405

(Scheme 12). The so-generated Δ^8-ene dione system tautomerized (Scheme 10, **C**), leading to a tedious isolation accompanied by decomposition. To prevent this problem, we decided to add another reducing reagent to the reaction mixture to convert one or both ketones to the corresponding alcohols. Interestingly, the initially formed lithium enolate protected the respective ketone against reduction with lithium aluminum hydride, and only the 6-oxo moiety was reduced to give β-hydroxy ketone **40**. Its treatment with BF_3•OEt_2 and acetic acid again resulted in an undesired side reaction, i.e., isomerization of Δ^8 into conjugation with the ketone to give $\Delta^{5,7}$-diene **41** as the major product (51%) and only minor quantities (12%) of the desired $\Delta^{5,8}$-diene **42**. Saponification (K_2CO_3, MeOH) proved to be difficult on **42**, and de-acetylation could only be achieved under reductive conditions (DIBAl-H) leading to concomitant reduction of the 14-oxo functionality to furnish **43**. To instead employ $\Delta^{5,7}$-diene **41**, several approaches were investigated, but isomerization of one or both of the two double bonds proved to be impossible. We suspected that isomerization of Δ^8 had occurred due to activation of the ketone with BF_3•OEt_2, and, thus, reduced **40** to 6,14-diol **44**. Fortunately, this time no isomerization was observed during *i*-steroid opening and subsequent de-acetylation (DIBAl-H) gave 3,14-diol **43** in a convincing yield of 74% over 2 steps. Employing Oppenauer conditions to achieve oxidation and isomerization to enone **45** did not lead to any conversion. Hence, a stepwise process using Dess–Martin periodinane and then DBU established key-intermediate **45** with a yield of 79% over 2 steps.



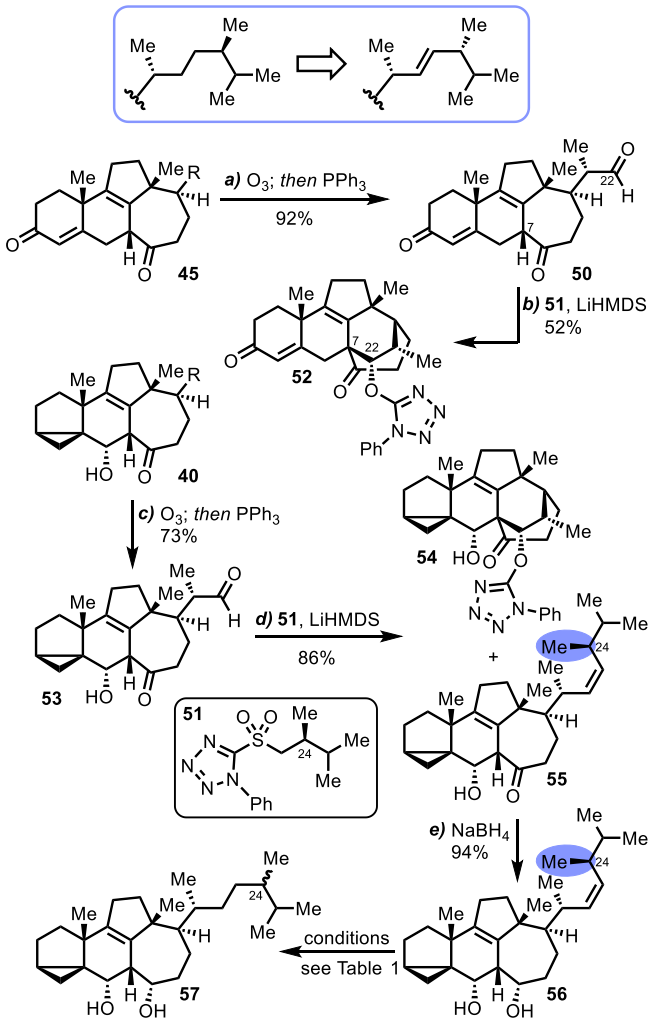
Scheme 12. *i*-Steroid opening and synthesis of key fragment **45**. Reagents and conditions: a) L-selectride (1.5 eq.), $LiAlH_4$ (2.5 eq.), THF, –78 to 0 °C, 2 h, 55%; b) BF_3•OEt_2/HOAc/Et_2O (1:1:2), 0 °C, 45 min, **41**: 51%, **42**: 12%; c) DIBAl-H, THF, –78 °C, 1.5 h, 76%; d) $NaBH_4$ (2.5 eq.), $CeCl_3$•$7H_2O$ (2.5 eq.), MeOH/CH_2Cl_2 (2:1), –10 °C, 30 min, 87%; e) BF_3•OEt_2/HOAc/Et_2O (1:1:2), 0 to 25 °C, 5 h, 88%; f) DIBAl-H, THF, –78 °C, 1.5 h, 89%; g) DMP, $NaHCO_3$, CH_2Cl_2, 25 °C, 1 h, 82%; h) DBU, CH_2Cl_2, 25 °C, 1 h, 91%. DIBAl-H = diisobutylaluminum hydride, R as in Scheme 3.



Scheme 13. Attempted reductive alkylation of enone **45**, successful conversion to hydroxymethylated **49** *via* Nishiyama–Stork reaction and elimination of the primary alcohol to Δ^{22}-24-*epi*-**2**. Reactions and conditions: Li•4 NH_3, –78 to 25 °C; *then* **45**, THF, –78 °C, 30 min; *then* TMSCl/Et_3N (1:2), –60 to –20 °C, 1 h; b) $NaBH_4$ (0.6 eq.), $CeCl_3$•7 H_2O (1.5 eq.), MeOH, –10 °C, 20 min; c) (chloromethyl)-chloromethylsilane (5.0 eq.), Et_3N (10 eq.), DMAP (0.2 eq.), CH_2Cl_2, 25 °C, 1 h; d) NaI (50 eq.), acetone, 60 °C, 16 h, 83% (3 steps); e) $n$$Bu_3SnCl$ (0.2 eq.), $NaBH_3CN$ (2.0 eq.), AIBN (0.1 eq.), *t*BuOH, 85 °C, 16 h; *then* KF (10 eq.), $KHCO_3$ (10 eq.), H_2O_2/MeOH/THF (2:2:1), 25 °C, 30 min, 36%; f) Tf_2O (2.5 eq.), 2,6-di-*tert*-butyl-4-methylpyridine (7.5 eq.), CH_2Cl_2, –78 °C, 5 min; *then* MeOH (30 eq.), DBU (20 eq.), –78 to 25 °C, 2 h, 62%. TMS = trimethylsilyl, DMAP = 4-(dimethylamino)pyridine, AIBN = 2,2'-azobis(isobutyronitrile), Tf = trifluoromethanesulfonyl, R as in Scheme 3.

As a handle to construct the requisite *exo*-methylene group along with the necessary *trans* ring junction of the A and B ring (Scheme 10, **B**), we envisioned the installation of a hydroxymethyl group at C4 and elimination of the primary alcohol to furnish the methylene unit. Initially, we intended to install the remaining carbon atom through a reductive alkylation protocol under dissolving metal conditions. As the direct addition of gaseous formaldehyde did not yield any of the desired hydroxy methylated product,[25] the trapping as a silyl enol ether was investigated. We applied a procedure described by Mueller and Gillick,[26] which involved the generation of so-called lithium bronze.[26c] Thus, enone **45** was readily converted into silyl enol ether **46** (Scheme 13). To introduce a suitable methylene precursor, a variety of conditions to alkylate **46** were tested. Methods using aqueous formaldehyde either in combination with Lewis acids such as $Sc(OTf)_3$[27] or $Yb(OTf)_3$[28] or by addition of a de-silylating reagent (e.g. TBAF[29]) have been described. Even though addition of formaldehyde could be detected by mass spectrometry, the isolation of the desired γ-hydroxy ketone was unsuccessful and instead, ketone **47** was obtained, the product of a retro-aldol reaction.[30] To circumvent this problem, we attempted to install a protected hydroxy methyl moiety. However, when treating silyl enol ether **46** with BOMCl and varying Lewis acids,[31] only α-halogenated ketones were isolated, yielding 4-chloro- and 4-fluoro-ketones

when using $SnCl_4$, $TiCl_4$, or BF_3•OEt_2, respectively. Consequently, the introduction of other functional groups known to be convertible into a methylene group was considered. Thus, treatment of silyl enol ether **46** with ethyl bromo acetate to give the corresponding ethyl ester[32] or Eschenmoser's salt to give the dimethylamine,[33] were attempted but did not yield any desired product other than ketone **47**.



Scheme 14. Attempts to install the necessary campestane side chain. Reagents and conditions: a) O_3, CH_2Cl_2/pyridine (99:1), –78 °C, 3 min; *then* PPh_3 (1.1 eq), –78 to 25 °C, 16 h, 92%; b) **51** (5.0 eq.), LiHMDS (5.0 eq.), THF, –78 to 25 °C, 22 h, 52%; c) O_3, CH_2Cl_2/pyridine (99:1), –78 °C, 45 min; *then* PPh_3 (2.0 eq.), –78 to 25 °C, 16 h, 73%; d) **51** (5.0 eq), LiHMDS (3.1 eq), THF, –78 to –65 °C, 2 h, 86%; e) $NaBH_4$ (2.5 eq), CH_2Cl_2/MeOH (1:1), –10 °C, 30 min, 94%. HMDS = 1,1,1,3,3,3-hexamethyldisilazide, R as in Scheme 3.

Alternatively, the method by Nishiyama and Stork[34] was considered and successfully executed to introduce the C4 hydroxy methyl moiety. Thus, enone **45** was selectively reduced under Luche conditions to the corresponding allylic alcohol, which was then treated with chloro(bromomethyl)dimethylsilane and triethyl amine to give the crucial precursor for a radical cyclization. Initial results employing the (bromomethyl)silyl ether (not shown) in the radical cyclization and subsequent Tamao oxidation[35] lacked reproducibility. An alternative procedure employing substoichiometric amounts of the tin reagent required the corresponding (iodomethyl)silyl ether **48**.[36] Hence, allylic alcohol was converted to the (chloromethyl)silyl ether (not shown) followed by Finkelstein reaction to give iodide **48**. Radical cyclization was then achieved by treatment with catalytic quantities of AIBN and $n$$Bu_3SnCl$ and stoichiometric amounts of $NaBH_3CN$ to result in the formation of a oxasilolane (not shown), which, upon oxidative work up (H_2O_2, KF), delivered diol **49** in 36% yield along with 16% of its undesired 5β-epimer. Finally, the primary alcohol was converted to the corresponding triflate with Tf_2O at –78 °C, which, upon warming to 25 °C, eliminated to yield the desired *exo*-methylene group in Δ^{22}-24-*epi*-swinhoeisterol A Δ^{22}-24-*epi*-**2**.[37]

With reliable route for swinhoeisterol A's tetracyclic core, one last synthetic challenge had to be overcome, i.e., the introduction of the correctly configurated side chain (Scheme 10, **A**). It was deemed strategically advantageous, to perform the necessary modifications at a late stage. Since we envisioned a sequence of oxidative C–C bond cleavage, olefination, and hydrogenation, many synthetic intermediates bearing easily accessible double bonds additional to Δ^{22} had to be excluded *a priori*. Thus, hydroxy methylated **49** and enone **45** presented themselves as promising candidates (Scheme 14). Oxidative Δ^{22} bond cleavage on the stage of diol **49** was achieved through ozonolysis and reductive work-up. Attempted Julia–Kocienski olefination proved unsuccessful due to low solubility of the starting material. Thus, the 1,3-diol functionality of **49** was protected as an acetonide, which was processed to the corresponding aldehyde. Again, no conversion of the starting material in an attempted Julia−Kocienski reaction could be observed. We, thus, shifted our attempts towards enone **45**. Ozonolysis gave aldehyde **50**, and this time, Julia−Kocienski olefination using sulfone **51** indeed led to conversion of starting material. Unfortunately, not the desired olefin, but tetrazole **52**, which presumably arose from aldol reaction between enolizable C7 and the 22-oxo functionality followed by trapping of the alcoholate by the tetrazole moiety of sulfone **51**, was isolated. As a consequence of this reactivity, *i*-steroid diol **44**, an intermediate without the oxo moiety at C14, was anticipated to adopt a less reactive conformation and, thus, seemed to be a better choice. However, treatment of the corresponding aldehyde of diol **44** with LiHMDS and sulfone **51** only led to isolation of material with the C6 hydroxyl bearing a tetrazole substituent. One of the few remaining intermediates to conduct the ozonolysis/olefination approach was β-hydroxy ketone **40**, which, after conversion to aldehyde **53** eventually afforded the desired olefin **55** (with the double bond being *Z* configurated) along with small quantities of aldol product **54**. Fortunately, it was possible to almost suppress formation of **54** (less than 5%) when increasing the amount of sulfone **51** (5.0 eq.). That way, olefin **55** was obtained in 86% yield. To furnish the desired saturated campestane side chain, hydrogenation conditions were tested on olefin **55**, but no conversion of starting material was observed under the conditions employed. Further reduction experiments were then carried out on diol **56**, which was obtained by reduction with $NaBH_4$.

Hydrogenation of a 22*Z* double bond is known to be more difficult than of the corresponding 22*E* isomer.[38] In agreement, in most experiments no conversion was achieved (Table 1, entries 3–9) and only elevated hydrogen pressure (40–60 bar) led to complete conversion to **57**. Unfortunately, varying degrees of epimerization at C24 occurred during the course of this reaction[39] yielding up to 50% of the undesired ergostane product when using Pd/C (entry 1) and still 25% when Pt/C was used (entry 2). Attempted

alternatives, such as Wilkinson's (entry 6) or Crabtree's catalyst (entry 7) as well as Shenvi's radical hydrogenation method (entries 8 and 9)[40] did not lead to any conversion of starting material.

Table 1: Attempted hydrogenation of Δ^{22} in **56**.

entry	catalyst	pressure H_2 [bar]	epimerization at C24[a]	conversion
1	Pd/C	40	~50%	complete
2	Pt/C	40	~25%	complete
3	PtO_2	60	-	none
4	Ir	60	-	none
5	Rh/C	60	-	none
6	$[RhCl(PPh_3)_3]$	60	-	none
7	Crabtree[b]	60	-	none
8	$Mn(dpm)_3$	-[c]	-	none
9	$Co(acac)_2$	-[c]	-	none

[a] Ratio of epimers determined from ^{13}C NMR spectra (see SI of ref. 13). [b] Crabtree catalyst: (*SP*-4)tris(cyclohexyl)phosphane[(1-2-*η*:5-6-*η*)-cycloocta-1,5-diene]pyridineiridium hexafluorophosphate. [c] 4.0 eq. of $PhSiH_3$; acac = acetylacetonate, dpm = 2,2,6,6-tetramethyl-3,5-heptanedionato.

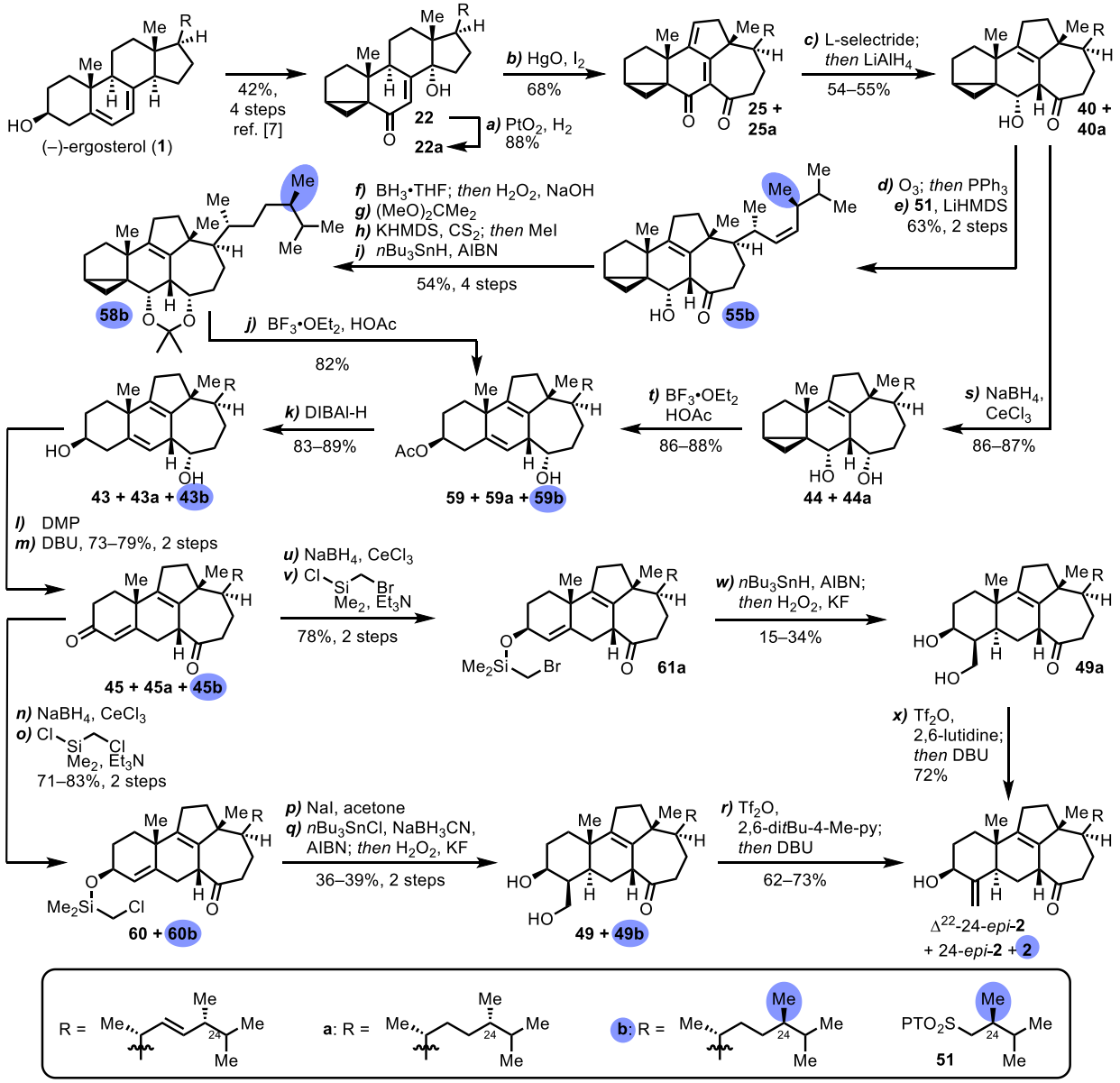
As hydrogenation of an 22*E*-configurated double bond without epimerization of C24 was deemed more promising, we carried out several isomerization experiments to convert 22*Z* to 22*E*, but could eventually not succeed in identifying a viable method. At this point, we turned our attention to rather functionalize the side chain double bond and remove the thus-installed functional group reductively in a separate step. Introduction of sulfur-containing functionalities failed and halogenation with bromine to the dibromide and subsequent treatment with AIBN/nBu$_3$SnH only led to a mixture of 22*E*- and 22*Z*-diol **56**. To our delight, hydroboration and subsequent oxidation with NaOH/H_2O_2 afforded primarily a 6,14,23-triol (not shown) under concomitant reduction of C14. Acetonide formation of the thus-obtained 1,3-diol unit and functionalization of the side chain alcohol (predominantly 23-OH) to a xanthate, followed by Barton–McCombie deoxygenation eventually gave the desired saturated campestane side chain without any epimerization (Scheme 15).

All synthetic challenges were thus coped with so that three very similar approaches led to the synthesis of natural swinhoeisterol A (**2**, b-series) and 24-*epi*-swinhoeisterol A (24-*epi*-**2**, a-series). As it was initially uncertain at which stage an installation of the correct side chain fragment would be feasible, the synthetic route had also been carried out in the ergostane series, starting from ergosterol (**1**) without hydrogenation of the Δ^{22} bond. This route enabled access to Δ^{22}-24-*epi*-swinhoeisterol A (Δ^{22}-24-*epi*-**2**) in 16 steps and a total yield of 1.5%.

In summary, access to the di*abeo*-skeleton (**25** and **25a**) *via* γ-hydroxy enones **22** or **22a** was accomplished in 5 to 6 steps, respectively, starting from ergosterol (**1**). β-Hydroxy ketones **40** and **40a**, obtained after reduction, were further processed following two different pathways. For the synthesis of swinhoeisterol A (**2**), **40a** was subjected to ozonolysis and Julia–Kocienski olefination to give **55b**, followed by a hydroboration, oxidation/Barton–McCombie deoxygenation sequence to yield the desired saturated campestane side chain as in **58b**. Opening of the *i*-steroid moiety led to acetate **59b**. **40** and **40a**, on the other hand, were reduced to diols **44** and **44a** and subsequent treatment with BF_3•OEt_2 under acidic conditions gave the corresponding acetates **59** and **59a**. De-acetylation was accomplished using DIBAl-H giving rise to **43**, **43a**, and **43b**. Oxidation with DMP and subsequent isomerization of the Δ^5 bond with DBU yielded enones **45**, **45a**, and **45b**. Luche reduction and silylation with chloro(chloromethyl)- or (bromomethyl)chlorodimethylsilane gave (chloromethyl)silyl ethers **60** and **60b**, and (bromomethyl)silyl ether **61a**, respectively. As classic Nishiyama−Stork conditions (**61a**, AIBN, *n*BuSnH) followed by Tamao oxidation gave crucial diol **49a** only in low and varying yields (15–34%), we adjusted the synthetic route towards Δ^{22}-24-*epi*-**2** and **2**. (Chloromethyl)silyl ethers **60** and **60b** were transformed to the corresponding (iodomethyl)silyl ethers using Finkelstein conditions and then treated with catalytic amounts of AIBN and nBu$_3$SnCl and a stoichiometric amount of $NaBH_3CN$ prior to oxidation, facilitating a reliable access to diols **49** and **49b**. Finally, triflation of the primary alcohol and subsequent elimination afforded **2**, 24-*epi*-**2**, and Δ^{22}-24-*epi*-**2**, respectively, bearing the characteristic *exo*-methylene group of the swinhoeisterols.

We herein detailed our efforts towards the synthesis of swinhoeisterol A (**2**) and discussed major challenges that were overcome during the development of a viable synthetic route. Additionally, the synthesis of the first analogue, Δ^{22}-24-*epi*-swinhoeisterol A (Δ^{22}-24-*epi*-**2**) was outlined as well as several experiments that were carried out to support our mechanistic proposal for the radical framework reconstruction. Two unexpected rearrangements of the steroid skeleton were observed, one of them leading to hydroxy lactone **20**, which had not been reported before. The synthesis of the remaining members of the swinhoeisterol class and the biological evaluation of all synthesized natural products are ongoing in our laboratory.

10.1002/chem.202001405



Scheme 15. Overview of the synthetic routes to swinhoeisterol A (**2**, b series), 24-*epi*-swinhoeisterol A (24-*epi*-**2**, a series) and Δ^{22}-24-*epi*-swinhoeisterol A (Δ^{22}-24-*epi*-**2**) starting from ergosterol (**1**). Reactions and conditions: a) PtO_2 (0.1 eq.), H_2 (20 bar), EtOAc, 25 °C, 24 h, **22a**: 88% b) HgO (2.7 eq.), I_2 (2.4 eq.), C_6H_6, 105 °C, 2 h, **25**: 68%, **25a**: 68%; c) L-selectride (2.0 eq.), THF, –78 °C, 1 h; *then* $LiAlH_4$ (2.0 eq.), –78 to 0 °C, 1 h, **40**: 55%, **40a**: 54%; d) O_3, CH_2Cl_2/pyridine (99:1), –78 °C, 45 min; *then* PPh_3 (2.0 eq.), –78 to 25 °C, 16 h; e) **51** (5.0 eq.), LiHMDS (3.1 eq.), THF, –65 °C, 1 h; *then* **40**, –65 °C, 1 h, **55b**: 63% (2 steps); f) BH_3•THF (10 eq.), THF, 0 to 25 °C, 16 h; *then* NaOH/H_2O_2 (1:1), 25 °C, 1 h; g) CSA (1.2 eq.), $(MeO)_2CMe_2$/CH_2Cl_2 (1:5), 0 °C, 1 h; h) KHMDS (2.0 eq.), CS_2 (5.0 eq.), THF, –78 to 25 °C, 1.5 h; *then* MeI (7.5 eq.), 25 °C, 45 min; i) AIBN (0.5 eq.), nBu$_3$SnH (5.0 eq.), C_6H_6, 85 °C, 3 h, **58b**: 54% (4 steps); j) BF_3•OEt_2/HOAc/Et_2O (1:1:2), 0 to 25 °C, 5 h, **59b**: 82%; k) DIBAl-H, THF, –78 °C, 1 h, **43**: 89%, **43a**: 86% **43b**: 83%; l) DMP (3.0 eq.), $NaHCO_3$ (6.6 eq.), CH_2Cl_2, 25 °C, 1 h; m) DBU (0.2 eq.), CH_2Cl_2, 25 °C, 1 h, **45**: 75% (2 steps), **45a**: 79% (2 steps), **45b**: 73% (2 steps); n) $NaBH_4$ (0.6 eq.), $CeCl_3$•7 H_2O (2.5 eq.), MeOH, –10 °C, 20 min; o) chloro(chloromethyl)dimethylsilane (5.0 eq.), Et_3N (10 eq.), DMAP (0.2 eq.), CH_2Cl_2, 25 °C, 1 h, **60**: 83% (2 steps), **60b**: 71% (2 steps); p) NaI (50 eq.), acetone, 60 °C, 16 h; q) nBu$_3$SnCl (0.2 eq.), $NaBH_3CN$ (2.0 eq.), AIBN (0.1 eq.), *t*BuOH, 85 °C, 16 h; *then* KF (10 eq.), $KHCO_3$ (10 eq.), H_2O_2/MeOH/THF (2:2:1), 25 °C, 30 min, **49**: 36% (2 steps), **49b**: 39% (2 steps); r) Tf_2O (2.5 eq.), 2,6-di-*t*butyl-4-methylpyridine (7.5 eq.), CH_2Cl_2, –78 °C, 5 min; *then* MeOH (30 eq.), DBU (20 eq.), –78 to 25 °C, 2 h, Δ^{22}-24-*epi*-**2**: 62%, **2**: 73%; s) $NaBH_4$ (2.5 eq.), $CeCl_3$•7 H_2O (2.5 eq.), MeOH, –10 °C, 30 min, **44**: 86%, **44a**: 87%; t) BF_3•OEt_2/HOAc/Et_2O (1:1:2), 0 to 25 °C, 5 h, **59**: 88% **59a**: 86%; u) $NaBH_4$ (0.6 eq.), $CeCl_3$•7 H_2O (2.5 eq.), MeOH, –10 °C, 20 min; v) (bromomethyl)chlorodimethylsilane (15 eq.), Et_3N (20 eq.), DMAP (0.2 eq.), CH_2Cl_2, 25 °C, 1 h, **61a**: 78% (2 steps); w) AIBN (1.0 eq.), nBu$_3$SnH (5.0 eq.), C_6H_6, 85 °C, 16 h; *then* KF (10 eq.), $KHCO_3$ (10 eq.), H_2O_2/MeOH/THF (2:2:1), 25 °C, 2.5 h, **49a**: 15–34%; x) Tf_2O (10 eq.), 2,6-lutidine (15 eq.), CH_2Cl_2, –78 °C, 10 min; *then* MeOH (10 eq.), DBU (20 eq.), –78 to –40 °C, 1.5 h, 24-*epi*-**2**: 72%. CSA = camphorsulfonic acid, py = pyridine, PT = 1-phenyl-1*H*-tetrazol-5-yl.

Experimental Section

(22*E*)-6-Oxo-5α(H)-ergosta-7,22-dien-3β-yl acetate (S1)

A suspension of Burawoy's ketone (**6**) (366 mg, 778 µmol, 1.0 eq.) in acetic acid (26 mL) was heated to 90 °C and zinc dust (1.50 g, 22.9 mmol, 29 eq.) was added to the mixture in three portions over 3 h. The mixture was allowed to cool to 25 °C, diluted with EtOAc (15 mL) and filtered through a plug of Celite®. The solvent was removed under reduced pressure and column chromatography (silica gel, *n*hexane/EtOAc 9:1) gave **S1** (167 mg, 367 µmol, 47%) as a colorless solid. R_f = 0.22 (*n*hexane/EtOAc 5:1); m.p. 173–175 °C ($CHCl_3$); $[\alpha]_D^{20}$ = –14.7 (*c* = 1.00,

$CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ [ppm] = 5.72 (t, *J* = 2.4 Hz, 1H), 5.24 (dd, *J* = 15.3, 7.5 Hz, 1H), 5.16 (dd, *J* = 15.3, 8.3 Hz, 1H), 4.76 – 4.68 (m, 1H), 2.30 (dd, *J* = 12.4, 3.7 Hz, 1H), 2.25 – 2.15 (m, 2H), 2.14 – 2.04 (m, 3H), 2.04 (s, 3H), 1.89 – 1.83 (m, 3H), 1.82 – 1.74 (m, 2H), 1.70 – 1.62 (m, 1H), 1.62 – 1.56 (m, 1H), 1.56 – 1.51 (m, 1H), 1.50 – 1.44 (m, 3H), 1.44 – 1.33 (m, 4H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.61 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$); δ [ppm] = 199.3, 170.7, 163.8, 135.1, 132.6, 123.1, 73.0, 56.2, 55.8, 53.2, 50.1, 44.5, 42.9, 40.4, 38.8, 38.3, 36.7, 33.2, 28.0, 26.9, 26.5, 22.7, 21.9, 21.5, 21.2, 20.1, 19.8, 17.7, 13.3, 12.7; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2922 (s), 2852 (m), 1739 (w), 1677 (w), 1459 (m), 1377 (w). 1240 (w), 1038 (w), 970 (w), 722 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{46}O_3Na^+$ [M+Na]$^+$: 477.3339, found: 477.3350.

(22*E*)-14-Hydroxy-6-oxo-5α(H)-ergosta-7,22-dien-3β-yl acetate (7)

Selenium dioxide (83.4 mg, 752 µmol, 4.75 eq.) was added to a solution of 5α-enone **S1** (71.8 mg, 158 mmol, 1.0 eq.) in *t*BuOH/pyridine (4:1, 2.5 mL) and the reaction mixture was heated to 80 °C for 4 h. It was cooled to 25 °C, the mixture was filtered through a plug of Celite® and rinsed with EtOAc (15 mL). The filtrate was washed sequentially with $Na_2S_2O_3$ (sat. aq., 10 mL), $NaHCO_3$ (sat. aq., 10 mL) and brine (sat., 10 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 4:1 g 3:1) gave γ-hydroxy enone **7** (43.7 mg, 92.8 µmol, 59%) as a colorless solid. R_f = 0.20 (*n*hexane/EtOAc 3:1); m.p. 187–189 °C ($CHCl_3$); $[\alpha]_D^{20}$ = +15.2 (*c* = 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ [ppm] = 5.90 (d, *J* = 2.8 Hz, 1H), 5.26 (dd, *J* = 15.3, 7.5 Hz, 1H), 5.19 (dd, *J* = 15.3, 8.2 Hz, 1H), 4.76 – 4.68 (m, 1H), 2.72 (ddd, *J* = 11.9, 7.2, 2.8 Hz, 1H), 2.34 (dd, *J* = 12.3, 3.8 Hz, 1H), 2.25 – 2.18 (m, 1H), 2.11 – 2.05 (m, 1H), 2.04 (s, 3H), 1.98 – 1.90 (m, 3H), 1.90 – 1.83 (m, 3H), 1.80 – 1.68 (m, 2H), 1.63 – 1.52 (m, 3H), 1.52 – 1.35 (m, 4H), 1.28 – 1.23 (m, 1H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 3H), 0.85 – 0.81 (m, 6H), 0.69 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$); δ [ppm] = 200.0, 170.7, 163.4, 135.4, 132.7, 122.9, 85.3, 72.9, 53.4, 50.4, 46.5, 46.1, 42.9, 40.1, 38.7, 36.7, 33.2, 32.1, 30.6, 26.9, 26.7, 26.4, 21.5, 21.4, 20.6, 20.1, 19.8, 17.7, 16.2, 13.1; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2922 (s), 2853 (m), 1739 (w), 1459 (w), 1377 (w), 1240 (w), 1038 (w), 972 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{46}O_4Na^+$ [M+Na]$^+$: 493.3288, found: 493.3287.

(22*E*)-15β-Iodo-6,14-dioxo-13(14→8),14(8→7)di*abeo*-5α(H)-ergosta-7,9(11),22-trien-3β-yl acetate (8),

(22*E*)-6,14-Dioxo-13(14→8),14(8→7)di*abeo*-5α(H)-ergosta-7,9(11),22-trien-3β-yl acetate (9) and

(22*E*)-6,14-Dioxo-5α,9α-endoperoxide-13(14→8),14(8→7)di*abeo*-ergosta-7,22-dien-3β-yl acetate (10)

To a solution of γ-hydroxy enone **7** (43 mg, 91 µmol, 1.0 eq.) in benzene (4 mL) were added $CaCO_3$ (18.2 mg, 182 µmol, 2.0 eq.) iodine (46.2 mg, 182 µmol, 2.0 eq.) and $Pb(OAc)_4$ (80.7 mg, 182 µmol, 2.0 eq.), and argon was bubbled through the solution *via* cannula for 15 min. The resulting mixture was heated to 85 °C for 2 h. The reaction mixture was cooled to 25 °C, filtered through a plug of Celite®, and rinsed with EtOAc (20 mL). The organic phase was washed sequentially with $Na_2S_2O_3$ (sat. aq., 25 mL) and brine (sat., 25 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc, 5:1g3:1) gave 15β-iodo diene dione **8** (9.5 mg, 16 µmol, 18%) diene dione **9** (24.9 mg, 53.4 µmol, 59%) and traces of endoperoxide **10**.

15β-Iodo diene dione 8: light-yellow oil, R_f = 0.29 (*n*hexane/EtOAc 3:1); $[\alpha]_D^{20}$ = –25.9 (*c* = 0.75, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.31 (t, *J* = 2.8 Hz, 1H), 5.34 – 5.23 (m, 2H), 4.87 (t, *J* = 3.9 Hz, 1H), 4.77 – 4.69 (m, 1H), 2.96 (dd, *J* = 17.9, 2.5 Hz, 1H), 2.70 – 2.63 (m, 1H), 2.50 (dd, *J* = 8.9, 3.3 Hz, 1H), 2.47 (t, *J* = 3.5 Hz, 1H), 2.31 – 2.24 (m, 1H), 2.19 – 2.14 (m, 1H), 2.05 (s, 3H), 2.04 – 2.01 (m, 2H), 2.00 – 1.93 (m, 2H), 1.93 – 1.85 (m, 1H), 1.80 – 1.71 (m, 1H), 1.64 – 1.57 (m, 1H), 1.51 – 1.44 (m, 1H), 1.10 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.02 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 4H), 0.82 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ [ppm] = 193.9, 193.0, 170.6, 167.6, 148.5, 137.5, 136.1, 131.9, 127.6, 72.7, 52.2, 49.1, 47.7, 45.3, 43.4, 39.4, 38.9, 36.0, 34.5, 33.2, 31.5, 26.7, 26.3, 22.7, 22.1, 21.5, 20.2, 19.9, 19.3, 17.6.; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2956 (s), 2925 (s), 2871 (m), 2855 (m), 1735 (s), 1702 (s), 1590 (w), 1458 (w), 1376 (m), 1291 (w), 1235 (s), 1185 (w), 1035 (m); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{41}O_4INa^+$ [M+Na]$^+$: 615.1942, found: 615.1933.

Diene dione 9: colorless needles (recrystallized from pentane/Et_2O), R_f = 0.15 (*n*hexane/EtOAc 3:1); $[\alpha]_D^{20}$ = –79.5 (*c* = 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.30 – 6.22 (m, 1H), 5.36 (dd, *J* = 15.3, 8.5 Hz, 1H), 5.28 (dd, *J* = 15.3, 7.9 Hz, 1H), 4.75 – 4.64 (m, 1H), 2.83 (dd, *J* = 17.7, 2.4 Hz, 1H), 2.69 (ddd, *J* = 11.9, 7.0, 3.5 Hz, 1H), 2.61 – 2.50 (m, 3H), 2.45 (dd, *J* = 17.6, 3.2 Hz, 1H), 2.40 (dd, *J* = 12.6, 3.4 Hz, 1H), 2.24 – 2.18 (m, 1H), 2.04 (s, 3H), 1.99 – 1.94 (m, 2H), 1.90 – 1.85 (m, 2H), 1.75 – 1.68 (m, 1H), 1.59 – 1.51 (m, 2H), 1.49 – 1.43 (m, 2H), 1.14 (s, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.01 (s, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$); δ [ppm] = 201.8, 193.6, 170.6, 170.2, 148.9, 136.3, 135.5, 131.8, 130.1, 72.7, 53.1, 50.5, 49.6, 48.1, 45.1, 43.4, 39.8, 36.3, 34.5, 33.2, 26.7, 26.2, 23.6, 22.9, 22.1, 21.4, 20.2, 19.8, 19.1, 17.6; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (m), 2924 (s), 2854 (m), 1735 (m), 1704 (s), 1659 (w), 1590 (w),1457 (m), 1375 (m), 1234 (s), 1186 (m), 1037 (m); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{42}O_4Na^+$ [M+Na]$^+$: 489.2975, found: 489.2992. CCDC 1991055 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Endoperoxide 10: colorless needles (recrystallized from pentane/Et_2O) R_f = 0.24 (*n*hexane/EtOAc 3:1); ^1H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.26 (t, *J* = 2.8 Hz, 1H), 5.36 (dd, *J* = 15.3, 8.6 Hz, 1H), 5.29 (dd, *J* = 15.2, 8.0 Hz, 1H), 4.71 (tt, *J* = 11.3, 4.5 Hz, 1H), 2.83 (dd, *J* = 17.6, 2.4 Hz, 1H), 2.70 (ddd, *J* = 12.0, 7.2, 3.6 Hz, 1H), 2.63 – 2.52 (m, 2H), 2.46 (dd, *J* = 17.5, 3.2 Hz, 1H), 2.41 (dd, *J* = 12.6, 3.4 Hz, 1H), 2.26 – 2.19 (m, 1H), 2.05 (s, 3H), 2.02 – 1.98 (m, 1H), 1.98 – 1.93 (m, 1H), 1.91 – 1.86 (m, 2H), 1.82 (dt, *J* = 11.6, 2.4 Hz, 1H), 1.73 (td, *J* = 14.0, 13.1, 4.4 Hz, 1H), 1.55 – 1.50 (m, 1H), 1.49 – 1.45 (m, 1H), 1.31 – 1.28 (m, 2H), 1.15 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.02 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ [ppm] = 201.8, 193.6, 170.7, 148.9, 131.8, 131.1, 130.2, 129.0, 72.8, 53.1, 50.5, 49.7, 48.2, 45.2, 43.4, 39.8, 36.3, 34.5, 33.2, 29.8, 26.7, 26.3, 23.7, 22.9, 22.2, 21.5, 20.2, 19.9, 19.2, 17.6; HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{42}O_6Na^+$ [M+Na]$^+$: 521.2874, found: 521.2892. CCDC 1991054 contains the supplementary crystallographic data for this paper. These data can be

obtained free of charge from The Cambridge Crystallographic Data Centre.

(22*E*)-6-Oxo-ergosta-4,7,22-trien-3β-yl acetate (11)

Through a solution of Burawoy's ketone (**6**) (1.00 g, 2.13 mmol, 1.0 eq.) in pyridine (30 mL) was bubbled argon *via* cannula for 10 min and the mixture was cooled to –15 °C. In a separate flask, $SOCl_2$ (694 µL, 9.56 mmol, 4.5 eq.) was added to pyridine (5 mL) at 0 °C, which was then added to the reaction mixture at –15 °C and the mixture was stirred at this temperature for 45 min. The solution was carefully poured into H_2O (30 mL) and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic phases were washed sequentially with HCl (1 M in H_2O, 3 × 35 mL), H_2O (2 × 50 mL) and brine (sat., 50 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 7:1) gave Δ⁴-enone **11** (724 mg, 1.60 mmol, 75%) as a colorless solid. R_f = 0.40 (*n*hexane/EtOAc 3:1); m.p. 127–129 °C (EtOAc); $[\alpha]_D^{20}$ = –100.7 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ [ppm] = 6.37 (dd, *J* = 2.3, 1.5 Hz, 1H), 5.85 (t, *J* = 2.3 Hz, 1H), 5.41 (ddd, *J* = 9.5, 6.0, 2.3 Hz, 1H), 5.24 (dd, *J* = 15.3, 7.7 Hz, 1H), 5.17 (dd, *J* = 15.2, 8.4 Hz, 1H), 2.28 (ddd, *J* = 11.7, 7.2, 2.5 Hz, 1H), 2.14 (ddd, *J* = 12.9, 4.6, 2.5 Hz, 1H), 2.07 (s, 3H), 2.06 – 2.01 (m, 2H), 1.93 – 1.89 (m, 1H), 1.88 – 1.84 (m, 1H), 1.81 – 1.78 (m, 1H), 1.77 – 1.70 (m, 1H), 1.67 – 1.63 (m, 2H), 1.53 – 1.46 (m, 2H), 1.46 – 1.40 (m, 1H), 1.39 – 1.33 (m, 2H), 1.17 (s, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.65 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$); δ [ppm] = 188.0, 170.8, 166.6, 145.0, 135.1, 132.8, 129.5, 123.9, 69.5, 56.2, 56.2, 47.7, 44.6, 43.0, 40.3, 38.7, 38.1, 34.5, 33.2, 27.9, 24.6, 22.7, 21.8, 21.3, 21.3, 20.9, 20.1, 19.8, 17.7, 12.9; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (s), 2926 (m), 2871 (m), 1740 (s), 1666 (m), 1624 (m), 1458 (w), 1371 (w), 1236 (s), 1057 (w), 1022 (w), 969 (w), 874 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{44}O_3Na^+$ [M+Na]$^+$: 475.3183, found: 473.3183.

(22E)-14-Hydroxy-6-oxo-ergosta-4,7,22-trien-3β-yl acetate (12)

Selenium dioxide (671 mg, 6.05 mmol, 4.75 eq.) was added to a solution of Δ⁴-enone **11** (574 mg, 1.27 mmol, 1.0 eq.) in dioxane/H_2O (50:1, 40.8 mL) and the resulting mixture was heated to 60 °C for 5 h. The mixture was cooled to 25 °C, filtered through a plug of Celite® and rinsed with EtOAc (25 mL). The filtrate was washed sequentially with $Na_2S_2O_3$ (sat. aq., 40 mL), $NaHCO_3$ (sat. aq., 40 mL) and brine (sat., 40 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 4:1) gave Δ⁴-hydroxy enone **12** (434 mg, 922 µmol, 73%) as a yellow solid. R_f = 0.30 (*n*hexane/EtOAc 3:1); m.p. 165–167 °C (EtOAc); $[\alpha]_D^{20}$ = –50.5 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.36 (t, *J* = 1.8 Hz, 1H), 6.00 (d, *J* = 2.6 Hz, 1H), 5.43 – 5.36 (m, 1H), 5.26 (dd, *J* = 15.2, 7.3 Hz, 1H), 5.18 (dd, *J* = 15.3, 8.0 Hz, 1H), 2.77 (ddd, *J* = 10.5, 7.3, 2.7 Hz, 1H), 2.15 – 2.08 (m, 1H), 2.07 (s, 3H), 2.05 – 2.02 (m, 1H), 2.02 – 1.83 (m, 5H), 1.78 – 1.60 (m, 6H), 1.58 – 1.51 (m, 1H), 1.51 – 1.44 (m, 1H), 1.44 – 1.36 (m, 1H), 1.15 (s, 3H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.86 – 0.80 (m, 6H), 0.71 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$); δ [ppm] = 188.8, 170.8, 166.4, 144.6, 135.4, 132.6, 130.4, 123.5, 85.2, 69.5, 50.4, 46.4, 43.8, 42.9, 40.1, 38.1, 34.3, 33.2, 32.1, 30.4, 26.6, 24.5, 21.4, 21.3, 20.6, 20.5, 20.1, 19.8, 17.7, 16.2; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 3458 (br w), 2954 (m), 2924 (s), 2853 (m), 1739 (m), 1666 (w), 1625 (w), 1458 (w), 1374 (w), 1236 (m), 1056 (w), 1021 (w), 969 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{44}O_4Na^+$ [M+Na]$^+$: 491.3132, found: 491.3131.

(22*E*)-6,14-Dioxo-13(14→8),14(8→7)di*abeo*-ergosta-4,7,9(11),22-tetraen-3β-yl acetate (13),

(22*E*)-15β-Iodo-6,14-dioxo-13(14→8),14(8→7)di*abeo*-ergosta-4,7,9(11),22-tetraen-3β-yl acetate (14),

(22*E*)-6,14-Oxo-13(14→8)*abeo*-ergosta-4,22-dien-3β-yl acetate (15),

(22*E*)-4β-Iodo-6,14-dioxo-5α,9α-endoperoxide-13(14→8),14(8→7)di*abeo*-ergosta-7,22-dien-3β-yl acetate (16) and

(22*E*)-4α-Iodo-6,14-dioxo-5α,9α-endoperoxide-13(14→8),14(8→7)di*abeo*-ergosta-7,22-dien-3β-yl acetate (17)

To a solution of Δ⁴-hydroxy enone **12** (60.0 mg, 128 µmol, 1.0 eq.) in benzene (3 mL) were added $CaCO_3$ (25.6 mg, 256 µmol, 2.0 eq.), iodine (49.0 mg, 192 µmol, 1.5 eq.) and $Pb(OAc)_4$ (114 mg, 256 µmol, 2.0 eq.), and the reaction mixture was heated to 85 °C for 2 h. The mixture was cooled to 25 °C, filtered through a plug of Celite®, and rinsed with EtOAc (10 mL). The filtrate was washed sequentially with $Na_2S_2O_3$ (sat. aq., 15 mL) and brine (sat., 15 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAC , 5:1 g 4:1 g 3:1 g 2:1) gave 4β-iodo endoperoxide **16** (9.9 mg, 16 µmol, 12%), 15β-iodo Δ⁴-diene dione **14** (10.9 mg, 18.5 µmol, 14%), Δ⁴-diene dione **13** (18.7 mg, 40.2 µmol, 31%) and 4α-iodo endoperoxide **17** (18.5 mg, 29.6 µmol, 23%). When the reaction mixture was subjected to three freeze-pump-thaw cycles prior to addition of $Pb(OAc)_4$ and heating the following product distribution was obtained (**15** was isolated instead of **14**): **16**: 9%, **17**: 13%, **15**: 11%, **13**: 44%.

4β-iodo endoperoxide 16: light-orange oil, R_f = 0.24 (*n*hexane/EtOAc 3:1); $[\alpha]_D^{20}$ = +37.0 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 5.31 (dd, *J* = 15.3, 8.4 Hz, 1H), 5.25 (dd, *J* = 15.3, 7.6 Hz, 1H), 4.72 (dd, *J* = 3.8, 1.7 Hz, 1H), 4.38 (dt, *J* = 11.1, 3.7 Hz, 1H), 2.72 (ddd, *J* = 11.7, 5.6, 2.8 Hz, 1H), 2.64 (dd, *J* = 12.8, 4.2 Hz, 1H), 2.62 – 2.55 (m, 1H), 2.11 (s, 3H), 2.08 – 2.05 (m, 2H), 2.04 – 1.99 (m, 2H), 1.97 – 1.93 (m, 3H), 1.91 – 1.85 (m, 2H), 1.82 – 1.76 (m, 2H), 1.49 – 1.42 (m, 1H), 1.39 (dt, *J* = 12.8, 3.3 Hz, 1H), 1.26 (s, 3H), 1.09 (s, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$); δ [ppm] = 202.8, 185.5, 169.8, 166.9, 135.5, 134.4, 131.6, 97.3, 89.6, 69.6, 53.0, 52.0, 51.9, 45.5, 43.4, 38.9, 38.7, 33.1, 28.3, 25.2, 24.4, 23.1, 22.9, 22.9, 21.3, 20.4, 20.2, 19.8, 19.1, 17.6; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (m), 2924 (s), 2854 (m), 1739 (m), 1714 (m), 1458 (w), 1376 (w), 1232 (m), 1067 (w), 1024 (w), 981 (w), 770 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{41}O_6Ina^+$ [M+Na]$^+$: 647.1840, found: 647.1845.

Δ⁴-dione 15: light-orange oil, R_f = 0.33 (*n*hexane/EtOAc 2:1); $[\alpha]_D^{20}$ = –26.2 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.42 (dd, *J* = 3.1, 1.0 Hz, 1H), 5.43 – 5.39 (m, 1H), 5.30 – 5.21 (m, 2H), 2.74 – 2.69 (m, 1H), 2.60 (d, *J* = 16.4 Hz, 1H), 2.53 – 2.47 (m, 2H), 2.39 – 2.31 (m, 2H), 2.04 (s, 3H), 1.99 – 1.93 (m, 1H), 1.91 – 1.80 (m, 4H), 1.78 – 1.67 (m, 5H), 1.58 – 1.55 (m, 1H), 1.50 – 1.43 (m, 1H), 1.30 (dt, *J* = 13.0, 2.8 Hz, 1H), 1.18 (s, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.97 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ [ppm] = 214.9, 199.5, 170.5, 143.5, 135.0, 132.8, 130.7, 68.9, 62.1, 53.4, 50.4, 48.9, 43.4, 41.9, 39.8, 38.0, 37.7, 37.6, 35.3, 33.2, 25.2, 24.8, 24.4, 23.5, 22.6, 21.3, 20.2, 19.8, 17.8, 17.2; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (s), 2925 (s), 2870 (m), 1737 (m), 1701 (m), 1631 (w), 1463 (w), 1371 (w), 1232 (s),

1044 (w), 1016 (w), 970 (w); HRMS (ESI-TOF); *m/z* calcd. For $C_{30}H_{44}O_4Na^+$ [M+Na]$^+$: 491.3132, found: 491.3134.

15β-iodo Δ^4-diene dione 14: light-yellow oil, R_f = 0.26 (*n*hexane/EtOAc 3:1); $[\alpha]_D^{20}$ = –30.4 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.53 – 6.48 (m, 1H), 6.35 (t, *J* = 2.8 Hz, 1H), 5.45 (ddd, *J* = 10.2, 6.3, 2.4 Hz, 1H), 5.32 – 5.26 (m, 2H), 4.91 (t, *J* = 3.9 Hz, 1H), 2.93 (dd, *J* = 17.9, 2.5 Hz, 1H), 2.70 – 2.63 (m, 1H), 2.50 (dd, *J* = 17.8, 3.2 Hz, 1H), 2.21 – 2.14 (m, 2H), 2.11 – 2.09 (m, 1H), 2.08 (s, 3H), 2.06 – 2.03 (m, 3H), 1.89 (q, *J* = 6.7 Hz, 1H), 1.79 (tdd, *J* = 13.6, 10.2, 3.5 Hz, 1H), 1.47 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.29 (s, 3H), 1.14 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ [ppm] = 194.8, 183.5, 170.8, 168.0, 147.2, 140.3, 137.9, 136.1, 132.4, 131.8, 128.3, 69.5, 52.6, 47.6, 45.1, 43.4, 39.4, 38.4, 36.0, 33.2, 32.9, 31.4, 28.9, 24.6, 22.5, 22.0, 21.3, 20.2, 19.9, 17.6; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2958 (m), 2927 (m), 2871 (w), 1737 (s), 1695 (s), 1625 (w), 1589 (w), 1456 (w), 1365 (m), 1293 (w), 1234 (s), 1024 (m), 984 (w), 914 (w), 797 (w), 735 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{39}O_4INa^+$ [M+Na]$^+$: 613.1785, found: 613.1801.

Δ^4-diene dione 13: light-yellow foam, R_f = 0.21 (*n*hexane/EtOAc 3:1); $[\alpha]_D^{20}$ = –128.1 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.46 – 6.41 (m, 1H), 6.31 (t, *J* = 2.8 Hz, 1H), 5.42 (ddd, *J* = 10.2, 6.4, 2.4 Hz, 1H), 5.35 (dd, *J* = 15.3, 8.4 Hz, 1H), 5.28 (dd, *J* = 15.3, 7.8 Hz, 1H), 2.81 (dd, *J* = 17.9, 2.5 Hz, 1H), 2.72 (ddd, *J* = 11.9, 6.5, 2.9 Hz, 1H), 2.60 – 2.53 (m, 2H), 2.48 (dd, *J* = 17.8, 3.2 Hz, 1H), 2.19 – 2.13 (m, 1H), 2.11 – 2.09 (m, 1H), 2.08 (s, 3H), 2.02 – 1.97 (m, 2H), 1.92 – 1.84 (m, 2H), 1.83 – 1.75 (m, 2H), 1.47 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.29 (s, 3H), 1.16 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ [ppm] = 203.5, 183.5, 170.8, 169.6, 147.5, 141.3, 136.9, 135.6, 131.9, 131.0, 69.5, 53.2, 49.8, 48.2, 45.4, 43.4, 39.8, 36.1, 33.2, 32.9, 28.9, 24.6, 24.0, 23.0, 22.0, 21.3, 20.2, 19.9, 17.6; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (m), 2922 (s), 2853 (m), 1739 (m), 1703 (w), 1458 (w), 1365 (w), 1234 (m), 1025 (w), 975 (w), 773 (w); HRMS (ESI-TOF); *m/z* calcd. for for $C_{30}H_{40}O_4Na^+$ [M+Na]$^+$: 487.2819, found: 487.2809.

4α-iodo endoperoxide 17: orange oil, R_f = 0.17 (*n*hexane/EtOAc 3:1); $[\alpha]_D^{23}$ = –64.7 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ [ppm] = 5.34 (dd, *J* = 15.3, 8.7 Hz, 1H), 5.31 – 5.25 (m, 2H), 4.14 (d, *J* = 10.7 Hz, 1H), 2.77 (td, *J* = 12.0, 4.1 Hz, 1H), 2.71 (ddd, *J* = 11.6, 5.7, 2.8 Hz, 1H), 2.66 – 2.59 (m, 1H), 2.31 – 2.25 (m, 1H), 2.15 (s, 3H), 2.11 – 2.03 (m, 3H), 2.02 – 1.93 (m, 2H), 1.93 – 1.86 (m, 4H), 1.50 – 1.43 (m, 3H), 1.11 – 1.07 (m, 6H), 1.04 (d, *J* = 0.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$); δ [ppm] = 201.4, 190.6, 170.1, 168.3, 135.6, 133.4, 131.6, 97.5, 92.0, 75.2, 56.2, 52.0, 51.9, 45.5, 43.4, 39.0, 38.7, 33.2, 28.5, 27.2, 25.0, 23.3, 22.9, 21.2, 21.2, 20.2, 19.8, 19.3, 17.6, 15.4; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (s), 2924 (s), 2854 (m), 1739 (m), 1718 (s), 1458 (m), 1376 (w), 1234 (m), 1041 (w), 983 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{41}O_6INa^+$ [M+Na]$^+$: 647.1840, found: 647.1841.

(22*E*)-5α,9α-Dihydroxy-4β-iodo-6,14-dioxo-13(14→8),14(8→7)di*abeo*-ergosta-7,22-dien-3β-yl acetate (S2)

To a solution of 4β-iodo endoperoxide **16** (11.1 mg, 17.8 µmol, 1.0 eq.) in EtOAc (1.5 mL) was added PtO_2 (0.8 mg, 3.6 µmol, 0.2 eq.). After stirring at 25 °C for 4 h under an atmosphere of hydrogen (balloon), the mixture was filtered through a plug of Celite®, rinsed with EtOAc (10 mL), and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 3:1) gave a mixture of diol **S2** and epoxide **18** (6.9 mg, **S2**/**18** 3.1:1 determined by integration of 4H-signals δ [ppm] = 4.77(major), 3.80 (minor) in ^{1}H-NMR) as a light-yellow oil. R_f = 0.26 (*n*hexane/EtOAc 2:1); $[\alpha]_D^{20}$ = –7.5 (*c* = 0.58, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ [ppm] = 5.31 (dd, *J* = 15.4, 8.8 Hz, 1H), 5.26 (dd, *J* = 15.3, 7.9 Hz, 1H), 5.12 (d, *J* = 2.5 Hz, 1H), 5.08 – 5.05 (m, 1H), 4.77 (dd, *J* = 4.6, 1.7 Hz, 1H), 4.54 (dt, *J* = 12.3, 4.5 Hz, 1H), 2.74 – 2.67 (m, 1H), 2.66 – 2.62 (m, 2H), 2.56 (td, *J* = 13.9, 4.0 Hz, 1H), 2.32 – 2.25 (m, 1H), 2.11 (s, 3H), 2.03 – 1.95 (m, 3H), 1.89 – 1.85 (m, 2H), 1.83 – 1.77 (m, 3H), 1.71 – 1.68 (m, 1H), 1.48 (s, 3H), 1.47 – 1.43 (m, 1H), 1.41 (dt, *J* = 13.7, 3.6 Hz, 1H), 1.06 – 1.04 (m, 6H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$); δ [ppm] = 204.4, 189.6, 173.1, 171.0, 135.2, 132.1, 130.3, 84.1, 78.6, 70.8, 51.2, 50.9, 45.5, 43.4, 42.2, 38.7, 37.3, 33.2, 29.8, 26.4, 26.1, 24.2, 24.1, 23.6, 22.8, 21.5, 20.8, 20.2, 19.9, 17.6; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2921 (s), 2852 (m), 1740 (w), 1460 (w), 1377 (w), 1243 (w), 759 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{43}O_6INa^+$ [M+Na]$^+$: 649.1997, found: 649.2004.

(22*E*)-4α,5α-Epoxy-9α-hydroxy-6,14-dioxo-13(14→8),14(8→7)di*abeo*-ergosta-7,22-dien-3β-yl acetate (18)

To a solution of diol **S2** and epoxide **18** (3.1:1, 6.90 mg.11.6 µmol, 1.0 eq.) in THF (1.0 mL) was added Ag_2O (8.1 mg, 35 µmol, 3.0 eq.) and the reaction mixture was stirred at 25 °C for 1 h. The mixture was filtered through a plug of Celite®, rinsed with EtOAc (10 mL), and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 3:1) gave epoxide **18** (5.0 mg, 10 µmol, 56% over 2 steps) as a colorless solid. R_f = 0.32 (*n*hexane/EtOAc 2:1); m.p. 169–171 °C (CH_2Cl_2); $[\alpha]_D^{20}$ = –53.7 (*c* = 0.35, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ [ppm] = 5.32 (dd, *J* = 15.3, 8.6 Hz, 1H), 5.28 (dd, *J* = 15.3, 7.7 Hz, 1H), 5.07 (dd, *J* = 9.4, 8.0 Hz, 1H), 3.81 (d, *J* = 1.0 Hz, 1H), 2.78 (d, *J* = 2.6 Hz, 1H), 2.71 (tt, *J* = 9.1, 5.9 Hz, 1H), 2.66 (ddd, *J* = 11.7, 5.4, 3.2 Hz, 1H), 2.60 (ddd, *J* = 12.7, 11.6, 4.5 Hz, 1H), 2.33 – 2.27 (m, 1H), 2.15 (td, *J* = 14.2, 3.6 Hz, 1H), 2.11 (s, 3H), 2.09 – 2.01 (m, 2H), 2.01 – 1.95 (m, 1H), 1.91 – 1.85 (m, 1H), 1.84 – 1.77 (m, 3H), 1.75 (ddd, *J* = 12.7, 6.3, 2.8 Hz, 1H), 1.50 – 1.43 (m, 2H), 1.22 – 1.18 (m, 4H), 1.09 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$); δ [ppm] = 203.9, 187.7, 175.0, 170.1, 135.4, 133.2, 131.9, 84.1, 66.6, 62.4, 56.1, 51.5, 51.1, 45.5, 43.4, 38.9, 37.9, 37.2, 33.2, 29.1, 23.9, 22.8, 22.4, 22.3, 21.2, 20.3, 20.2, 20.1, 19.9, 17.6; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (m), 2922 (s), 2853 (m), 1740 (m), 1712 (m), 1458 (w), 1376 (w), 1233 (m), 1025 (w), 979 (w), 801 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{42}O_6Na^+$ [M+Na]$^+$: 521.2874, found: 521.2877.

(22*E*)-5α,9α-Dihydroxy-4α-iodo-6,14-dioxo-13(14→8),14(8→7)di*abeo*-ergosta-7,22-dien-3β-yl acetate (19): To a solution of 4α-iodo endoperoxide **17** (6.9 mg, 11 µmol, 1.0 eq.) in EtOAc (1.5 mL) was added PtO_2 (0.5 mg, 2.2 µmol, 0.2 eq.). After stirring at 25 °C for 4 h under an atmosphere of hydrogen (balloon), the mixture was filtered through a plug of Celite®, rinsed with EtOAc (10 mL), and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 3:1) gave 4α-iodo diol **19** (4.8 mg, 7.7 µmol, 70%) as a colorless solid. R_f = 0.28 (*n*hexane/EtOAc 2:1); m.p. 237–239 °C ($CHCl_3$); $[\alpha]_D^{22}$ = –39.3 (*c* = 0.63, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 5.31 (dd, *J* = 15.3, 8.5

Hz, 1H), 5.28 – 5.24 (m, 1H), 5.24 – 5.19 (m, 1H), 4.91 (d, *J* = 2.5 Hz, 1H), 4.57 (d, *J* = 11.1 Hz, 1H), 3.78 (s, 1H), 2.72 – 2.64 (m, 2H), 2.64 – 2.56 (m, 2H), 2.36 – 2.29 (m, 1H), 2.12 (s, 3H), 2.06 – 2.00 (m, 3H), 1.90 – 1.84 (m, 2H), 1.79 – 1.74 (m, 1H), 1.70 – 1.63 (m, 3H), 1.46 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.40 (dt, *J* = 14.0, 3.5 Hz, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.03 (s, 3H), 0.95 (s, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ [ppm] = 202.3, 190.2, 173.3, 170.1, 135.2, 132.2, 130.1, 83.3, 80.0, 75.4, 51.1, 50.9, 45.5, 43.7, 43.4, 40.1, 38.6, 37.6, 33.2, 29.6, 27.7, 25.8, 24.5, 22.8, 21.9, 21.3, 20.2, 19.9, 19.7, 17.6; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2952 (m), 2922 (s), 2852 (m), 1740 (w), 1460 (w), 1377 (w), 1215 (w), 760 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{43}O_6INa^+$ [M+Na]$^+$: 649.1997, found: 649.2021.

Hydroxy lactone (20): Ag_2O (4.4 mg, 19 µmol, 3.0 eq.) was added to a solution of 4α-iodo diol **19** (4.0 mg, 6.4 µmol, 1.0 eq.) in THF (2.0 mL) and the reaction mixture was heated to 60 °C for 16 h. The mixture was cooled to 25 °C, filtered through Celite®, and it was rinsed with EtOAc (10 mL). The solvent was removed under reduced pressure and column chromatography (silica gel, *n*hexane/EtOAc 3:1) gave hydroxy lactone **20** (2.7 mg, 5.4 µmol, 85%) as a crystalline solid (crystallized from *n*hexane/EtOAc). R_f = 0.28 (*n*hexane/EtOAc 2:1); m.p. 152–154 °C; $[\alpha]_D^{22}$ = +31.0 (*c* = 0.26, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ [ppm] = 5.93 (s, 1H), 5.40 (dd, *J* = 14.8, 8.9 Hz, 1H), 5.30 (dd, *J* = 15.3, 8.2 Hz, 1H), 5.19 (td, *J* = 5.1, 3.4 Hz, 1H), 2.80 (ddd, *J* = 12.4, 10.5, 8.5 Hz, 1H), 2.61 (ddd, *J* = 12.4, 7.6, 2.8 Hz, 1H), 2.55 (ddt, *J* = 9.6, 7.0, 3.7 Hz, 1H), 2.29 (d, *J* = 3.5 Hz, 1H), 2.17 (ddd, *J* = 13.4, 12.1, 6.8 Hz, 1H), 2.13 – 2.04 (m, 3H), 2.04 – 1.98 (m, 6H), 1.93 – 1.86 (m, 2H), 1.85 – 1.79 (m, 1H), 1.61 (dt, *J* = 13.1, 7.6 Hz, 1H), 1.50 – 1.45 (m, 2H), 1.27 (s, 3H), 1.23 (s, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$); δ [ppm] = 201.4, 174.5, 170.5, 170.0, 135.8, 132.7, 131.0, 95.2, 77.8, 77.1, 60.8, 52.8, 51.7, 48.7, 43.5, 42.8, 39.8, 38.7, 33.2, 33.0, 32.8, 28.3, 26.4, 22.7, 21.4, 21.3, 20.3, 19.9, 17.6, 16.6; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2922 (s), 2853 (m), 1740 (w), 1460 (w), 1377 (w), 1246 (w), 1082 (w), 966 (w), 721 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{42}O_6Na^+$ [M+Na]$^+$: 521.2874, found: 521.2881.

(22*E*)-3β-Hydroxy-13(14→8)*abeo*-ergosta-4,22-diene-6,14-dione (S3)

To a solution of acetate **15** (33 mg, 70 µmol, 1.0 eq.) in MeOH (1.5 mL) at 25 °C was added K_2CO_3 (49 mg, 0.35 mmol, 5.0 eq.) and the reaction mixture was stirred at this temperature for 1 h. The mixture was diluted with H_2O (3 mL) and EtOAc (5 mL), and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (sat., 15 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 1:1) gave 3β-allylic alcohol **S3** (16.6 mg, 38.9 µmol, 56%) as a colorless oil. R_f = 0.18 (*n*hexane/EtOAc 1:1); $[\alpha]_D^{22}$ = +7.0 (*c* = 0.90, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.50 (dd, *J* = 2.9, 1.2 Hz, 1H), 5.30 – 5.20 (m, 2H), 4.35 (td, *J* = 7.0, 5.6, 2.6 Hz, 1H), 2.73 – 2.67 (m, 1H), 2.62 (d, *J* = 16.3 Hz, 1H), 2.54 – 2.46 (m, 2H), 2.40 – 2.29 (m, 2H), 1.98 – 1.91 (m, 1H), 1.89 – 1.80 (m, 4H), 1.77 – 1.70 (m, 3H), 1.67 – 1.59 (m, 2H), 1.58 – 1.52 (m, 1H), 1.46 (dq, *J* = 13.4, 6.7 Hz, 1H), 1.28 (dt, *J* = 12.9, 2.8 Hz, 1H), 1.17 (s, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.97 (s, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ [ppm] = 215.2, 199.9, 141.9, 135.0, 134.7, 132.8, 66.9, 62.1, 53.3, 50.6, 49.1, 43.4, 42.1, 40.0, 38.1, 38.0, 37.6, 35.4, 33.2, 28.4, 25.3, 24.5, 23.5, 22.5, 20.2, 19.8, 17.8, 17.3; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 3431 (br w), 2955 (s), 2925 (s), 2870 (m), 1737 (m), 1791 (s), 1625 (w), 458 (m), 1368 (m), 1267 (w), 1231 (m), 1079 (w), 974 (w), 756 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_3Na^+$ [M+Na]$^+$: 449.3026, found: 449.3035.

Dankasterone A (3)[10a, 13]

To a solution of 3β-allylic alcohol **S3** (16.6 mg, 38.9 µmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) at 25 °C was added Dess–Martin periodinane (33.0 mg, 77.8 µmol, 2.0 eq.) and the reaction mixture was stirred at this temperature for 1 h. The mixture was diluted with CH_2Cl_2 (2 mL), $Na_2S_2O_3$ (sat. aq., 5 mL) was added and the mixture was vigorously stirred at 25 °C for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 20 mL) and brine (sat., 20 mL), and it was dried over $MgSO_4$. The solvent was removed under reduced pressure and column chromatography (silica gel, *n*hexane/EtOAc 1:1) gave dankasterone A (**3**) (16.5 mg, 38.9 µmol, quant.) as a colorless solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ [ppm] = (700 MHz, $CDCl_3$); δ [ppm] = 6.36 (d, *J* = 0.8 Hz, 1H), 5.31 – 5.22 (m, 2H), 2.84 – 2.79 (m, 1H), 2.65 (dd, *J* = 16.8, 1.6 Hz, 1H), 2.56 – 2.43 (m, 5H), 2.41 (td, *J* = 7.4, 2.6 Hz, 1H), 2.10 – 1.98 (m, 3H), 1.92 – 1.82 (m, 3H), 1.77 (dt, *J* = 13.0, 7.4 Hz, 1H), 1.74 – 1.66 (m, 2H), 1.50 – 1.46 (m, 2H), 1.26 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.98 (s, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H). All characterization data were consistent with those reported in the literature.[13]

(22*E*)-3α-Hydroxy-13(14g8)*abeo*-ergosta-4,22-diene-6,14-dione (21)

L-Selectride (1 M in THF, 46µL, 46 µmol, 2.0 eq.) was added dropwise to a solution of dankasterone A (**3**) (9.8 mg, 23 µmol, 1.0 eq.) in THF (1 mL) at –78 °C and the reaction mixture was stirred at this temperature for 1 h. After addition of MeOH (0.5 mL), the mixture was warmed to 0 °C before NaOH (3 m in H_2O, 2 mL) and H_2O_2 (35% *w*/*w*, 2 mL) were carefully added. The mixture was vigorously stirred at 25 °C for 1 h and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (sat., 25 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 1:1) gave 3α-allylic alcohol **21** (8.6 mg, 20 µmol, 87%) as a colorless oil. R_f = 0.23 (*n*hexane/EtOAc 1:1); $[\alpha]_D^{21}$ = +37.0 (*c* = 0.55, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ [ppm] = 6.43 (d, *J* = 2.9 Hz, 1H), 5.26 – 5.24 (m, 2H), 4.20 – 4.16 (m, 1H), 2.79 (t, *J* = 8.7 Hz, 1H), 2.53 – 2.50 (m, 2H), 2.48 (ddd, *J* = 15.8, 6.5, 2.3 Hz, 1H), 2.44 – 2.38 (m, 2H), 1.96 – 1.89 (m, 2H), 1.87 – 1.83 (m, 2H), 1.79 – 1.75 (m, 2H), 1.71 – 1.67 (m, 2H), 1.65 – 1.61 (m, 1H), 1.57 (dtd, *J* = 13.1, 6.9, 3.5 Hz, 1H), 1.48 – 1.45 (m, 1H), 1.43 – 1.41 (m, 1H), 1.39 (dt, *J* = 13.0, 2.7 Hz, 1H), 1.06 (t, *J* = 3.5 Hz, 6H), 0.95 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$); δ [ppm] = 215.1, 201.3, 143.1, 135.0, 134.7, 132.7, 66.0, 61.9, 54.2, 49.7, 48.3, 43.4, 41.9, 39.5, 38.2, 37.5, 35.3, 35.0, 33.2, 28.4, 25.7, 24.7, 23.6, 23.1, 20.2, 19.8, 17.8, 17.2; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 3458 (br w), 2954 (s), 2925 (s), 2855 (m),1736 (s), 1457 (w), 1366 (m), 1217 (m), 977 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_3Na^+$ [M+Na]$^+$: 449.3026, found: 449.3041.

(22*E*)-3β-Iodo-5α(H)-ergosta-6,14,22-trien-6-one (27) and **(22*E*)-3α,5-Cyclo-5α-ergosta-6,14,22-trien-6-one (28)**[7]

To a solution of γ-hydroxy enone **22** (80.0 mg, 195 µmol, 1.0 eq.) in benzene (5 mL) were added iodine (74.1 mg, 292 µmol, 1.5 eq.) and

silver(I) oxide (90.4 mg, 390 µmol, 2.0 eq.) and the reaction mixture was heated to 85 °C for 2 h. The mixture was cooled to 25 °C, filtered through a plug of Celite® and rinsed with EtOAc (10 mL). The filtrate was washed sequentially with $Na_2S_2O_3$ (sat. aq., 15 mL) and brine (sat., 15 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 99:1 g 50:1) gave iodide **27** (37.6 mg, 72.2 µmol, 37%) as a mixture of diastereomers (5α/5β 2.3:1 determined by integration of 15H-signals δ [ppm] = 6.16 (minor), 6.10 (major) in ^{1}H-NMR) and Δ^{14}-enone **28** (14.6 mg, 37.2 µmol, 19%).

Iodide 27: light-yellow solid, R_f = 0.29 (*n*hexane/EtOAc 12:1); m.p. 137–139 °C, $[\alpha]_D^{21}$ = –251.6 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.10 (d, *J* = 2.8 Hz, 1H), 5.95 – 5.89 (m, 1H), 5.28 (dd, *J* = 15.3, 7.8 Hz, 1H), 5.17 (dd, *J* = 15.1, 8.4 Hz, 1H), 4.14 – 4.01 (m, 1H), 2.73 – 2.65 (m, 1H), 2.36 (dd, *J* = 12.0, 3.4 Hz, 1H), 2.32 – 2.18 (m, 5H), 2.13 – 2.04 (m, 3H), 1.90 – 1.84 (m, 1H), 1.76 – 1.68 (m, 3H), 1.66 – 1.58 (m, 1H), 1.51 – 1.43 (m, 2H), 1.36 (td, *J* = 13.5, 3.9 Hz, 1H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.93 – 0.91 (m, 6H), 0.90 (s, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$); δ [ppm] = 198.1, 154.7, 149.4, 134.9, 132.9, 129.4, 121.5, 58.6, 57.0, 50.9, 46.5, 42.9, 40.6, 39.0, 39.0, 38.8, 36.7, 35.7, 34.8, 33.2, 27.3, 21.1, 20.6, 20.1, 19.8, 17.7, 17.4, 13.5; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (s), 2926 (s), 2870 (m), 1666 (s), 1615 (w), 1593 (w), 1566 (w), 1457 (m), 1368 (w), 1330 (w), 1265 (m), 1121 (w), 971 (w)823 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{28}H_{41}OINa^+$ [M+Na]$^+$: 543.2094, found: 543.2118.

Δ^{14}-enone 28[7]: R_f = 0.18 (*n*hexane/EtOAc 12:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.24 (d, *J* = 2.7 Hz, 1H), 6.04 (dd, *J* = 3.7, 2.2 Hz, 1H), 5.29 (dd, *J* = 15.1, 7.8 Hz, 1H), 5.19 (dd, *J* = 15.4, 8.5 Hz, 1H), 2.36 (ddd, *J* = 12.4, 5.9, 2.7 Hz, 1H), 2.33 – 2.23 (m, 2H), 2.10 (dt, *J* = 13.0, 3.4 Hz, 1H), 2.07 – 2.01 (m, 1H), 1.97 (dtd, *J* = 12.3, 8.0, 4.0 Hz, 1H), 1.91 – 1.84 (m, 1H), 1.84 – 1.79 (m, 1H), 1.77 – 1.68 (m, 6H), 1.52 – 1.46 (m, 1H), 1.44 (dd, *J* = 13.4, 3.5 Hz, 1H), 1.16 – 1.11 (m, 1H), 1.09 (s, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.96 (s, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.78 (t, *J* = 4.7 Hz, 1H).

(22*E*)-3α,5-Cyclo-5α-ergosta-8(14),22-dien-6-one (29)

Through a solution of γ-hydroxy enone **22** (75.5 mg, 184 µmol, 1.0 eq.) in toluene (5 mL) in a pressure tube was bubbled argon *via* cannula for 10 min. $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}d(CF_3)bpy)]PF_6$ (6.3 mg, 5.5 µmol, 0.03 eq.) and $(n Bu_4)NCOOCF_3$ (26 mg, 74 µmol, 0.4 eq.) were added and the tube was sealed. The reaction mixture was irradiated with two Kessil lamps (Kessil H150B LED Grow Light) and stirred at 35 °C, which was the internal temperature of the reaction set up, for 3 d. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, *n*hexane/EtOAc 50:1 g 9:1) to give $\Delta^{8(14)}$-ketone **29** (12.7 mg, 32.3 µmol, 17%) as a colorless oil and recovered starting material **22** (42.5 mg, 103 µmol, 56%) as a light-yellow solid. R_f = 0.32 (*n*hexane/EtOAc 19:1); $[\alpha]_D^{22}$ = –31.4(*c* = 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 5.24 – 5.19 (m, 2H), 3.03 (dt, *J* = 21.8, 1.4 Hz, 1H), 2.96 (dd, *J* = 21.7, 1.6 Hz, 1H), 2.30 – 2.23 (m, 1H), 2.23 – 2.18 (m, 1H), 2.18 – 2.13 (m, 1H), 2.13 – 2.08 (m, 2H), 2.08 – 2.03 (m, 1H), 2.01 (dt, *J* = 12.5, 3.4 Hz, 1H), 1.89 – 1.80 (m, 4H), 1.76 – 1.71 (m, 2H), 1.67 – 1.63 (m, 1H), 1.62 – 1.56 (m, 2H), 1.49 – 1.44 (m, 1H), 1.44 – 1.38 (m, 1H), 1.30 (td, *J* = 13.4, 3.5 Hz, 1H), 1.20 – 1.14 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.94 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ [ppm] = 210.5, 145.8, 135.5, 132.3, 121.6, 56.9, 47.1, 44.4, 43.3, 43.0, 42.7, 42.3, 39.5, 37.3, 36.8, 33.2, 32.2, 28.1, 25.9, 25.1, 21.3, 21.2, 20.1, 19.8, 18.9, 18.7, 17.8, 16.3; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2922 (s), 2852 (m), 1460 (w), 1377 (w), 1246 (w), 1082 (w), 970 (w), 760 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}ONa^+$ [M+Na]$^+$: 417.3128, found: 417.3143.

(22*E*)-14α-Hydroperoxy-3α,5-cyclo-5α-ergosta-7,22-dien-6-one (32) and **(22*E*)-14β-Hydroperoxy-3α,5-cyclo-5α-ergosta-7,22-dien-6-one (33)**

To a solution of enone **30** (100 mg, 253 µmol, 1.0 eq.) in CH_2Cl_2 (1 mL) were added triethylamine (71 µL, 0.51 µmol, 2.0 eq.) and trimethylsilyl trifluoromethanesulfonate (68 µL, 0.38 mmol, 1.5 eq.) at 0 °C and the reaction mixture was stirred at this temperature for 1 h. It was diluted with CH_2Cl_2 (5 mL) and $NaHCO_3$ (sat. aq., 15 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were washed with brine (sat., 30 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification.

Crude silyl enol ether **31** (253 µmol, 1.0 eq.) was dissolved in CH_2Cl_2 (3.5 mL), *meso*-tetraphenylporphyrin (0.3 mg, 0.5 µmol, 0.2 mol%) was added, and the reaction mixture was cooled to –78 °C. Oxygen was bubbled through the solution and the mixture was irradiated with white light (300 W) for 15 min. The solution was allowed to warm to 25 °C, the solvent was removed under reduced pressure, and the residue was adsorbed on silica gel. Column chromatography (silica gel, *n*hexane/EtOAc 9:1) gave 14β-hydroperoxide **33** (13.3 mg, 31.2 µmol, 12%) and 14α-hydroperoxide **32** (60.4 mg, 142 µmol, 56%).

14β-Hydroperoxide 33: light-yellow oil, R_f = 0.26 (*n*hexane/EtOAc 5:1); $[\alpha]_D^{21}$ = +17.9 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.71 (s, 1H), 6.38 (d, *J* = 2.7 Hz, 1H), 5.32 – 5.21 (m, 2H), 2.46 (ddd, *J* = 10.1, 5.5, 2.8 Hz, 1H), 2.31 – 2.24 (m, 1H), 2.03 – 1.95 (m, 2H), 1.90 – 1.84 (m, 2H), 1.79 – 1.69 (m, 4H), 1.67 – 1.62 (m, 3H), 1.57 – 1.52 (m, 3H), 1.50 – 1.44 (m, 2H), 1.14 (s, 3H), 1.11 – 1.08 (m, 1H), 1.06 (s, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.83 – 0.81 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$); δ [ppm] = 198.3, 160.8, 134.4, 133.3, 125.9, 95.5, 55.0, 49.1, 47.5, 44.1, 43.1, 42.0, 39.8, 39.2, 35.1, 34.1, 33.3, 33.0, 26.6, 26.5, 22.1, 20.9, 20.1, 19.8, 18.8, 18.3, 17.8, 14.4; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 3348 (br w), 2957 (s), 2925 (s), 2870 (m), 1737 (w), 1646 (m), 1457 (w), 1379 (m), 974 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_3Na^+$ [M+Na]$^+$: 449.3026, found: 449.3006.

14α-Hydroperoxide 32: colorless solid, R_f = 0.22 (*n*hexane/EtOAc 5:1); m.p. 184–186 °C ($CHCl_3$); $[\alpha]_D^{21}$ = +87.3 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.90 (s, 1H), 5.93 (d, *J* = 2.6 Hz, 1H), 5.26 (dd, *J* = 15.3, 7.6 Hz, 1H), 5.16 (dd, *J* = 15.2, 8.4 Hz, 1H), 2.65 (ddd, *J* = 10.5, 7.6, 2.6 Hz, 1H), 2.22 – 2.15 (m, 1H), 2.12 – 1.99 (m, 3H), 1.99 – 1.89 (m, 3H), 1.89 – 1.83 (m, 2H), 1.79 (dt, *J* = 8.8, 4.5 Hz, 1H), 1.72 – 1.68 (m, 3H), 1.66 – 1.59 (m, 2H), 1.51 – 1.45 (m, 1H), 1.44 – 1.38 (m, 1H), 1.10 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.85 – 0.81 (m, 9H), 0.80 – 0.77 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$); δ [ppm] = 198.0, 159.2, 135.4, 132.7, 127.3, 97.1, 50.7, 47.8, 45.5, 44.1, 42.9, 40.0, 38.1, 35.6, 33.7, 33.2, 30.1, 26.9, 26.9, 24.9, 22.0, 21.4, 20.1, 19.8, 19.4, 17.6, 17.2, 13.8; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2952 (w), 2923 (m), 2852 (w), 1736 (s),

1634 (w), 1456 (w), 1371 (m), 1229 (m), 1217 (m), 887 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_3Na^+$ [M+Na]$^+$: 449.3026, found: 449.3012.

(22*E*)-14β-Hydroxy-3α,5-cyclo-5α-ergosta-7,22-dien-6-one (34):

Triphenylphosphine (9.2 mg, 35 µmol, 1.0 eq.) was added to a solution of 14β-hydroperoxide **33** (15 mg, 35 µmol, 1.0 eq.) in CH_2Cl_2 (1 mL) at 25 °C and the resulting mixture was stirred at this temperature for 1 h. The solvent was removed under reduced pressure and the colorless residue was adsorbed on silica gel. Column chromatography (silica gel, *n*hexane/EtOAc 9:1 g 5:1) gave 14β-γ-hydroxy enone **34** (10.3 mg, 25 µmol, 71%) as a colorless solid. R_f = 0.18 (*n*hexane/EtOAc 5:1); m.p. 136–138 °C ($CHCl_3$); $[\alpha]_D^{22}$ = +13.1 (*c* = 0.72, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.50 (d, *J* = 2.5 Hz, 1H), 5.40 (dd, *J* = 15.4, 8.2 Hz, 1H), 5.35 (dd, *J* = 15.4, 7.7 Hz, 1H), 2.42 (ddd, *J* = 9.9, 7.2, 2.6 Hz, 1H), 2.39 – 2.34 (m, 1H), 2.05 – 1.95 (m, 2H), 1.91 (q, *J* = 6.8 Hz, 1H), 1.85 – 1.79 (m, 2H), 1.73 – 1.68 (m, 6H), 1.66 – 1.63 (m, 1H), 1.54 – 1.46 (m, 4H), 1.15 – 1.11 (m, 1H), 1.06 (s, 3H), 1.05 (s, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.77 – 0.74 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$); δ [ppm] = 197.8, 165.1, 135.4, 133.2, 124.6, 84.7, 55.3, 49.4, 46.2, 43.5, 43.5, 41.1, 40.6, 40.5, 38.8, 35.0, 33.6, 33.2, 26.7, 25.7, 22.8, 22.1, 20.2, 19.9, 19.3, 17.9, 16.5, 13.7; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2921 (s), 2852 (m), 1740 (w), 1459 (w), 1377 (w), 1168 (w), 1082 (w), 970 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_2Na^+$ [M+Na]$^+$: 433.3077, found: 433.3079.

(22*E*)-7α-Iodo-8β,14β-epoxy-3α,5-cyclo-5α-ergosta-22-en-6-one (35)

Through a solution of 14β-γ-hydroxy enone **34** (9.9 mg, 24 µmol, 1.0 eq.) in benzene (1 mL) was bubbled argon *via* cannula for 10 min. $CaCO_3$ (4.8 mg, 48 µmol, 2.0 eq.), iodine (12 mg, 48 µmol, 2.0 eq.) and $Pb(OAc)_4$ (21 mg, 48 µmol, 2.0 eq.) were added and the reaction mixture was heated to 85 °C for 2 h. The mixture was cooled to 25 °C, filtered through a plug of Celite®, and rinsed with EtOAc (10 mL). The filtrate was washed sequentially with $Na_2S_2O_3$ (sat. aq., 15 mL) and brine (sat., 15 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAC 19:1) gave iodo-epoxide **35** (5.5 mg, 10 µmol, 42%) as a colorless solid. R_f = 0.42 (*n*hexane/EtOAc 9:1); m.p. 113–115 °C ($CHCl_3$); $[\alpha]_D^{19}$ = –31.8 (*c* = 0.82, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 5.26 (dd, *J* = 15.2, 7.5 Hz, 1H), 5.20 (dd, *J* = 15.2, 8.4 Hz, 1H), 3.99 (s, 1H), 2.77 – 2.71 (m, 1H), 2.20 – 2.12 (m, 2H), 2.04 – 1.98 (m, 1H), 1.98 – 1.95 (m, 1H), 1.91 – 1.85 (m, 1H), 1.85 – 1.79 (m, 2H), 1.79 – 1.73 (m, 3H), 1.62 – 1.56 (m, 1H), 1.53 – 1.45 (m, 2H), 1.45 – 1.39 (m, 3H), 1.22 (td, *J* = 12.8, 4.2 Hz, 1H), 1.08 – 1.00 (m, 7H), 0.95 – 0.92 (m, 6H), 0.88 (t, *J* = 5.2 Hz, 1H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ [ppm] = 204.3, 134.8, 133.1, 74.2, 67.5, 57.1, 47.7, 43.4, 43.0, 41.7, 40.7, 39.3, 37.7, 36.6, 34.3, 33.2, 30.5, 27.1, 26.0, 26.0, 21.5, 20.3, 20.1, 19.8, 18.0, 17.7, 15.0, 11.5; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2956 (s), 2925 (s), 2871 (m), 2853 (m), 1692 (m), 1458 (w), 1370 (w), 1291 (w), 1143 (w), 974 (w), 878 (w), 756 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{28}H_{41}O_2INa^+$ [M+Na]$^+$:559.2043, found: 559.2042.

(22*E*)-14-Triethylsilyloxy-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α-ergosta-7,9(11),14,22-tetraen-6-one (36)

To a solution of diene dione **25** (20 mg, 50 µmol, 1.0 eq.) in CH_2Cl_2 (1.25 mL) were added 2,6-lutidine (58 µL, 0.50 mmol, 10 eq.) and triethylsilyl trifluoromethanesulfonate (56 µL, 0.25 mmol, 5.0 eq.) at 0 °C and the reaction mixture was stirred at this temperature for 1 h. The mixture was diluted with CH_2Cl_2 (5 mL), and $NaHCO_3$ (sat. aq., 10 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were washed with brine (sat., 30 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and column chromatography (silica gel, *n*hexane/EtOAc 14:1) gave silyl enol ether **36** (22.4 mg, 43 µmol, 86%) as a light-yellow solid. R_f = 0.53 (*n*hexane/EtOAc 5:1); m.p. 85–87 °C ($CHCl_3$); $[\alpha]_D^{20}$ = –83.1 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.15 (t, *J* = 2.9 Hz, 1H), 5.39 (dd, *J* = 15.3, 8.2 Hz, 1H), 5.31 (dd, *J* = 15.3, 7.7 Hz, 1H), 5.07 (t, *J* = 6.8 Hz, 1H), 2.66 (dd, *J* = 18.6, 2.7 Hz, 1H), 2.53 – 2.46 (m, 1H), 2.38 (dd, *J* = 18.6, 3.2 Hz, 1H), 2.07 – 2.03 (m, 2H), 1.95 – 1.87 (m, 2H), 1.86 – 1.76 (m, 1H), 1.72 (dd, *J* = 8.3, 4.6 Hz, 1H), 1.66 – 1.62 (m, 1H), 1.55 – 1.47 (m, 1H), 1.46 – 1.38 (m, 1H), 1.22 – 1.19 (m, 6H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.99 – 0.94 (m, 12H), 0.93 – 0.88 (m, 2H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.78 (t, *J* = 4.8 Hz, 1H), 0.72 – 0.67 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$); δ [ppm] = 194.1, 169.9, 146.9, 146.7, 134.9, 134.2, 133.7, 126.9, 108.5, 56.6, 51.6, 50.9, 43.3, 42.9, 41.7, 38.8, 36.1, 35.8, 33.3, 27.1, 26.3, 26.2, 22.6, 21.2, 20.1, 19.9, 17.5, 13.0, 7.0, 5.3; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (m), 2924 (s), 2853 (m), 1738 (w), 1658 (w), 1459 (w), 1378 (w), 1208 (w), 1173 (w), 1005 (w), 969 (w), 823 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{34}H_{52}O_2SiNa^+$ [M+Na]$^+$: 543.3629, found: 543.3627.

(22*E*)-9α-Hydroxy-14-triethylsilyloxy-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α-ergosta-7,14,22-trien-6-one (37)

L-Selectride (317 µL, 317 µmol, 3.0 eq.) was added dropwise to a solution of silyl enol ether **36** (55.0 mg, 106 µmol, 1.0 eq.) in THF (1.5 mL) at –78 °C and the reaction mixture was stirred at this temperature for 1 h. Methanol (0.2 mL) was added and the mixture was warmed to 0 °C before NaOH (3 M in H_2O, 2 mL) and H_2O_2 (35% *w*/*w*, 2 mL) were carefully added. The mixture was vigorously stirred at 25 °C for 1 h and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 7:1 g 5:1) gave 9-hydroxy silyl enol ether **37** (30 mg, 56 µmol, 53%) as a light-yellow oil. R_f = 0.28 (*n*hexane/EtOAc 5:1); $[\alpha]_D^{19}$ = –49.1 (*c* = 0.67, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ [ppm] = 5.40 (dd, *J* = 15.4, 8.7 Hz, 1H), 5.32 – 5.26 (m, 2H), 2.65 – 2.59 (m, 1H), 2.30 (dt, *J* = 17.8, 5.4 Hz, 1H), 2.20 (td, *J* = 12.5, 6.5 Hz, 1H), 2.13 (ddd, *J* = 17.8, 9.7, 6.0 Hz, 1H), 2.09 – 2.03 (m, 2H), 2.02 – 1.96 (m, 1H), 1.93 – 1.85 (m, 2H), 1.82 – 1.78 (m, 2H), 1.75 (dd, *J* = 12.0, 6.5 Hz, 1H), 1.68 (dd, *J* = 12.1, 8.8 Hz, 1H), 1.60 (ddd, *J* = 8.2, 4.2, 1.3 Hz, 1H), 1.50 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.24 – 1.20 (m, 1H), 1.15 – 1.12 (m, 3H), 1.07 (s, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.95 – 0.93 (m, 9H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.78 (dd, *J* = 5.2, 4.1 Hz, 1H), 0.69 – 0.58 (m, 6H); ^{13}C NMR (176 MHz, $CDCl_3$); δ [ppm] = 196.1, 169.2, 143.7, 134.7, 132.4, 131.0, 113.6, 85.2, 54.2, 50.4, 46.8, 43.5, 42.4, 38.4, 37.9, 36.5, 34.0, 33.3, 31.3, 27.7, 25.5, 22.6, 22.6, 20.2, 19.9, 19.3, 17.6, 16.2, 7.0, 5.3; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 3455 (br w), 2954 (m), 2924 (s), 2872 (m), 2854 (m), 1737 (s), 1667 (w), 1456 (w), 1372 (s), 1217 (s), 1011 (w), 887 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{34}H_{54}O_3Na^+$ [M+Na]$^+$: 561.3734, found: 561.3727.

(22*E*)-6α,9α-Dihydroxy-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α-ergosta-7,22-dien-14-one (38)

Lithium aluminum hydride (1 M in THF, 70 µL, 70 µmol, 5.0 eq.) was added dropwise to a solution of 9-hydroxy silyl enol ether **37** (7.5 mg, 14 µmol, 1.0 eq.) in THF (1.0 mL) at 0 °C and the reaction mixture was stirred at this temperature for 1 h. EtOAc (5 mL) and Rochelle's salt (½ sat. aq., 5 mL) were carefully added and the resulting mixture was vigorously stirred at 25 °C for 5 h. The aqueous phase was extracted with EtOAc (3 × 10 mL), the combined organic phases were washed with brine (sat., 25 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and column chromatography (silica gel, *n*hexane/EtOAc 3:1) gave 6,9-diol **38** (2.4 mg, 5.6 µmol, 40%) as a colorless oil. R_f = 0.32 (*n*hexane/EtOAc 3:1); $[\alpha]_D^{20}$ = +37.3 (*c* = 0.21, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ [ppm] = 5.34 (dd, *J* = 15.3, 8.8 Hz, 1H), 5.28 (dd, *J* = 15.3, 8.0 Hz, 1H), 4.24 (s, 1H), 3.72 (s, 1H), 2.74 – 2.68 (m, 2H), 2.62 (ddd, *J* = 13.2, 11.5, 4.7 Hz, 1H), 2.17 – 2.11 (m, 1H), 2.02 – 1.95 (m, 2H), 1.91 – 1.79 (m, 3H), 1.79 – 1.74 (m, 3H), 1.59 (dd, *J* = 12.3, 8.9 Hz, 1H), 1.51 – 1.48 (m, 1H), 1.46 (dd, *J* = 13.1, 6.5 Hz, 1H), 1.28 – 1.26 (m, 1H), 1.20 – 1.14 (m, 1H), 1.08 (s, 3H), 1.07 – 1.04 (m, 6H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.85 – 0.81 (m, 7H), 0.54 (dd, *J* = 5.2, 3.7 Hz, 1H);^{13}C NMR (176 MHz, $CDCl_3$); δ [ppm] = 212.0, 163.6, 135.1, 132.2, 130.7, 85.6, 70.6, 52.8, 51.2, 45.7, 44.7, 43.5, 38.9, 37.7, 35.3, 33.3, 32.9, 29.9, 29.0, 28.0, 23.0, 22.9, 22.9, 22.3, 20.3, 19.9, 17.7, 11.5; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2921 (s), 2852 (m), 1740 (w), 1460 (m), 1377 (w), 1238 (w), 1168 (w), 974 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_3Na^+$ [M+Na]$^+$: 449.3026, found: 449.3042.

(22*E*)-14-Oxo-1(10→6),13(14→8),14(8→7)tri*abeo*-anthraergosta-5,7,9,22-tetraen-3α-yl acetate (39)

To a solution of 6,9-diol **38** (2.3 mg, 5.4 µmol, 1.0 eq.) in Et_2O (0.4 mL) at 0 °C were added acetic acid (0.2 mL) and BF_3•OEt_2 (0.2 mL), and the resulting mixture was stirred at this temperature for 1 h. The mixture was diluted with EtOAc (5 mL) and carefully poured into $NaHCO_3$ (sat. aq., 20 mL) at 0 °C. The aqueous phase was extracted with EtOAc (3 × 10 mL), the combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 25 mL) and brine (sat., 25 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and column chromatography (silica gel, *n*hexane/EtOAc 7:1) gave anthrasteroid **39** (2.1 mg, 4.7 µmol, 87%) as a colorless oil. R_f = 0.24 (*n*hexane/EtOAc 7:1); $[\alpha]_D^{22}$ = –46.4 (*c* = 0.20, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ [ppm] = 5.39 (dd, *J* = 15.3, 8.8 Hz, 1H), 5.29 (dd, *J* = 15.3, 8.5 Hz, 1H), 5.19 – 5.12 (m, 1H), 3.12 – 3.03 (m, 2H), 2.90 (dd, *J* = 15.9, 9.0 Hz, 1H), 2.83 – 2.78 (m, 1H), 2.76 (dd, *J* = 16.5, 9.5 Hz, 1H), 2.74 – 2.68 (m, 2H), 2.64 – 2.57 (m, 2H), 2.16 – 2.10 (m, 4H), 2.06 (s, 3H), 2.05 – 1.99 (m, 2H), 2.00 – 1.95 (m, 2H), 1.92 – 1.85 (m, 1H), 1.78 – 1.70 (m, 2H), 1.51 – 1.45 (m, 1H), 1.07 (s, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$); δ [ppm] = 209.8, 170.9, 146.1, 139.6, 135.3, 134.9, 134.9, 132.5, 131.9, 130.9, 70.3, 54.1, 53.9, 46.3, 43.5, 40.5, 38.3, 33.3, 33.1, 29.0, 28.0, 25.3, 24.4, 23.3, 21.6, 20.7, 20.2, 19.9, 17.7, 16.1; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (m), 2924 (s), 2853 (m), 1739 (w), 1684 (w), 1458 (w), 1377 (w), 1241 (w), 772 (w), 757 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{42}O_3Na^+$ [M+Na]$^+$: 473.3026, found: 473.3029.

14-Oxo-13(14→8),14(8→7)di*abeo*-ergosta-5,7-dien-3β-yl acetate (41) and **14-Oxo-13(14→8),14(8→7)di*abeo*-7β(H)-ergosta-5,8-dien-3β-yl acetate (42)**

To a solution of β-hydroxy ketone **40** (123 mg, 298 µmol, 1.0 eq.) in Et_2O (6 mL) at 0 °C were added acetic acid (3 mL) and BF_3•OEt_2 (3 mL). After stirring for 45 min at this temperature, the reaction mixture was diluted with EtOAc (10 mL) and carefully added to $NaHCO_3$ (sat. aq., 50 mL) at 0 °C. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed sequentially with $NaHCO_3$ (5% aq., 2 × 30 mL) and brine (sat., 30 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 19:1 g 12:1 g 9:1) gave $\Delta^{5,8}$-diene **42** (16.1 mg, 35.4 µmol, 12%) and $\Delta^{5,7}$-diene **41** (69.3 mg, 152 µmol, 51%).

$\Delta^{5,8}$-diene 42: colorless oil, R_f = 0.38 (*n*hexane/EtOAc 5:1); $[\alpha]_D^{23}$ = –71.9 (*c* = 1.02, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ [ppm] = 5.24 (dd, *J* = 3.0, 1.7 Hz, 1H), 4.61 (tt, *J* = 10.9, 5.1 Hz, 1H), 3.49 – 3.47 (m, 1H), 2.49 – 2.38 (m, 3H), 2.36 – 2.29 (m, 1H), 2.27 – 2.21 (m, 1H), 2.21 – 2.16 (m, 1H), 2.16 – 2.11 (m, 1H), 2.04 (s, 3H), 1.96 – 1.91 (m, 1H), 1.81 – 1.77 (m, 1H), 1.77 – 1.74 (m, 1H), 1.74 – 1.67 (m, 1H), 1.60 (dd, *J* = 10.7, 7.0 Hz, 1H), 1.56 – 1.52 (m, 1H), 1.51 – 1.44 (m, 2H), 1.44 – 1.38 (m, 2H), 1.34 (td, *J* = 13.7, 4.1 Hz, 1H), 1.29 – 1.25 (m, 2H), 1.23 (s, 3H), 1.22 – 1.15 (m, 2H), 0.95 (d, *J* = 6.9 Hz, 2H), 0.91 (s, 3H), 0.90 – 0.87 (m, 1H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$); δ [ppm] = 212.4, 170.5, 143.4, 141.4, 134.9, 119.0, 73.7, 53.7, 51.3, 50.5, 40.8, 39.2, 38.2, 37.3, 36.9, 35.8, 35.5, 33.7, 31.8, 31.0, 27.5, 27.5, 22.8, 22.6, 21.5, 21.4, 20.5, 19.6, 17.9, 15.6; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (w), 2937 (w), 2870 (w), 1739 (m), 1713 (m), 1464 (w), 1373 (w), 1236 (s), 1162 (w), 1046 (m); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{46}O_3Na^+$ [M+Na]$^+$: 477.3339, found: 477.3345.

$\Delta^{5,7}$-diene 41: colorless oil, R_f = 0.33 (*n*hexane/EtOAc 5:1); $[\alpha]_D^{24}$ = –30.9 (*c* = 1.01, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 5.95 (d, *J* = 2.5 Hz, 1H), 4.67 (tt, *J* = 11.4, 4.5 Hz, 1H), 2.79 – 2.72 (m, 1H), 2.58 (ddd, *J* = 14.6, 4.9, 2.4 Hz, 1H), 2.51 (ddd, *J* = 13.9, 9.1, 5.3 Hz, 1H), 2.46 (dd, *J* = 11.4, 7.8 Hz, 1H), 2.32 – 2.25 (m, 1H), 2.03 (s, 3H), 1.96 – 1.87 (m, 2H), 1.86 – 1.81 (m, 3H), 1.76 – 1.71 (m, 2H), 1.62 – 1.58 (m, 2H), 1.58 – 1.52 (m, 4H), 1.45 – 1.36 (m, 2H), 1.24 – 1.18 (m, 1H), 1.11 (s, 3H), 0.93 (d, *J* = 6.9 Hz, 4H), 0.91 – 0.87 (m, 1H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.79 – 0.75 (m, 9H); ^{13}C NMR (151 MHz, $CDCl_3$); δ [ppm] = 203.4, 170.6, 161.9, 141.6, 128.1, 120.3, 72.9, 55.8, 52.6, 51.3, 44.7, 40.3, 39.0, 38.0, 36.3, 36.3, 35.7, 33.5, 31.7, 29.8, 28.0, 22.1, 21.5, 21.5, 21.1, 20.7, 20.5, 17.8, 15.6, 15.2; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2953 (m), 2922 (s), 2853 (m), 1739 (w), 1463 (w), 1377 (w), 1241 (w), 759 (m); HRMS (ESI-TOF); *m/z* calcd. for $C_{30}H_{46}O_3Na^+$ [M+Na]$^+$: 477.3339, found: 477.3342.

3β,14α-Dihydroxy-13(14→8),14(8→7)di*abeo*-7β(H)-ergosta-5,8-dien-3β-yl acetate (44)[13]

To a solution of $\Delta^{5,8}$-diene **42** (75.0 mg, 165 µmol, 1.0 eq.) in THF (4 mL) at –78 °C was added DIBAl-H (1 M in hexanes, 1.65 mL, 1.65 mmol, 10.0 eq.) and the resulting solution was stirred at this temperature for 1.5 h. EtOAc (2.5 mL) and Rochelle's salt (½ sat. aq., 5 mL) were added carefully and the mixture was vigorously stirred for 30 minutes while warming to 25 °C. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (sat., 15 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 1:1) gave 3,14-diol **44** (51.8 mg, 125 µmol, 76%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 5.40 – 5.28 (m, 1H), 3.79 (d, *J* = 6.2 Hz, 1H), 3.61 – 3.52 (m, 1H), 3.03 – 2.95 (m, 1H), 2.41 (dd, *J* = 12.2, 5.0 Hz, 1H), 2.37 – 2.29 (m, 2H), 2.24 (dd, *J* = 15.5, 8.4 Hz, 1H), 2.00 – 1.93 (m, 1H), 1.93 – 1.86 (m,

2H), 1.86 – 1.80 (m, 2H), 1.74 – 1.63 (m, 2H), 1.62 – 1.51 (m, 6H), 1.49 – 1.44 (m, 2H), 1.41 (dt, *J* = 12.7, 4.1 Hz, 1H), 1.36 (d, *J* = 10.5 Hz, 1H), 1.24 – 1.16 (m, 2H), 1.14 (s, 3H), 0.96 (s, 3H), 0.95 – 0.91 (m, 1H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.80 – 0.76 (m, 6H).

13(14→8),14(8→7)di*abeo*-5α(H),7β(H)-ergosta-8,22-diene-3,14-dione (47)

Lithium (3.0 mg, 0.43 mmol, 18 eq.) was added to liquid ammonia (3 mL) at –78 °C before it was warmed to room temperature and the residual ammonia was blown out with a stream of argon. To the resulting lithium bronze, THF (1.5 mL) was added and the resulting suspension was cooled to –78 °C. A solution of enone **45** (10 mg, 24 µmol, 1.0 eq) in THF (0.75 mL) was added dropwise and the reaction mixture was stirred at this temperature until complete conversion was observed (0.5–1 h). Triethyl amine (0.2 mL) and TMSCl (0.1 mL) were added at –60 °C and the reaction mixture was allowed to warm to –20 °C. Phosphate buffer (2 mL) in THF (2 mL) was added carefully and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (sat., 25 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Crude silyl enol ether was used in the next step without further purification.

Independent from the consecutive reaction conditions chosen, the only isolable product was ketone **47**, which was obtained as a colorless oil after column chromatography (silica gel, *n*hexane/EtOAc 4:1). R_f = 0.26 (*n*hexane/EtOAc 3:1); $[\alpha]_D^{22}$ = +66.3 (*c* = 0.39, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = (600 MHz, $CDCl_3$); δ [ppm] = 5.26 (dd, *J* = 15.4, 7.7 Hz, 1H), 5.20 (dd, *J* = 15.4, 7.7 Hz, 1H), 2.78 (dd, *J* = 14.1, 2.4 Hz, 1H), 2.63 (td, *J* = 13.7, 7.1 Hz, 1H), 2.48 (d, *J* = 9.2 Hz, 1H), 2.46 – 2.45 (m, 1H), 2.33 – 2.26 (m, 2H), 2.23 – 2.16 (m, 1H), 2.16 – 2.08 (m, 2H), 2.08 – 2.03 (m, 1H), 1.95 – 1.89 (m, 2H), 1.89 – 1.82 (m, 2H), 1.73 (d, *J* = 8.9 Hz, 1H), 1.50 – 1.40 (m, 4H), 1.38 (s, 3H), 1.31 – 1.22 (m, 2H), 1.02 (s, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.95 (dt, *J* = 11.6, 2.1 Hz, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ [ppm] = 212.2, 149.6, 136.3, 134.3, 133.1, 85.6, 60.8, 52.1, 51.9, 43.4, 42.7, 41.3, 40.6, 38.8, 38.7, 37.9, 37.7, 34.0, 33.3, 32.9, 26.5, 23.1, 22.9, 22.5, 20.2, 19.8, 19.5, 17.7; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (s), 2924 (s), 2853 (m), 1714 (w), 1457 (m), 1375 (w), 1074 (w), 1016 (w), 800 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_2Na^+$ [M+Na]$^+$: 433.3077, found: 433.3074.

Δ^{22}-24-*epi*-swinhoeisterol A (Δ^{22}-24-*epi*-2)

To a solution of diol **49** (7.4 mg, 17 µmol, 1.0 eq) in CH_2Cl_2 (1.5 mL) was added 2,6-di-*tert*-butyl-4-methylpyridine (18.5 mg, 90.0 µmol, 7.5 eq.) and it was cooled to –78 °C. Triflic anhydride (1 M in CH_2Cl_2, 42 µL, 42 µmol, 2.5 eq.) was added dropwise and the reaction was stirred at this temperature for 5 min before MeOH (20 µL, 0.50 mmol, 30 eq.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (50 µL, 0.33 µmol, 20 eq.) were added. The reaction mixture was allowed to warm to 25 °C over 1.5 h, and then stirred at this temperature for 1 h before HCl (1 M in H_2O, 5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were washed sequentially with HCl (1 M in H_2O, 20 mL), $NaHCO_3$ (sat. aq., 20 mL), and brine (sat., 20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 4:1) gave Δ^{22}-24-*epi*-swinhoeisterol A (Δ^{22}-24-*epi*-**2**) (4.5 mg, 10 µmol, 62%) as a colorless oil. R_f = 0.25 (*n*hexane/EtOAc 3:1); $[\alpha]_D^{22}$ = +84.4 (*c* = 0.25, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 5.35 (dd, *J* = 15.4, 7.8 Hz, 1H), 5.25 (dd, *J* = 15.3, 8.1 Hz, 1H), 5.09 (s, 1H), 4.69 (s, 1H), 4.05 (dd, *J* = 11.4, 5.8 Hz, 1H), 3.19 – 3.15 (m, 1H), 2.55 (dt, *J* = 16.6, 4.1 Hz, 1H), 2.49 (p, *J* = 7.3 Hz, 1H), 2.36 (dd, *J* = 9.3, 6.7 Hz, 1H), 2.34 – 2.26 (m, 2H), 2.20 (dtd, *J* = 15.7, 7.6, 2.9 Hz, 1H), 2.13 (d, *J* = 13.2 Hz, 1H), 2.07 – 2.01 (m, 2H), 1.87 (h, *J* = 6.7 Hz, 2H), 1.72 – 1.67 (m, 2H), 1.57 (td, *J* = 12.8, 6.3 Hz, 3H), 1.49 – 1.44 (m, 2H), 1.36 (td, *J* = 12.8, 4.3 Hz, 1H), 1.04 – 1.01 (m, 6H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.78 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ [ppm] = 213.3, 152.0, 146.8, 136.1, 134.7, 132.7, 102.9, 73.1, 55.6, 53.6, 45.4, 45.2, 44.3, 43.6, 38.8, 38.4, 37.6, 34.8, 33.3, 32.5, 27.8, 24.3, 23.0, 20.9, 20.2, 19.9, 19.7, 17.9, 17.8; IR (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (m), 2923 (s), 2853 (m), 1740 (w), 1459 (w), 1377 (w), 1010 (w), 970 (w); HRMS (ESI-TOF); *m/z* calcd. for $C_{29}H_{44}O_2Na^+$ [M+Na]$^+$: 447.3234, found: 447.3228.

Acknowledgements

Financial support for this work was provided by Deutsche Forschungsgemeinschaft (Grant No. HE 7133/7-1), the Boehringer Ingelheim Stiftung (exploration grant to P.H.), and Studienstiftung des Deutschen Volkes (Ph.D. scholarship to R.C.H.). We acknowledge the assistance of the Core Facility BioSupraMol supported by the DFG.

Keywords: biomimetic synthesis • natural product synthesis • radical reactions • rearrangement • steroids

[1] a) R. Ebel, *Mar. Drugs*. **2010**, *8*, 2340–2368; b) M. E. Rateb, R. Ebel, *Nat. Prod. Rep.* **2011**, *28*, 290–344; c) J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro, M. R. Prinsep, *Nat. Prod. Rep.* **2014**, *31*, 160–258.

[2] a) X. Wang, Z. Ma, J. Lu, X. Tan, C. Chen, *J. Am. Chem. Soc.* **2011**, *133*, 15350–15353; b) H. C. Lam, J. T. J. Spence, J. H. George, *Angew. Chem.* **2016**, *128*, 10524–10527; *Angew. Chem. Int. Ed.* **2016**, *55*, 10368–10371; c) Y. Wang, W. Ju, H. Tian, W. Tian, J. Gui, *J. Am. Chem. Soc.* **2018**, *140*, 9413–9416; d) Y. Wang, B. Chen, X. He, J. Gui, *J. Am. Chem. Soc.* **2020**, 10.1021/jacs.0c00363.

[3] a) M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 12692–12714; b) J. M. Smith, S. J. Harwood, P. S. Baran, *Acc. Chem. Res.* **2018**, *51*, 1807–1817; c) K. J. Romero, M. S. Galliher, D. A. Pratt, C. R. J. Stephenson, *Chem. Soc. Rev.* **2018**, *47*, 7851–7866.

[4] a) F. L. Duecker. F. Reuß, P. Heretsch, *Org. Biomol. Chem.* **2019**, *17*, 1624–1633; b) F. Noack, R. C. Heinze, P. Heretsch, *Synthesis*, **2019**, *51*, 2039–2057.

[5] R. A. Shenvi, C. A. Guerrero, J. Shi, C.-C. Li, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 7241–7243.

[6] Z. Lu, X. Zhang, Z. Guo, Y. Chen, T. Mu, A. Li, *J. Am. Chem. Soc.* **2018**, *140*, 9211–9218.

[7] R. C. Heinze, D. Lentz, P. Heretsch, *Angew. Chem.* **2016**, *128*, 11828–11831; *Angew. Chem. Int. Ed.* **2016**, *55*, 11656–11659.

[8] R. C. Heinze, P. Heretsch, *J. Am. Chem. Soc.* **2019**, *141*, 1222–1226.

[9] F. L. Duecker, R. C. Heinze, M. Mueller, S. Zhang, P. Heretsch, *Org. Lett.* **2020**, *22*, 1585–1588.

[10] a) T. Amagata, M. Doi, M. Tohgo, K. Minoura, A. Numata, *Chem. Commun.* **1999**, 1321–1322; b) T. Amagata, M. Tanaka, T. Yamada, M. Doi, K. Minoura, H. Ohishi, T. Yamori, A. Numata, *J. Nat. Prod.* **2007**, *70*, 1731–1740.

[11] a) J. Gong, P. Sun, N. Jiang, R. Riccio, G. Lauro, G. Bifulco, T.-J. Li, W. H. Gerwick, W. Zhang, *Org. Lett.* **2014**, *16*, 2224–2227; b) J. Li, H. Tang, T. Kurtán, A. Mándi, C.-L. Zhuang, L. Su, G.-L. Zheng, W. Zhang, *J. Nat. Prod.* **2018**, *81*, 1645–1650.

[12] W. Gao, C. Chai, Y. He, F. Li, X. Hao, F. Cao, L. Gu, J. Liu, Z. Hu, Y. Zhang, *Org. Lett.* **2019**, *21*, 8469–8472.

[13] F. L. Duecker, R. C. Heinze, P. Heretsch, *J. Am. Chem. Soc.* **2020**, *142*, 104–108.

[14] a) L. Canonica, B. Danieli, G. Lesma, G. Palmisano, *J. Chem. Soc., Chem. Commun.* **1985**, 1321–1322; b) L. Canonica, B. Danieli, G. Lesma, G. Palmisano, A. Mugnoli, *Helv. Chim. Acta* **1987**, *70*, 701–716.

[15] a) P. Dowd, S.-C. Choi, *J. Am. Chem. Soc.* **1987**, *109*, 6548–6549; b) A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood; c) A. L. J. Beckwith, D. M. O'Shea, S. W. Westwood, *J. Am. Chem. Soc.* **1988**, *110*, 2565–2575; d) P. Dowd, W. Zhang, *Chem. Rev.* **1993**, *93*, 2091–2115.

[16] a) A. Burawoy, *J. Chem. Soc.* **1937**, 409–411; b) D. H. R. Barton, C. H. Robinson, *J. Chem. Soc.* **1954**, 3045–3051; c) E. V. Yablonskaya, G. M. Segal, *Chem. Nat. Compd.* **1971**, *7*, 476–480; d) C. Brosa, R. Puig, X. Comas, C. Fernández, *Steroids* **1996**, *61*, 540–543.

[17] D. H. R. Barton, P. G. Feakins, J. P. Poyser, P. G. Sammes, *J. Chem. Soc. (C) Org.* **1970**, 1584–1591.

[18] a) C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, A. Wettstein, *Helv. Chim. Acta* **1962**, *45*, 1317–1343; b) V. A. Khripach, V. N. Zhabinskii, G. P. Fando, N. B. Khripach, B. Schneider, *ARKIVOC* **2008**, *ix*, 20–28.

[19] a) J. S. Guo, X. T. Liang, *Chin. Chem. Lett.* **1991**, *2*, 189–190; b) Guo, J. S.; X. T. Liang, *Youji Huaxue* **1991**, *11*, 425–430; c) F. Noack, B. Hartmayer, P. Heretsch, *Synthesis* **2018**, *50*, 809–820.

[20] a) R. A. Sneen, N. P Matheny, *J. Am. Chem. Soc.* **1964**, *86*, 3905–3906; b) M. Ottolenghi, K. Bar-Eli, H. Linschitz, *J. Am. Chem. Soc.* **1965**, *87*, 1807–1809; c) M. L. Mihailović, Ž. Čeković, J. Stanković, *J. Chem. Soc., Chem. Commun.* **1969**, 981–982.

[21] Y. Wang, W. Ju, H. Tian, S. Sun, X. Li, W. Tian, J. Gui, *J. Am. Chem. Soc.* **2019**, *141*, 5021–5033.

[22] K. Zhao, K. Yamashita, J. E. Carpenter, T. C. Sherwood, W. R. Ewing, P. T. W. Cheng, R. R. Knowles, *J. Am. Chem. Soc.* **2019**, *141*, 8752–8757.

[23] H. Hosoda, K. Yamashita, N. Chino, T. Nambara, *Chem. Pharm. Bull.* **1976**, *24*, 1860–1864.

[24] a) W. R. Nes, E. Mosettig, *J. Am. Chem. Soc.* **1954**, *76*, 3182–3186; b) N. Bosworth, A. Emke, J. M. Midgley, C. J. Moore, W. B. Whalley, G. Ferguson, W. C. Marsh, *J. Chem. Soc. Perkin Trans. 1* **1977**, 805–809; c) W. R. Nes, J. A. Steele, E. Mosettig, *J. Am. Chem. Soc.* **1958**, *80*, 5230–5232; d) T. Nakada, S. Yamamura, *Tetrahedron* **2000**, *56*, 2595–2602; e) H. Koshino, T. Yoshihara, S. Sakamura, T. Shimanuki, T. Sato, A. Tajimi, *Phytochemistry* **1989**, *28*, 771–772; f) S. Kosemura, S. Uotsu, S. Yamamura, *Tetrahedron Letters* **1995**, *36*, 7481–7482; g) X. Luo, F. Li, P. B. Shinde, J. Hong, C.-O. Lee, K. S. Im. J. H. Jung, *J. Nat. Prod.* **2006**, *69*, 1760–1768.

[25] a) G. Stork, J. d'Angelo, *J. Am. Chem. Soc.* **1974**, *96*, 7114–7116; b) J. E. McMurry, A. Andrus, G. M. Ksander, J. H. Musser, M. A. Johnson, *J. Am. Chem. Soc.* **1979**, *101*, 1330–1332.

[26] a) R. H. Mueller, J. G. Gillick, *J. Org. Chem.* **1978**, *43*, 4647–4648; b) M. J. Taschner, A. Shahripour, *J. Am. Chem. Soc.* **1985**, *107*, 5570–5572; c) The benefits of this approach are the possibility to easily accomplish stochiometric reductions as well as circumventing the sometimes tedious removal of ammonia from the reaction mixture.

[27] a) S. Kobayashi, I. Hachiya, H. Ishitani, M. Araki, *Synlett* **1993**, 472–474; b) A. B. Smith III, L. Kürti, A. H. Davulcu, Y. S. Cho, *Org. Process Res. Dev.* **2007**, *11*, 19–24; c) K. Fukaya, Y. Tanaka, A. Y. Sato, K. Kodama, H. Yamazaki, T. Ishimoto, Y. Nozaki, Y. M. Iwaki, Y. Yuki, K. Umei, T. Sugai, Y. Yamaguchi, A. Watanabe, T. Oishi, T. Sato, N. Chida, *Org. Lett.* **2015**, *17*, 2570–2573.

[28] K. Fujioka, N. Miyamoto, H. Toya, K. Okano, H. Tokuyama, *Synlett* **2016**, *27*, 621–625.

[29] N. Ozasa, M. Wadamoto, K. Ishihara, H. Yamamoto, *Synlett* **2003**, *3*, 2219–2221.

[30] a) B. M. Trost, H. Hiemstra, *Tetrahedron* **1986**, *42*, 3323–3332; b) M. R. Tremblay, A. Lescarbeau, M. J. Grogan, E. Tan, G. Lin, B. C. Austad, L.-C. Yu, M. L. Behnke, S. J. Nair, M. Hagel, K. White, J. Colney, J. D. Manna, T. M. Alvarez-Diez, J. Hoyt, C. N. Woodward, J. R. Sydor, M. Pink, J. MacDougall, M. J. Campbell, J. Cushing, J. Ferguson, M. S. Curtis, K. McGovern, M. A. Read, V. J. Palombella, J. Adams, A. C. Castro, *J. Med. Chem.* **2009**, *52*, 4400–4418.

[31] a) F. H. Bottom, F. J. McQuillin, *Tetrahedron Lett.* **1968**, *9*, 459–462; b) T. Kaneko, H. Wong, *Tetrahedron Lett.* **1987**, *28*, 517–520; c) D. V. Patel, R. J. Schmidt, E. M. Gordon, *J. Org. Chem.* **1992**, *57*, 7143–7151; d) H. Nakamura, K. Ishihara, H. Yamamoto, *J. Org. Chem.* **2002**, *67*, 5124–5137.

[32] M. J. Taschner, A. Shahripour, *J. Am. Chem. Soc.* **1985**, *107*, 5570–5572.

[33] a) J. Schreiber, H. Maag, N. Hashimoto, A. Eschenmoser, *Angew. Chem.* **1971**, *83*, 355–357; *Angew. Chem. Int. Ed.* **1971**, *10*, 330–331; b) S. Danishefsky, T. Kitahara, R. McKee, P. F. Schuda, *J. Am. Chem. Soc.* **1976**, 6715–6717.

[34] a) H. Nishiyama, T. Kitajima, M. Matsumoto, K. Itoh, *J. Chem. Soc.* **1984**, *49*, 2298–2300; b) G. Stork, M. Kahn, *J. Am. Chem. Soc.* **1985**, *107*, 500–501.

[35] K. Tamao, N. Ishida, M. Kumada, *J. Org. Chem.* **1983**, *48*, 2120–2122.

[36] a) M. Sawamura, Y. Kawaguchi, E. Nakamura, *Synlett* **1997**, *38*, 1543–1546; b) E. J. Corey, J. W. Suggs, *J. Org. Chem.* **1975**, *40*, 2554–2555.

[37] M. L. Landry, G. M. McKenna, N. Z. Burns, *J. Am. Chem. Soc.* **2019**, *141*, 2867–2871.

[38] D. Zhu, B. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 15098–15101.

[39] a) W. C. Dow, T. Gebreysus, S. Popov, R. M. K. Carlson, C. Djerassi, *Steroids* **1983**, *42*, 217–230; b) V. A. Khripach, V. N. Zhabinskii, O. V. Konstantinova, N. B. Khripach, A. P. Antonchick, B. Schneider, *Steroids* **2002**, *67*, 597–603; c) F. O. McCarthy, J. Chopra, A. Ford, S. A. Hogan, J. P. Kerry, N. M. O'Brien, E. Ryan, A. R. Maguire, *Org. Biomol. Chem.* **2005**, *3*, 3059–3065.

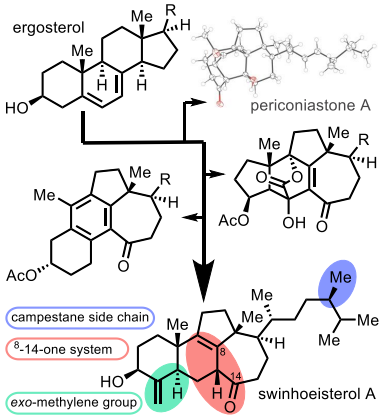
[40] C. Obradors, R. M. Martinez, R. A. Shenvi, *J. Am. Chem. Soc.* **2016**, *138*, 4962–4971.

10.1002/chem.202001405

WILEY-VCH

FULL PAPER

Entry for the Table of Contents



Institute and/or researcher Twitter usernames: @HeretschPhilipp

Supporting Information

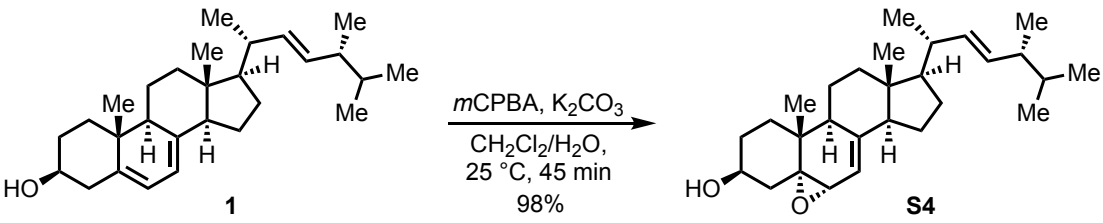
Table of Contents

1 General Methods

All reactions sensitive to moisture and/or air were carried out using heat gun dried glassware, an argon atmosphere, and dry solvents. Dry dichloromethane, toluene, and Et_2O were taken from a M. Braun GmbH MB SPS-800 solvent purification system. THF was distilled from sodium and stored over 4 Å molecular sieves. Triethylamine was distilled from CaH_2 and stored over KOH. Ethyl acetate and *n*hexane were purified by distillation on a rotary evaporator. All other solvents and commercially available reagents were used without further purification unless otherwise stated. In case reactions required heating, this was carried out using silicone oil baths. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck Silica Gel 50 F245-plates and visualized by fluorescence quenching under UV-light or an aqueous solution of cerium sulfate and phosphomolybdic acid and heat as developing agent. Column chromatographic purification was performed on Macherey-Nagel Silica Gel 60 M (40–60 μm). HPLC separation was performed on a Knauer system with DAD detection at 254 nm. Concentration under reduced pressure was performed by rotary evaporation at 45 °C and appropriate pressure, followed by exposure to high vacuum (10^{-3} mbar) at 25 °C. NMR spectra were recorded on either a Jeol ECX400 (400 MHz), a Jeol ECP500 (500 MHz), a Bruker AVANCE III 500 (500 MHz), a Varian INOVA600 (600 MHz) or a Bruker AVANCE III 700 (700 MHz, with CryoProbe) spectrometer. Chemical shifts δ are reported in parts per million (ppm) and are referenced using residual undeuterated solvent ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; DMSO-d_6: δ_H = 8.74 ppm, δ_C = 150.35 ppm pyridine-d_5: δ_H = 2.50 ppm, δ_C = 39.52 ppm; unless otherwise stated) as an internal reference at 298 K. The given multiplicities are phenomenological; thus the actual appearance of the signals is stated and not the theoretically expected one. The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, and combinations thereof. In case no multiplicity could be identified, the chemical shift range of the signal is given (m = multiplet). Infrared (IR) spectra were measured on a Jasco FT/IR-4100 Type A spectrometer with a TGS detector. Wavenumbers $\tilde{\nu}$ are given in cm^{-1} and intensities are as follows: s = strong, m = medium, w = weak. High-resolution mass spectra (HRMS) were recorded using an Agilent 6210 ESI-TOF or an Ionspec QFT-7 ESI-TOF spectrometer. Optical rotations were measured on a JASCO P-2000 polarimeter at 589 nm using 100 mm cells and the solvent and concentration (g/100 mL) indicated. Melting points were measured on a Stuart SMP30.

2 Experimental Procedures and Characterization Data

(22*E*)-5α,6α-Epoxyergosta-7,22-dien-3β-ol (**S4**)

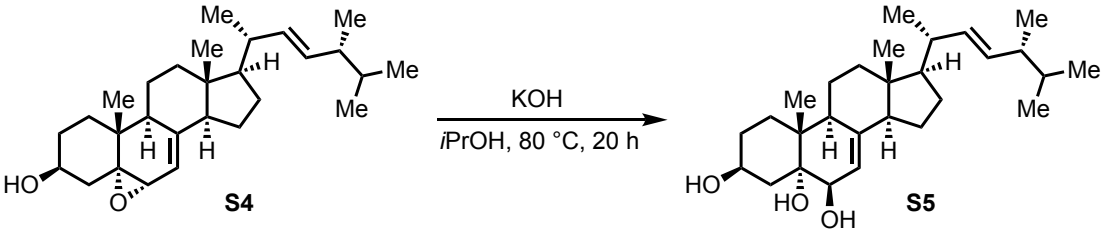


To a suspension of (–)-ergosterol (**1**) (5.00 g, 12.6 mmol, 1.0 eq.) in CH_2Cl_2 (125 mL) was added a solution of K_2CO_3 (3.48 g, 25.3 mmol, 2.0 eq.) in H_2O (125 mL). In a separate flask, *m*CPBA (70% *w/w*, 3.10 g, 12.6 mmol, 1.0 eq.) was suspended in CH_2Cl_2 (50 mL) by sonication to give a turbid solution, which was then added dropwise to the reaction mixture over a period of 5 min. After vigorous stirring for 45 min at 25 °C the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic phases were sequentially washed with $NaHCO_3$ (sat. aq., 250 mL) and brine (sat., 250 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure to give epoxide **S4** (5.10 g, 12.4 mmol, 98%) as a white solid, which was used in the next step without further purification.

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.45 – 5.41 (m, 1H), 5.24 – 5.12 (m, 2H), 4.01 – 3.91 (m, 1H), 3.00 (d, *J* = 4.1 Hz, 1H), 2.26 (dd, *J* = 13.0, 11.5 Hz, 1H), 2.06 – 1.99 (m, 3H), 1.99 – 1.92 (m, 2H), 1.87 – 1.80 (m, 2H), 1.75 – 1.66 (m, 2H), 1.57 – 1.50 (m, 3H), 1.51 – 1.38 (m, 3H), 1.35 – 1.20 (m, 4H), 1.02 (s, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.55 (s, 3H).

All characterization data were consistent with those reported in the literature.[1]

(22*E*)-Ergosta-7,22-diene-3β,5α,6β-triol/cerevisterol (**S5**)



To epoxide **S4** (5.10 g, 12.4 mmol, 1.0 eq.) were added KOH (1 M in H_2O, 50 mL) and *i*PrOH (50 mL). The suspension was heated to 80 °C and stirred at this temperature for 18 h. The reaction mixture was allowed to cool to 25 °C and neutralized with HCl (1 M in H_2O). The layers were separated, and the aqueous phase was extracted with $CHCl_3$/*i*PrOH (4:1, 3 × 75 mL). The combined organic phases were

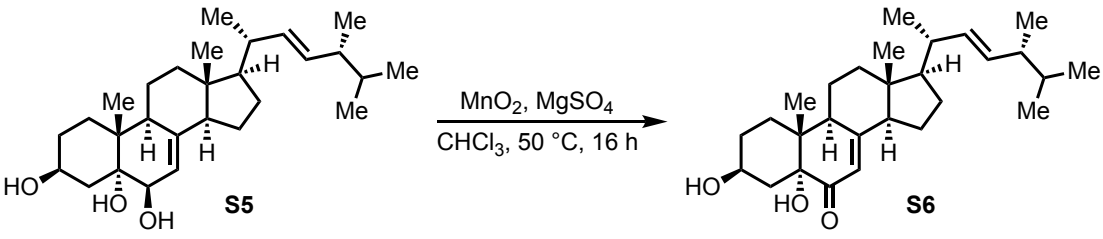
washed with brine (sat., 250 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure to give crude triol **S5** (5.33 g, 12.4 mmol, quant.) as a light yellow solid, which was used in the next step without further purification.

Analytically pure triol **S5** could be obtained by column chromatography (silica gel, EtOAc) as a colorless solid.

^{1}H-NMR: (500 MHz, DMSO-d_6); δ [ppm] = 5.23 (dd, *J* = 15.3, 7.2 Hz, 1H), 5.17 (dd, *J* = 15.3, 8.0 Hz, 1H), 5.10 – 5.06 (m, 1H), 4.49 (d, *J* = 5.5 Hz, 1H), 4.22 (d, *J* = 5.7 Hz, 1H), 3.81 – 3.72 (m, 1H), 3.58 (s, 1H), 3.39 – 3.35 (m, 1H), 2.04 – 1.91 (m, 3H), 1.90 – 1.77 (m, 3H), 1.70 – 1.57 (m, 2H), 1.52 – 1.43 (m, 5H), 1.42 – 1.34 (m, 2H), 1.31 – 1.21 (m, 5H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.54 (s, 3H).

All characterization data were consistent with those reported in the literature.[1]

(22*E*)-3β,5α-Dihydroxyergosta-7,22-dien-6-one (**S6**)



To a stirred suspension of triol **S5** (5.33 g, 12.4 mmol, 1.0 eq.) in $CHCl_3$ (125 mL) were added $MgSO_4$ (1.25 g) and MnO_2 (8.58 g, 98.8 mmol, 8.0 eq.). The resulting mixture was heated to 50 °C and stirred at this temperature for 16 h. The reaction mixture was allowed to cool to 25 °C and $CHCl_3$/*i*PrOH (4:1, 65 mL) and silica gel were added. The solvent was removed under reduced pressure and the residue was added onto a short plug of silica gel (10 cm) to remove manganese solids. It was rinsed with $CHCl_3$/*i*PrOH (4:1) until all product was recovered from the column to give a mix of crude α-ketol **S6** along with the over oxidized side product as a yellow solid (5.3 g).

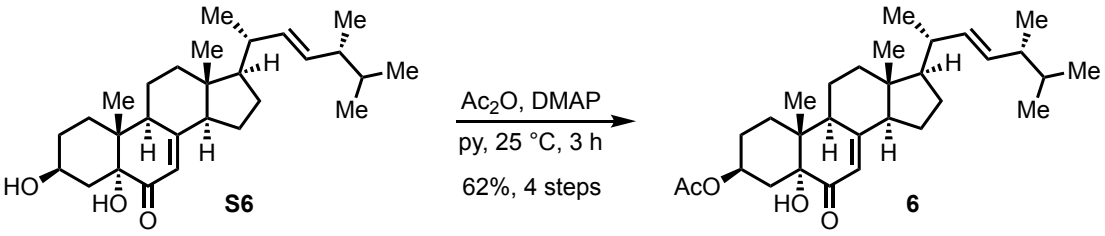
Analytically pure α-ketol **S6** could be obtained by column chromatography (silica gel, *n*hexane/EtOAc 1:2) as a colorless solid.

^{1}H-NMR: (500 MHz, pyridine-d_5); δ [ppm] = 7.23 (s, 1H), 6.24 – 6.11 (m, 1H), 5.94 (t, *J* = 2.3 Hz, 1H), 5.29 (dd, *J* = 15.2, 7.7 Hz, 1H), 5.21 (dd, *J* = 15.3, 8.5 Hz, 1H), 4.76 – 4.66 (m, 1H), 3.02 – 2.91 (m, 2H), 2.33 (dd, *J* = 13.8, 11.4 Hz, 1H), 2.27 – 2.18 (m, 2H), 2.09 – 2.00 (m, 3H), 1.95 – 1.87 (m, 1H), 1.87 – 1.81 (m, 1H), 1.79 – 1.74 (m, 1H), 1.74 – 1.68 (m, 2H), 1.62 (qd, *J* = 13.4, 4.3 Hz, 1H), 1.54 – 1.45 (m, 3H), 1.41 – 1.34 (m, 1H), 1.33

– 1.23 (m, 2H), 1.12 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 4.3 Hz, 3H), 0.89 (d, *J* = 4.4 Hz, 3H), 0.63 (s, 3H).

All characterization data were consistent with those reported in the literature.[1]

(22*E*)-5α-Hydroxyergosta-7,22-dien-6-on-3β-yl acetate/Burawoy ketone (**6**)

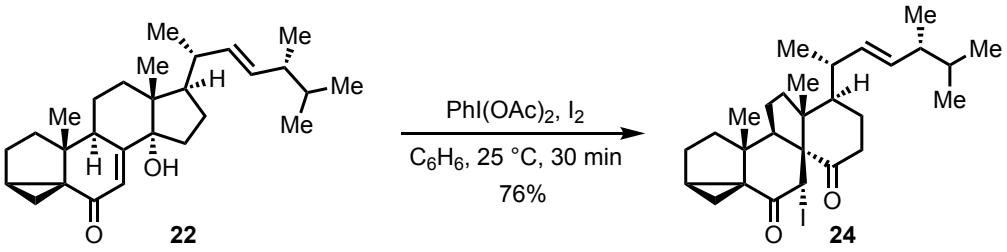


To a stirred solution of crude α-ketol **S6** (5.3 g, 12.4 mmol, 1.0 eq.) in pyridine (50 mL) were added 4-dimethylaminopyridine (150 mg, 1.23 mmol, 0.1 eq.) and acetic anhydride (3.3 mL, 34 mmol, 2.75 eq.) at 25 °C and stirring was continued at this temperature for 3 h. The reaction mixture was poured into H_2O (50 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL) and the combined organic phases were washed with HCl (1 M in H_2O, 3 × 200 mL) and brine (sat., 400 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a yellow residue (5.7 g). Recrystallization of the crude product from EtOAc gave Burawoy ketone (**6**) (3.68 g, 7.80 mmol, 62% over 4 steps) as colorless needles.

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.63 (t, *J* = 2.3 Hz, 1H), 5.23 (dd, *J* = 15.2, 7.7 Hz, 1H), 5.14 (dd, *J* = 15.3, 8.2 Hz, 1H), 5.11 – 5.04 (m, 1H), 2.77 (s, 1H), 2.54 (ddd, *J* = 12.2, 6.9, 2.5 Hz, 1H), 2.17 (ddd, *J* = 16.1, 6.0, 2.8 Hz, 1H), 2.14 – 2.07 (m, 2H), 2.01 (s, 3H), 1.89 – 1.82 (m, 3H), 1.78 – 1.68 (m, 2H), 1.77 (dd, *J* = 14.0, 11.8 Hz, 1H), 1.64 – 1.56 (m, 3H), 1.52 – 1.43 (m, 4H), 1.41 (dd, *J* = 13.1, 4.4 Hz, 1H), 1.36 – 1.31 (m, 2H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.94 (s, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.59 (s, 3H).

All characterization data were consistent with those reported in the literature.[1]

(22*E*)-7α-Iodo-13(14→8)*abeo*-3α,5-cyclo-5α-ergosta-22-en-6,14-dione (**24**)

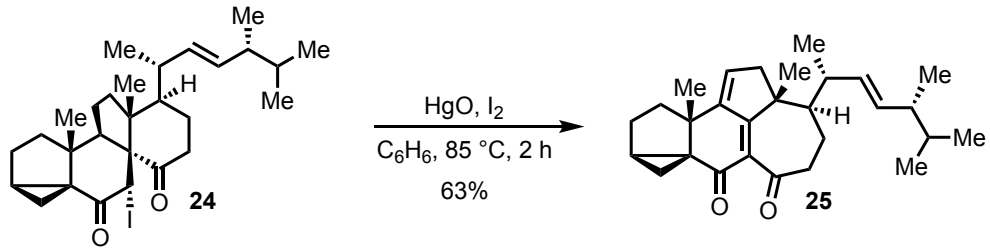


A solution of γ-hydroxy enone **22**[2] (30 mg, 73 *µ*mol, 1.0 eq.) in benzene (1.5 mL) was degassed applying three freeze-pump-thaw cycles. (Diacetoxyiodo)benzene (47.0 mg, 146 *µ*mol, 2.0 eq.) and iodine (18 mg, 73 *µ*mol, 1.0 eq.) were added, and the resulting mixture was stirred at 25 °C for 30 min. $Na_2S_2O_3$ (sat. aq., 5 mL) was added and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (sat., 15 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and column chromatography (silica gel, *n*hexane/EtOAc 19:1 → 9:1) gave iodo ketone **24** (30 mg, 55 mmol, 76%) as colorless needles.

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.40 (dd, *J* = 15.3, 7.8 Hz, 1H), 5.29 (dd, *J* = 15.4, 8.2 Hz, 1H), 5.13 (s, 1H), 2.73 (dd, *J* = 19.2, 4.9 Hz, 1H), 2.56 (t, *J* = 7.3 Hz, 1H), 2.53 (d, *J* = 9.3 Hz, 1H), 2.24 (dt, *J* = 8.3, 5.2 Hz, 1H), 2.16 – 2.08 (m, 1H), 2.07 – 2.03 (m, 1H), 2.00 (td, *J* = 12.9, 5.1 Hz, 1H), 1.93 – 1.85 (m, 2H), 1.78 – 1.71 (m, 2H), 1.69 (dd, *J* = 8.4, 4.2 Hz, 1H), 1.65 (dd, *J* = 13.2, 7.6 Hz, 1H), 1.63 – 1.57 (m, 2H), 1.53 – 1.47 (m, 2H), 1.42 (s, 3H), 1.35 (d, *J* = 12.4 Hz, 1H), 1.19 – 1.14 (m, 1H), 1.13 (s, 3H), 1.09 (d, *J* = 7.1 Hz, 3H), 0.97 – 0.95 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

All characterization data were consistent with those reported in the literature.[3]

(22*E*)-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α-ergosta-7,9(11),22-trien-6,14-dione (**25**)



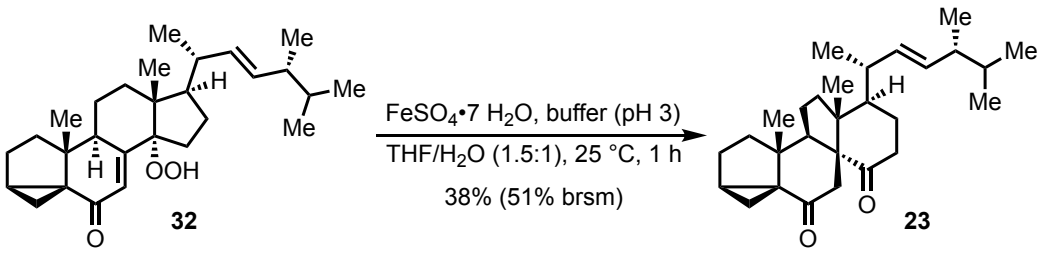
Through a solution of iodide **24** (12.0 mg, 22.4 *µ*mol, 1.0 eq.) in benzene (2 mL) was bubbled argon *via* cannula for 10 min. Iodine (13.6 mg, 53.8 *µ*mol, 2.4 eq.) and mercury oxide (yellow, 13.1 mg, 60.4 *µ*mol, 2.7 eq.) were added and the reaction mixture was heated to 85 °C for 2 h. The mixture was cooled to

25 °C, filtered through Celite®, and rinsed with EtOAc (10 mL). The organic phase was washed sequentially with $Na_2S_2O_3$ (sat. aq., 15 mL) and brine (sat., 15 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAC 4:1) gave diene dione **25** (5.7 mg, 14 μmol, 63%) as a light-yellow foam.

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 6.34 (t, *J* = 2.9 Hz, 1H), 5.36 (dd, *J* = 15.3, 8.4 Hz, 1H), 5.28 (dd, *J* = 15.3, 7.9 Hz, 1H), 2.78 (dd, *J* = 17.7, 2.4 Hz, 1H), 2.74 – 2.68 (m, 1H), 2.62 – 2.54 (m, 2H), 2.45 (dd, *J* = 17.6, 3.4 Hz, 1H), 2.11 – 2.03 (m, 1H), 2.03 – 1.95 (m, 1H), 1.93 – 1.81 (m, 4H), 1.77 – 1.72 (m, 2H), 1.69 (dd, *J* = 12.9, 7.6 Hz, 1H), 1.50 – 1.37 (m, 2H), 1.16 (s, 6H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.77 (t, *J* = 7.1 Hz, 1H).

All characterization data were consistent with those reported in the literature.[3]

(22*E*)-13(14→8)*abeo*-3α,5-Cyclo-5α-ergosta-22-ene-6,14-dione (**23**)

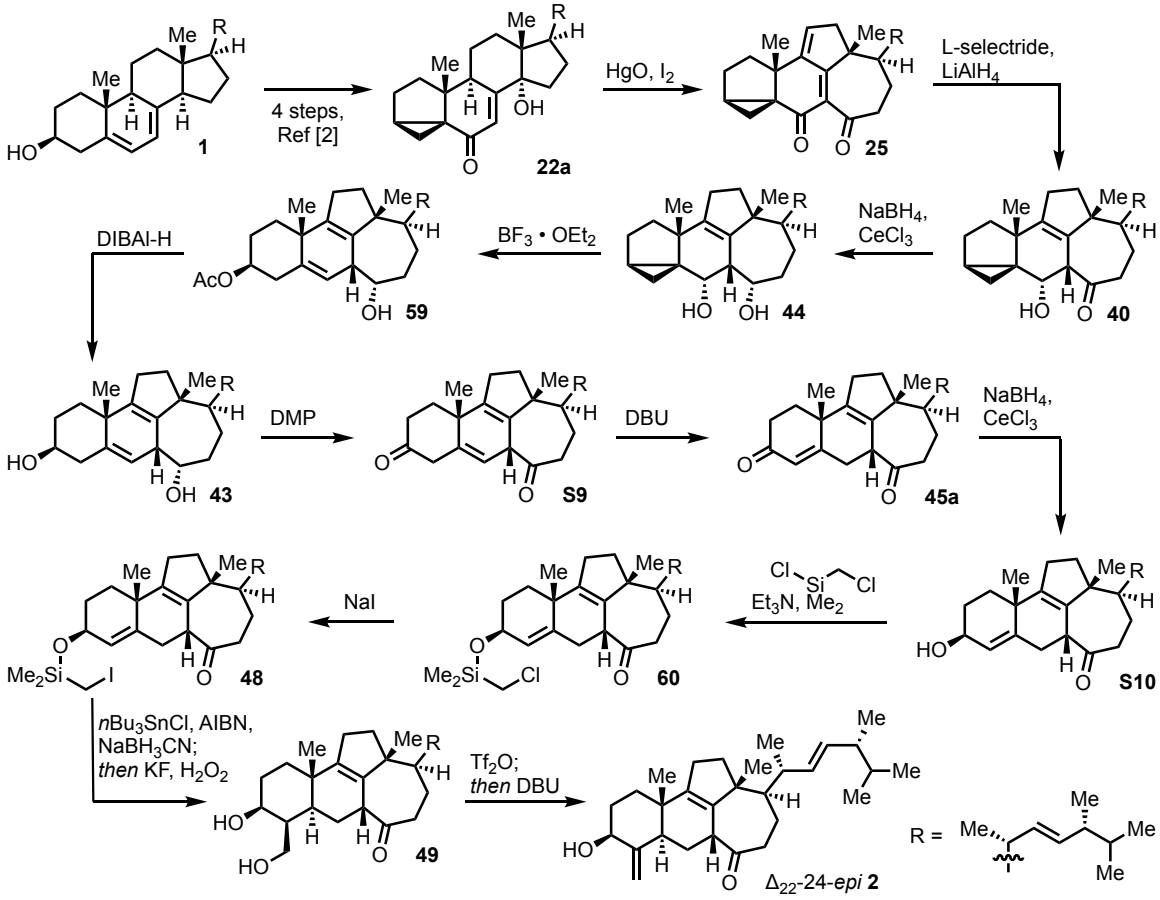


To a solution of 14α-hydroperoxide **32** (100 mg, 234 μmol, 1.0 eq.) in THF/H_2O (1.5:1, 12 mL) at 25 °C was added a solution of $FeSO_4$•7 H_2O (68.4 mg, 246 μmol, 1.05 eq.) in acetic buffer (pH 3, 2.9 mL) and the resulting mixture was stirred at this temperature for 1 h. The reaction mixture was poured into H_2O (10 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (sat., 25 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 19:1 → 9:1) gave dione **23** (37 mg, 90 μmol, 38%) as a colorless oil and starting material **32** (25 mg, 59 μmol, 25%) as a colorless solid.

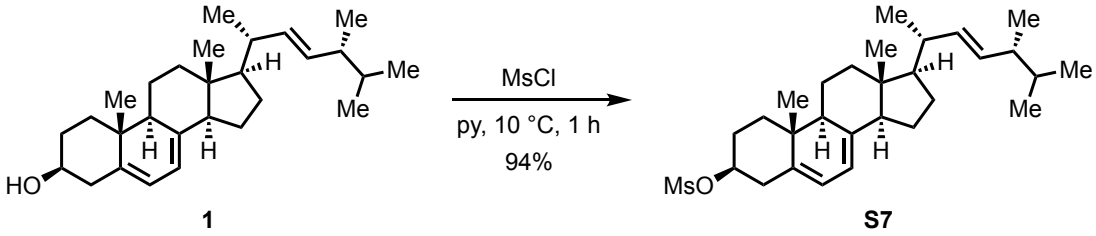
^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.27 – 5.24 (m, 2H), 2.93 (dd, *J* = 11.0, 8.2 Hz, 1H), 2.73 (d, *J* = 14.5 Hz, 1H), 2.61 (ddd, *J* = 17.1, 6.0, 3.2 Hz, 1H), 2.52 (d, *J* = 14.6 Hz, 1H), 2.38 – 2.31 (m, 1H), 2.28 – 2.18 (m, 2H), 1.91 – 1.82 (m, 2H), 1.82 – 1.75 (m, 3H), 1.75 – 1.70 (m, 1H), 1.67 – 1.61 (m, 3H), 1.51 (dd, *J* = 8.3, 4.3 Hz, 1H), 1.50 – 1.44 (m, 1H), 1.31 (td, *J* = 12.0, 6.3 Hz, 1H), 1.20 – 1.12 (m, 1H), 1.10 (s, 3H), 1.09 – 1.03 (m, 1H), 1.03 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.84 – 0.82 (m, 1H), 0.82 (d, *J* = 6.8 Hz, 3H).

All characterization data were consistent with those reported in the literature.[3]

2.1 Synthesis of Δ^{22}-24-*epi*-Swinhoeisterol A (Δ^{22}-24-*epi*-**2**)



Ergosterol mesylate (**S7**)



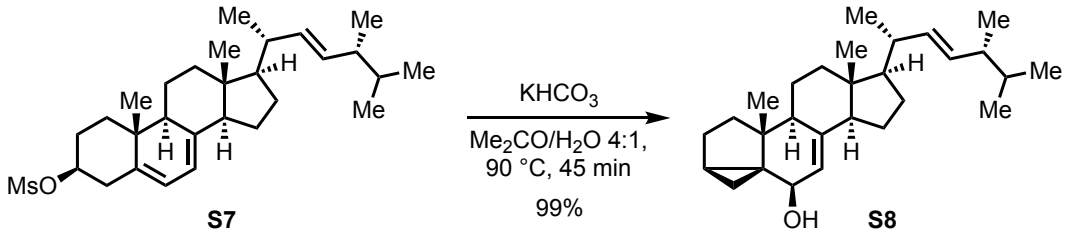
To a stirred solution of ergosterol (**1**) (53.7 g, 135 mmol, 1.0 eq.) in pyridine (1.0 L) was added methanesulfonyl chloride (52.4 mL, 677 mmol, 5.0 eq.) dropwise at 10 °C. After stirring at this temperature for 1 h, the reaction mixture was poured into a mixture of ice and H_2O (1.5 L) under stirring. The precipitate was filtered off, washed with H_2O (3 × 1 L), and dried under vacuum to give mesylate **S7** (60.0 g, 126 mmol, 94%) as a colorless solid, which was used in the next step without further purification.

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.60 (dd, *J* = 5.7, 2.3 Hz, 1H), 5.39 (dt, *J* = 5.3, 2.6 Hz, 1H), 5.23 (dd, *J* = 15.2, 7.1 Hz, 1H), 5.17 (dd, *J* = 15.2, 7.8 Hz, 1H), 4.63 (tt, *J* = 11.4, 4.7 Hz, 1H), 3.02 (s, 3H), 2.65 (ddd, *J* = 14.4, 5.1, 2.4 Hz, 1H), 2.62 – 2-50 (m, 1H),

2.15 – 1.21 (m, 18H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.95 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.62 (s, 3H).

All characterization data were consistent with those reported in the literature.[2]

(22*E*)-3α,5-Cyclo-5α-ergosta-7,22-dien-6β-ol (**S8**)

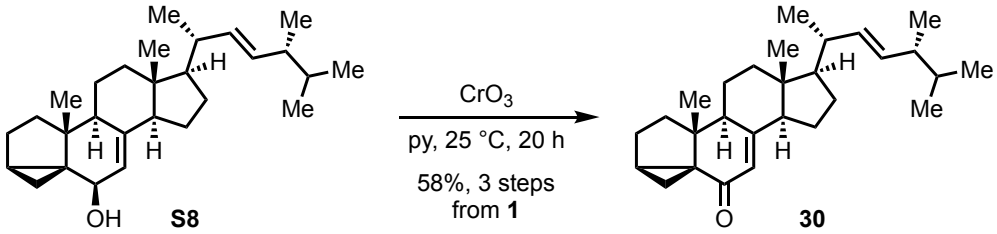


Finely powdered mesylate **S7** (60.0 g, 126 mmol, 1.0 eq.) was added portion wise to a refluxing solution of $KHCO_3$ (14.6 g, 145 mmol, 1.15 eq.) in acetone/ H_2O (4:1, 1.8 L) at 80 °C. After stirring for 45 min at 90 °C, the reaction mixture was allowed to cool to 40 °C and a mixture of ice and H_2O (1 L) was added. After further cooling to 0 °C, the precipitate was filtered off, washed with H_2O (2 × 500 mL), and dried under vacuum to give *i*-sterol **S8** (49.6 g, 125 mmol, 99%) as a colorless solid, which was used in the next step without further purification.

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.52 – 5.42 (m, 1H), 5.23 (dd, *J* = 15.2, 7.3 Hz, 1H), 5.17 (dd, *J* = 15.3, 8.1 Hz, 1H), 3.42 (s, 1H), 2.10 – 1.18 (m, 20H), 1.08 (s, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz), 3H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.66 – 0.60 (m, 4H), 0.48 (dd, *J* = 7.9, 5.0 Hz, 1H).

All characterization data were consistent with those reported in the literature.[2]

(22*E*)-3α,5-Cyclo-5α-ergosta-7,22-dien-6-one (**30**)



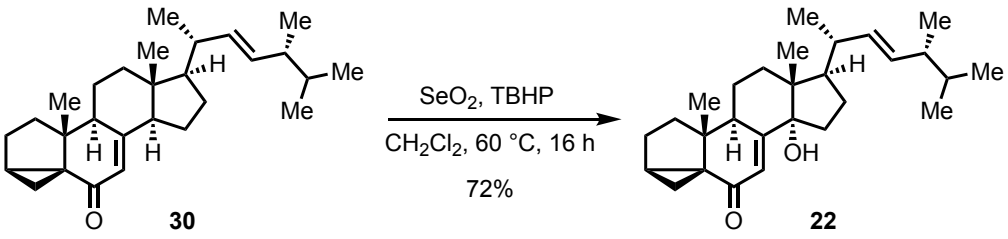
Under stirring CrO_3 (50.0 g, 500 mmol, 4.0 eq.) was added portion wise to pyridine (500 mL). To the resulting red-brown suspension was added *i*-sterol **S8** (49.6 g, 125 mmol, 1.0 eq.) in pyridine (500 mL) *via* cannula over 10 min. After stirring at 25 °C for 20 h, Et_2O (1.2 L) was added, the resulting mixture was filtered through Celite® and rinsed with Et_2O (2 × 200 mL). The filtrate was washed sequentially with H_2O (2 × 1 L) and brine (sat., 1 L), dried over $MgSO_4$, and concentrated under reduced pressure.

Crystallization from acetone (250 mL) gave enone **30** (30.9 g, 78.3 mmol, 58% over 3 steps) as a crystalline solid.

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.82 (t, *J* = 2.2 Hz, 1H), 5.27 (dd, *J* = 15.3, 7.6 Hz, 1H), 5.20 (dd, *J* = 15.7, 8.3 Hz, 1H), 2.28 (ddd, *J* = 11.7, 7.2, 2.3 Hz, 1H), 2.19 – 2.05 (m, 3H), 2.00 (tdd, *J* = 12.3, 8.0, 4.4 Hz, 1H), 1.93 – 1.85 (m, 1H), 184 – 1.64 (m, 8H), 1.58 – 1.47 (m, 2H), 1.47 – 1.33 (m, 3H), 1.19 – 1.13 (m, 1H), 1.12 (s, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.78 (t, *J* = 4.6 Hz, 1H), 0.71 (s, 3H).

All characterization data were consistent with those reported in the literature.[2]

(22*E*)-14-Hydroxy-3α,5-cyclo-5α-ergosta-7,22-dien-6-one (**22**)

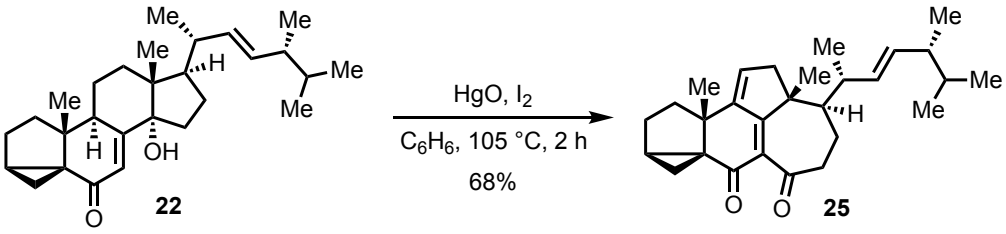


To a stirred suspension of SeO_2 (1.13 g, 10.2 mmol, 0.5 eq.) in CH_2Cl_2 (18 mL) was added *t*BuOOH (70% in H_2O, 11.2 mL, 81.8 mmol, 4.0 eq.) at 0 °C. After stirring at 25°C for 15 min, enone **30** (8.07 g, 20.4 mmol, 1.0 eq.) in CH_2Cl_2 (22 mL) was added. The vessel was sealed, and the mixture was stirred at 60 °C for 16 h. The reaction mixture was allowed to cool to 25 °C and was carefully added to $NaHSO_3$ (10% *w/w* in H_2O, 200 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (2 × 250 mL) and the combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 250 mL) and brine (sat., 250 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was adsorbed on silica and the mixture was purified by column chromatography (silica gel, *n*hexane/EtOAc 5:1 → 4:1) to give γ-hydroxy enone **22** (6.05 g, 14.7 mmol, 72%) as a crystalline solid.

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.97 (d, *J* = 2.7 Hz, 1H), 5.27 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.20 (ddd, *J* = 15.2, 8.5, 0.9 Hz, 1H), 2.79 – 2.75 (m, 1H), 2.13 – 1.84 (m, 7H), 1.80 (dt, *J* = 8.8, 4.6 Hz, 1H), 1.75 – 1.65 (m, 6H), 1.55 (ddd, *J* = 13.7, 9.8, 5.1 Hz, 1H), 1.48 (qd, *J* = 6.8, 5.7 Hz, 1H), 1.43 (s, 1H), 1.43 – 1.37 (m, 1H), 1.15 – 1.11 (m, 1H), 1.10 (s, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.79 (t, *J* = 4.7 Hz, 1H), 0.76 (s, 3H).

All characterization data were consistent with those reported in the literature.[2]

(22*E*)-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α-ergosta-7,9(11),22-triene-6,14-dione (**25**)

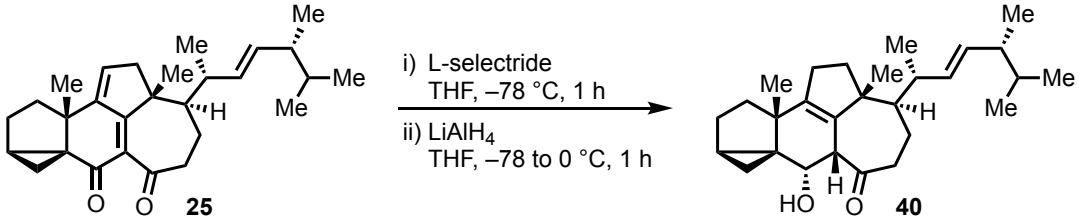


Through a solution of γ-hydroxy enone **22** (3.00 g, 7.31 mmol, 1.0 eq.) in benzene (300 mL) was bubbled argon *via* cannula for 10 min. Iodine (4.45 g, 17.5 mmol, 2.4 eq.) and HgO (yellow, 4.27 g, 19.7 mmol, 2.7 eq.) were added at 60 °C and the resulting mixture was stirred at 105 °C for 2 h. The reaction mixture was cooled to 25 °C, filtered through a plug of Celite®, and rinsed with EtOAc (100 mL). The organic phase was washed sequentially with $Na_2S_2O_3$ (sat. aq., 250 mL) and brine (sat., 250 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1 → 3:1) gave diene dione **25** (2.02 g, 4.97 mmol, 68%) as a light-yellow foam.

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 6.34 (t, *J* = 2.9 Hz, 1H), 5.36 (dd, *J* = 15.3, 8.4 Hz, 1H), 5.28 (dd, *J* = 15.3, 7.9 Hz, 1H), 2.78 (dd, *J* = 17.7, 2.4 Hz, 1H), 2.74 – 2.68 (m, 1H), 2.62 – 2.54 (m, 2H), 2.45 (dd, *J* = 17.6, 3.4 Hz, 1H), 2.11 – 2.03 (m, 1H), 2.03 – 1.95 (m, 1H), 1.93 – 1.81 (m, 4H), 1.77 – 1.72 (m, 2H), 1.69 (dd, *J* = 12.9, 7.6 Hz, 1H), 1.50 – 1.37 (m, 2H), 1.16 (s, 6H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.77 (t, *J* = 7.1 Hz, 1H).

All characterization data were consistent with those reported in the literature.[3]

(22*E*)-6α-Hydroxy-13(14→8),14(8→7)di*abeo*-3α,5-cyclo-5α,7β(H)-ergosta-8,22-dien-14-one (**40**)



A solution of diene dione **25** (630 mg, 1.55 mmol, 1.0 eq.) in THF (15 mL) was degassed applying three freeze-pump-thaw cycles. After cooling to –78 °C, L-selectride (1 M in THF, 2.3 mL, 2.3 mmol, 1.5 eq.) was added dropwise over 30 min and the resulting solution was stirred at this temperature for 30 min. Lithium aluminum hydride (1 M in THF, 3.1 mL, 3.1 mmol, 2.0 eq.) was added dropwise over 30 min, and the reaction mixture was warmed to 0 °C. After stirring for 30 min at this temperature, EtOAc (20 mL)

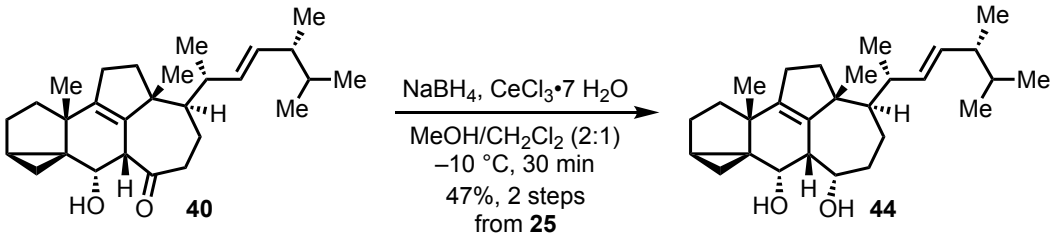
and Rochelle's salt (½ sat. aq., 30 mL) were added carefully, and the mixture was vigorously stirred at 25 °C for 16 h. A solution of $NaBO_3$•$4H_2O$ (0.48 g, 3.1 mmol, 2.0 eq.) in H_2O (10 mL) was added and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc (3 × 25 mL) and the combined organic phases were washed with brine (sat., 50 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude residue was used in the next step without further purification.

Analytically pure β-hydroxy ketone **40** could be obtained by column chromatography (silica gel, *n*hexane/EtOAc 50:1 → 19:1) as a colorless oil.

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.31 – 5.21 (m, 2H), 4.44 (d, *J* = 8.5 Hz, 1H), 4.25 – 4.19 (m, 1H), 3.16 (d, *J* = 6.4 Hz, 1H), 2.60 – 2.52 (m, 1H), 2.51 – 2.40 (m, 2H), 2.35 – 2.26 (m, 1H), 2.21 – 2.13 (m, 2H), 2.12 – 2.06 (m, 1H), 1.87 – 1.82 (m, 1H), 1.74 – 1.67 (m, 1H), 1.66 – 1.62 (m, 1H), 1.62 – 1.58 (m, 2H), 1.58 – 1.54 (m, 1H), 1.53 – 1.47 (m, 2H), 1.46 – 1.39 (m, 2H), 1.09 (s, 3H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.98 (s, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.77 – 0.73 (m, 1H), 0.31 (t, *J* = 4.2 Hz, 1H).

All characterization data were consistent with those reported in the literature.[3]

(22*E*)-13(14→8),14(8→7)Di*abeo*-3α,5-cyclo-5α,7β(H)-ergosta-8,22-dien-6α,14α-diol (**44**)



To a solution of crude β-hydroxy ketone **40** (1.55 mmol, 1.0 eq.) in MeOH/CH_2Cl_2 (2:1, 15 mL) at –10 °C were added $CeCl_3$•$7\ H_2O$ (1.45 g, 3.88 mmol, 2.5 eq.) and $NaBH_4$ (147 mg, 3.88 mmol, 2.5 eq.) and the reaction mixture was stirred at this temperature for 30 min. HCl (1 M in H_2O, 10 mL) was added carefully and the mixture was stirred vigorously for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic phases were washed with brine (sat., 30 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1) gave diol **44** (301 mg, 729 μmol, 47%) as a colorless solid.

M.p.: 136–139 °C (EtOAc).

TLC: R_f = 0.24 (*n*hexane/EtOAc 5:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.36 (dd, *J* = 15.2, 8.1 Hz, 1H), 5.20 (dd, *J* = 15.3, 8.2 Hz, 1H), 4.28 – 4.22 (m, 2H), 2.66 (d, *J* = 6.0 Hz, 1H), 2.42 (p, *J* = 7.1 Hz, 1H), 2.30 – 2.18

(m, 2H), 1.95 – 1.82 (m, 4H), 1.76 (dd, *J* = 13.6, 7.7 Hz, 1H), 1.73 – 1.65 (m, 2H), 1.63 – 1.53 (m, 5H), 1.47 – 1.43 (m, 2H), 1.04 (s, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.96 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.68 (dd, *J* = 8.4, 5.0 Hz, 1H), 0.30 – 0.26 (m, 1H).

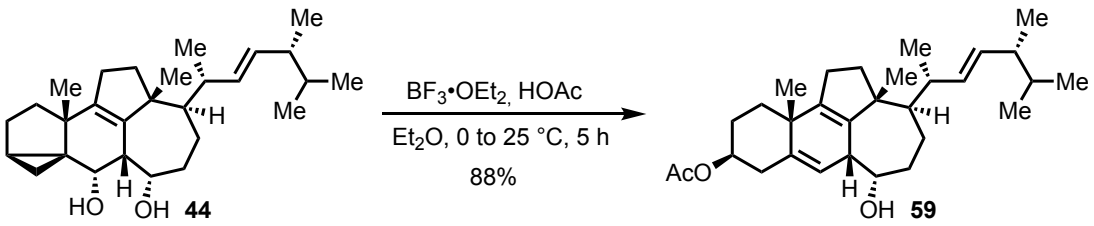
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 144.5, 140.1, 134.0, 133.3, 66.3, 64.0, 53.4, 51.8, 45.4, 43.6, 42.6, 39.4, 38.4, 37.3, 35.8, 33.3, 33.2, 28.7, 26.1, 23.8, 23.2, 21.4, 20.4, 20.3, 19.8, 17.9, 17.8, 7.1.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3384 (br w), 2953 (s), 2925 (s), 2869 (m), 1740 (w), 1450 (m), 1410 (w), 1367 (m), 1073 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{44}O_2Na^+$ $[M+Na]^+$: 435.3234, found: 435.3248.

Opt. act. $[\alpha]_D^{25}$ = +92.2 (*c* = 1.00, $CHCl_3$).

(22*E*)-14α-Hydroxy-13(14→8),14(8→7)di*abeo*-7β(H)-ergosta-5,8,22-trien-3β-yl acetate (**59**)



To a solution of diol **44** (248 mg, 601 μmol, 1.0 eq.) in Et_2O (6 mL) were added acetic acid (3 mL) and BF_3•OEt_2 (3 mL) at 0 °C. The resulting solution was warmed to 25 °C and stirred for 5 h, before diluting with EtOAc (10 mL). The reaction mixture was then carefully poured into $NaHCO_3$ (sat. aq., 50 mL) and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 20 mL) and brine (sat., 20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1) gave acetate **59** (240 mg, 528 μmol, 88%) as a colorless solid.

M.p.: 108–111 °C (EtOAc)

TLC: R_f = 0.28 (*n*hexane/EtOAc 5:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.41 – 5.31 (m, 2H), 5.25 – 5.17 (m, 1H), 4.69 – 4.59 (m, 1H), 3.85 – 3.78 (m, 1H), 3.00 – 2.93 (m, 1H), 2.50 – 2.39 (m, 3H), 2.39 – 2.29 (m, 1H), 2.28 – 2.21 (m, 1H), 2.04 (s, 3H), 1.99 – 1.90 (m, 3H), 1.89 – 1.82 (m, 2H), 1.79 – 1.68 (m, 2H), 1.68 – 1.62 (m, 1H), 1.62 – 1.59 (m, 1H), 1.51 – 1.46 (m, 2H), 1.46 – 1.42 (m, 1H), 1.26 (td, *J* = 13.5, 4.2 Hz, 1H), 1.15 (s, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

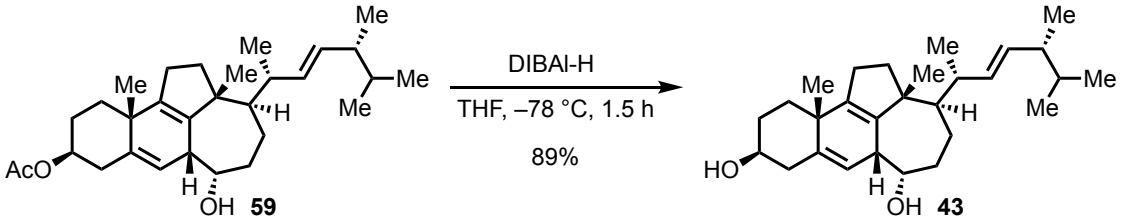
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 170.5, 143.6, 140.0, 137.8, 133.9, 133.4, 124.5, 74.2, 72.6, 53.6, 51.4, 43.5, 39.8, 39.0, 38.6, 37.3, 36.7, 36.5, 35.4, 33.3, 27.9, 27.7, 23.1, 22.8, 22.0, 21.5, 20.3, 19.8, 18.4, 17.7.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3452 (br w), 2956 (s), 2928 (s), 2871 (m), 1737 (s), 1457 (m), 1366 (s), 1242 (s), 1032 (m), 755 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{30}H_{46}O_3Na^+$ [M+Na]$^+$: 477.3339, found: 477.3339.

Opt. act. $[\alpha]_D^{25}$ = +38.1 (*c* = 1.00, $CHCl_3$).

(22*E*)-13(14→8),14(8→7)Di*abeo*-7β(H)-ergosta-5,8,22-trien-3β,14α-diol (**43**)



To a solution of acetate **59** (186 mg, 413 μmol, 1.0 eq.) in THF (4 mL) at –78 °C was added DIBAl-H (1 M in hexanes, 2.1 mL, 2.1 mmol, 5.0 eq.) and the resulting solution was stirred at this temperature for 1.5 h. EtOAc (2.5 mL) and Rochelle's salt (½ sat. aq., 5 mL) were added carefully and the mixture was vigorously stirred for 30 minutes while warming to 25 °C. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (sat., 15 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 1:1) gave diol **43** (152 mg, 368 μmol, 89%) as a colorless solid.

M.p.: 117–120 °C ($CHCl_3$).

TLC: R_f = 0.23 (*n*hexane/EtOAc 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.38 – 5.30 (m, 2H), 5.20 (dd, *J* = 15.4, 8.1 Hz, 1H), 3.81 – 3.77 (m, 1H), 3.61 – 3.51 (m, 1H), 2.99 – 2.94 (m, 1H), 2.48 – 2.37 (m, 2H), 2.37 – 2.28 (m, 2H), 2.28 – 2.21 (m, 1H), 2.01 – 1.91 (m, 2H), 1.91 – 1.83 (m, 3H), 1.76 – 1.68 (m, 1H), 1.64 – 1.57 (m, 3H), 1.57 – 1.52 (m, 1H), 1.48 – 1.42 (m, 2H), 1.23 – 1.15 (m, 1H), 1.13 (s, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

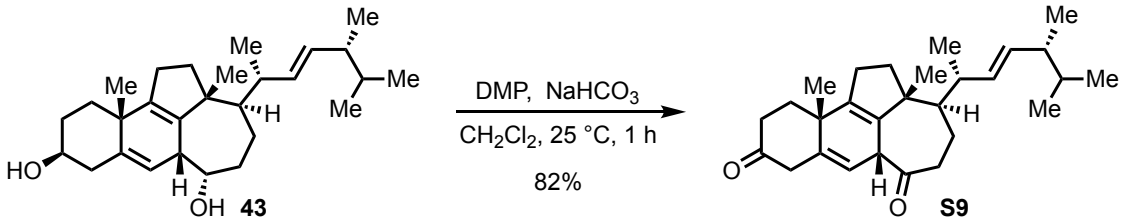
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 144.3, 141.0, 137.4, 134.0, 133.3, 123.5, 72.6, 72.4, 53.6, 51.7, 43.5, 41.4, 39.8, 39.0, 38.6, 36.8, 36.7, 35.5, 33.3, 31.6, 28.0, 23.1, 23.0, 21.9, 20.3, 19.9, 18.4, 17.7.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3363 (br w), 2956 (s), 2928 (s), 2871 (m), 1738 (w), 1458 (m), 1371 (m), 1217 (w), 1058 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{44}O_2Na^+$ [M+Na]$^+$: 435.3234, found: 435.3227.

Opt. act. $[\alpha]_D^{24}$ = +49.6 (*c* = 1.00, $CHCl_3$).

(22*E*)-13(14→8),14(8→7)di*abeo*-7β(H)-Ergosta-5,8,22-trien-3,14-dione (**S9**)



To a solution of diol **43** (137 mg, 332 μmol, 1.0 eq.) in CH_2Cl_2 (3.3 mL) were added $NaHCO_3$ (181 mg, 2.16 mmol, 6.5 eq.) and Dess–Martin periodinane (422 mg, 996 μmol, 3.0 eq.), and the resulting suspension was stirred at 25 °C. After 1 h, $Na_2S_2O_3$ (sat. aq., 3 mL) was added and after further stirring for 15 min, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 15 mL) and brine (sat., 15 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 5:1) gave dione **S9** (111 mg, 272 μmol, 82%) as a colorless foam.

TLC: R_f = 0.37 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.29 – 5.19 (m, 3H), 3.58 – 3.52 (m, 1H), 3.36 (dt, *J* = 16.1, 3.0 Hz, 1H), 2.97 (dd, *J* = 16.1, 2.2 Hz, 1H), 2.63 – 2.57 (m, 1H), 2.54 (dd, *J* = 14.9, 6.9 Hz, 1H), 2.45 – 2.42 (m, 1H), 2.42 – 2.37 (m, 1H), 2.37 – 2.33 (m, 2H), 2.23 (ddd, *J* = 11.7, 7.6, 1.6 Hz, 1H), 2.17 (ddd, *J* = 12.4, 6.6, 2.5 Hz, 1H), 2.02 (ddd, *J* = 13.2, 6.5, 2.4 Hz, 1H), 1.86 – 1.81 (m, 1H), 1.81 – 1.74 (m, 1H), 1.62 – 1.54 (m, 2H), 1.48 – 1.43 (m, 2H), 1.39 (s, 3H), 1.28 (dd, *J* = 12.0, 2.8 Hz, 1H), 1.03 (d, *J* = 7.1 Hz, 3H), 0.94 (s, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H).

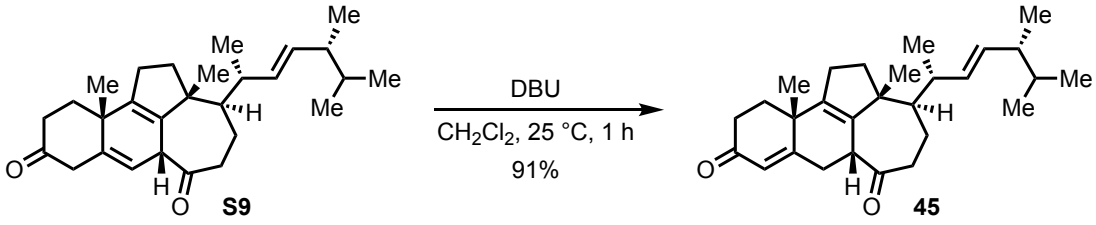
^{13}C-NMR: (126 MHz, $CDCl_3$); δ [ppm] = 211.6, 207.9, 142.1, 139.6, 136.0, 134.7, 132.5, 119.3, 53.6, 51.6, 50.3, 48.2, 43.4, 41.6, 38.8, 38.1, 38.0, 37.1, 35.9, 33.2, 27.7, 23.4, 23.0, 22.1, 20.2, 19.9, 19.2, 17.7.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2955 (m), 2923 (s), 2852 (m), 1737 (m), 1457 (m), 1376 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{40}O_2Na^+$ [M+Na]$^+$: 431.2921, found: 431.2940.

Opt. act. $[\alpha]_D^{25}$ = –33.0 (*c* = 1.00, $CHCl_3$).

(22*E*)-13(14→8),14(8→7)di*abeo*-7β(H)-Ergosta-4,8,22-trien-3,14-dione (**45**)



To a solution of dione **S9** (80.0 mg, 196 μmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (5.9 mg, 39 μmol, 0.2 eq.) and the resulting solution was stirred at 25 °C for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (2 mL), and NH_4Cl (sat. aq., 5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine (sat., 25 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 4:1 → 3:1) gave enone **45** (128 mg, 312 μmol, 91%) as a light-yellow oil.

TLC: R_f = 0.24 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.87 (s, 1H), 5.32 (dd, *J* = 15.4, 7.6 Hz, 1H), 5.27 – 5.22 (m, 1H), 3.24 (dd, *J* = 6.9, 1.6 Hz, 1H), 2.88 – 2.83 (m, 1H), 2.56 – 2.44 (m, 4H), 2.40 (ddd, *J* = 17.7, 4.5, 1.6 Hz, 1H), 2.32 – 2.28 (m, 2H), 2.17 (ddd, *J* = 16.0, 12.4, 2.2 Hz, 1H), 2.02 – 1.95 (m, 2H), 1.86 (h, *J* = 6.8 Hz, 1H), 1.81 – 1.77 (m, 1H), 1.77 – 1.71 (m, 1H), 1.71 – 1.65 (m, 1H), 1.61 – 1.53 (m, 1H), 1.46 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.29 (s, 3H), 1.28 – 1.24 (m, 1H), 1.08 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

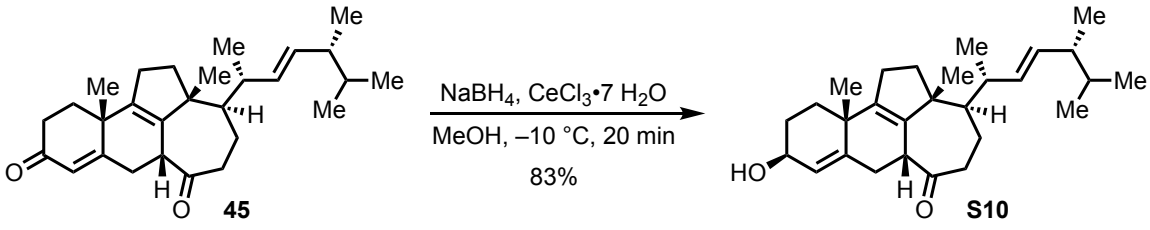
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 211.2, 198.6, 166.9, 143.3, 137.7, 135.0, 132.4, 126.1, 54.9, 53.5, 46.0, 44.9, 43.5, 38.3, 38.1, 37.5, 34.1, 33.7, 33.2, 32.7, 27.3, 23.0, 22.4, 21.0, 20.4, 20.2, 19.9, 17.8.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (s), 2926 (s), 2869 (m), 1708 (s), 1672 (s), 1457 (m), 1371 (m), 1233 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{40}O_2Na^+$ [M+Na]$^+$: 431.2921, found: 431.2926.

Opt. act. $[\alpha]_D^{24}$ = +96.2 (*c* = 1.00, $CHCl_3$).

(22*E*)-3β-Hydroxy-13(14→8),14(8→7)di*abeo*-7β(H)-ergosta-4,8,22-trien-14-one (**S10**)



To a solution of enone **45** (44.0 mg, 108 μmol, 1.0 eq.) in MeOH (2.5 mL) at –10 °C were added $CeCl_3$•7 H_2O (60.4 mg, 162 μmol, 1.5 eq.) and $NaBH_4$ (2.45 mg, 64.8 μmol, 0.6 eq.) in three portions over 15 min at this temperature. The reaction mixture was diluted with EtOAc (5 mL), and HCl (1 M in H_2O, 5 mL) was added. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 15 mL) and brine (sat., 15 mL), and

dried over $MgSO_4$. The solvent was removed under reduced pressure and column chromatography (silica gel, *n*hexane/EtOAc 2:1) gave allylic alcohol **S10** (36.5 mg, 88.9 μmol, 83%) as a colorless oil.

TLC: R_f = 0.24 (*n*hexane/EtOAc 2:1).

^{1}H-NMR: (500 MHz, $CDCl_3$); δ [ppm] = 5.41 – 5.34 (m, 1H), 5.30 (dd, *J* = 15.3, 7.4 Hz, 1H), 5.23 (dd, *J* = 15.3, 7.6 Hz, 1H), 4.21 – 4.11 (m, 1H), 3.01 – 2.93 (m, 1H), 2.66 – 2.57 (m, 1H), 2.52 – 2.44 (m, 1H), 2.43 – 2.37 (m, 1H), 2.34 (ddt, *J* = 12.8, 6.9, 1.7 Hz, 1H), 2.27 – 2.20 (m, 2H), 2.20 – 2.15 (m, 1H), 2.05 – 1.96 (m, 2H), 1.89 – 1.81 (m, 1H), 1.71 – 1.62 (m, 3H), 1.62 – 1.55 (m, 2H), 1.50 – 1.41 (m, 2H), 1.35 (td, *J* = 13.8, 2.9 Hz, 1H), 1.19 (s, 3H), 1.03 (d, *J* = 7.1 Hz, 3H), 1.01 (s, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H).

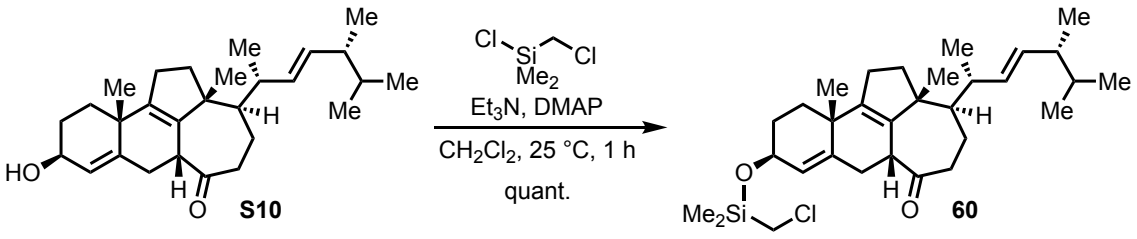
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 214.0, 145.2, 142.8, 137.4, 134.7, 132.5, 125.6, 67.9, 54.0, 53.3, 46.6, 45.5, 43.5, 38.3, 37.9, 36.4, 33.2, 33.1, 32.6, 28.8, 27.1, 23.9, 22.9, 21.4, 20.4, 20.2, 19.9, 17.8.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3370 (br w), 2954 (s), 2926 (s), 2868 (s), 1707 (s), 1456 (m), 1372 (m), 1066 (m), 1011 (m), 983 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{28}H_{42}O_2Na^+$ [M+Na]$^+$: 433.3077, found: 433.3075.

Opt. act. $[\alpha]_D^{22}$ = +17.5 (*c* = 1.00, $CHCl_3$).

(22*E*)-3β-(Chloromethyl)dimethylsilyloxy-13(14→8),14(8→7)di*abeo*-7β(H)-ergosta-4,8,22-trien-14-one (**60**)



To a solution of allylic alcohol **S10** (36.5 mg, 88.9 μmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) at 0 °C were added Et_3N (123 μL, 889 μmol, 10 eq.), 4-(dimethylamino)pyridine (2.2 mg, 18 μmol, 0.2 eq.) and (chloromethyl)-chlorodimethylsilane (58 μL, 0.44 mmol, 5.0 eq.) and the resulting solution was stirred at 25 °C for 1 h. The mixture was diluted with CH_2Cl_2 (5 mL), and NH_4Cl (sat. aq., 10 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed sequentially with NH_4Cl (sat. aq., 4 × 25 mL), $NaHCO_3$ (sat. aq., 25 mL) and brine (sat., 25 mL). The organic phase was dried over $MgSO_4$, the solvent was removed under reduced pressure and column chromatography (silica gel, *n*hexane/EtOAc 19:1) gave chloride **60** (46.0 mg, 88.9 μmol, quant.) as a colorless oil.

TLC: R_f = 0.18 (*n*hexane/EtOAc 19:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.32 – 5.26 (m, 2H), 5.23 (dd, *J* = 15.4, 7.8 Hz, 1H), 4.28 – 4.22 (m, 1H), 2.98 (dd, *J* = 7.0, 1.9 Hz, 1H), 2.78 (s, 2H), 2.61 (dd, *J* = 12.9, 1.6 Hz, 1H), 2.51 – 2.45 (m, 1H), 2.41 (ddd, *J* = 14.6, 7.8, 1.3 Hz, 1H), 2.33 (ddt, *J* = 12.9, 6.8, 1.7 Hz, 1H), 2.28 – 2.16 (m, 3H), 2.01 (ddd, *J* = 12.6, 7.5, 3.8 Hz, 1H), 1.92 – 1.87 (m, 1H), 1.87 – 1.82 (m, 1H), 1.72 – 1.61 (m, 4H), 1.50 – 1.42 (m, 2H), 1.37 – 1.30 (m, 1H), 1.28 – 1.24 (m, 1H), 1.18 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.00 (s, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.24 (d, *J* = 1.2 Hz, 6H).

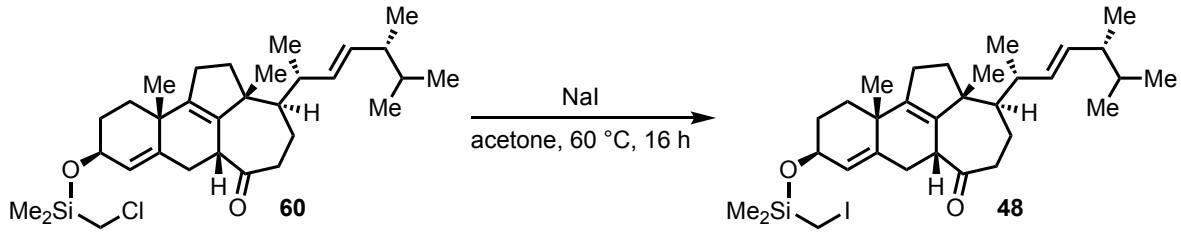
^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 213.9, 145.2, 142.6, 137.4, 134.7, 132.5, 125.6, 69.2, 54.1, 53.4, 46.6, 45.5, 43.5, 38.4, 38.0, 36.3, 33.2, 33.1, 32.6, 30.2, 29.0, 27.1, 23.8, 22.9, 21.4, 20.4, 20.2, 19.9, 17.8, –2.6, –2.7.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (s), 2924 (s), 2853 (m), 1709 (m), 1458 (w), 1377 (w), 1254 (m), 1127 (w), 1073 (m), 888 (m).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{31}H_{49}ClO_2SiNa^+$ $[M+Na]^+$: 539.3083, found: 539.3069.

Opt. act. $[\alpha]_D^{24}$ = +7.7 (*c* = 1.00, $CHCl_3$).

(22*E*)-3β-(Iodomethyl)dimethylsilyloxy-13(14→8),14(8→7)di*abeo*-7β(H)-ergosta-4,8,22-trien-14-one (**48**)



Sodium iodide (previously dried under reduced pressure at 120 °C for 24 h, 666 mg, 4.45 mmol, 50 eq.) was added to a solution of chloride **60** (46.0 mg, 88.9 μmol, 1.0 eq.) in acetone (5 mL) and the mixture was stirred at 60 °C for 16 h. The reaction mixture was allowed to cool to 25 °C, diluted with H_2O (5 mL) and EtOAc (5 mL), and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (sat., 30 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Crude iodide **48** was used in the next step without further purification

TLC: R_f = 0.19 (*n*hexane/EtOAc 19:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.32 – 5.27 (m, 2H), 5.23 (dd, *J* = 15.4, 7.6 Hz, 1H), 4.24 (ddt, *J* = 9.1, 6.5, 2.0 Hz, 1H), 2.98 (dt, *J* = 7.0, 1.9 Hz, 1H), 2.61 (dd, *J* = 12.9, 1.6 Hz, 1H), 2.51 – 2.45 (m, 1H), 2.41 (ddd, *J* = 14.6, 7.8, 1.3 Hz, 1H), 2.33 (ddt, *J* = 12.8, 6.8, 1.7 Hz, 1H), 2.28 – 2.18 (m, 3H), 2.04 (d, *J* = 1.5 Hz, 2H), 2.03 – 1.98 (m, 1H), 1.93 – 1.88 (m, 1H), 1.88 – 1.82 (m, 1H), 1.68 – 1.62 (m, 3H), 1.50 – 1.42 (m, 2H), 1.37 – 1.30 (m, 1H), 1.28 – 1.24 (m, 2H), 1.18 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.00 (s, 3H), 0.90

(d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H), 0.32 – 0.28 (m, 6H).

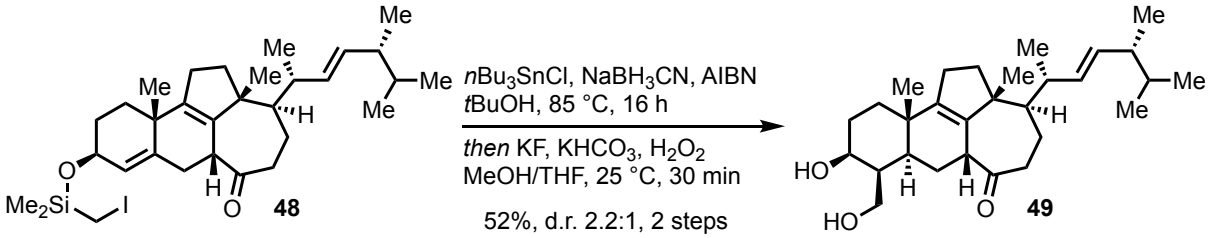
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 213.9, 145.2, 142.5, 137.4, 134.7, 132.5, 125.7, 69.2, 54.1, 53.4, 46.6, 45.5, 43.5, 38.4, 38.0, 36.3, 33.3, 33.2, 32.6, 29.1, 27.1, 23.8, 22.9, 21.4, 20.4, 20.2, 19.9, 17.8, –1.8, –1.8, –13.9.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (m), 2924 (s), 2853 (m), 1711 (w), 1456 (w), 1376 (w), 1253 (w), 1076 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{31}H_{49}IO_2SiNa^+$ [M+Na]$^+$: 631.2439, found: 631.2414.

Opt. act. $[\alpha]_D^{25}$ = +4.5 (c = 1.00, $CHCl_3$).

(22*E*)-3β-Hydroxy-4β-(hydroxymethyl)-13(14→8),14(8→7)di*abeo*-5α(H),7β(H)-ergosta-4,8,22-trien-14-one (**49**)



A solution of crude iodide **48** (88.9 μmol, 1.0 eq.), azobisisobutyronitrile (1.5 mg, 8.9 μmol, 0.1 eq.), nBu$_3$SnCl (4.8 μL, 18 μmol, 0.2 eq.) and $NaBH_3CN$ (11.2 mg, 178 μmol, 2.0 eq.) in tBuOH (2.5 mL) was degassed applying three freeze-pump-thaw cycles and then stirred at 85 °C for 16 h. The reaction mixture was cooled to 25 °C and diluted with EtOAc (5 mL) and brine (sat., 15 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (sat., 30 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was taken up in MeOH/THF (2:1, 2.25 mL) and KF (51.7 mg, 889 μmol, 10 eq.), $KHCO_3$ (89.0 mg, 889 μmol, 10 eq.), and H_2O_2 (35% w/w, 1.5 mL) were added at 25 °C and the reaction mixture was stirred at this temperature for 30 min. It was diluted with EtOAc (5 mL) and cooled in a H_2O bath to maintain the temperature at 25 °C before $Na_2S_2O_3$ (sat. aq., 5 mL) was added carefully. The aqueous phase was extracted with EtOAc (3 × 10 mL), the combined organic phases were washed sequentially with $NaHCO_3$ (sat. aq., 30 mL) and brine (sat., 30 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 2:1 → 1:1 → 1:2) gave 5α-epimer **49** (14.2 mg, 32 μmol, 36%) and 5β-epimer **S11** (6.4 mg, 14 μmol, 16%) both as colorless oils.

major 5α-epimer **49**

TLC: R_f = 0.26 (*n*hexane/EtOAc 1:2).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.33 (dd, J = 15.5, 8.0 Hz, 1H), 5.23 (dd, J = 15.4, 7.9 Hz, 1H), 4.02 (dd, J = 11.0, 9.8 Hz, 1H), 3.98 – 3.91 (m, 1H), 3.57 – 3.52 (m, 1H), 3.17 –

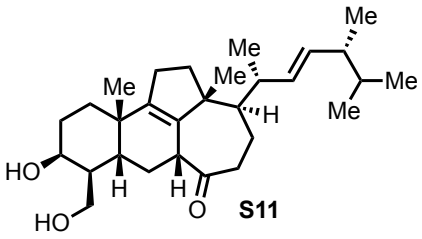
3.12 (m, 1H), 2.55 (ddd, *J* = 16.8, 5.0, 3.1 Hz, 1H), 2.46 (p, *J* = 7.2 Hz, 1H), 2.38 – 2.27 (m, 2H), 2.20 – 2.15 (m, 2H), 1.96 (d, *J* = 12.0 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.79 – 1.71 (m, 4H), 1.68 – 1.62 (m, 4H), 1.46 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.24 – 1.19 (m, 2H), 1.18 – 1.11 (m, 1H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.98 (s, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.78 (s, 3H).

^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 213.3, 146.9, 136.1, 134.7, 132.7, 74.5, 60.3, 55.5, 53.5, 48.0, 45.7, 45.4, 43.5, 41.5, 38.6, 38.4, 35.1, 34.7, 33.2, 27.5, 26.9, 26.7, 23.0, 20.6, 20.3, 19.9, 19.6, 19.1, 17.8.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3357 (br w), 2952 (m), 2925 (m), 2853 (w), 1738 (s), 1456 (w), 1366 (m), 1229 (m), 1217 (m), 715 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{29}H_{46}O_3Na^+$ $[M+Na]^+$: 465.3339, found: 465.3335.

Opt. act. $[\alpha]_D^{22}$ = +42.3 (*c* = 0.68, $CHCl_3$).



S11

major 5b-epimer **S11**

TLC: R_f = 0.19 (*n*hexane/EtOAc 1:1).

^{1}H-NMR: (700 MHz, $CDCl_3$); δ [ppm] = 5.30 (dd, *J* = 15.6, 7.4 Hz, 1H), 5.24 (dd, *J* = 15.2, 8.0 Hz, 1H), 4.13 (dt, *J* = 4.2, 2.6 Hz, 1H), 3.88 (dd, *J* = 11.1, 5.2 Hz, 1H), 3.74 (dd, *J* = 11.2, 2.4 Hz, 1H), 2.84 – 2.79 (m, 1H), 2.53 – 2.47 (m, 2H), 2.45 – 2.40 (m, 2H), 2.34 – 2.28 (m, 1H), 2.27 – 2.21 (m, 1H), 2.03 – 1.97 (m, 2H), 1.88 (dt, *J* = 11.7, 3.6 Hz, 1H), 1.87 – 1.83 (m, 1H), 1.76 – 1.68 (m, 3H), 1.63 (dq, *J* = 13.7, 3.7 Hz, 1H), 1.57 – 1.53 (m, 2H), 1.49 – 1.43 (m, 2H), 1.36 (dt, *J* = 11.5, 1.9 Hz, 1H), 1.28 (ddd, *J* = 13.8, 3.4, 2.2 Hz, 1H), 1.07 (s, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.98 (s, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

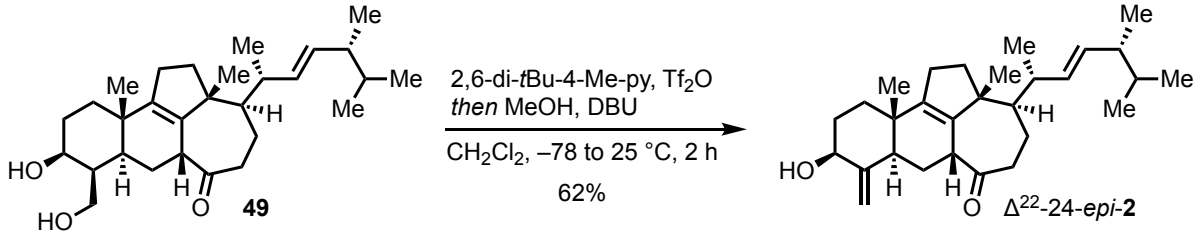
^{13}C-NMR: (176 MHz, $CDCl_3$); δ [ppm] = 215.3, 143.3, 137.9, 134.7, 132.6, 70.7, 64.7, 56.3, 54.9, 45.3, 43.5, 43.5, 41.6, 38.7, 38.0, 36.4, 35.0, 33.3, 30.2, 29.4, 29.1, 28.4, 24.4, 23.1, 21.7, 21.5, 20.2, 19.9, 17.7.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 3356 (br w), 2953 (m), 2923 (s), 2853 (m), 1740 (w), 1459 (w), 1376 (w), 1229 (w), 1217 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{29}H_{46}O_3Na^+$ $[M+Na]^+$: 465.3339, found: 465.3344.

Opt. act. $[\alpha]_D^{22}$ = +1.5 (*c* = 0.23, $CHCl_3$).

Δ[22]-24-*epi*-Swinhoeisterol A (Δ[22]-24-*epi*-**2**)



To a solution of diol **49** (7.4 mg, 17 μmol, 1.0 eq) in CH_2Cl_2 (1.5 mL) was added 2,6-di-*tert*-butyl-4-methyl-pyridine (18.5 mg, 90.0 μmol, 7.5 eq.) and it was cooled to –78 °C. Triflic anhydride (1 M in CH_2Cl_2, 42 μL, 42 μmol, 2.5 eq.) was added dropwise and the reaction was stirred at this temperature for 5 min before MeOH (20 μL, 0.50 mmol, 30 eq.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (50 μL, 0.33 μmol, 20 eq.) were added. The reaction mixture was allowed to warm to 25 °C over 1.5 h, and then stirred at this temperature for 1 h before HCl (1 M in H_2O, 5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were washed sequentially with HCl (1 M in H_2O, 20 mL), $NaHCO_3$ (sat. aq., 20 mL), and brine (sat., 20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (silica gel, *n*hexane/EtOAc 4:1) gave Δ[22]-24-*epi*-swinhoeisterol A (Δ[22]-24-*epi*-**2**) (4.5 mg, 10 μmol, 62%) as a colorless oil.

TLC: R_f = 0.25 (*n*hexane/EtOAc 3:1).

^{1}H-NMR: (600 MHz, $CDCl_3$); δ [ppm] = 5.35 (dd, *J* = 15.4, 7.8 Hz, 1H), 5.25 (dd, *J* = 15.3, 8.1 Hz, 1H), 5.09 (s, 1H), 4.69 (s, 1H), 4.05 (dd, *J* = 11.4, 5.8 Hz, 1H), 3.19 – 3.15 (m, 1H), 2.55 (dt, *J* = 16.6, 4.1 Hz, 1H), 2.49 (p, *J* = 7.3 Hz, 1H), 2.36 (dd, *J* = 9.3, 6.7 Hz, 1H), 2.31 – 2.26 (m, 1H), 2.20 (dtd, *J* = 15.7, 7.6, 2.9 Hz, 1H), 2.13 (d, *J* = 13.2 Hz, 1H), 2.07 – 2.03 (m, 2H), 1.86 (p, *J* = 6.7 Hz, 1H), 1.83 – 1.79 (m, 2H), 1.72 – 1.67 (m, 3H), 1.58 (dd, *J* = 12.7, 6.3 Hz, 1H), 1.49 – 1.44 (m, 2H), 1.36 (td, *J* = 12.8, 4.3 Hz, 1H), 1.30 – 1.26 (m, 1H), 1.04 – 1.01 (m, 6H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.78 (s, 3H).

^{13}C-NMR: (151 MHz, $CDCl_3$); δ [ppm] = 213.3, 152.0, 146.8, 136.1, 134.7, 132.7, 102.9, 73.1, 55.6, 53.6, 45.4, 45.2, 44.3, 43.6, 38.8, 38.4, 37.6, 34.8, 33.3, 32.5, 27.8, 24.3, 23.0, 20.9, 20.2, 19.9, 19.7, 17.9, 17.8.

IR: (neat); $\tilde{\nu}$ [cm^{-1}] = 2954 (m), 2923 (s), 2853 (m), 1740 (w), 1459 (w), 1377 (w), 1010 (w), 970 (w).

HRMS: (ESI-TOF); *m/z* calcd. for $C_{29}H_{44}O_2Na^+$ $[M+Na]^+$: 447.3234, found: 447.3228.

Opt. act. $[\alpha]_D^{22}$ = +84.4 (*c* = 0.25, $CHCl_3$).

3 NMR Comparisons

Table S1. ^{1}H-NMR comparison of synthetic swinhoeisterol A, natural swinhoeisterol A (**2**)[4], and synthetic Δ^{22}-24-*epi*-swinhoeisterol A (Δ^{22}-24-*epi*-**2**).

#	**Synthetic**[3],a	**Natural**[4],b	**Synthetic Δ^{22}-24-*epi***c
1	1.71 m; 1.36 td (13.3, 4.2)	1.70 ov; 1.35 m	1.72 m; 1.37 td (12.8, 4.3)
2	2.04 m; 1.48 qd (12.7, 4.3)	2.05 m; 1.46 ov	2.05 m; 1.48 m
3	4.04 dd (11.9, 5.8)	4.03 dd (14.5, 5.8)	4.05 dd (11.4, 5.8)
4		-	-
5	2.00 d (12.6)	2.01 d (13.0)	2.05 d (14.0)
6	2.15 d (13.1); 1.60 dd (12.9, 6.4)	2.14 d (12.8); 1.61 dd (12.8, 6.3)	2.13 d (13.2); 1.58 dd (12.7, 6.3)
7	3.14 m	3.14 m	3.17 m
8	-	-	-
9	-	-	-
10	-	-	-
11	2.29 m; 2.20 m	2.27 m; 2.21 ddd (9.1, 6.3, 2.9)	2.29 m; 2.19 dtd (15.7, 7.6, 2.9)
12	1.80 m; 1.76 m	1.80 ov; 1.77 ov	1.81 m
13	-	-	-
14	-	-	-
15	2.53 ddd (16.3, 6.1, 2.4); 2.36 ddd (15.9, 11.7, 3.5)	2.54 m; 2.35 m	2.55 dt (16.6, 4.1); 2.36 dd (9.3, 6.7)
16	1.68 m (2D); 1.66 m	1.68 ov; 1.65 ov	1.69 m
17	1.26 m	1.25 ov	1.26 m
18	1.01 s	1.00 s	1.02 s
19	0.78 s	0.78 s	0.78 s
20	1.56 m	1.56 ov	2.49 p (7.3)
21	0.93 d (6.9)	0.92 d (6.8)	1.03 d (6.8)
22	0.91 m; 1.39 m	0.91 m; 1.39 ov	5.35 dd (15.4, 7.8)
23	1.19 m	1.19 ov	5.25 dd (15.3, 8.1)
24	1.20 m	1.20 ov	1.87 p (6.7)
24^{1}	0.78 d (6.5)	0.78 d (6.8)	0.92 d (6.8)
25	1.55 m	1.55 ov	1.48 m
26	0.86 d (6.8)	0.85 d (6.8)	0.84 d (6.7)
27	0.80 d (6.8)	0.80 d (7.1)	0.82 d (6.8)
28	5.09 s; 4.69 s	5.09 s; 4.68 s	5.09 s; 4.69 s

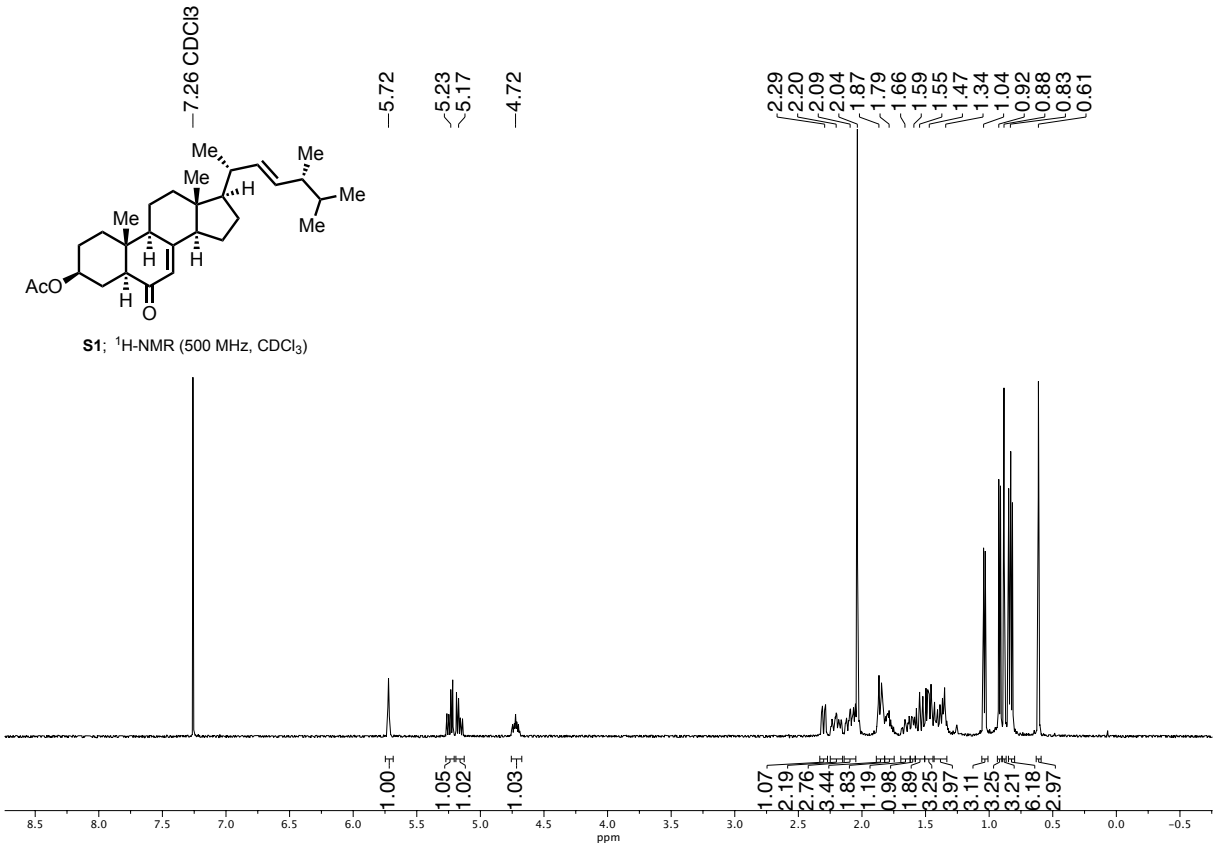
All chemical shifts are reported in ppm. Coupling constants are in parentheses and are reported in Hz. m = centered multiplet, ov = overlain. All spectra were measured in $CDCl_3$ and are referenced to the residual solvent peak at δ_H = 7.26 ppm. [a] Recorded at 700 MHz. [b] recorded at 500 MHz. [c] recorded at 600 MHz

Table S2. ^{13}C-NMR comparison of synthetic swinhoeisterol A, natural swinhoeisterol A (**2**)[4], and synthetic Δ^{22}-24-*epi*-swinhoeisterol A (Δ^{22}-24-*epi*-**2**).

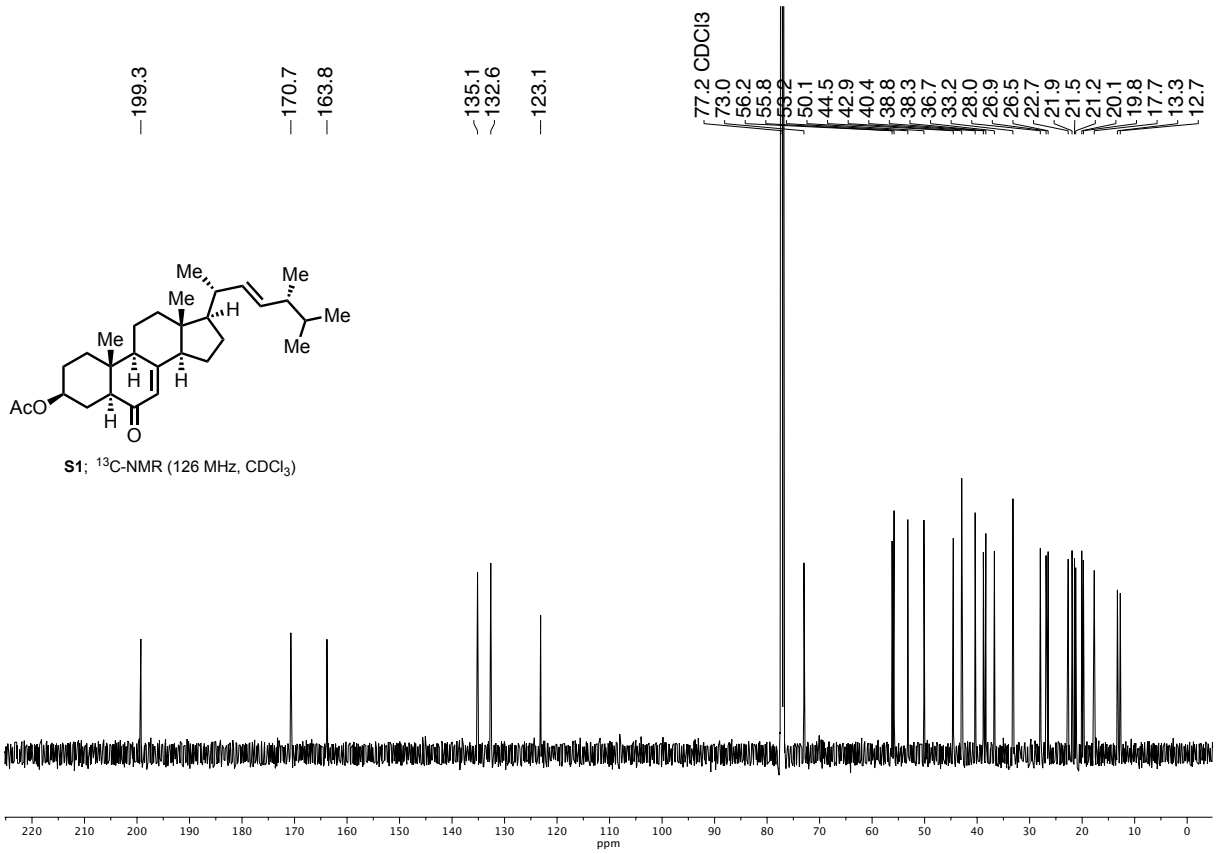
#	**Synthetic**[3],a	**Natural**[4],b	**Synthetic Δ^{22}-24-*epi***a
1	34.8	34.7	34.8
2	32.5	32.4	32.5
3	73.1	73.1	73.1
4	151.9	151.9	152.0
5	44.4	44.3	44.3
6	24.5	24.5	24.3
7	45.3	45.3	45.2
8	136.0	135.9	136.1
9	146.9	146.9	146.8
10	37.7	37.7	37.6
11	27.8	27.8	27.8
12	38.7	38.7	38.8
13	53.8	53.8	53.6
14	213.6	213.7	213.3
15	45.4	45.4	45.4
16	20.1	20.1	20.9
17	55.8	55.8	55.6
18	20.0	20.0	19.7
19	17.9	17.9	17.9
20	35.2	35.1	38.4
21	21.6	21.6	23.0
22	30.5	30.5	132.7
23	33.5	33.4	134.7
24	39.1	39.1	43.6
24[1]	15.6	15.6	17.8
25	32.2	32.3	33.3
26	20.4	20.4	20.2
27	18.2	18.2	19.9
28	102.9	102.9	102.9

All chemical shifts are reported in ppm. All spectra were measured in $CDCl_3$ and are referenced to the residual solvent peak at δ_C = 77.16 ppm. [a] Recorded at 176 MHz. [b] recorded at 126 MHz. [c] recorded at 151 MHz.

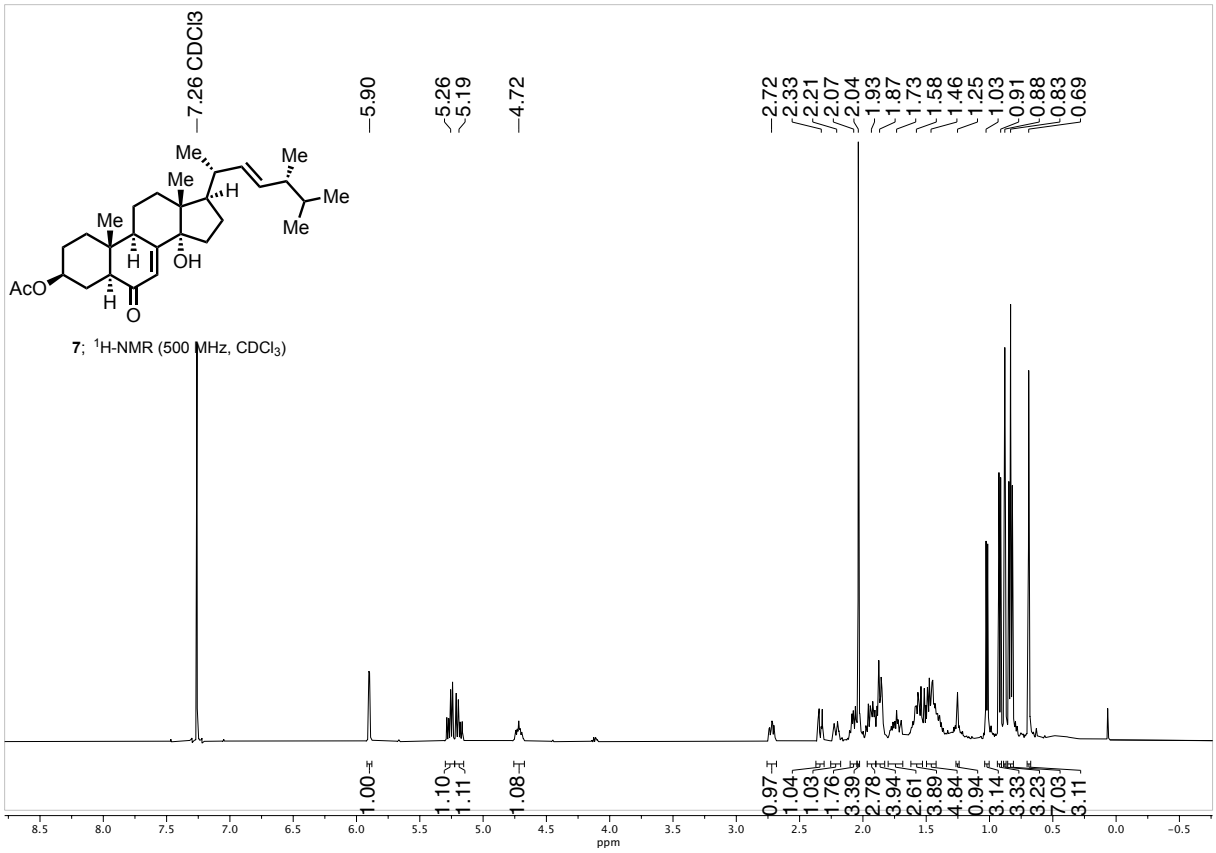
4 NMR Spectra



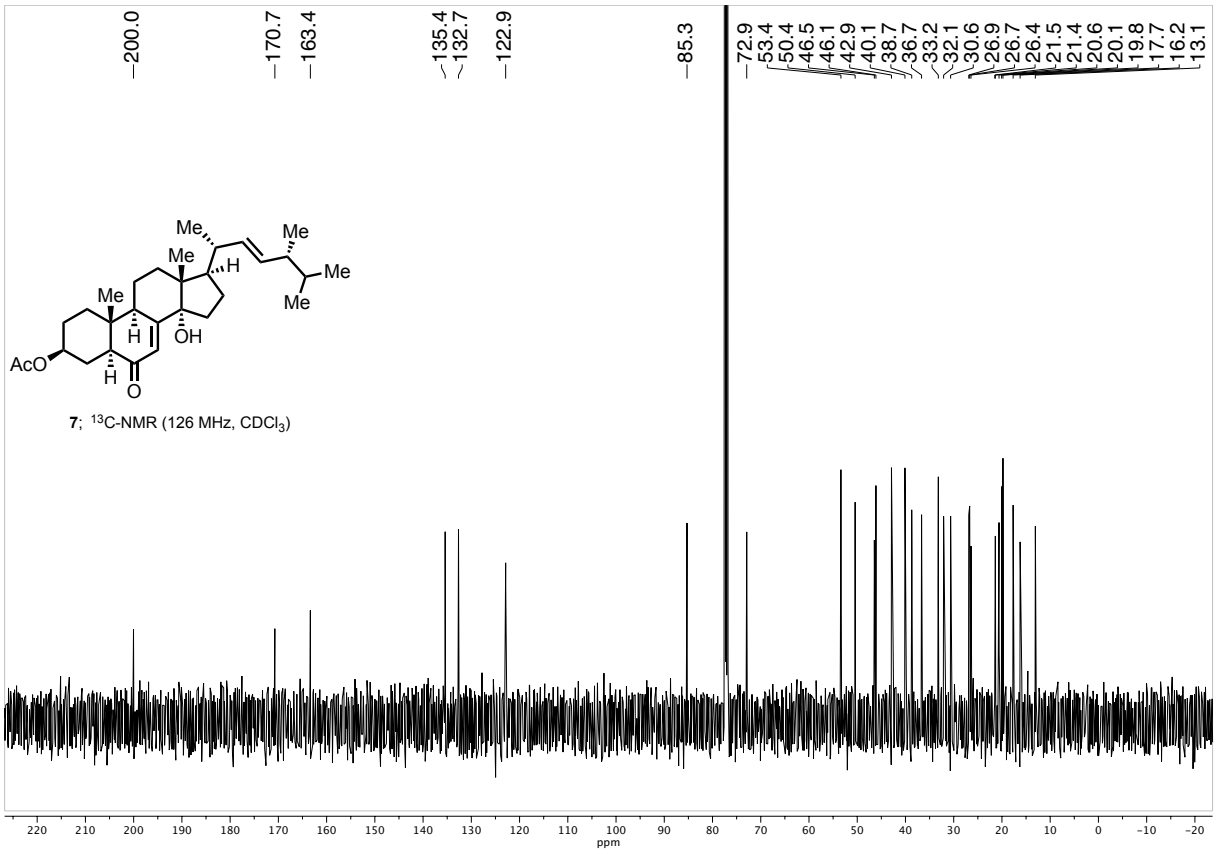
S1; ^{1}H-NMR (500 MHz, $CDCl_3$)



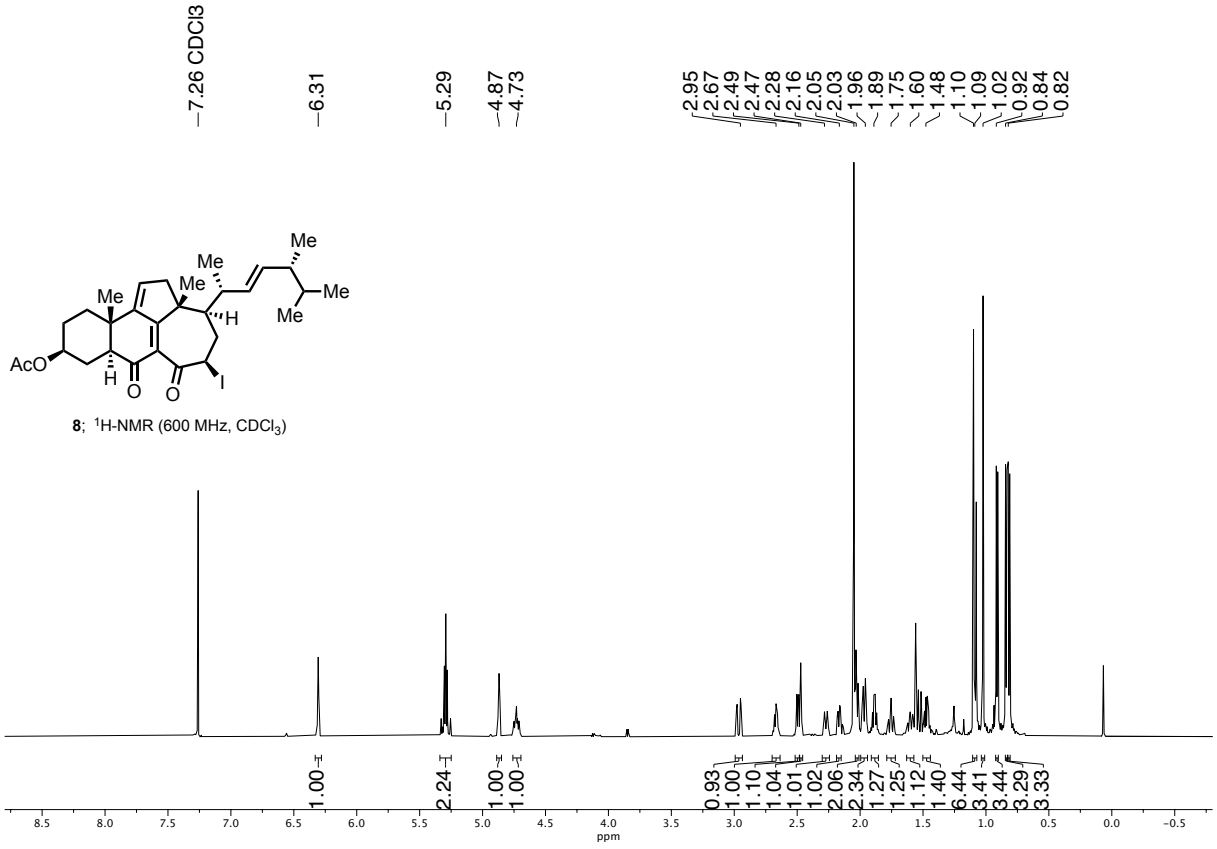
S1; ^{13}C-NMR (126 MHz, $CDCl_3$)



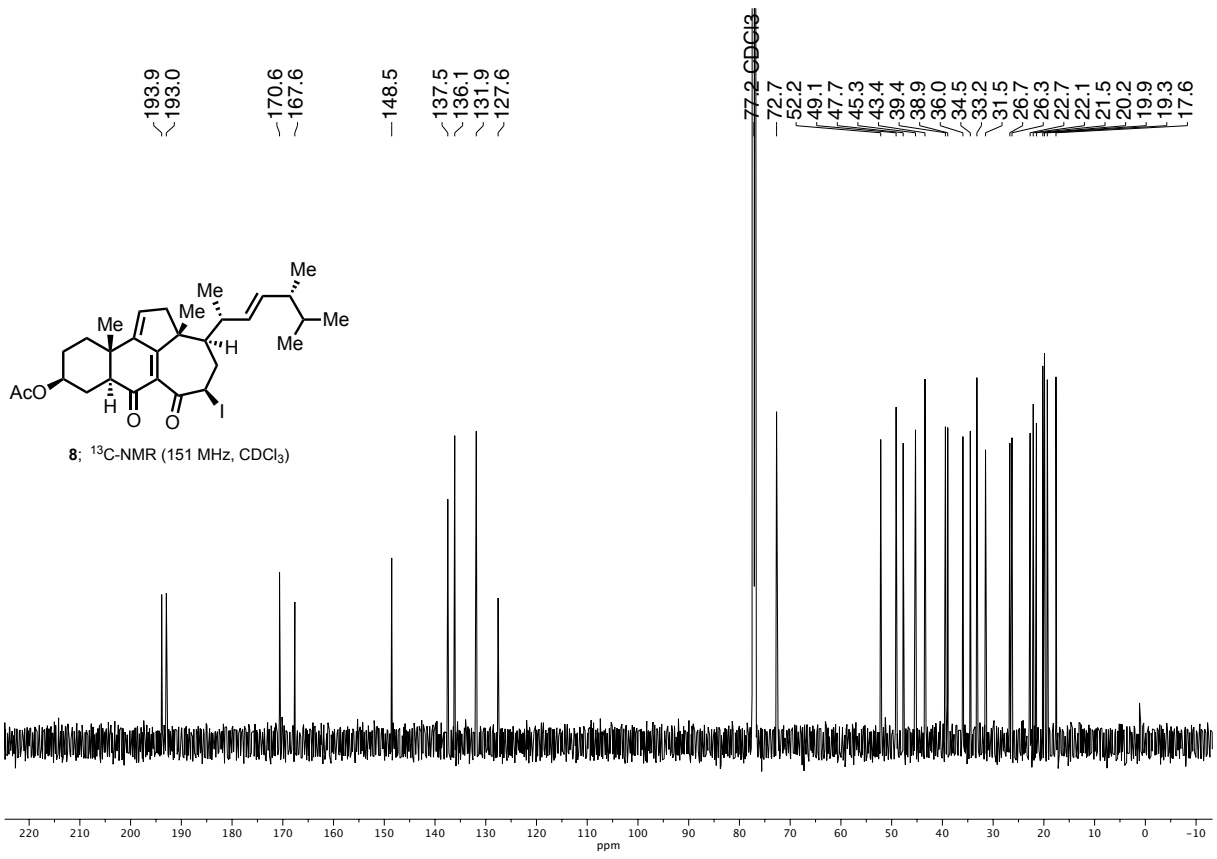
7; ^{1}H-NMR (500 MHz, $CDCl_3$)



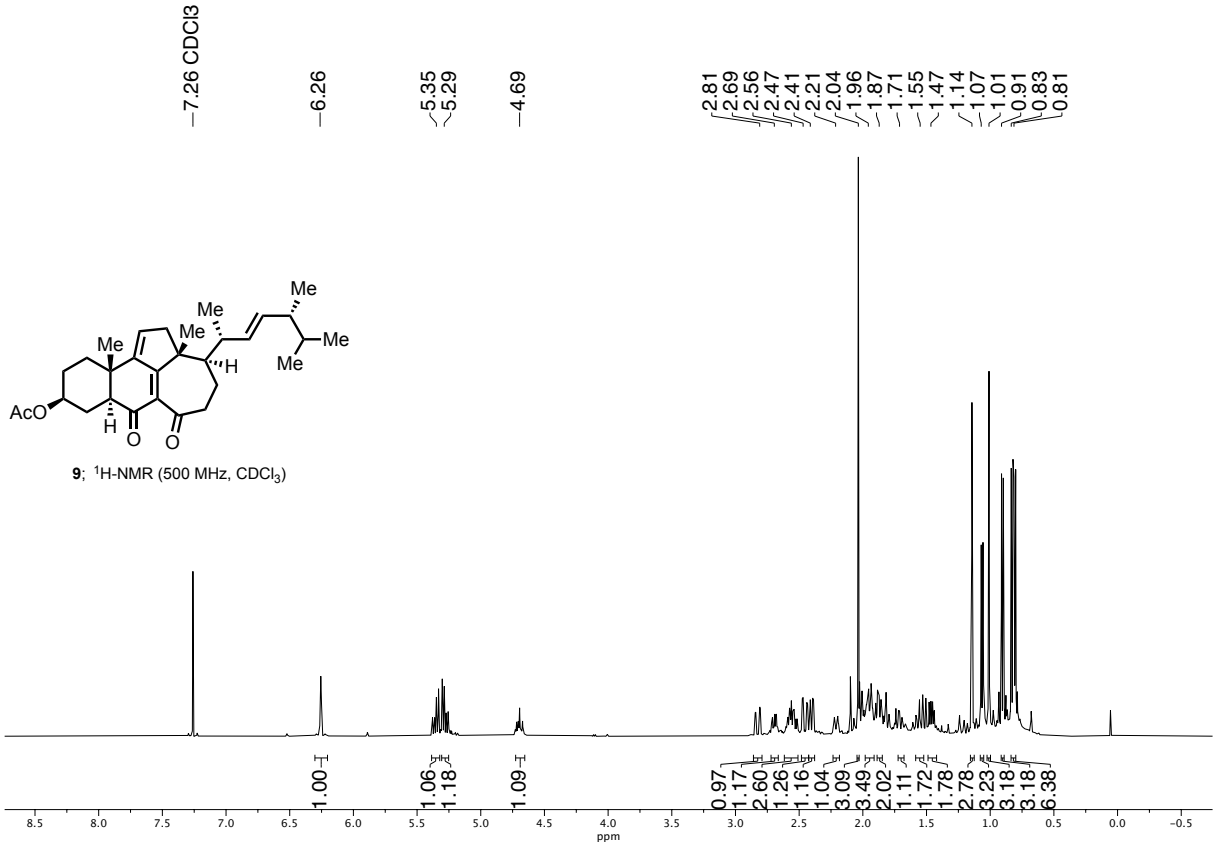
7; ^{13}C-NMR (126 MHz, $CDCl_3$)



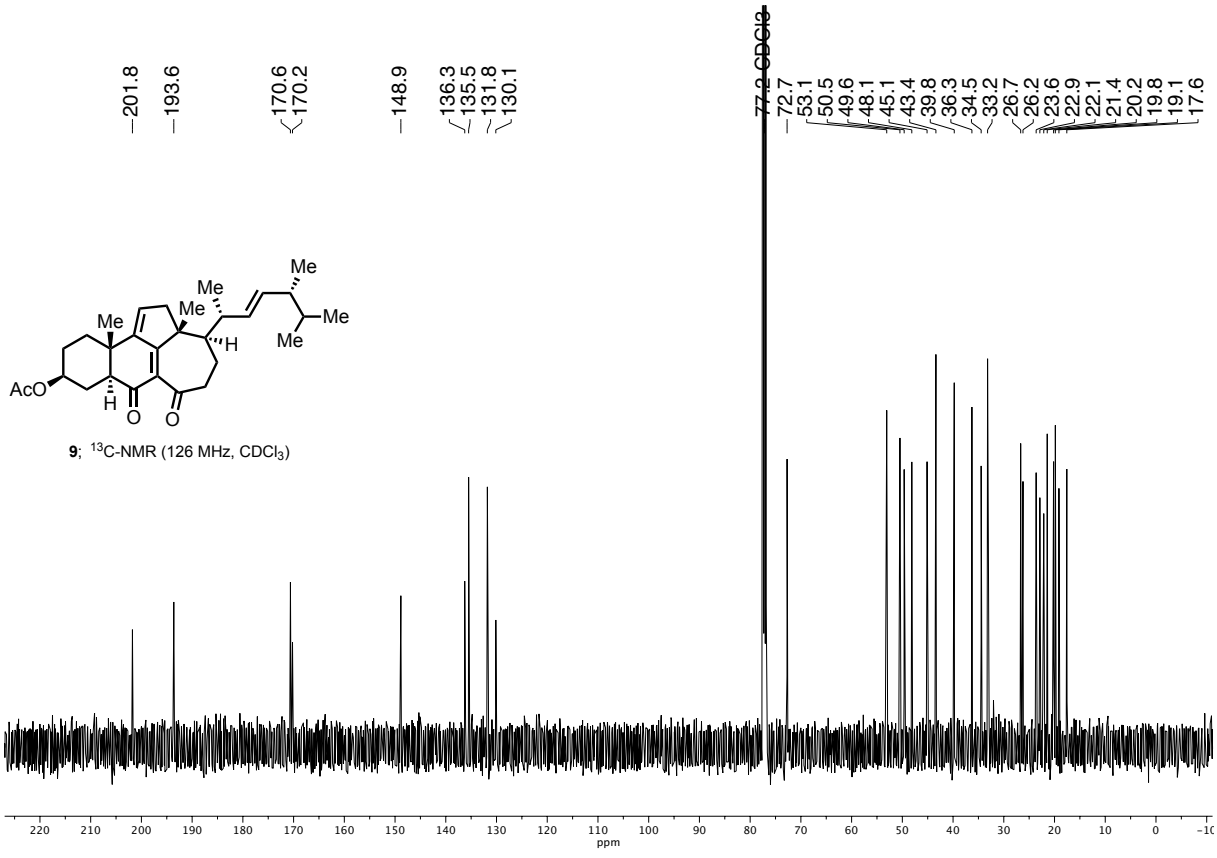
8; ^{1}H-NMR (600 MHz, $CDCl_3$)



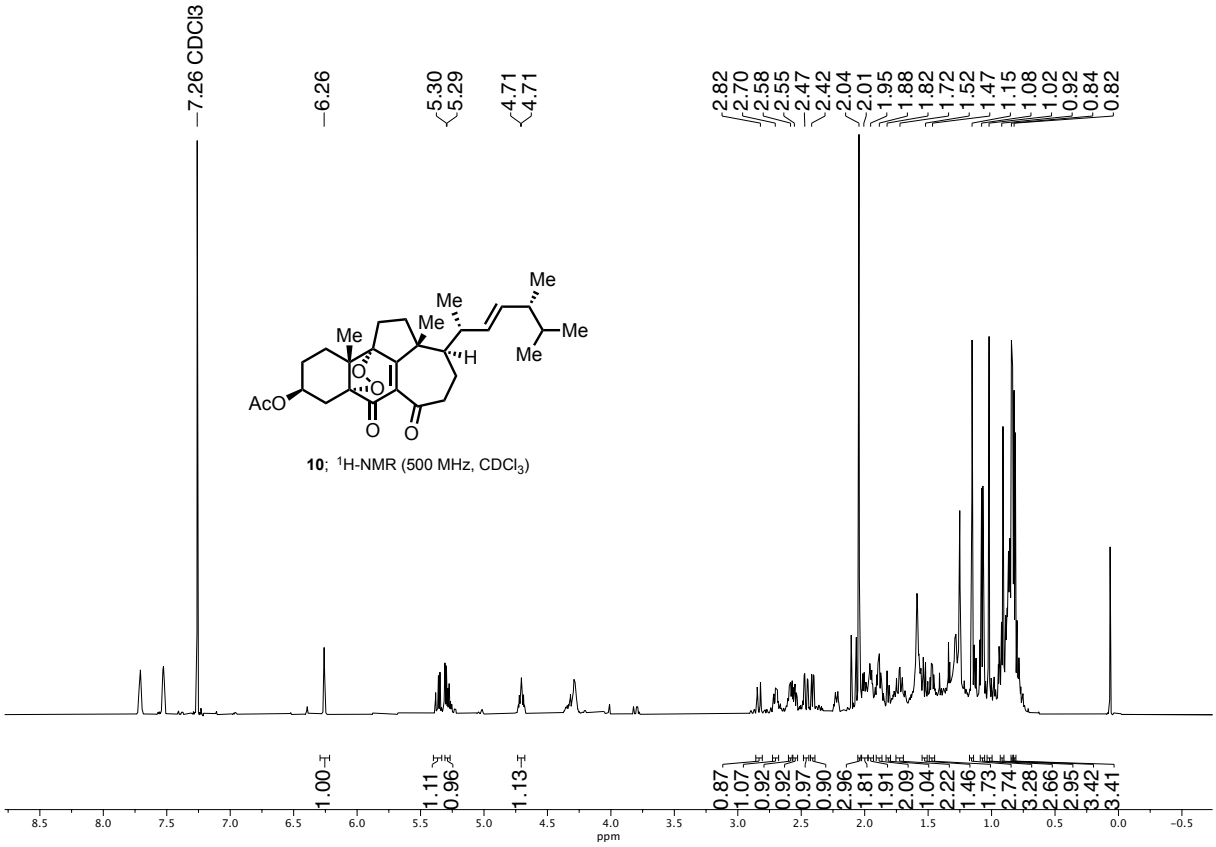
8; ^{13}C-NMR (151 MHz, $CDCl_3$)



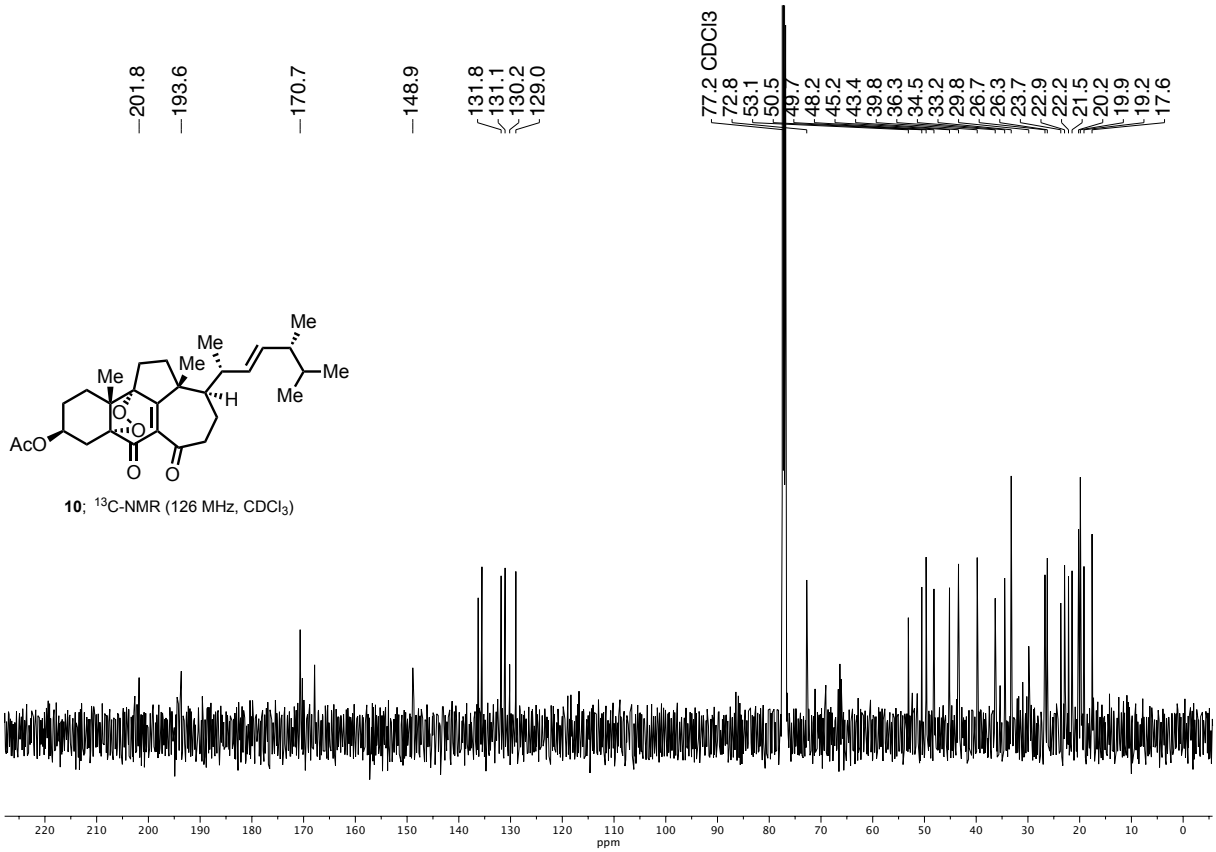
9; ^{1}H-NMR (500 MHz, $CDCl_3$)



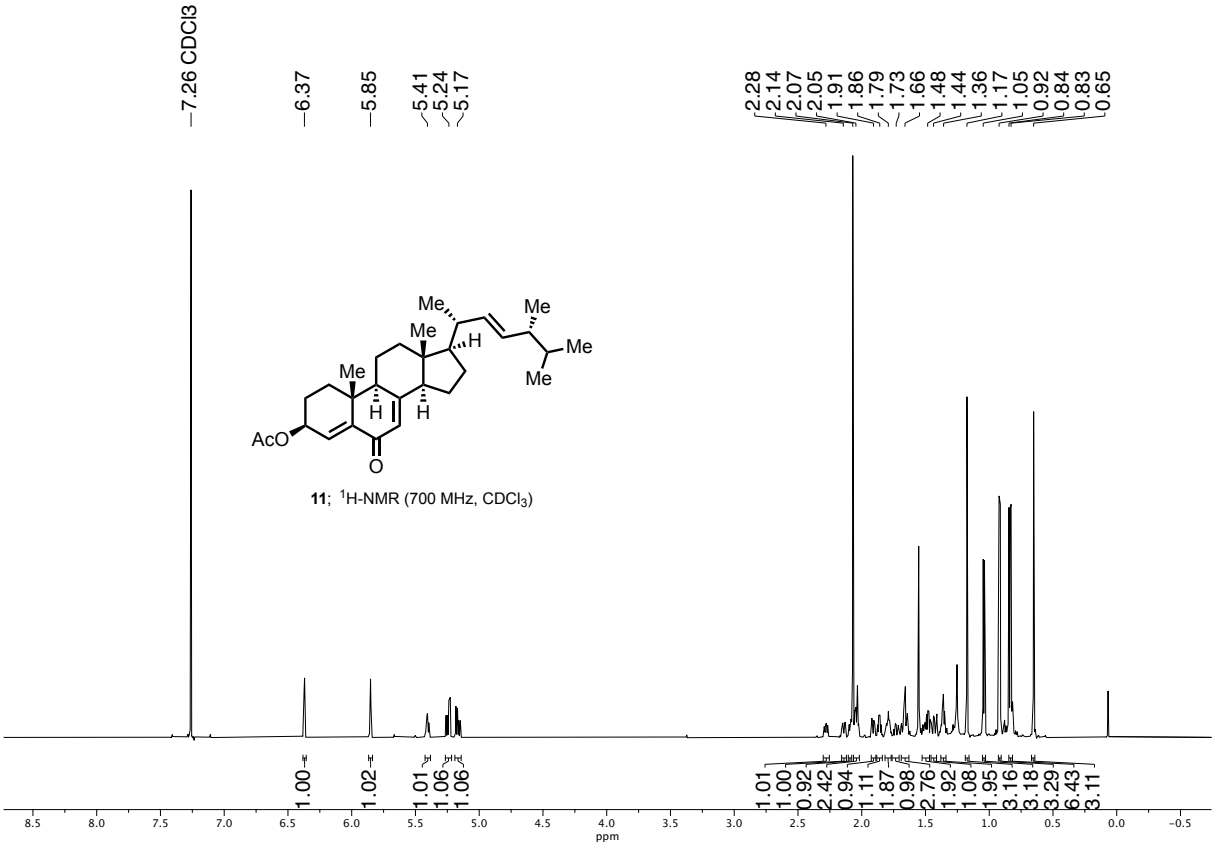
9; ^{13}C-NMR (126 MHz, $CDCl_3$)



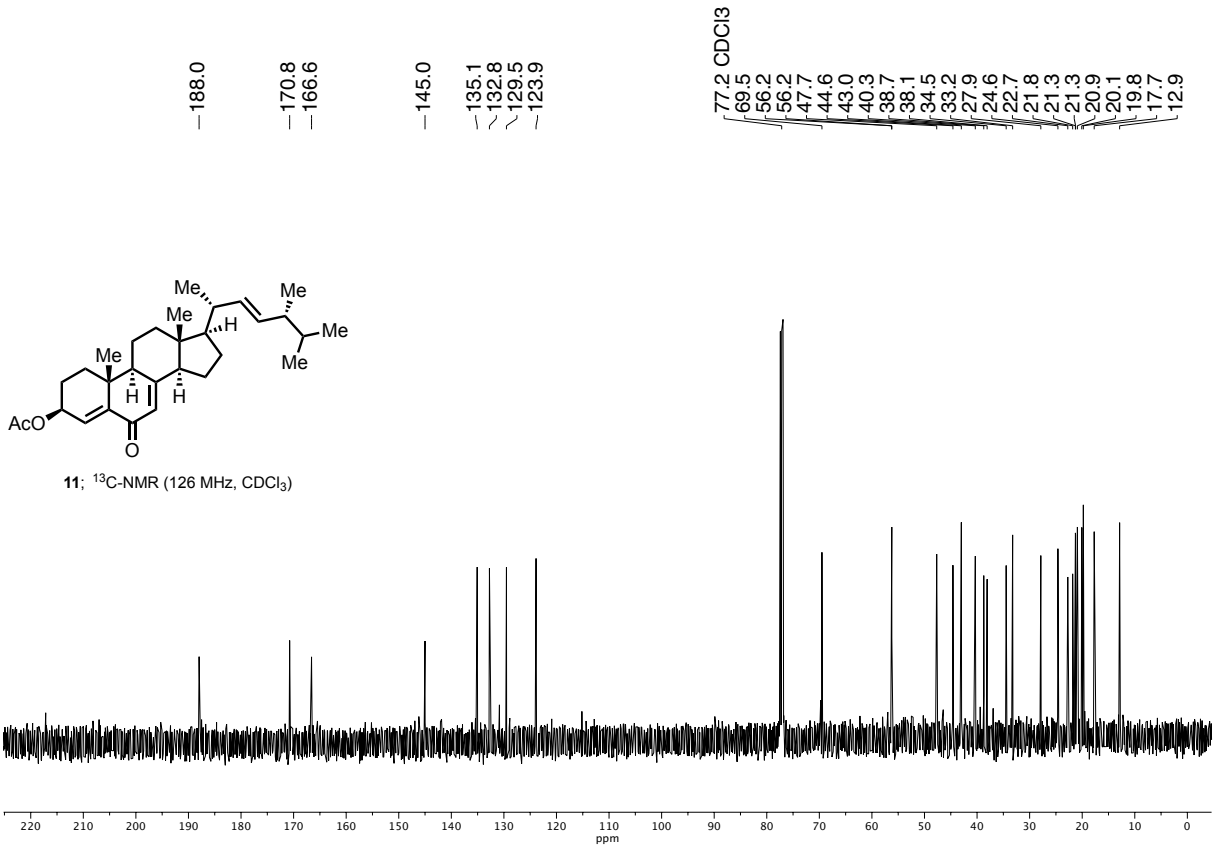
10; ^{1}H-NMR (500 MHz, $CDCl_3$)



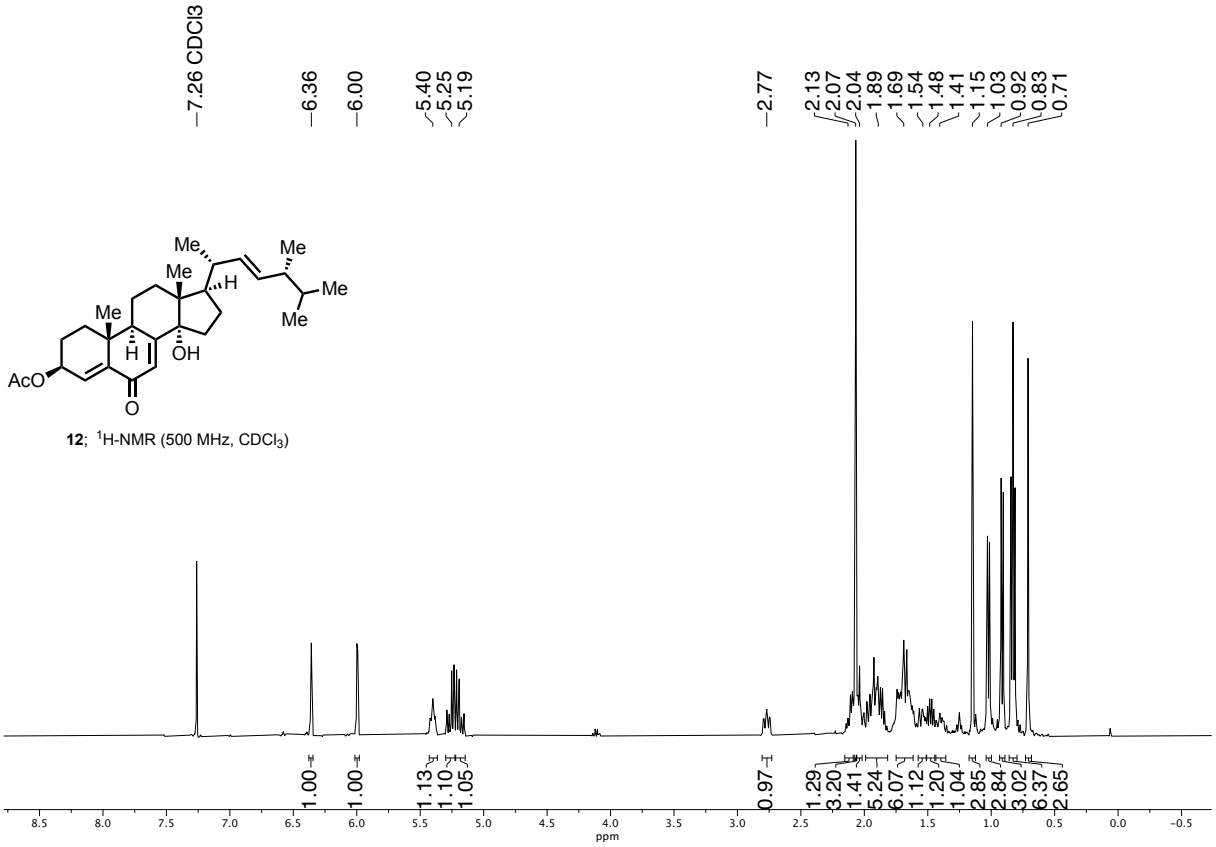
10; ^{13}C-NMR (126 MHz, $CDCl_3$)



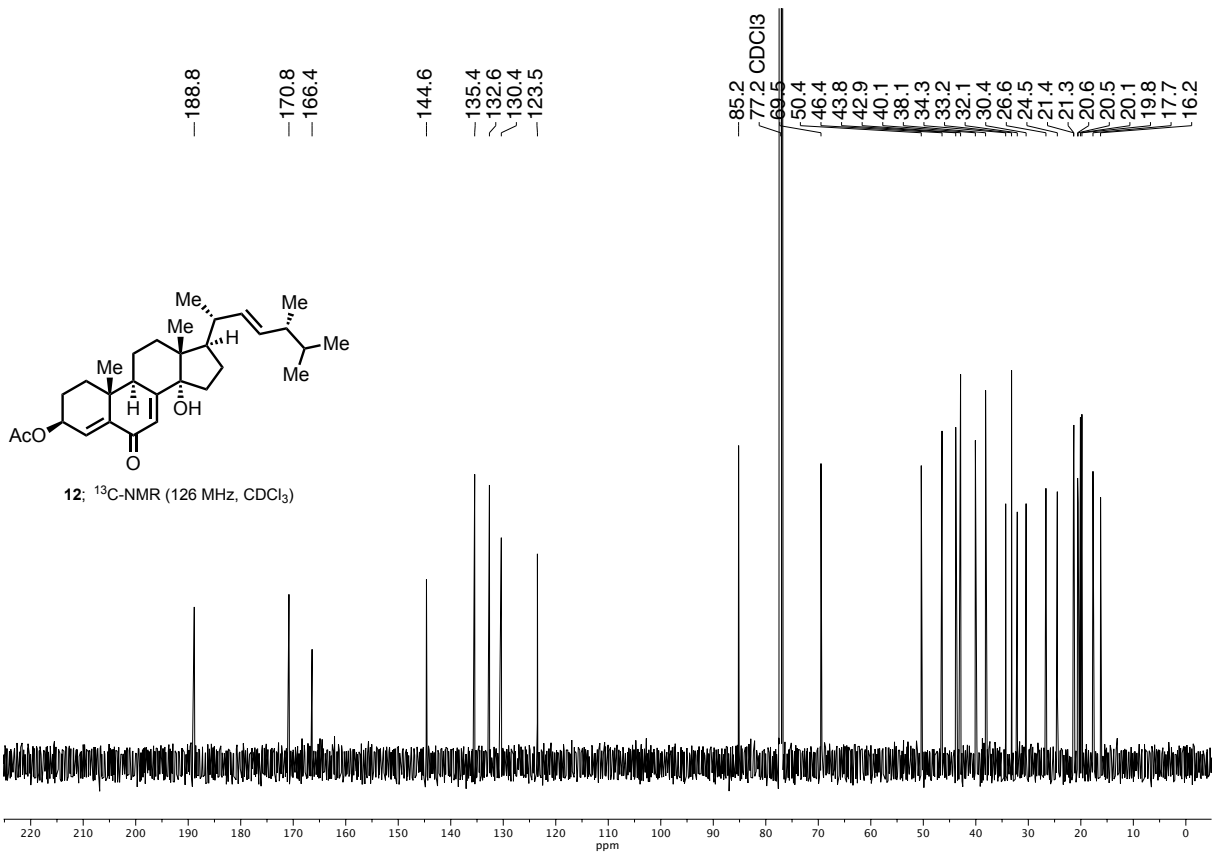
11; ^{1}H-NMR (700 MHz, $CDCl_3$)



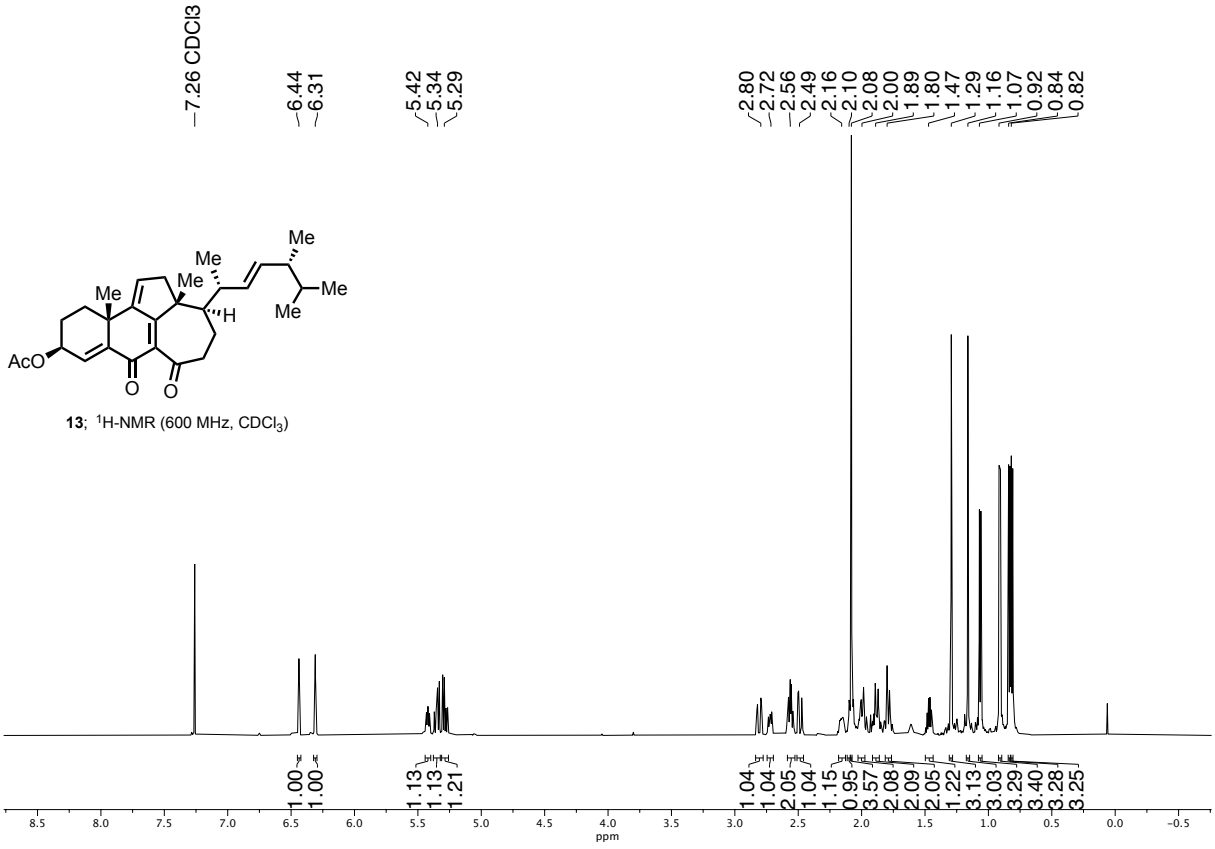
11; ^{13}C-NMR (126 MHz, $CDCl_3$)



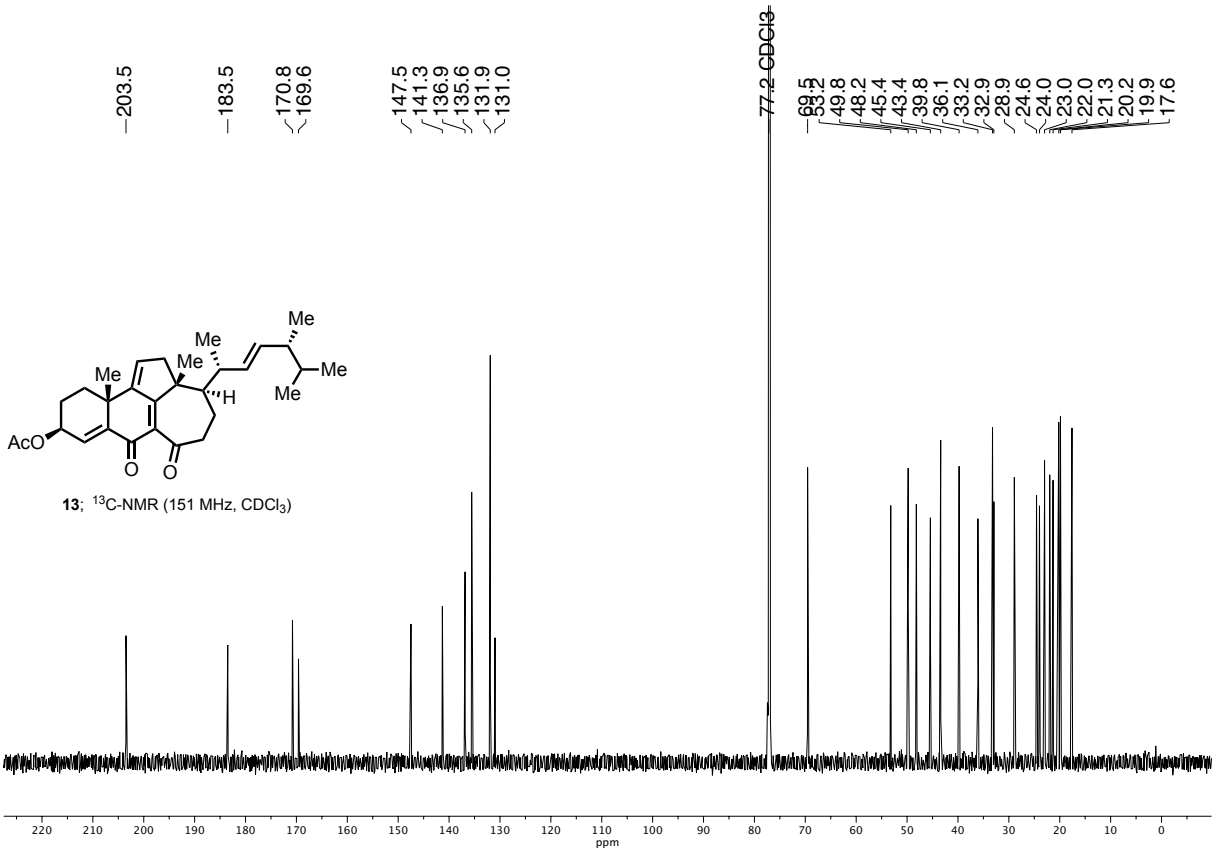
12; ^{1}H-NMR (500 MHz, $CDCl_3$)



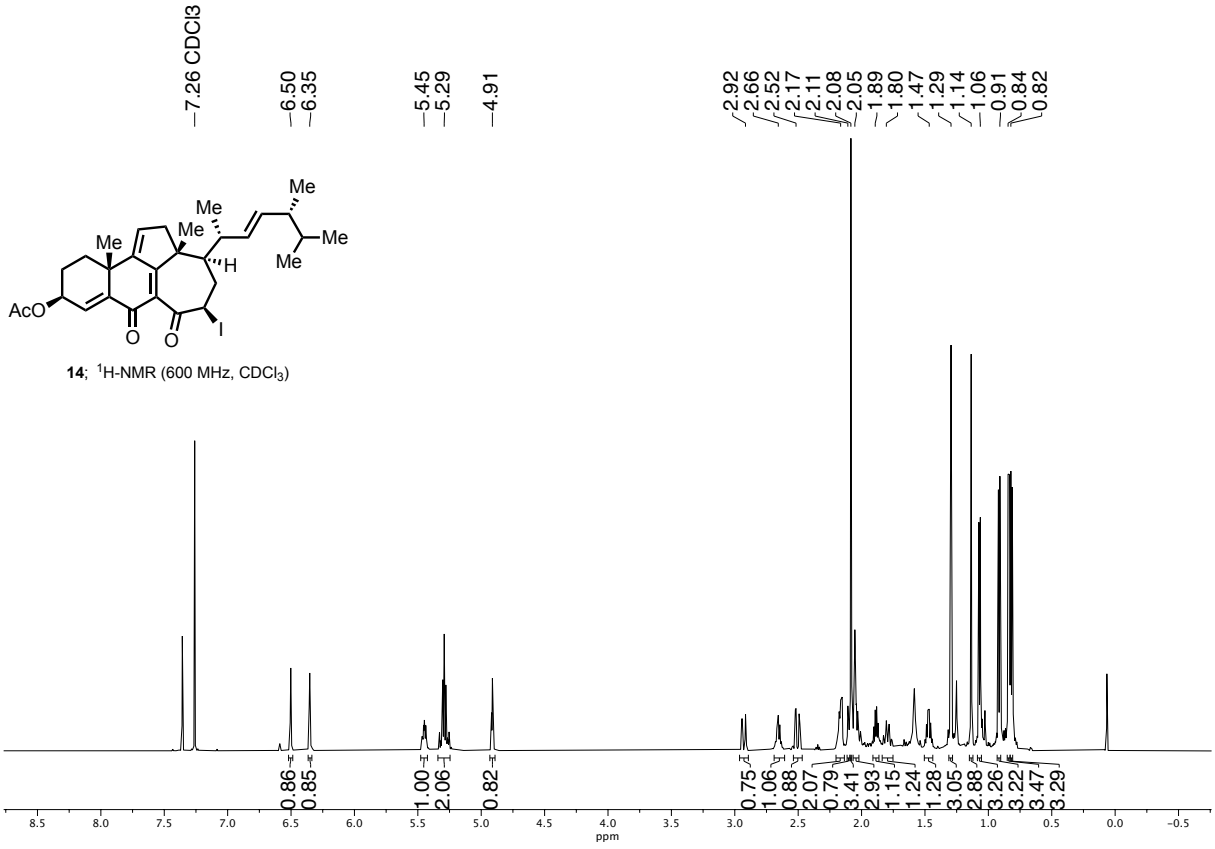
12; ^{13}C-NMR (126 MHz, $CDCl_3$)



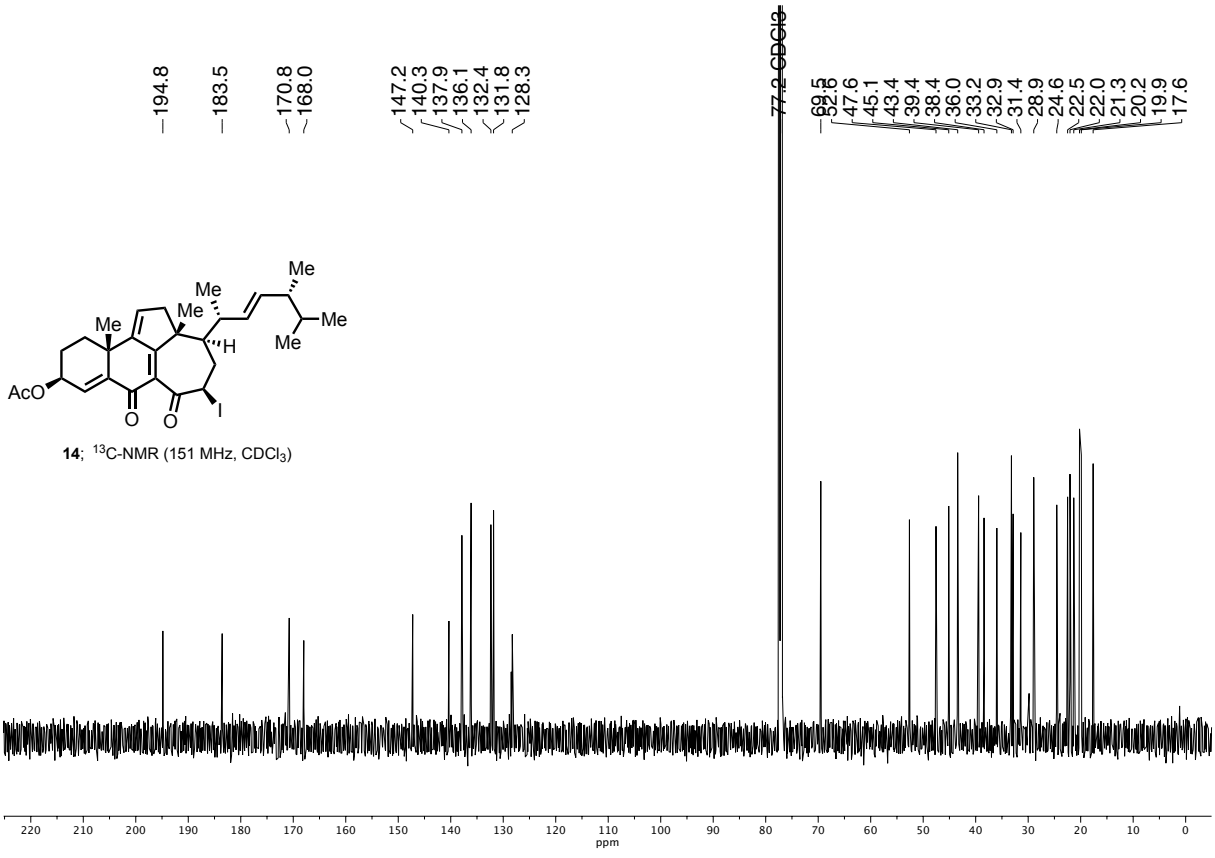
13; ^{1}H-NMR (600 MHz, $CDCl_3$)



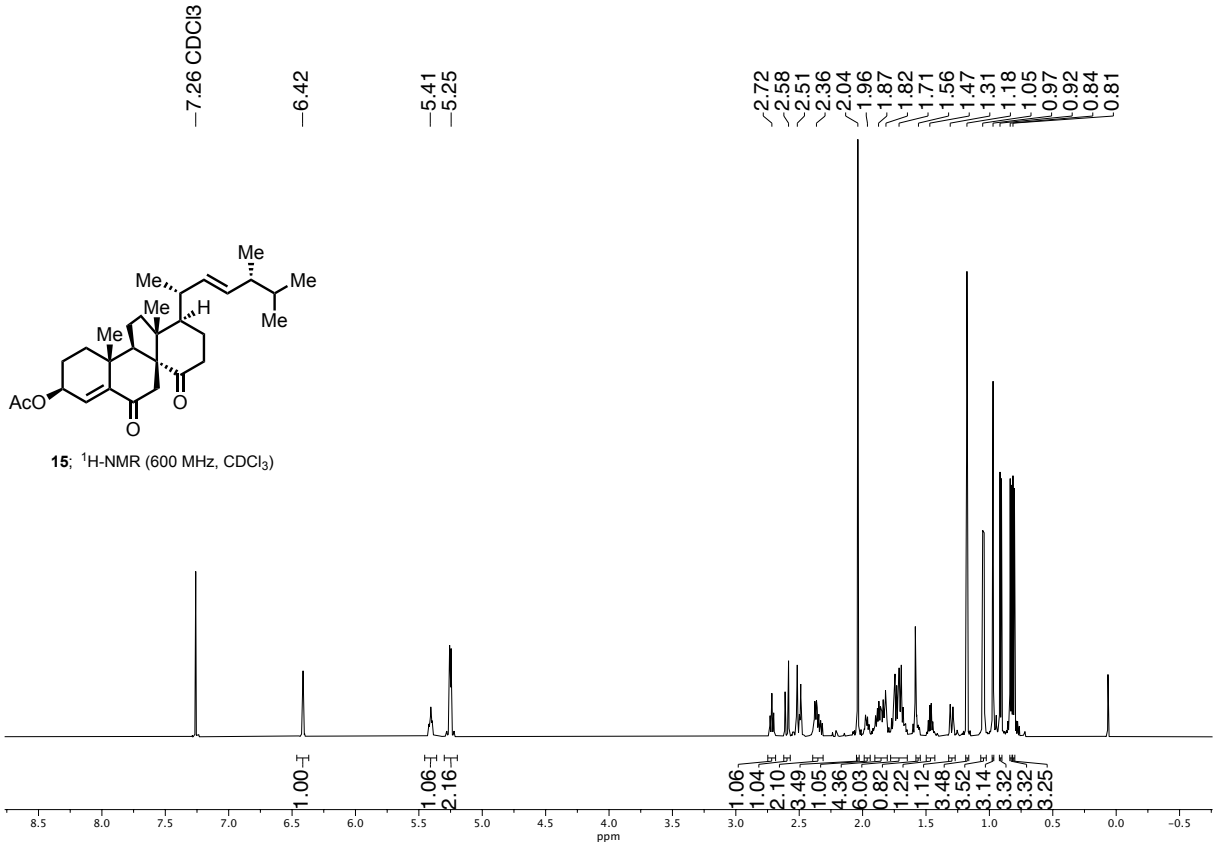
13; ^{13}C-NMR (151 MHz, $CDCl_3$)



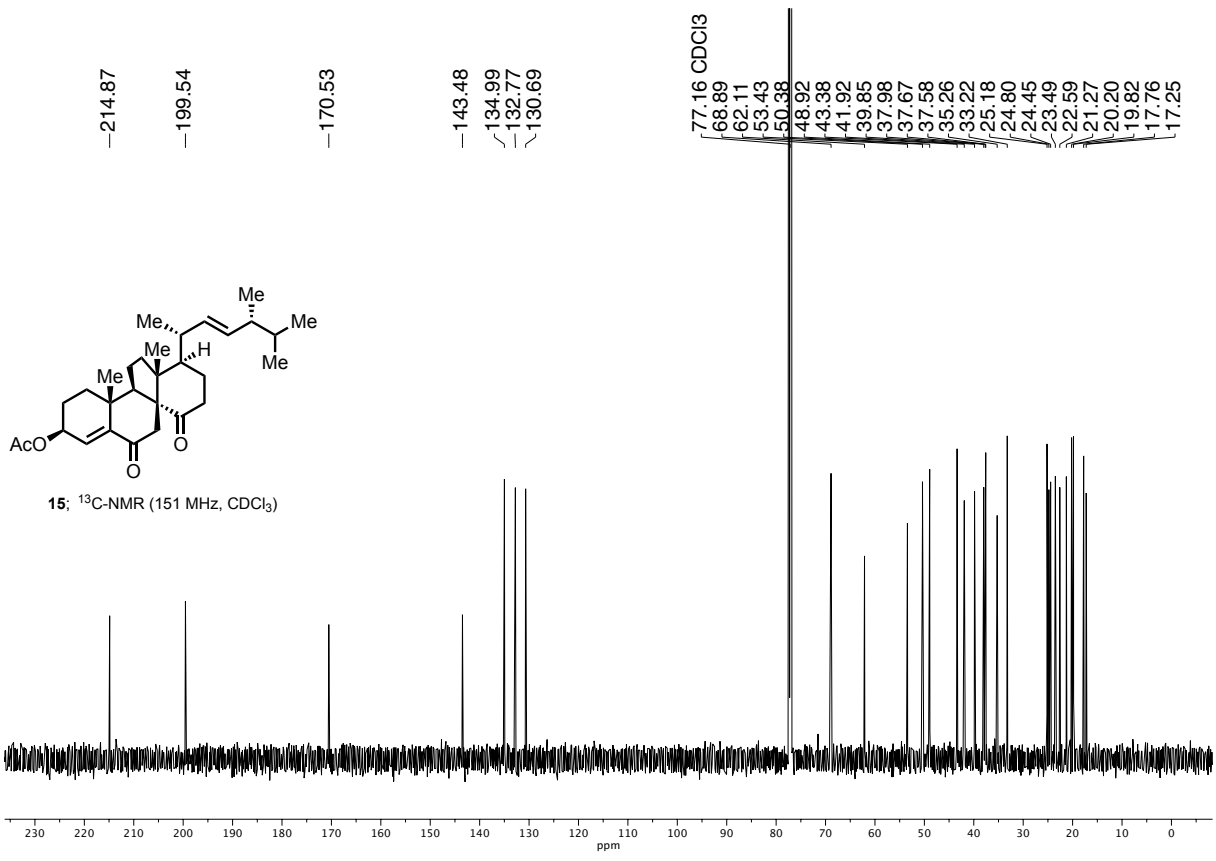
14; ^{1}H-NMR (600 MHz, $CDCl_3$)



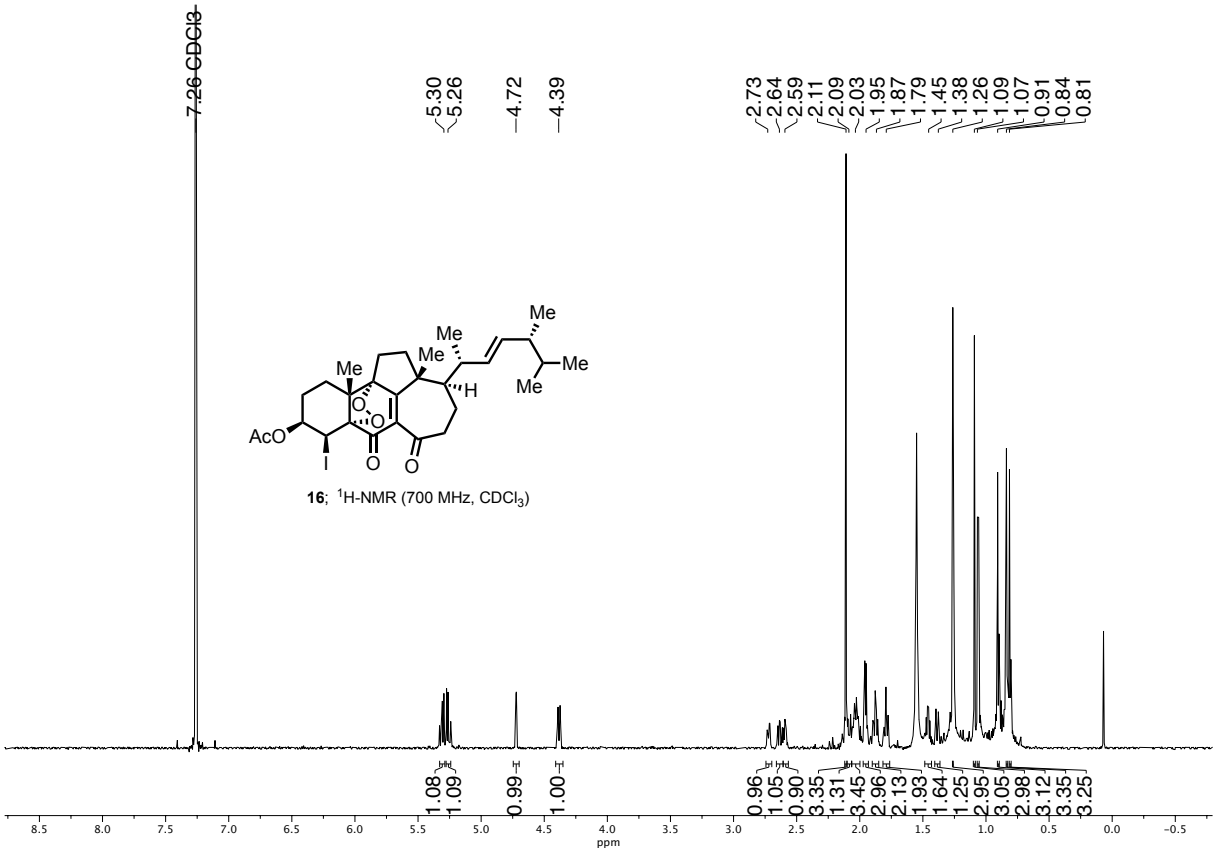
14; ^{13}C-NMR (151 MHz, $CDCl_3$)



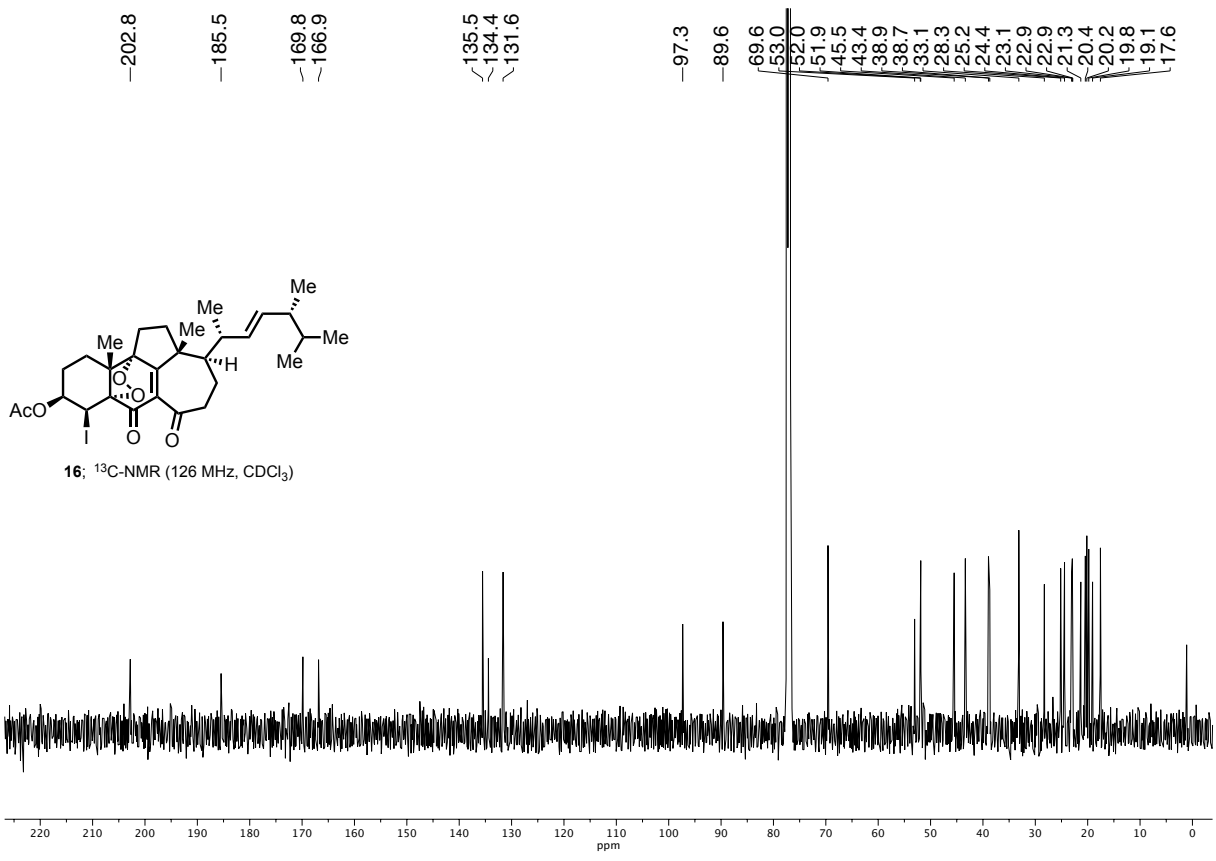
15; ^{1}H-NMR (600 MHz, $CDCl_3$)



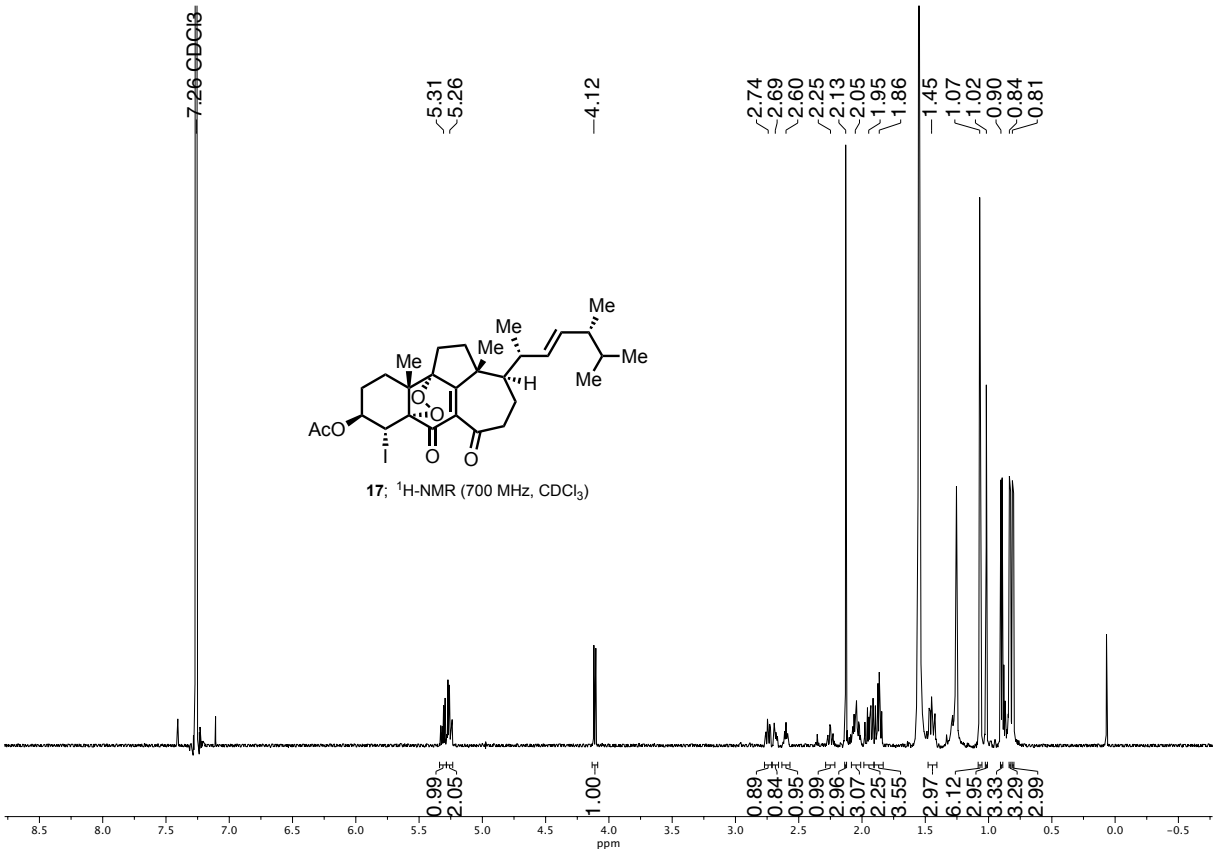
15; ^{13}C-NMR (151 MHz, $CDCl_3$)



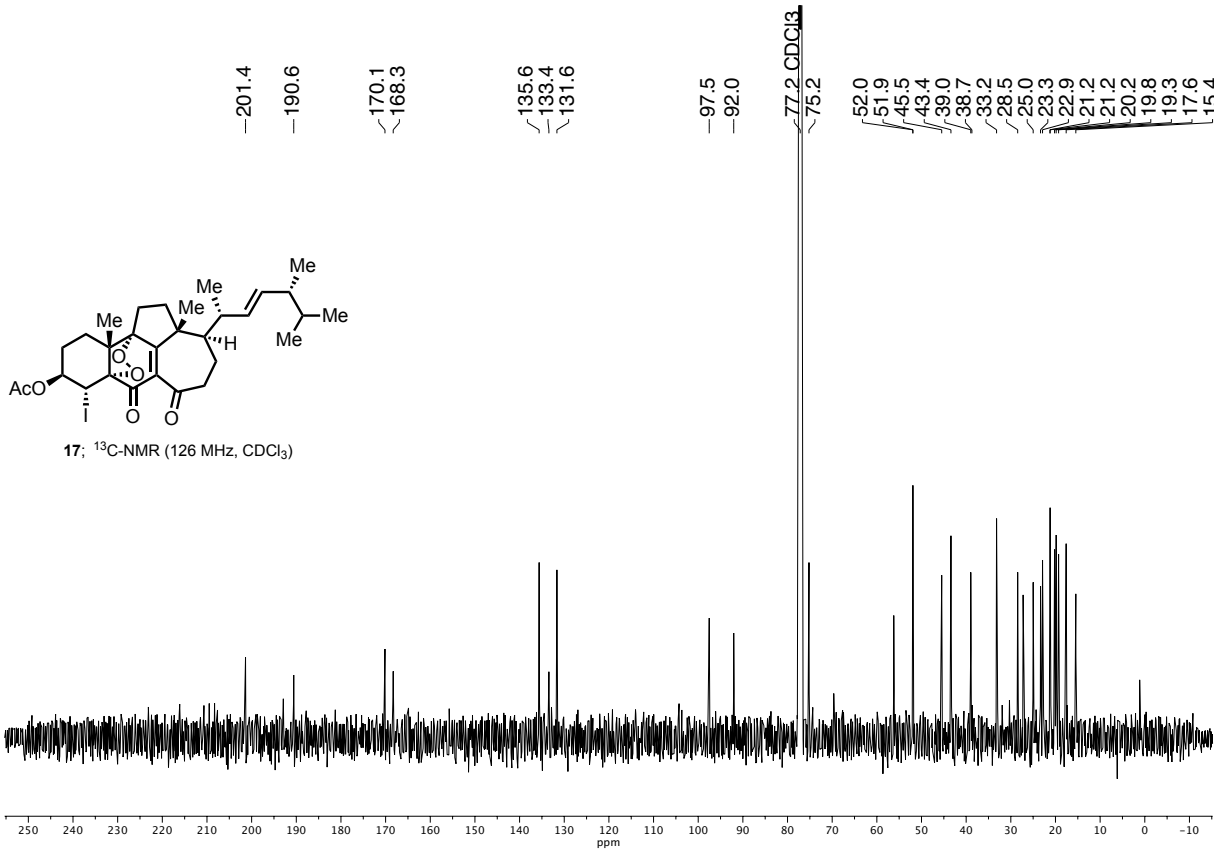
16; ^{1}H-NMR (700 MHz, $CDCl_3$)



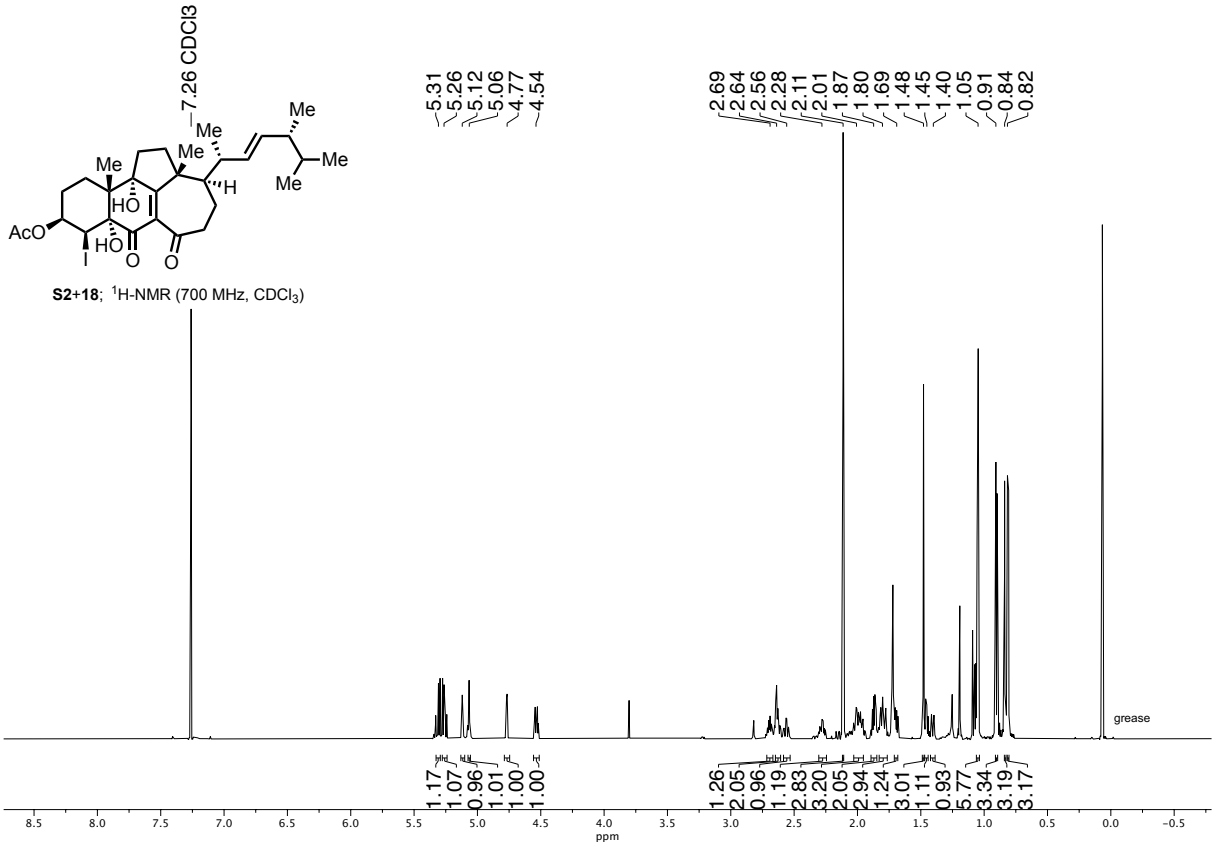
16; ^{13}C-NMR (126 MHz, $CDCl_3$)



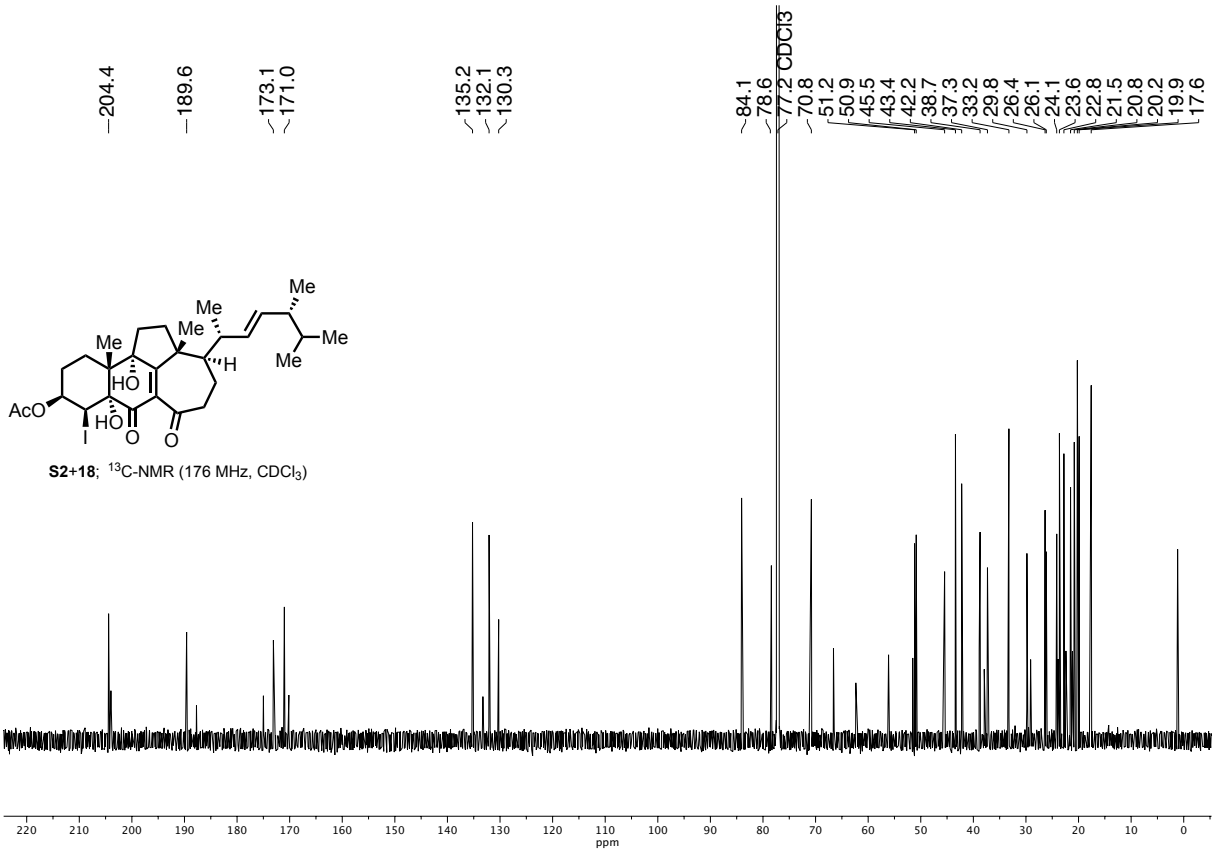
17; ^{1}H-NMR (700 MHz, $CDCl_3$)



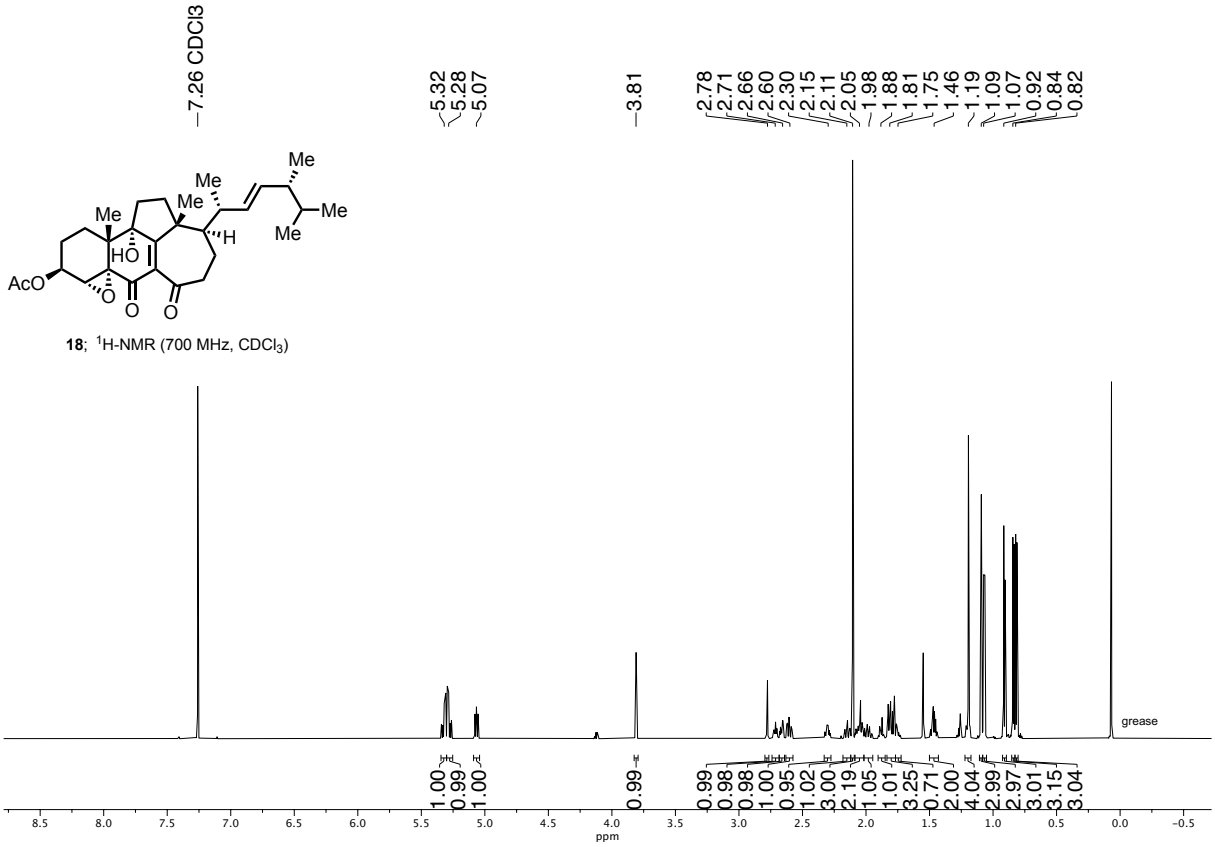
17; ^{13}C-NMR (126 MHz, $CDCl_3$)



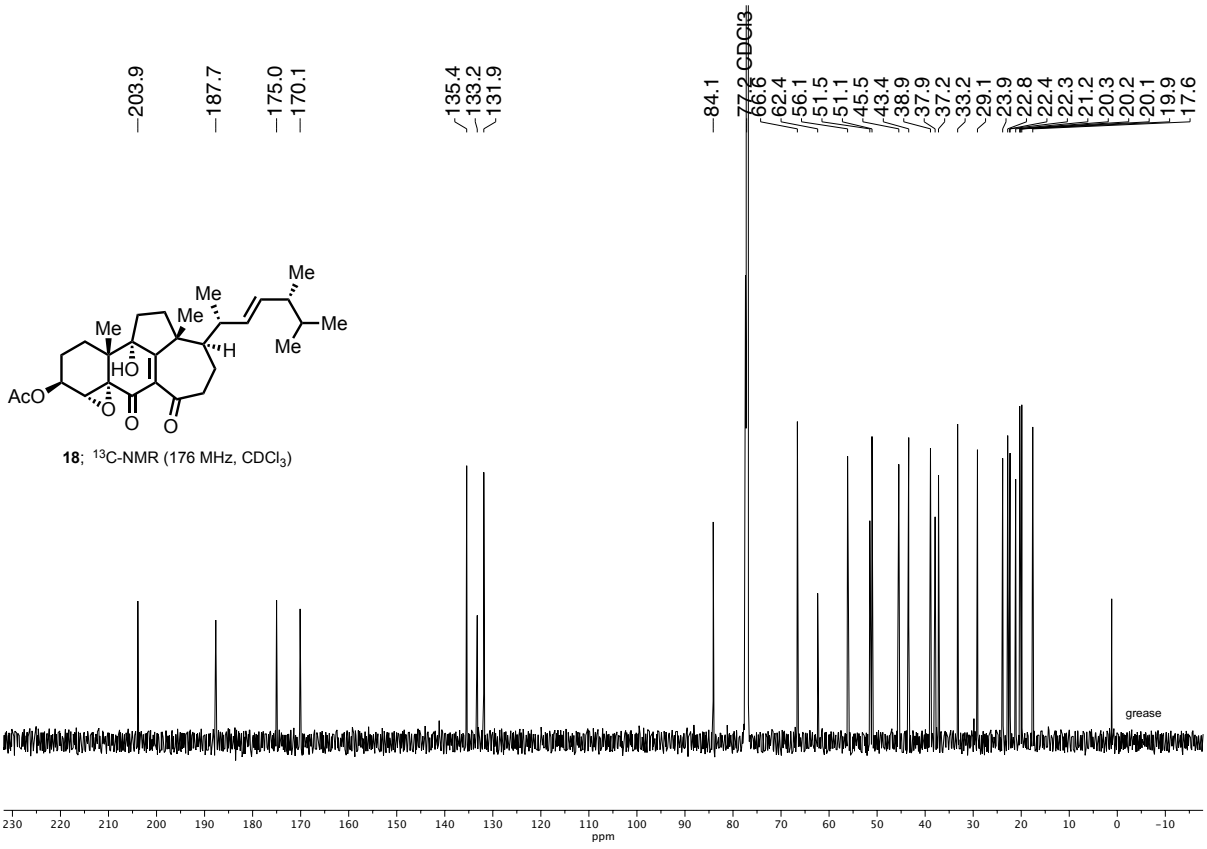
S2+18; ^{1}H-NMR (700 MHz, $CDCl_3$)



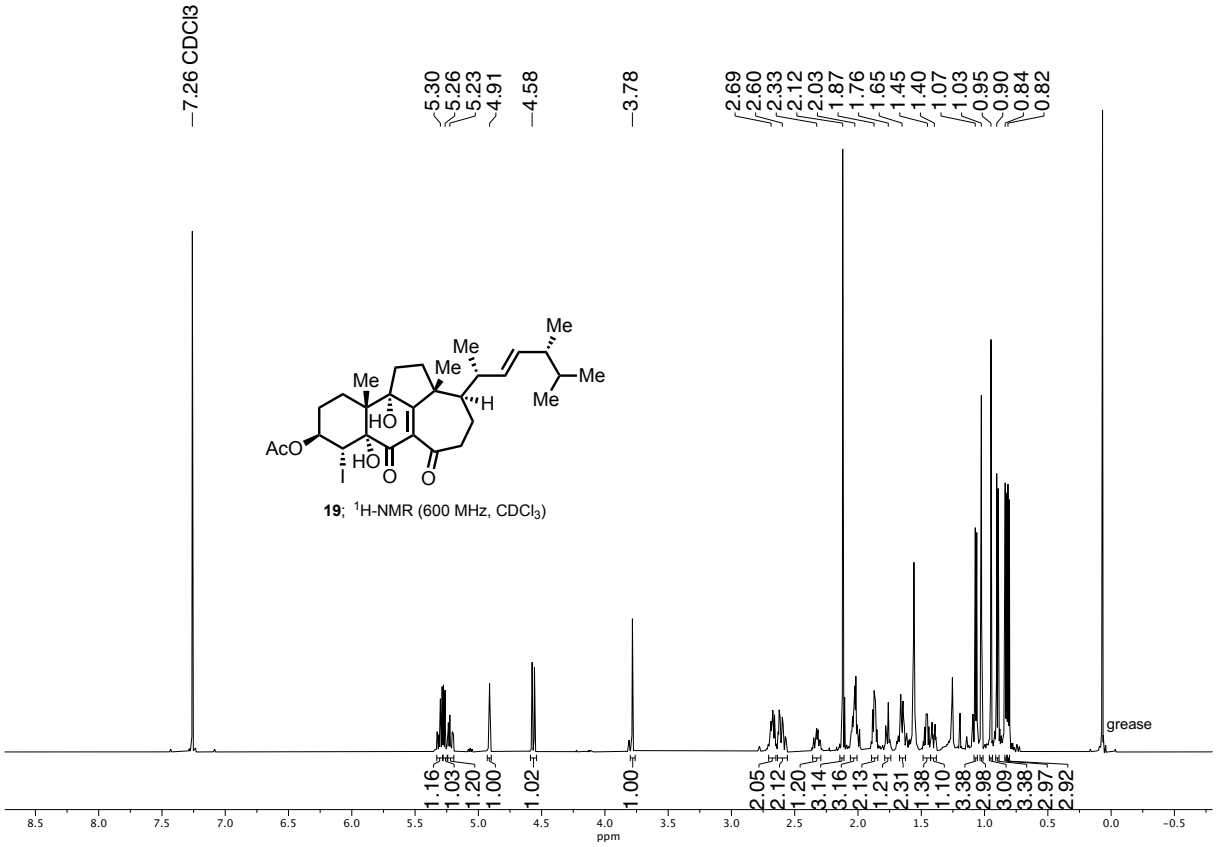
S2+18; ^{13}C-NMR (176 MHz, $CDCl_3$)



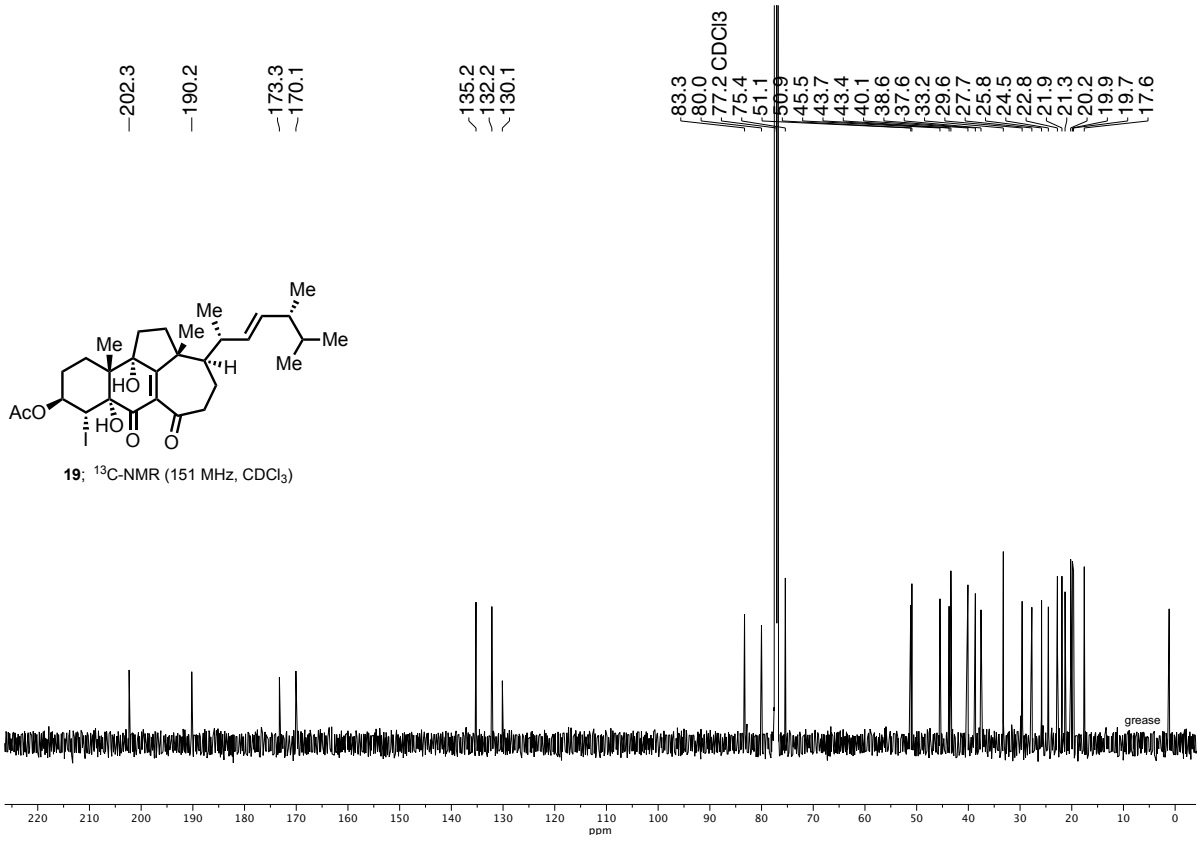
18; ^{1}H-NMR (700 MHz, $CDCl_3$)



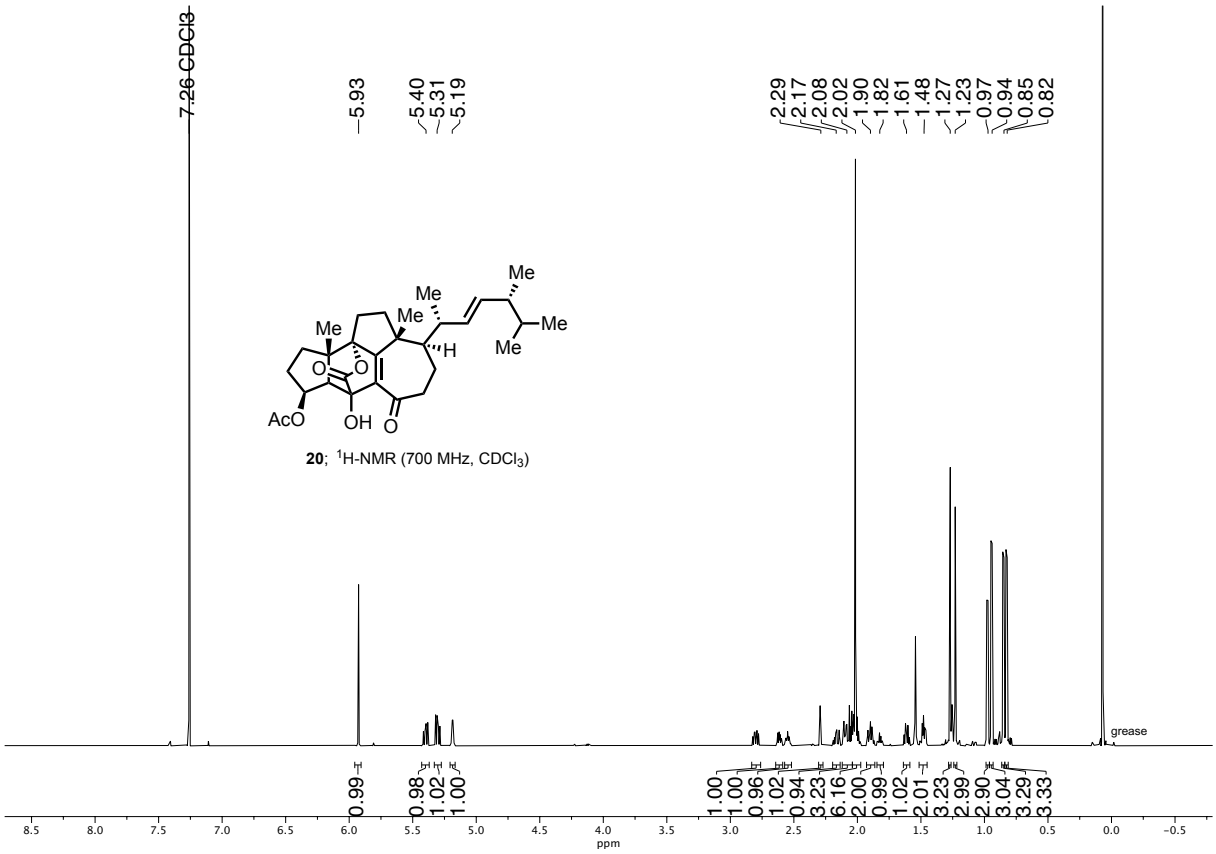
18; ^{13}C-NMR (176 MHz, $CDCl_3$)



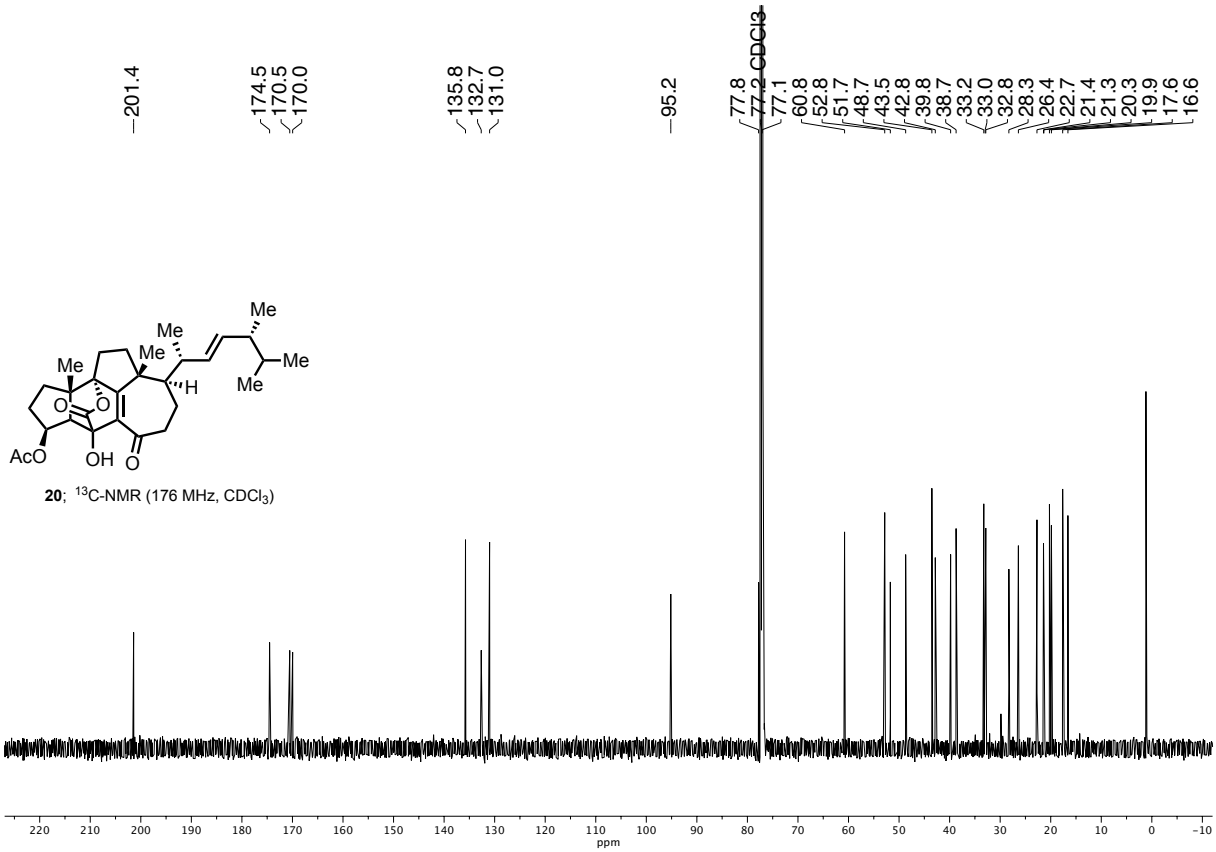
19; ^{1}H-NMR (600 MHz, $CDCl_3$)



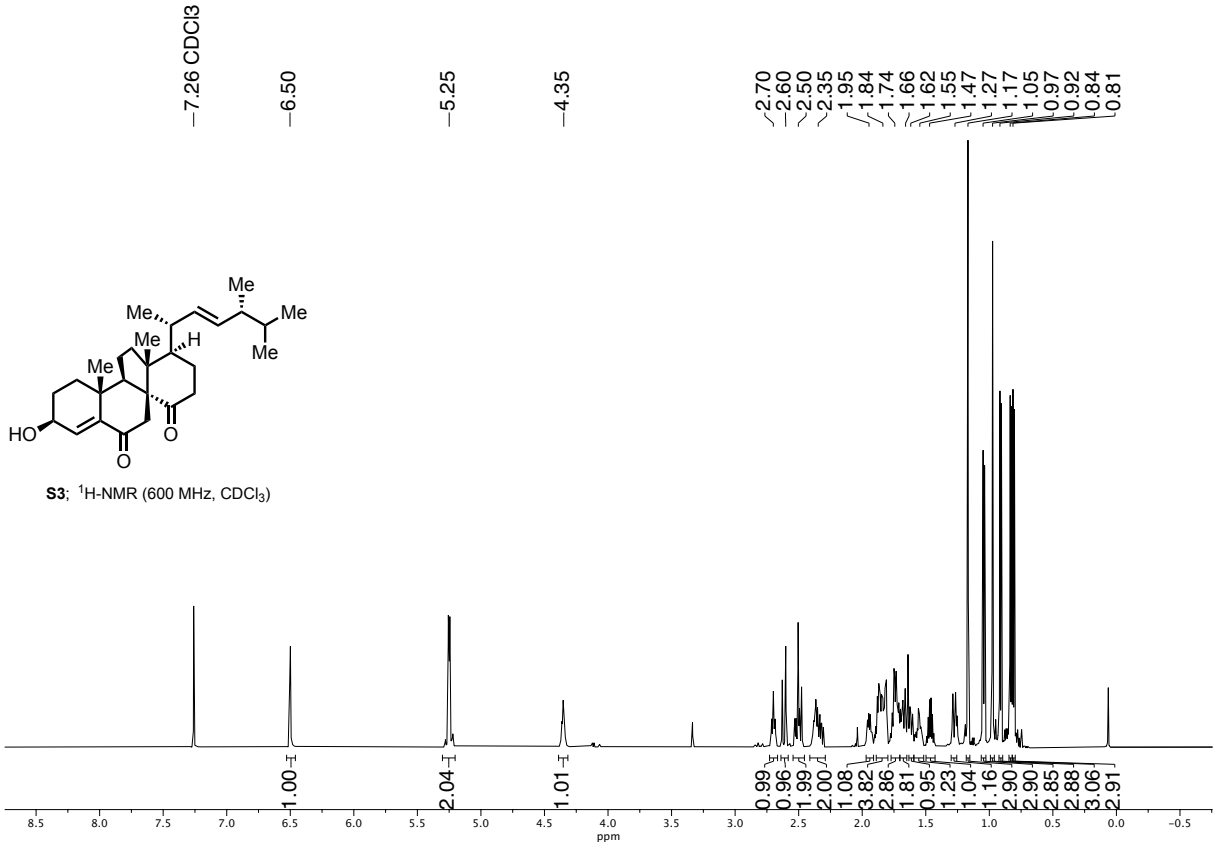
19; ^{13}C-NMR (151 MHz, $CDCl_3$)



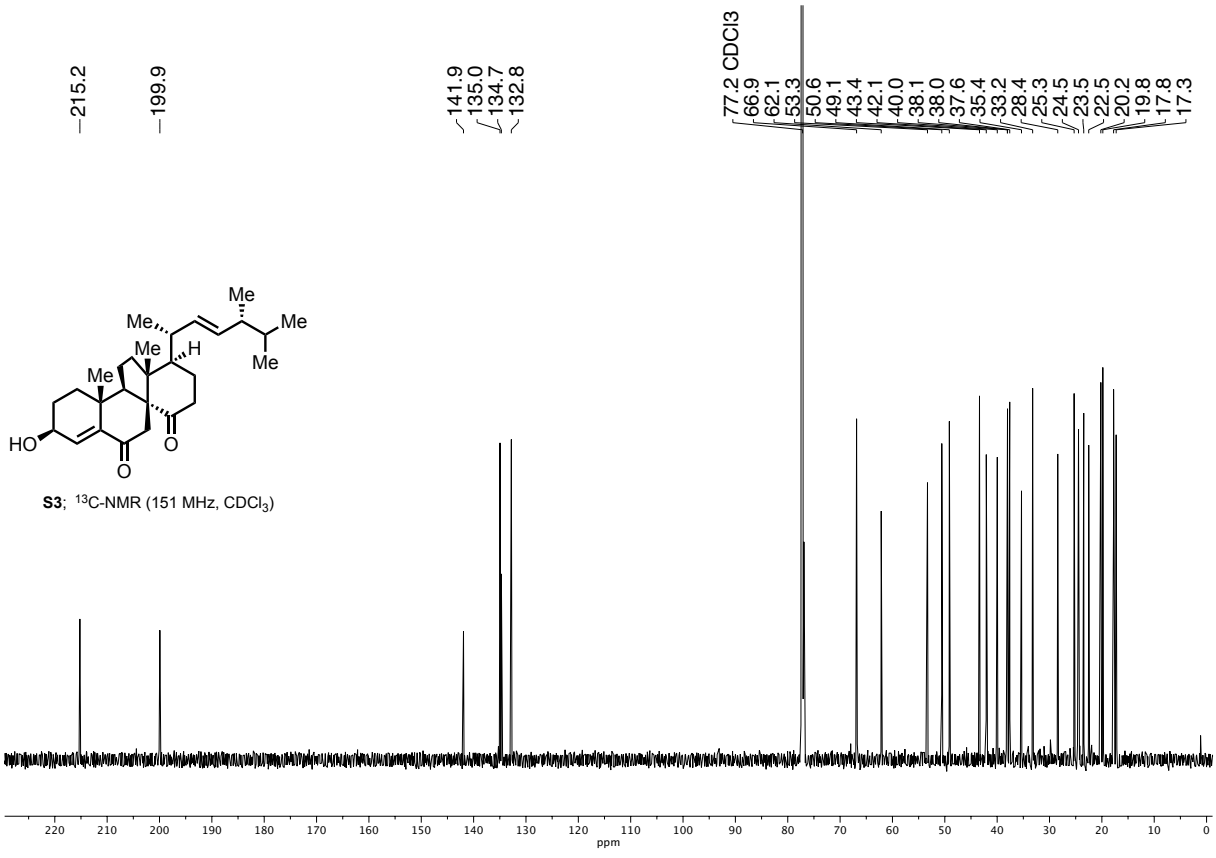
20; ^{1}H-NMR (700 MHz, $CDCl_3$)



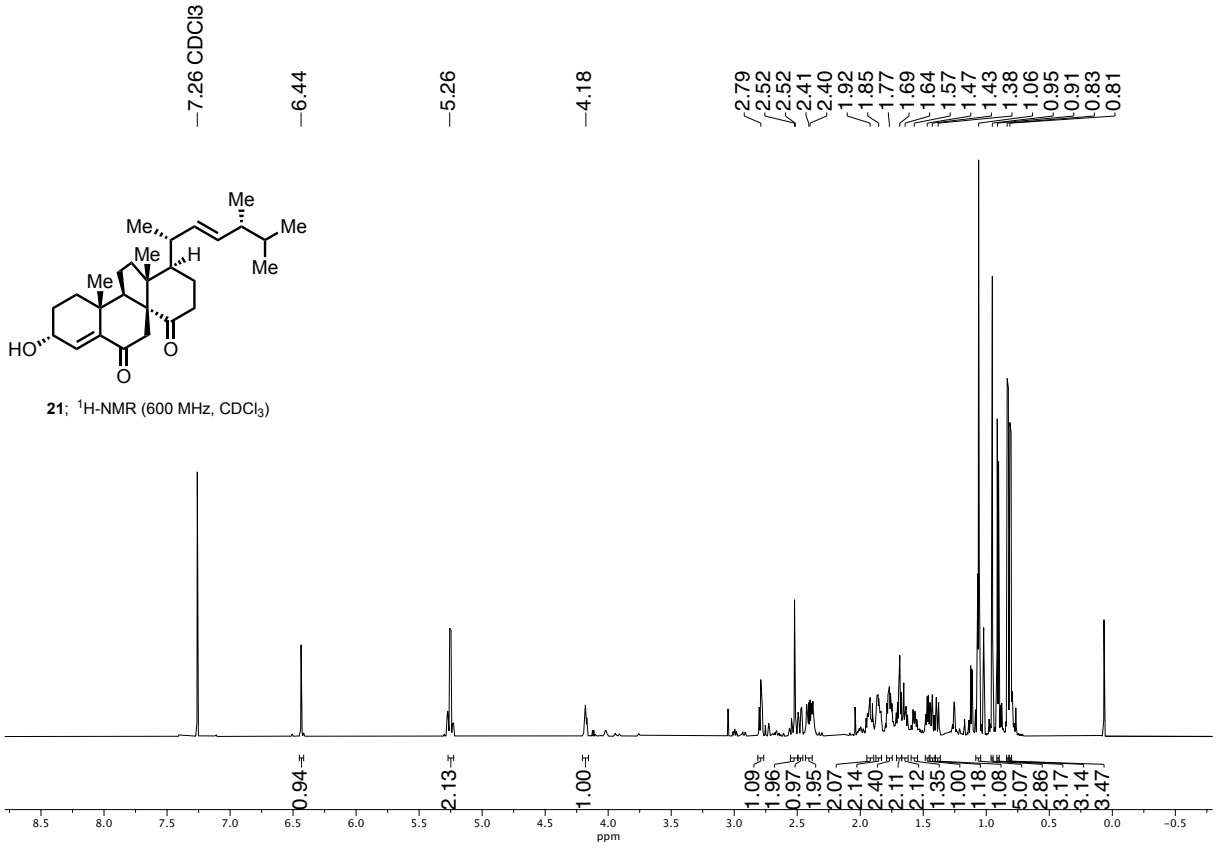
20; ^{13}C-NMR (176 MHz, $CDCl_3$)



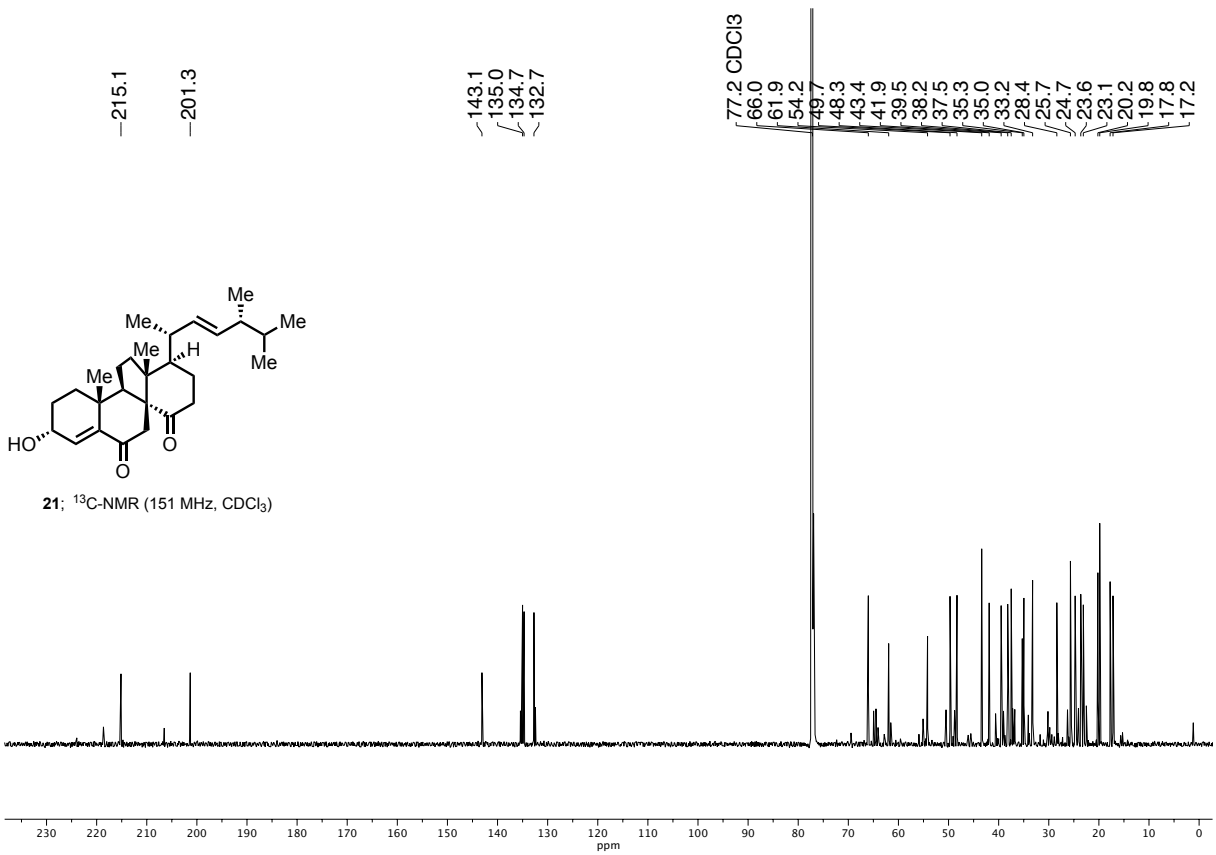
S3; ^{1}H-NMR (600 MHz, $CDCl_3$)



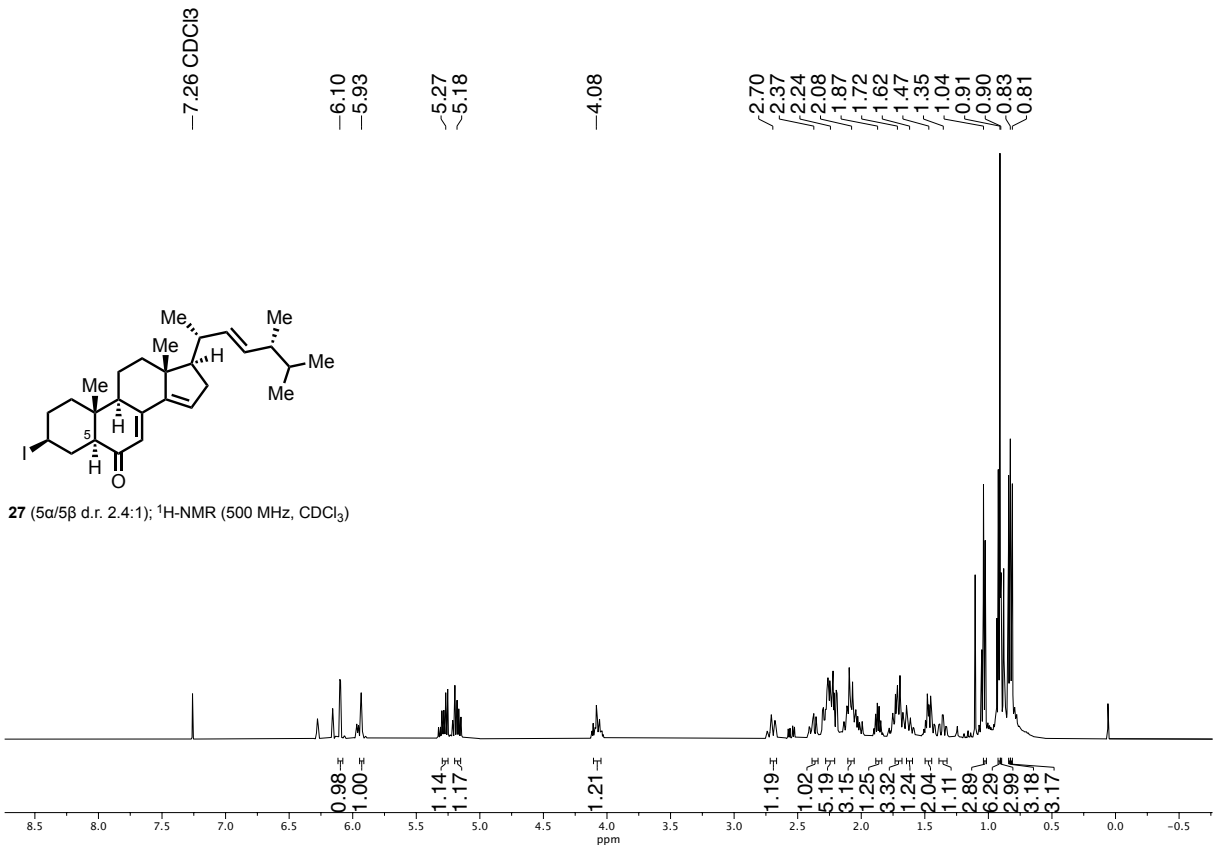
S3; ^{13}C-NMR (151 MHz, $CDCl_3$)



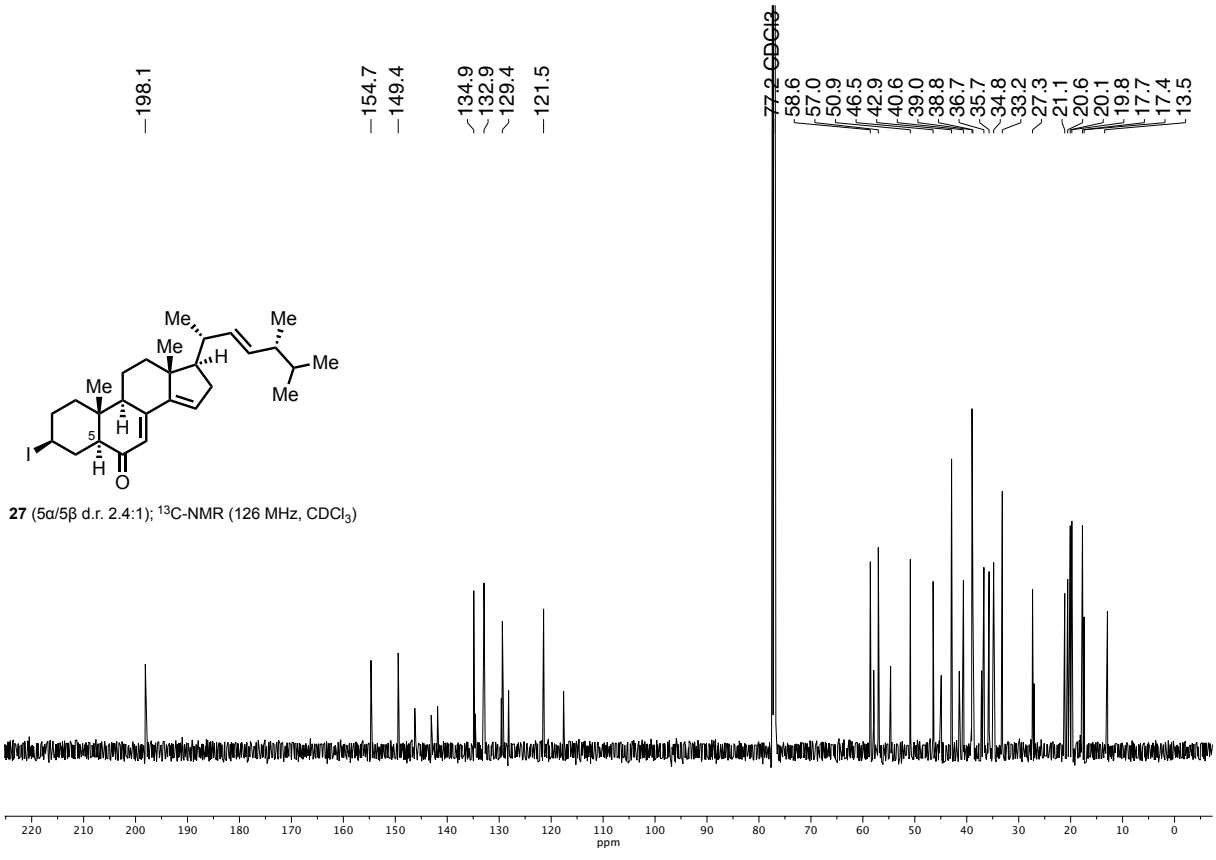
21; ^{1}H-NMR (600 MHz, $CDCl_3$)



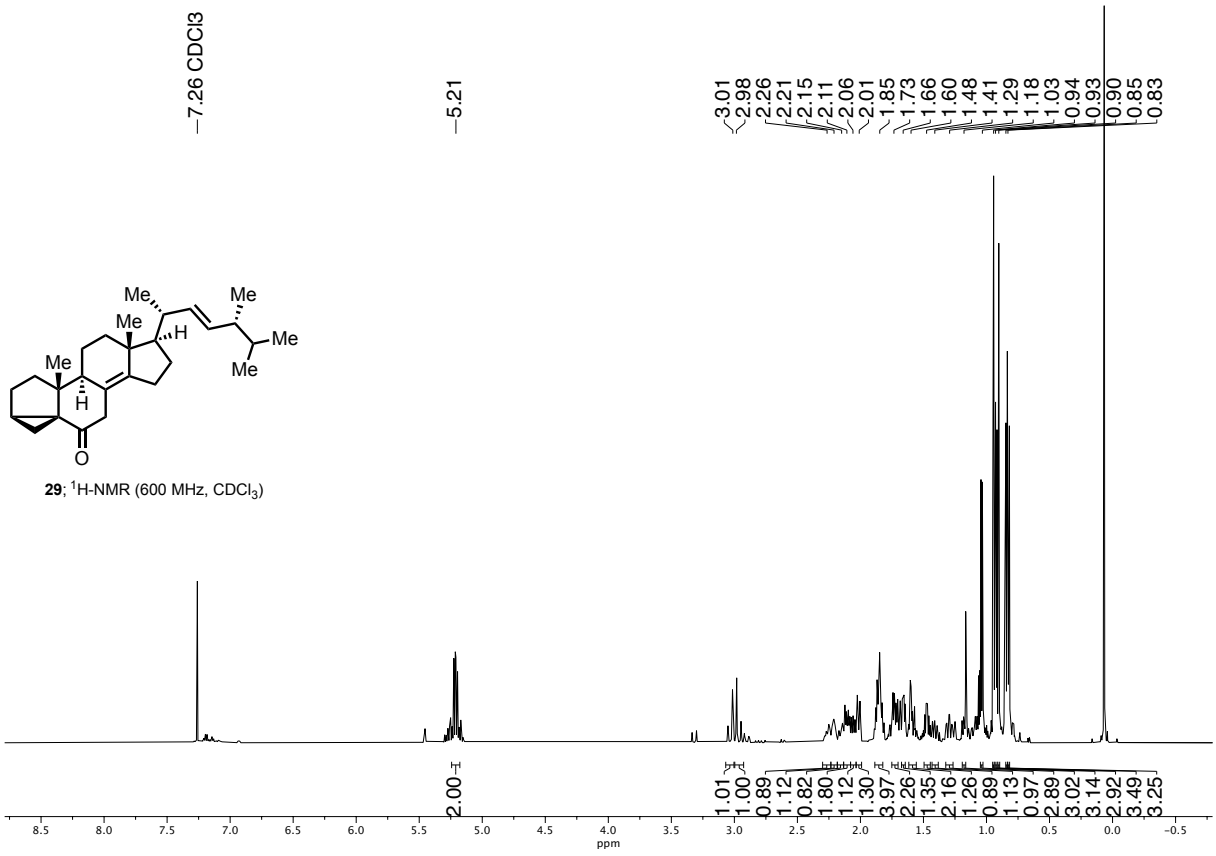
21; ^{13}C-NMR (151 MHz, $CDCl_3$)



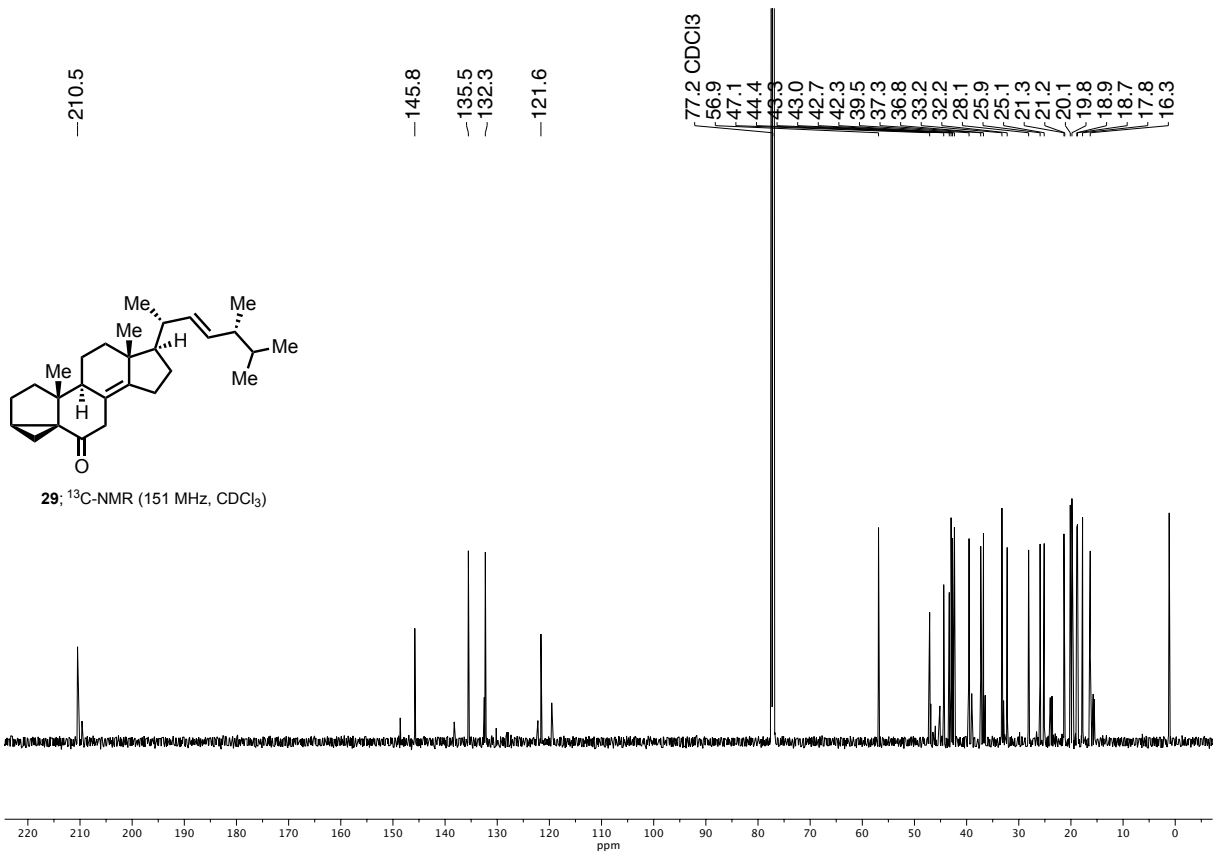
27 (5α/5β d.r. 2.4:1); ^{1}H-NMR (500 MHz, $CDCl_3$)



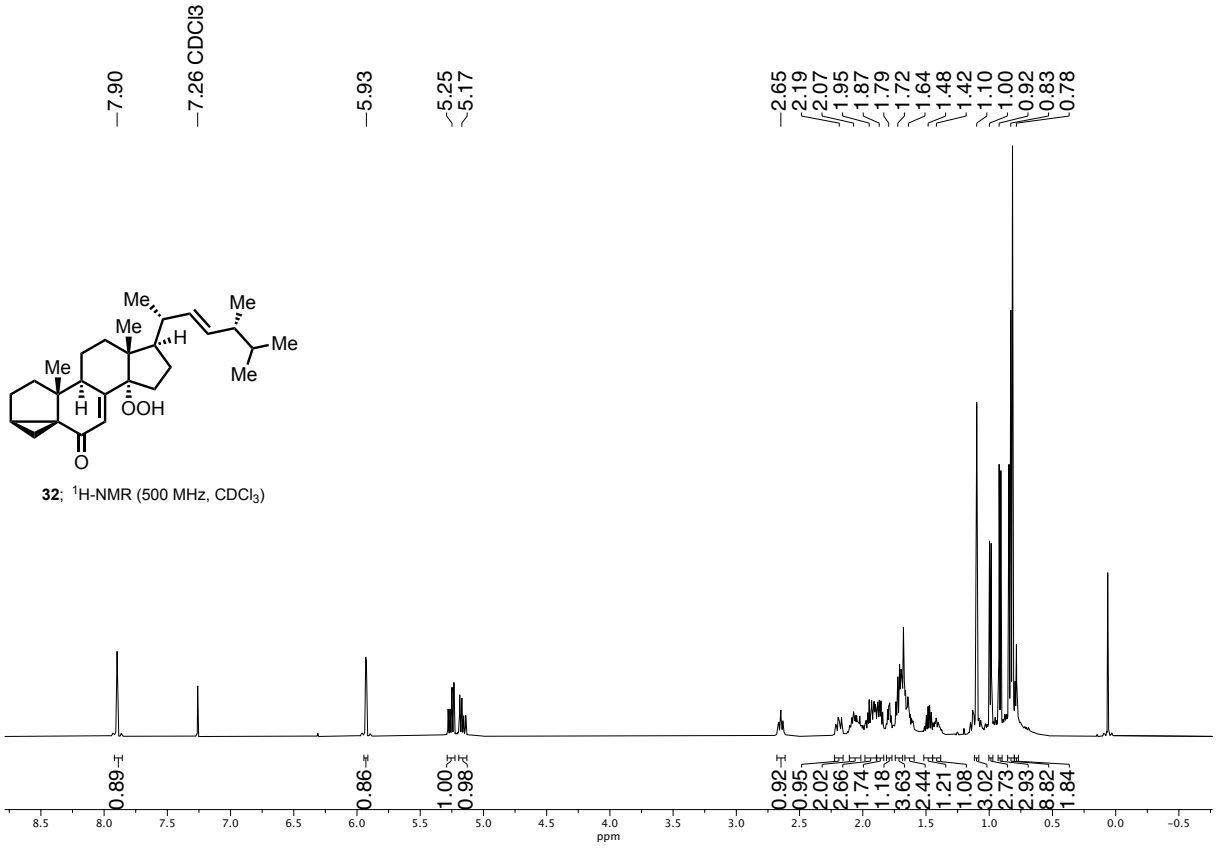
27 (5α/5β d.r. 2.4:1); ^{13}C-NMR (126 MHz, $CDCl_3$)



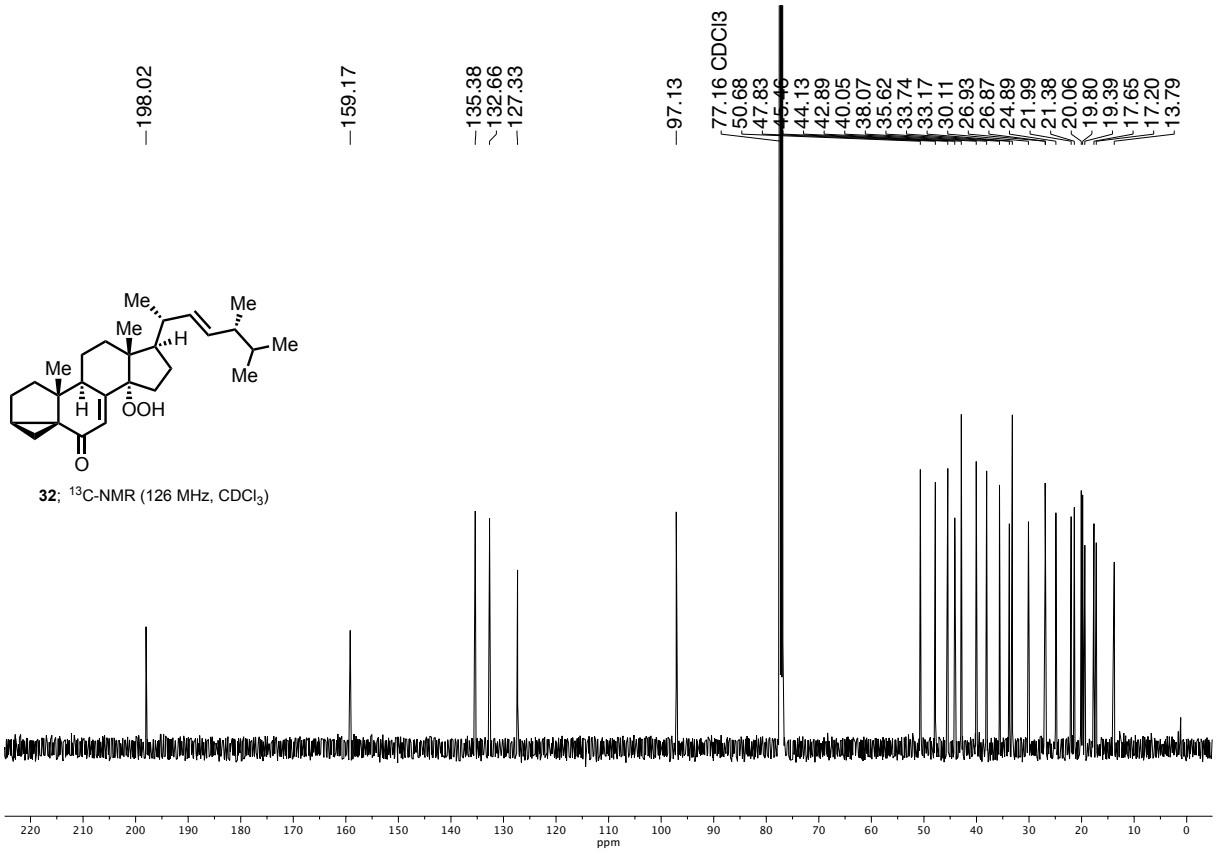
29; ^{1}H-NMR (600 MHz, $CDCl_3$)



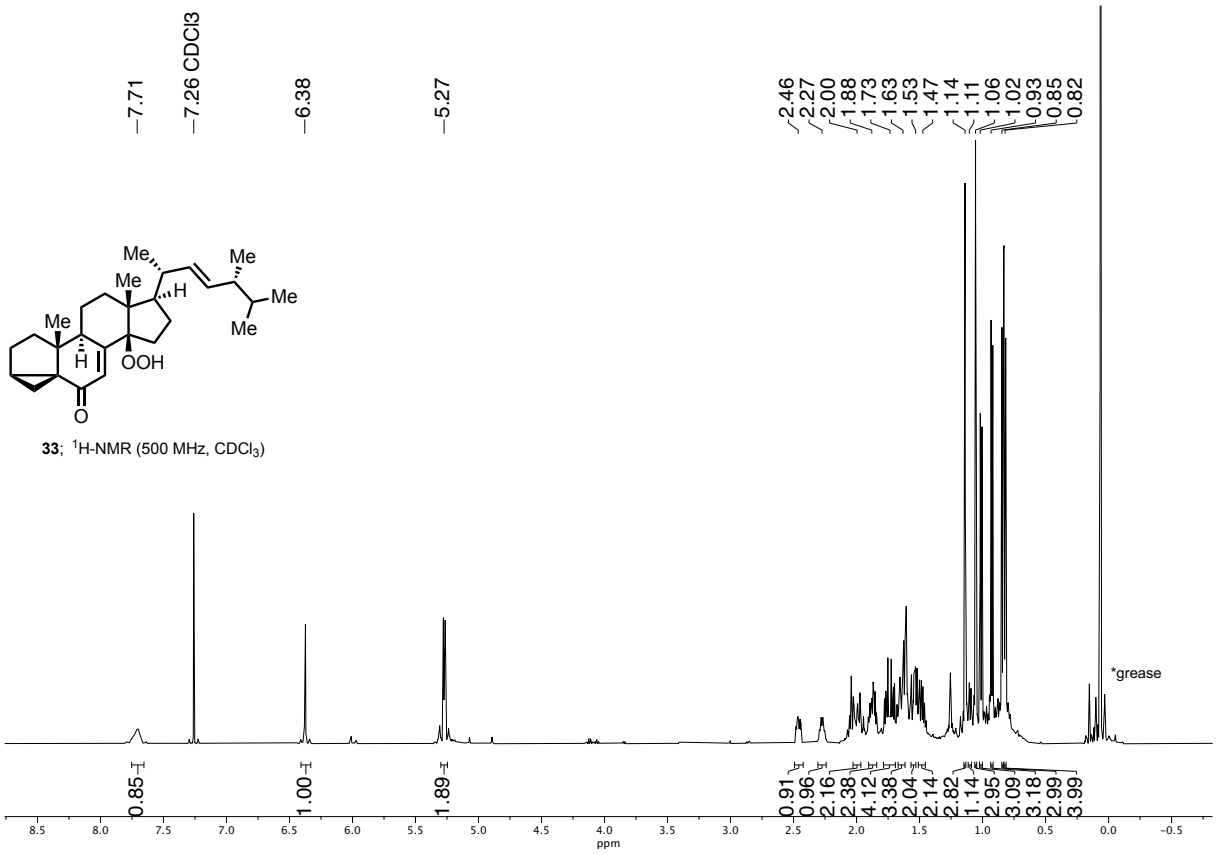
29; ^{13}C-NMR (151 MHz, $CDCl_3$)



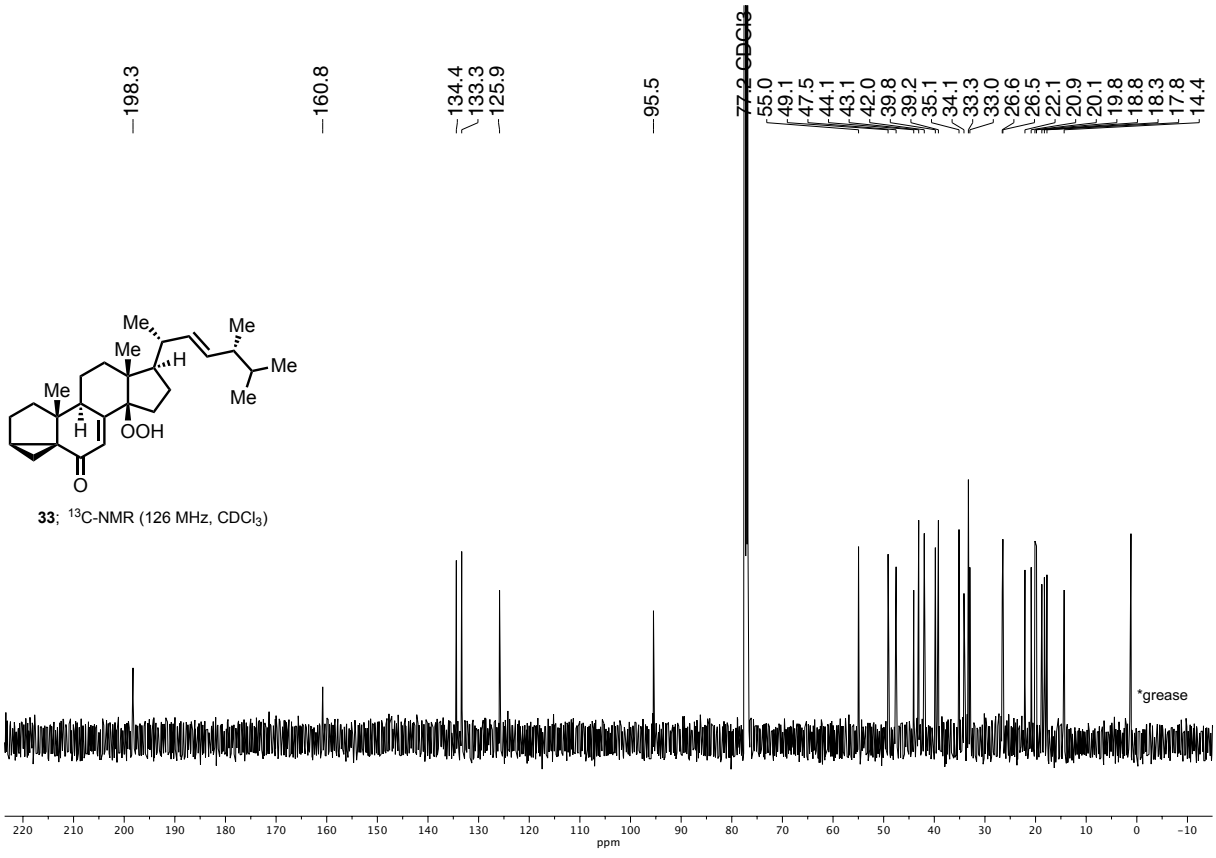
32; ^{1}H-NMR (500 MHz, $CDCl_3$)



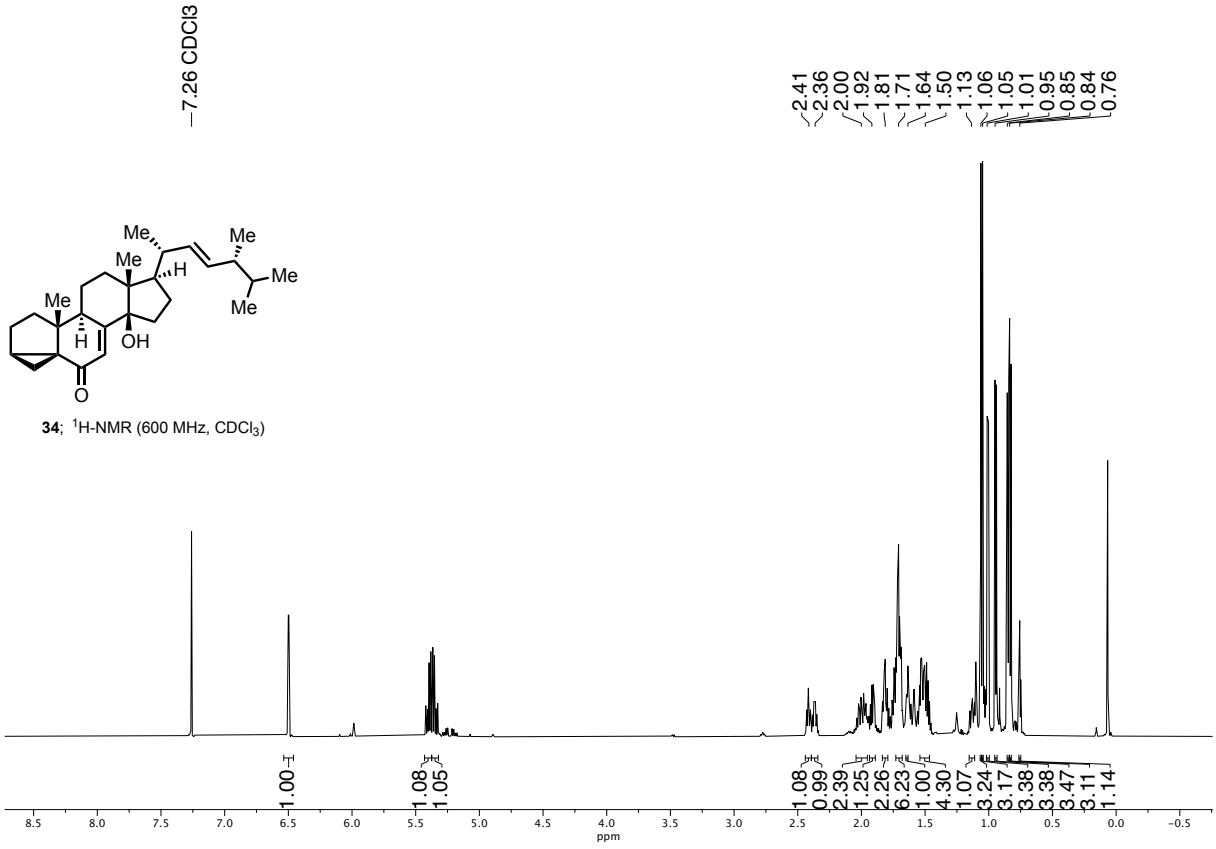
32; ^{13}C-NMR (126 MHz, $CDCl_3$)



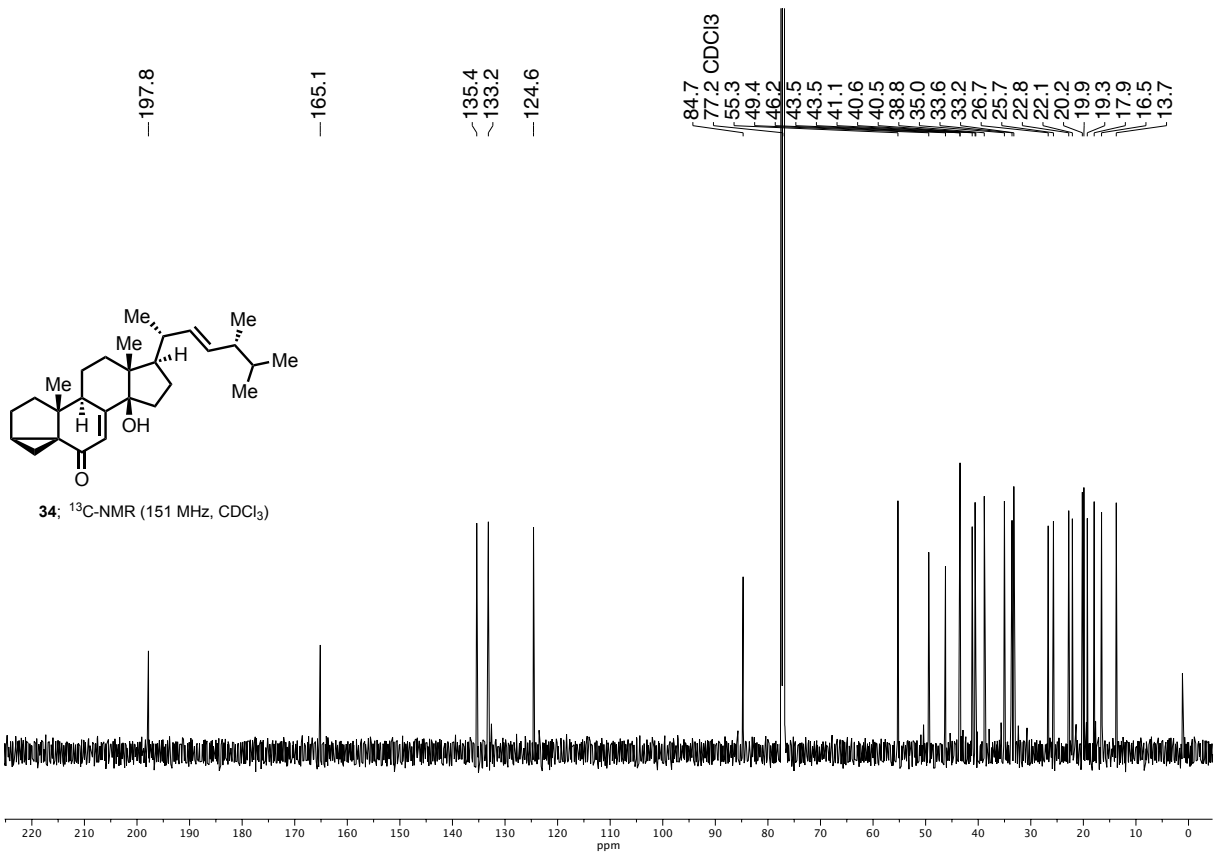
33; ^{1}H-NMR (500 MHz, $CDCl_3$)



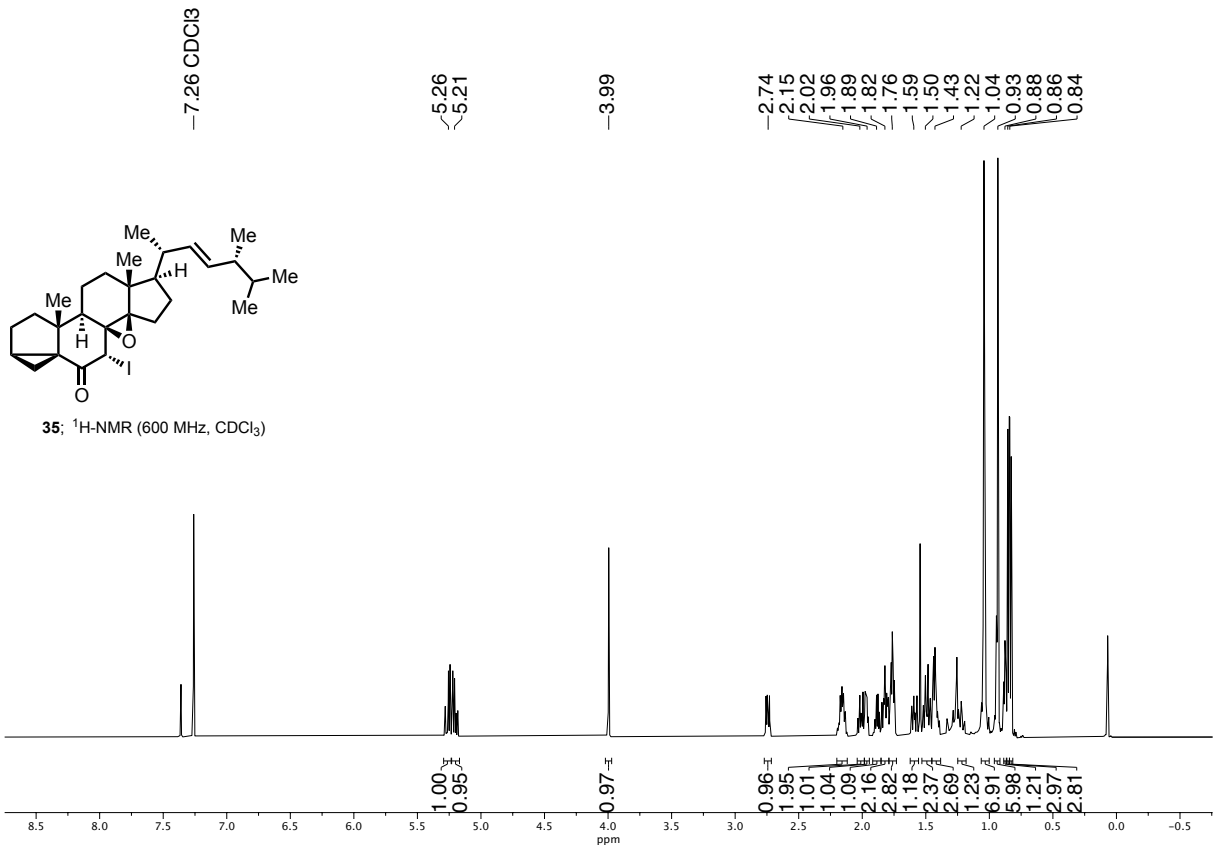
33; ^{13}C-NMR (126 MHz, $CDCl_3$)



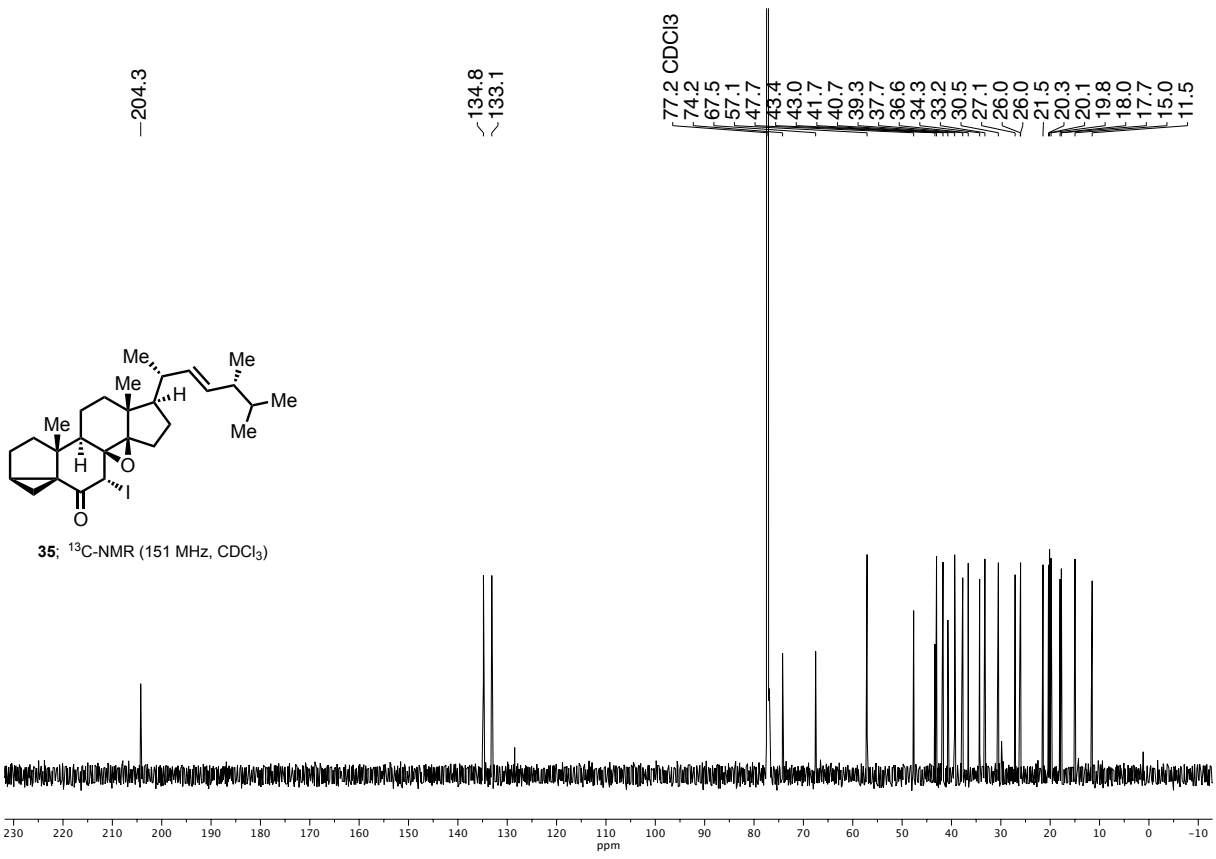
34; ^{1}H-NMR (600 MHz, $CDCl_3$)



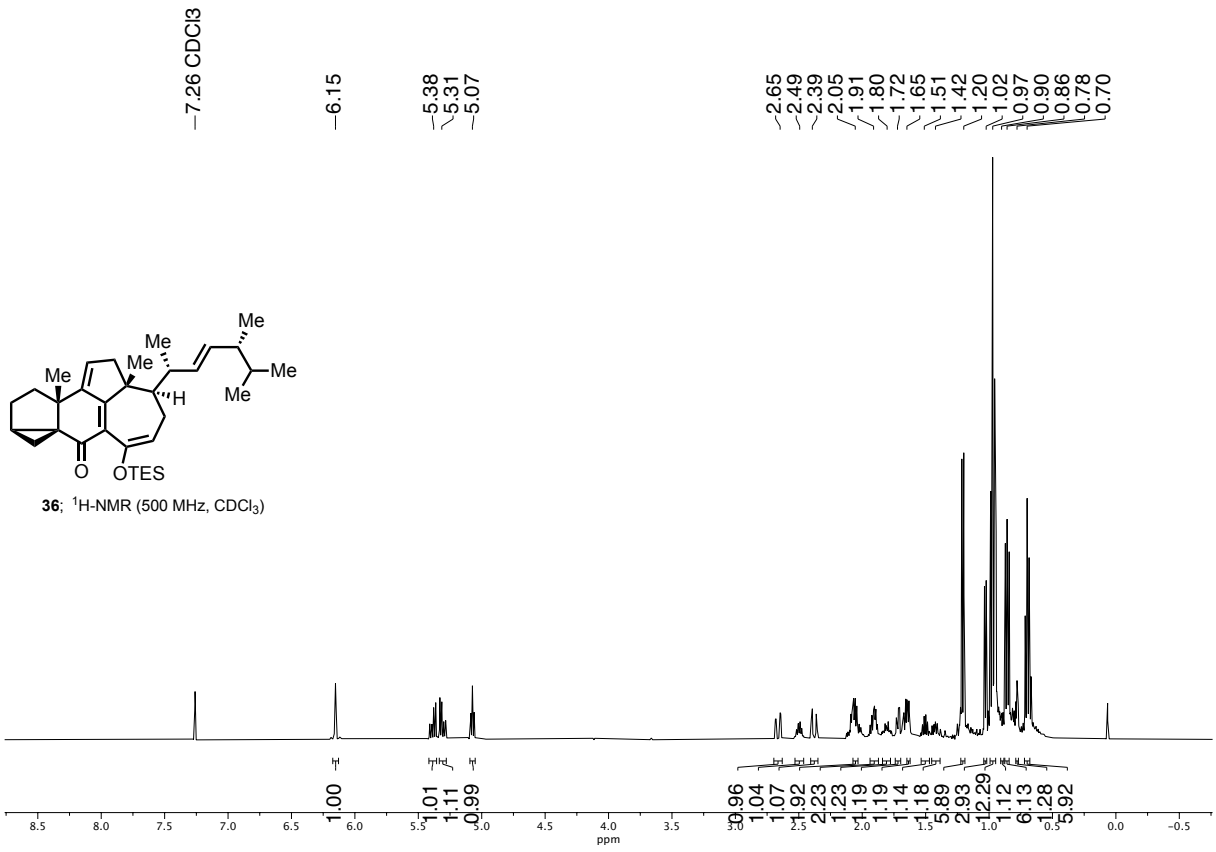
34; ^{13}C-NMR (151 MHz, $CDCl_3$)



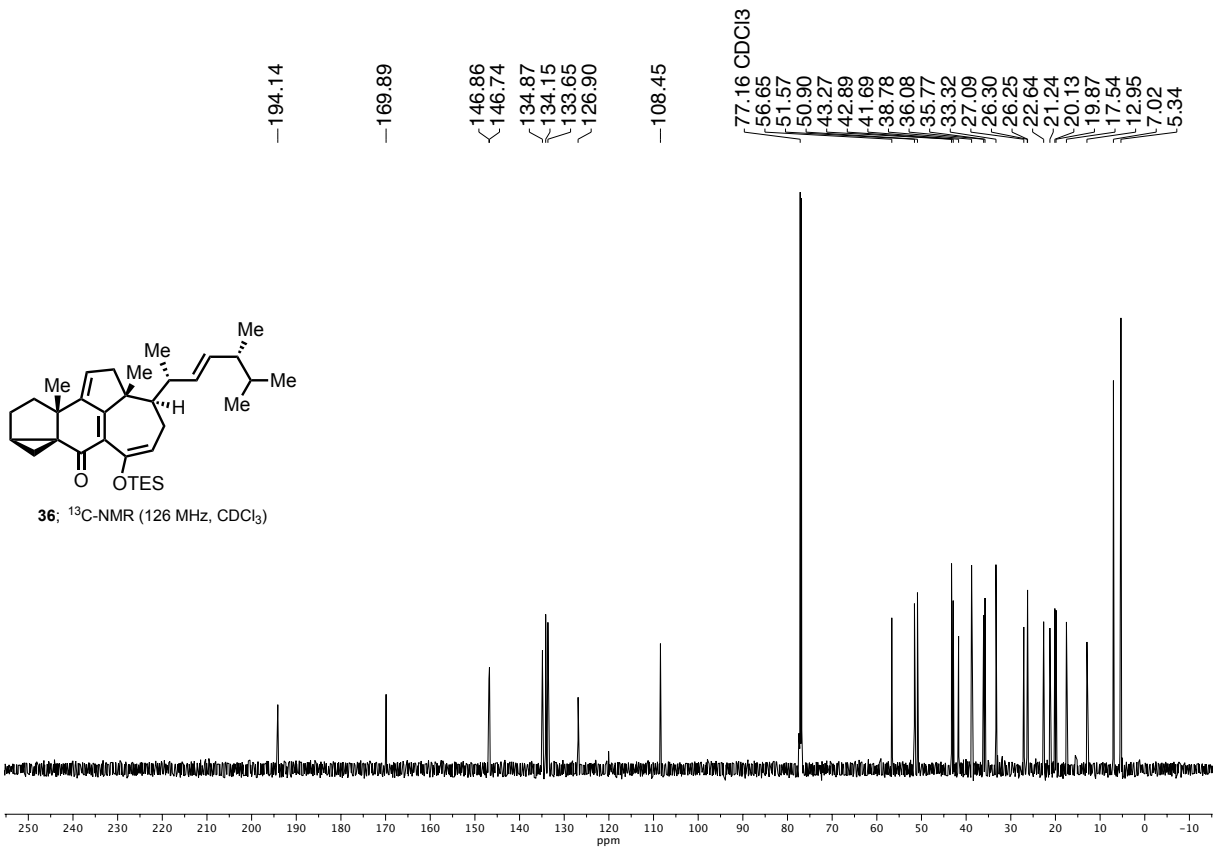
35; ^{1}H-NMR (600 MHz, $CDCl_3$)



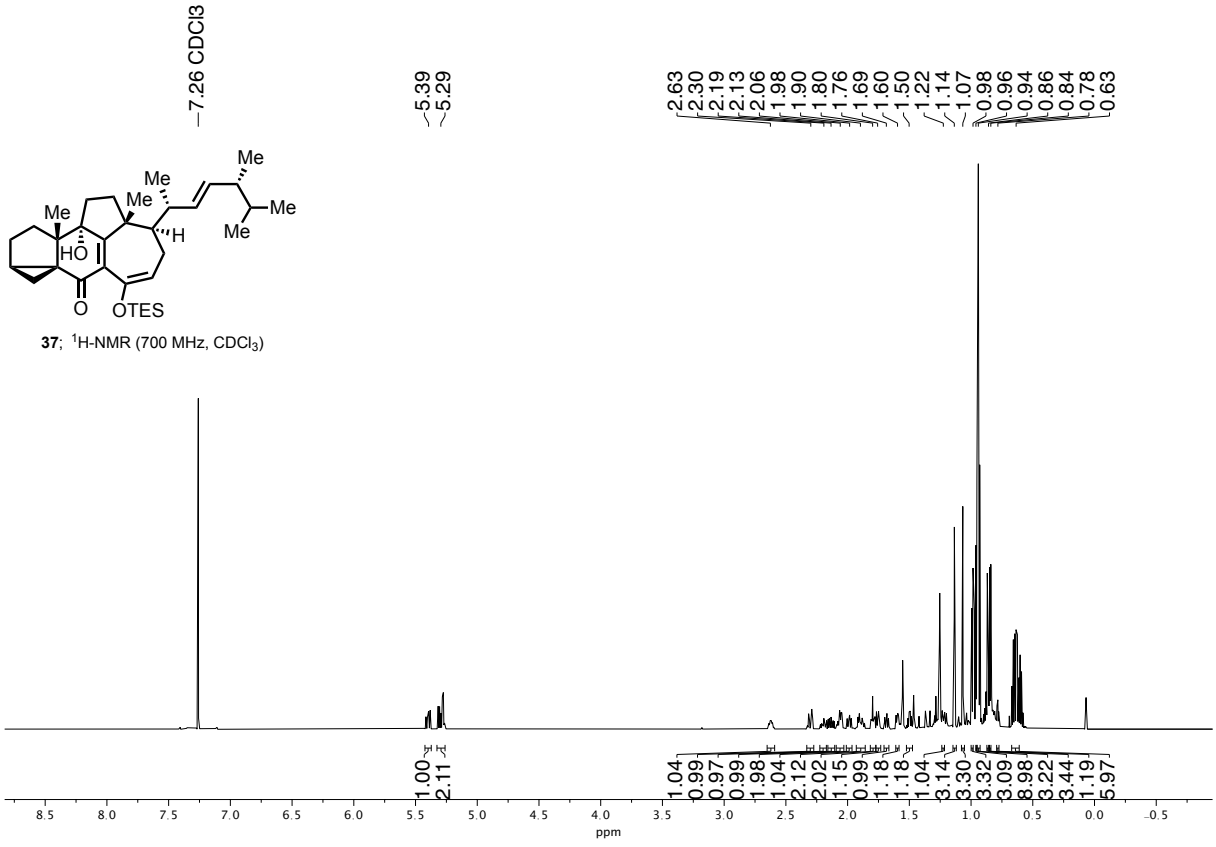
35; ^{13}C-NMR (151 MHz, $CDCl_3$)



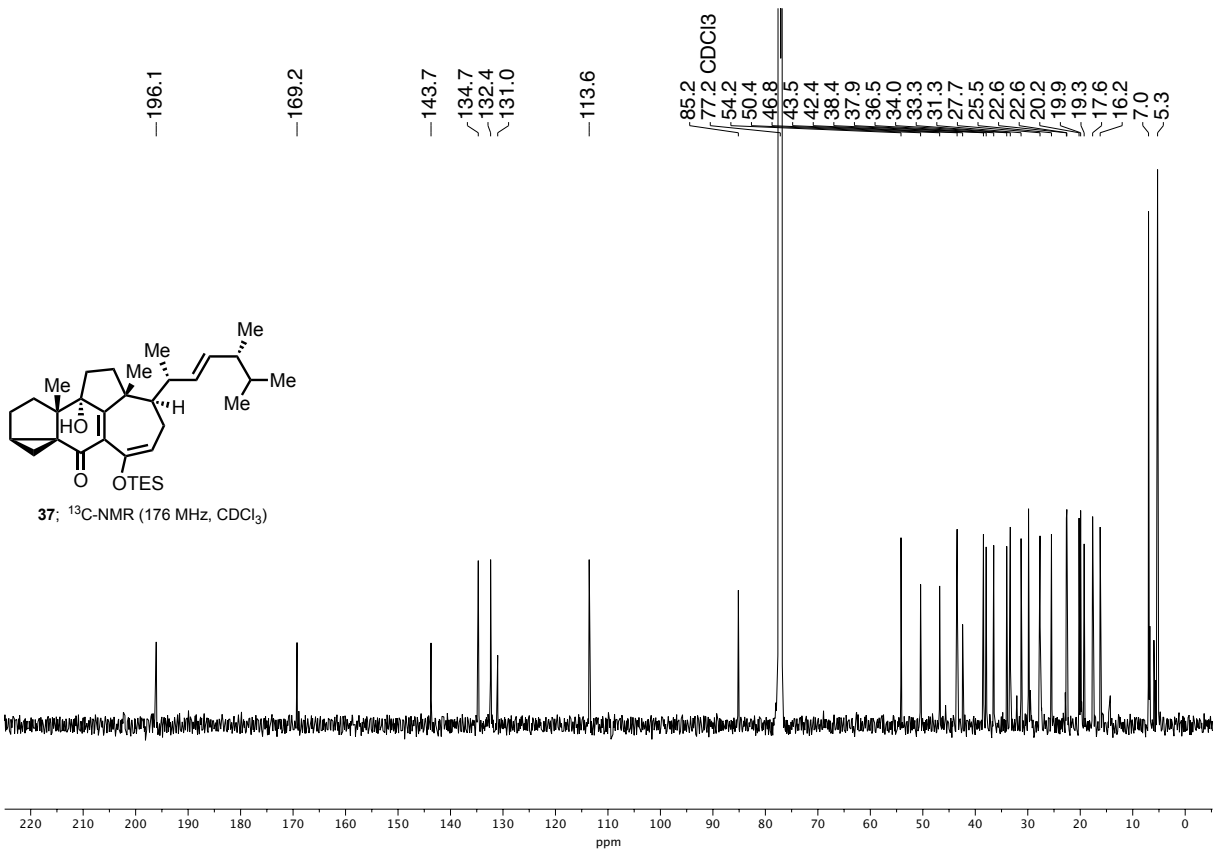
36; ^{1}H-NMR (500 MHz, $CDCl_3$)



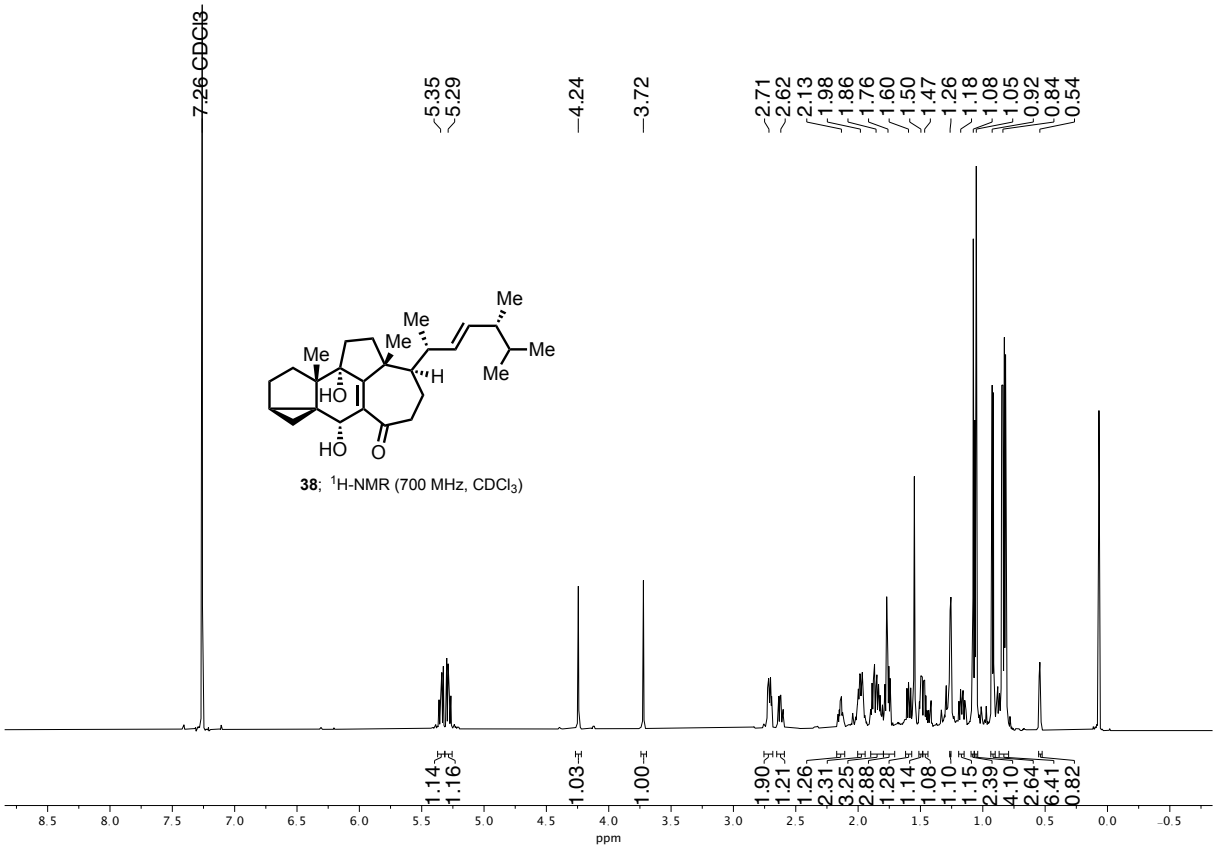
36; ^{13}C-NMR (126 MHz, $CDCl_3$)



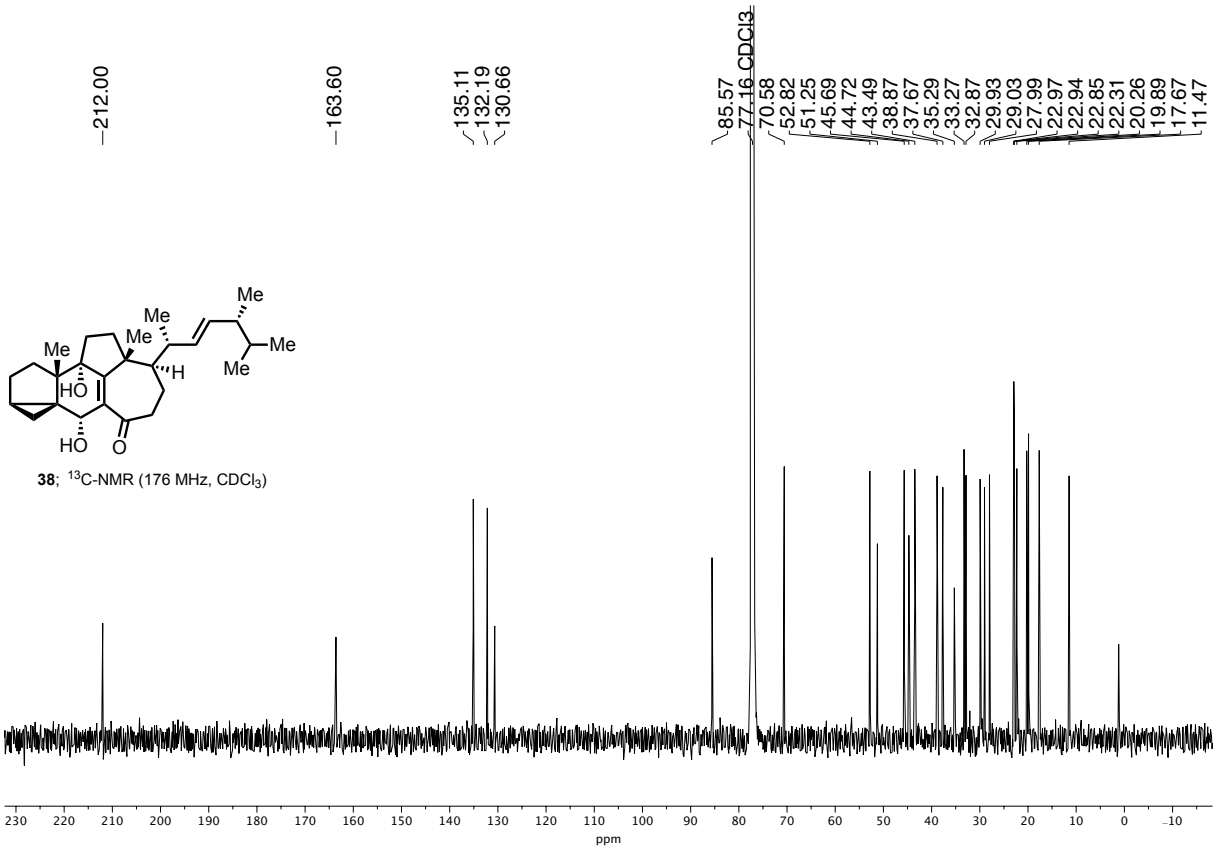
37; ^{1}H-NMR (700 MHz, $CDCl_3$)



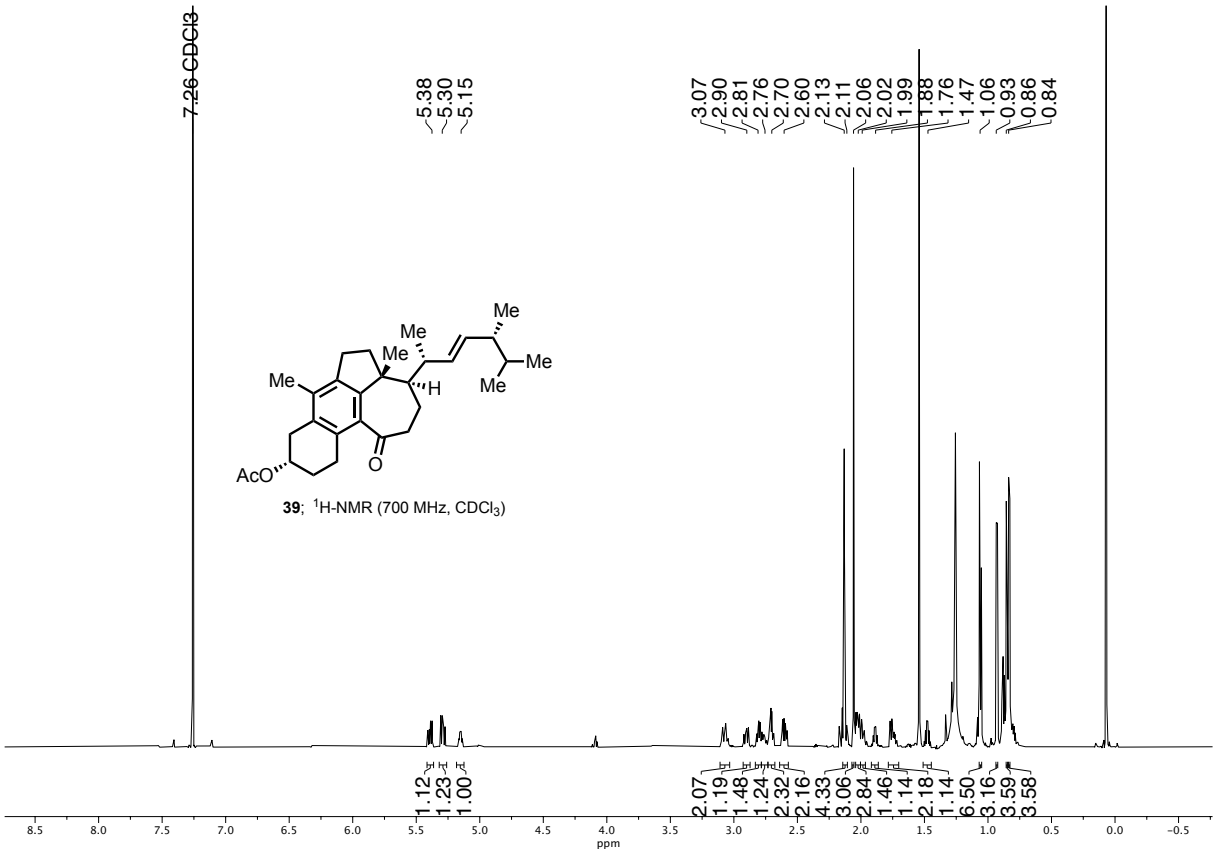
37; ^{13}C-NMR (176 MHz, $CDCl_3$)



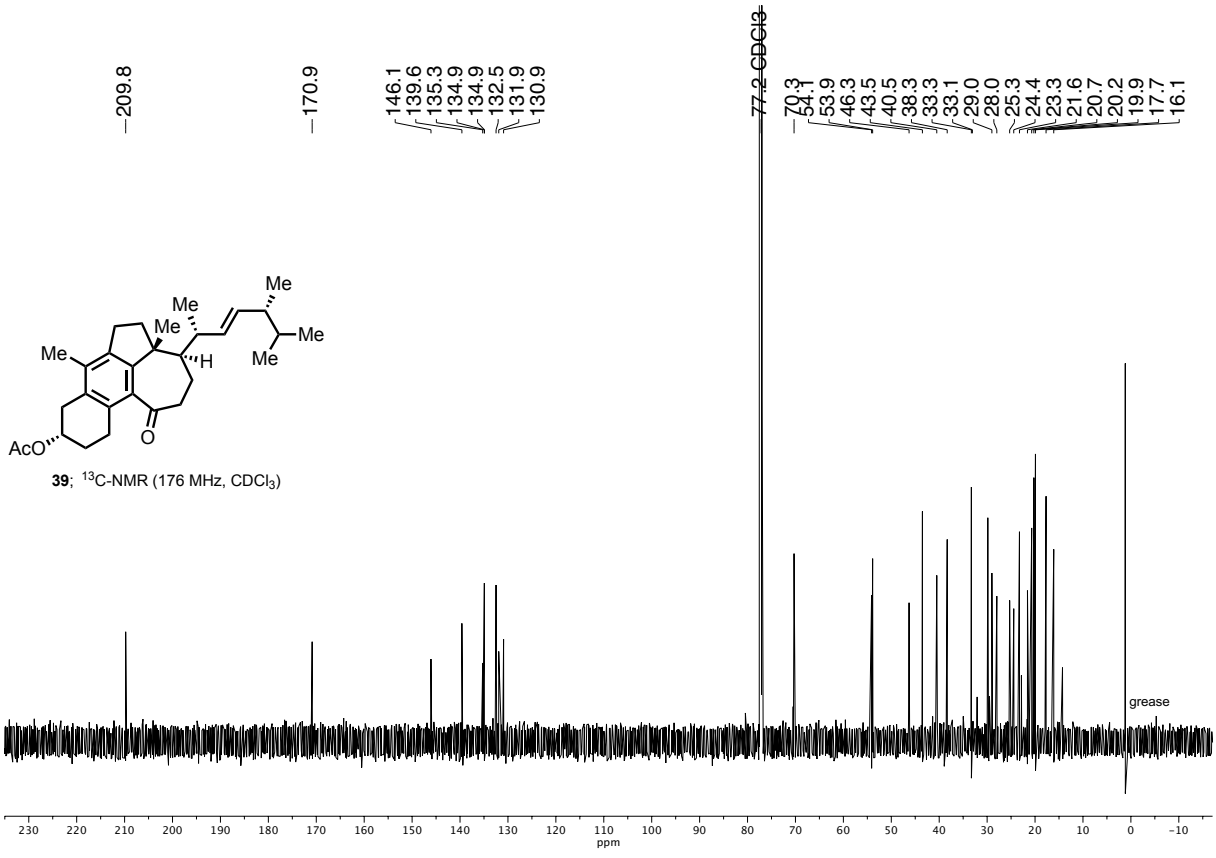
38; ^{1}H-NMR (700 MHz, $CDCl_3$)



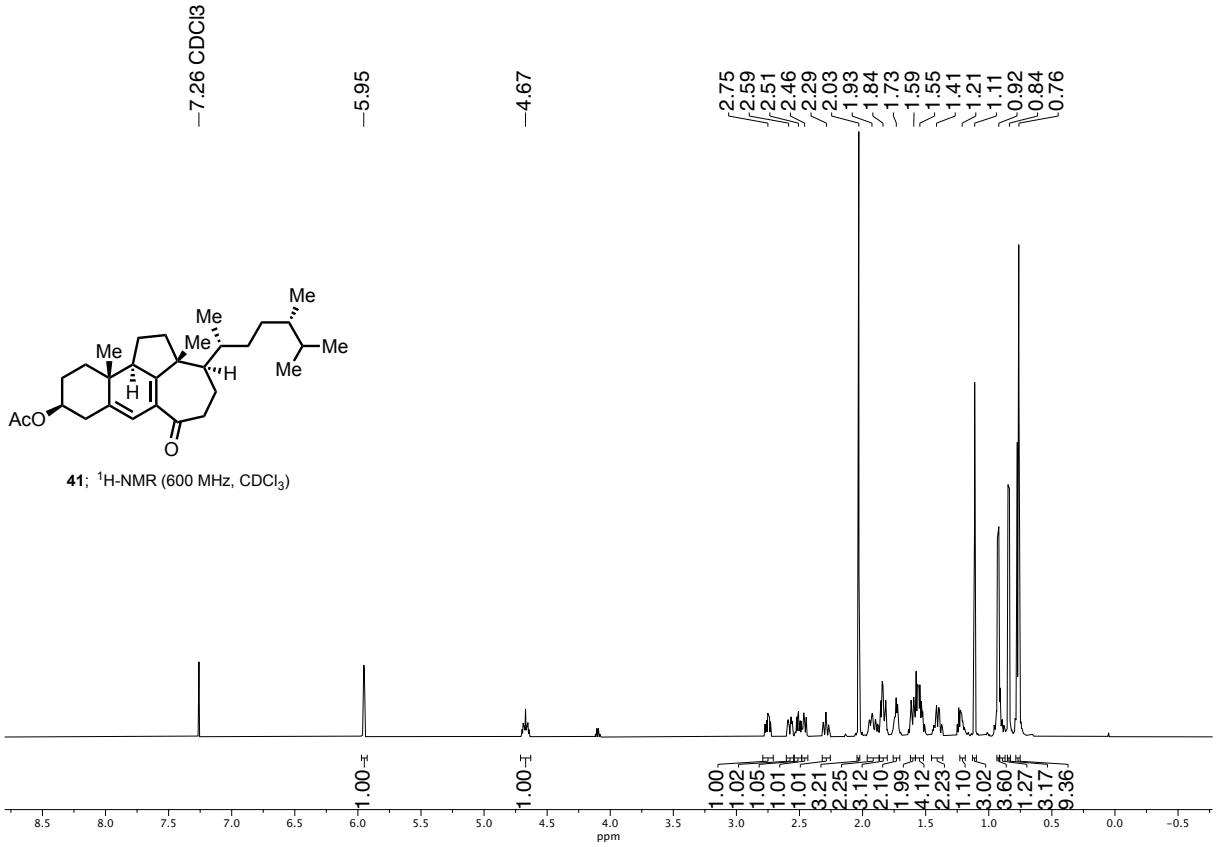
38; ^{13}C-NMR (176 MHz, $CDCl_3$)



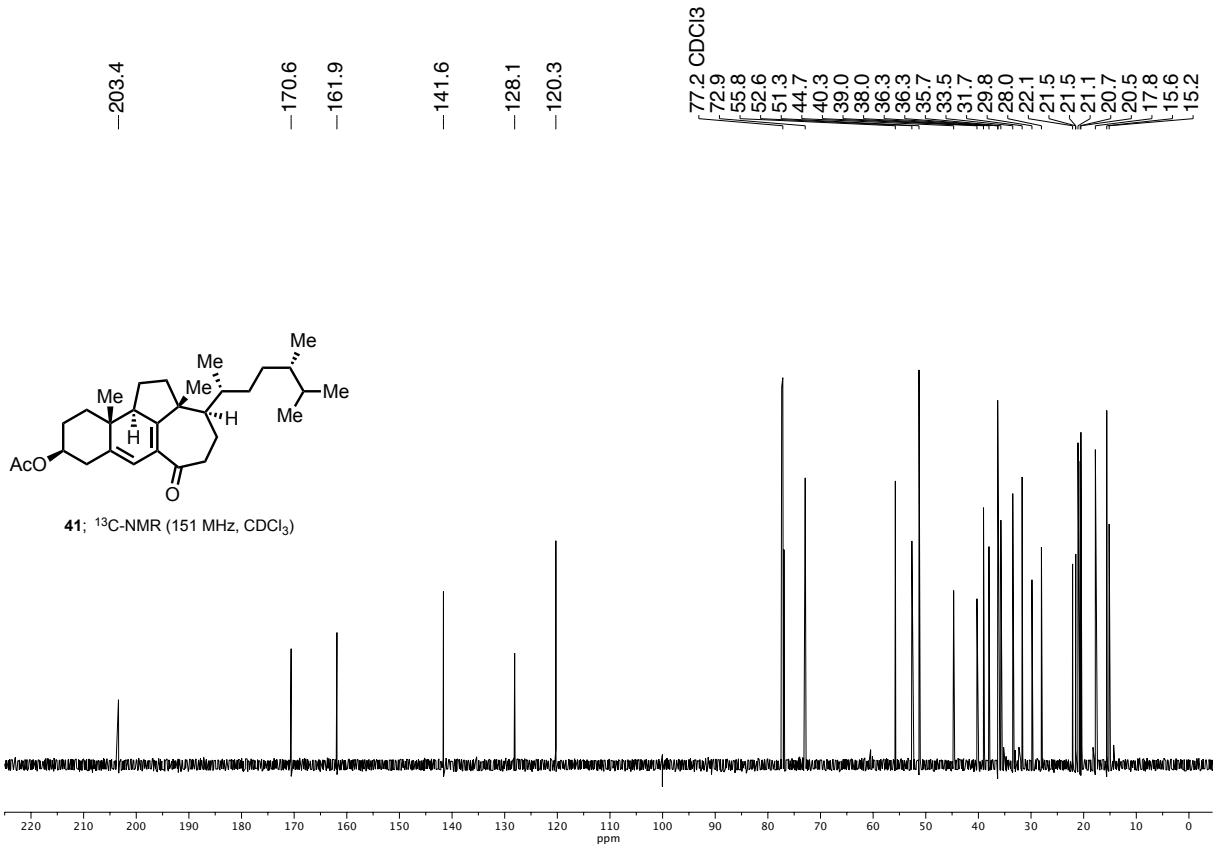
39; ^{1}H-NMR (700 MHz, $CDCl_3$)



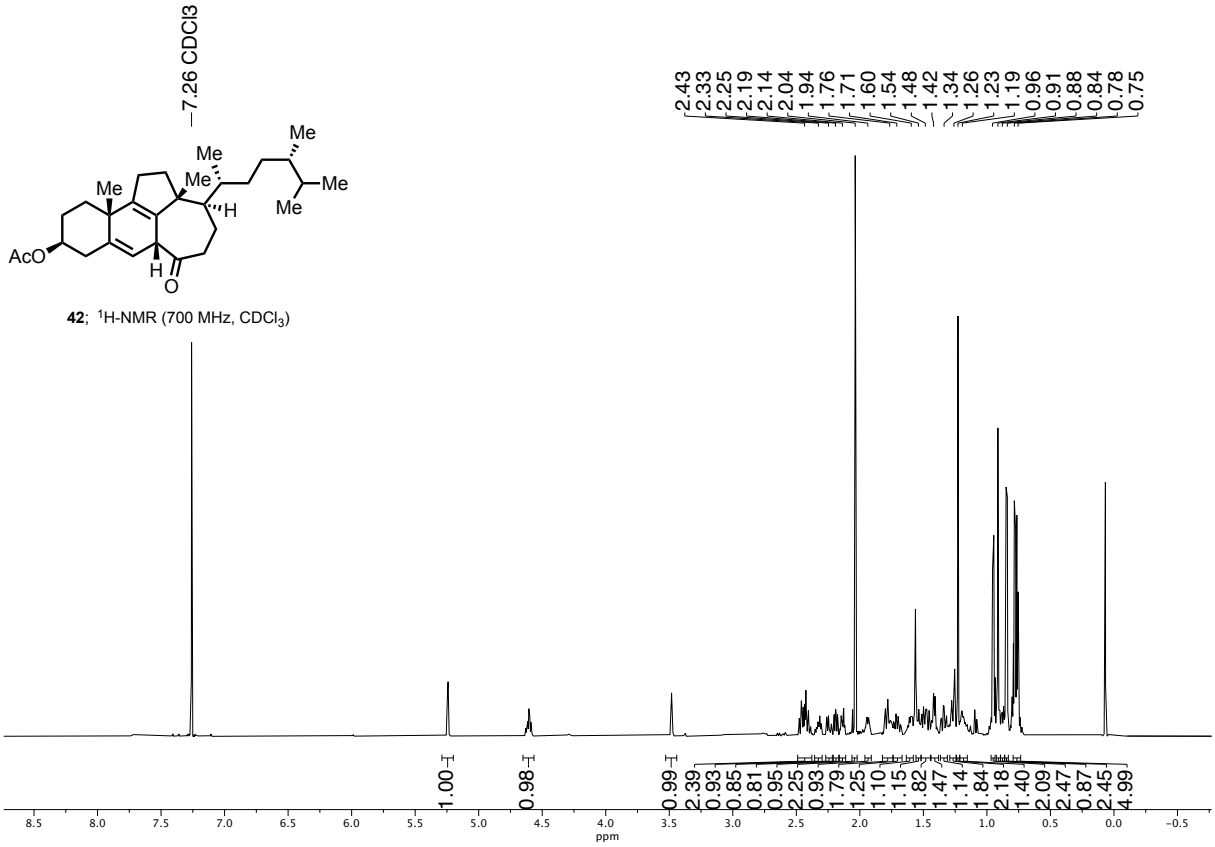
39; ^{13}C-NMR (176 MHz, $CDCl_3$)



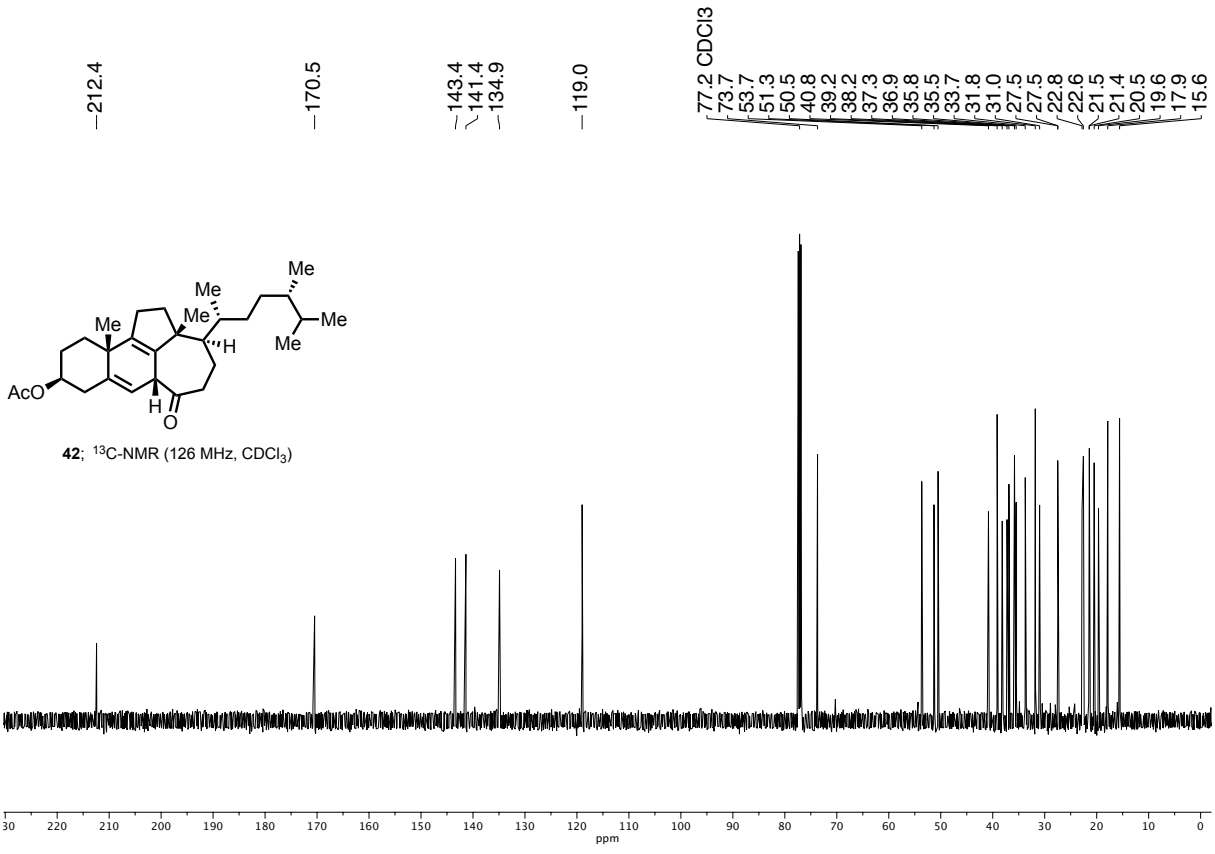
41; ^{1}H-NMR (600 MHz, $CDCl_3$)



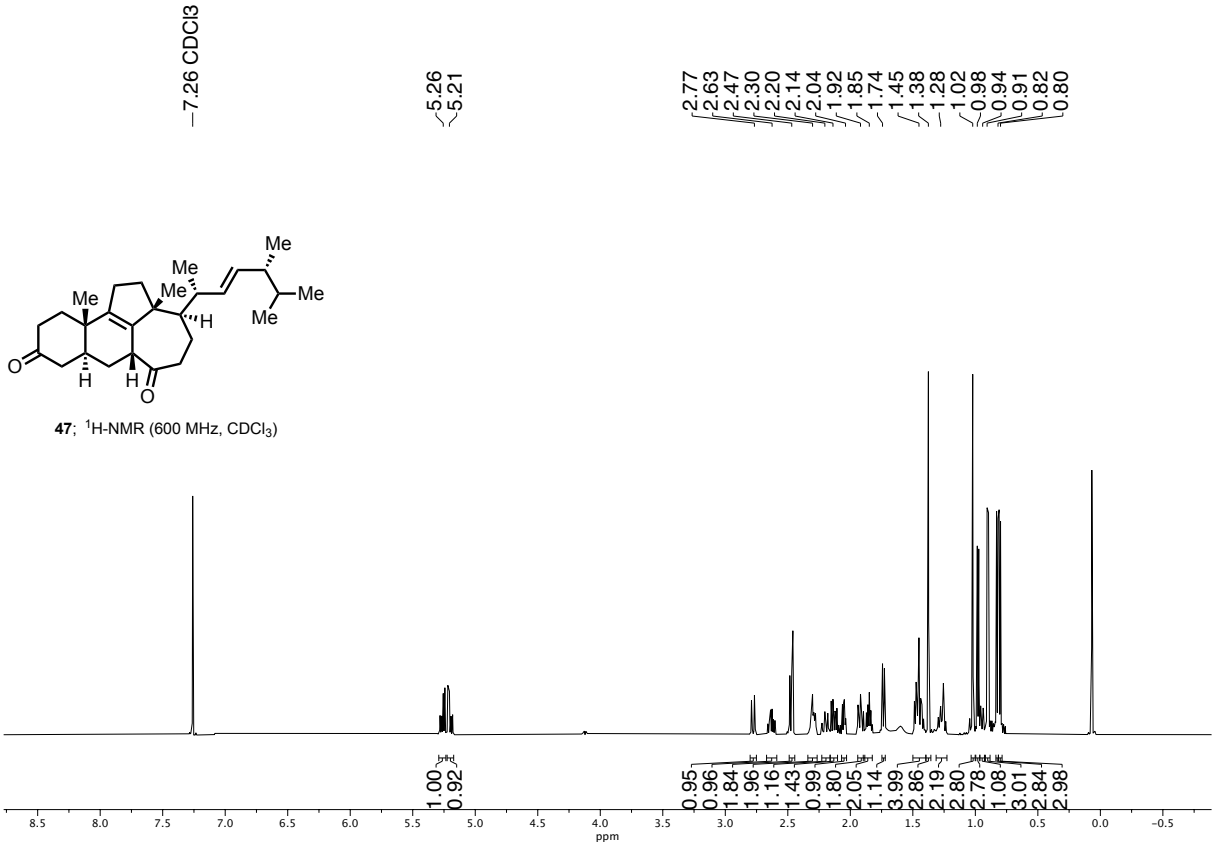
41; ^{13}C-NMR (151 MHz, $CDCl_3$)



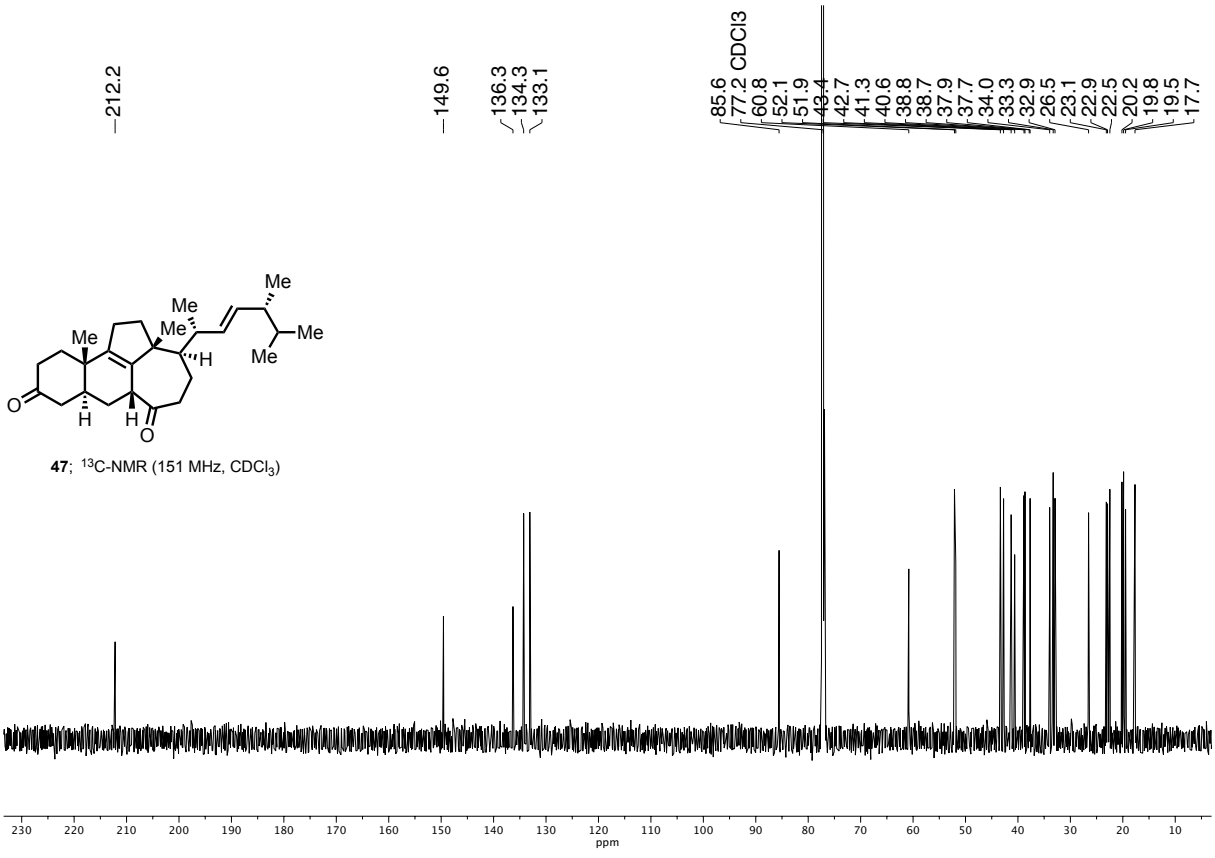
42; ^{1}H-NMR (700 MHz, $CDCl_3$)



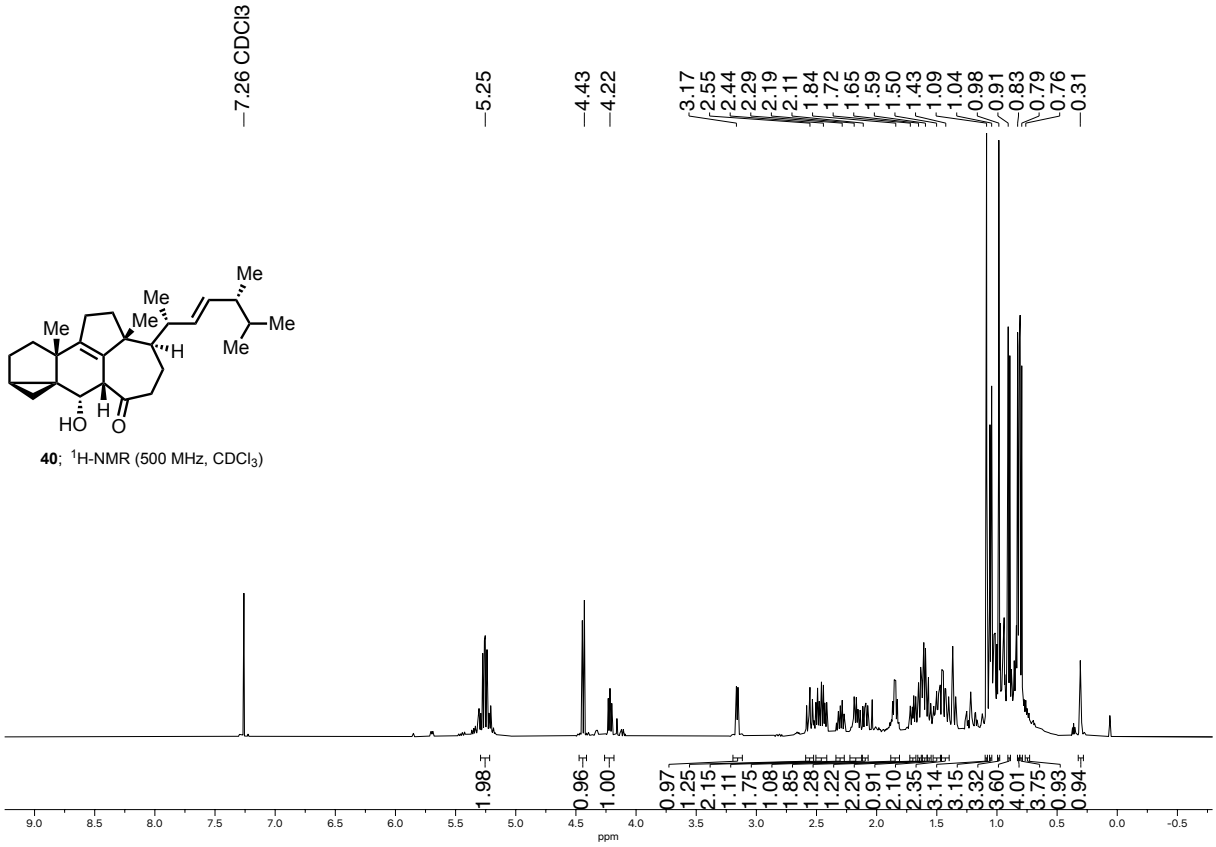
42; ^{13}C-NMR (126 MHz, $CDCl_3$)



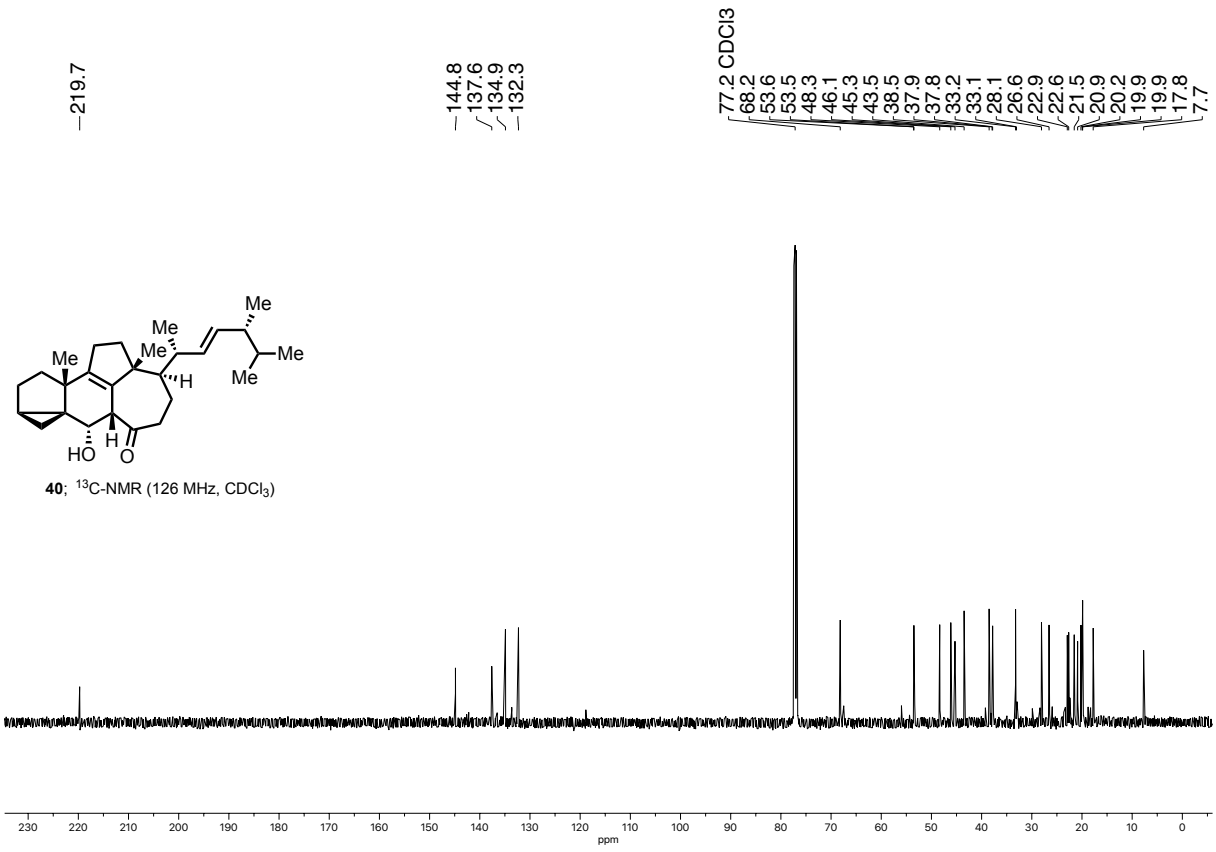
47; ^{1}H-NMR (600 MHz, $CDCl_3$)



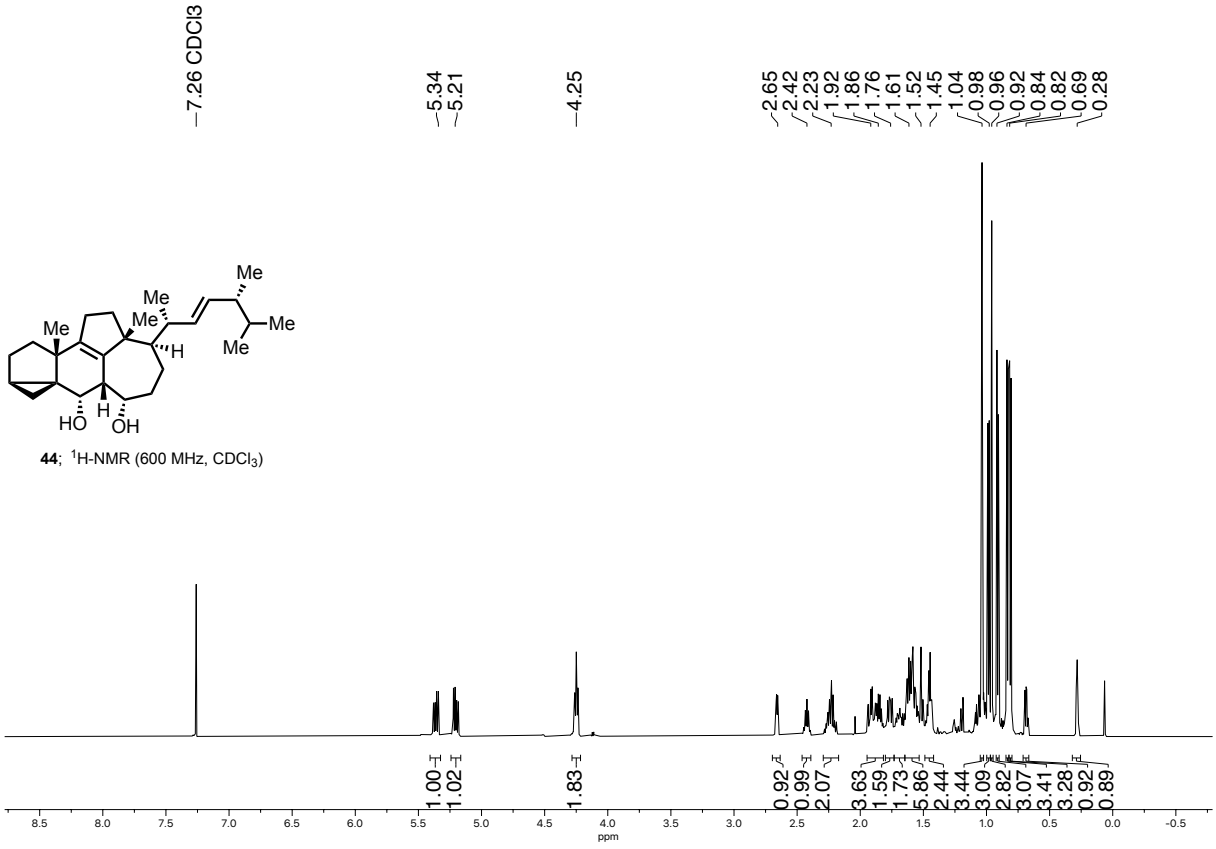
47; ^{13}C-NMR (151 MHz, $CDCl_3$)



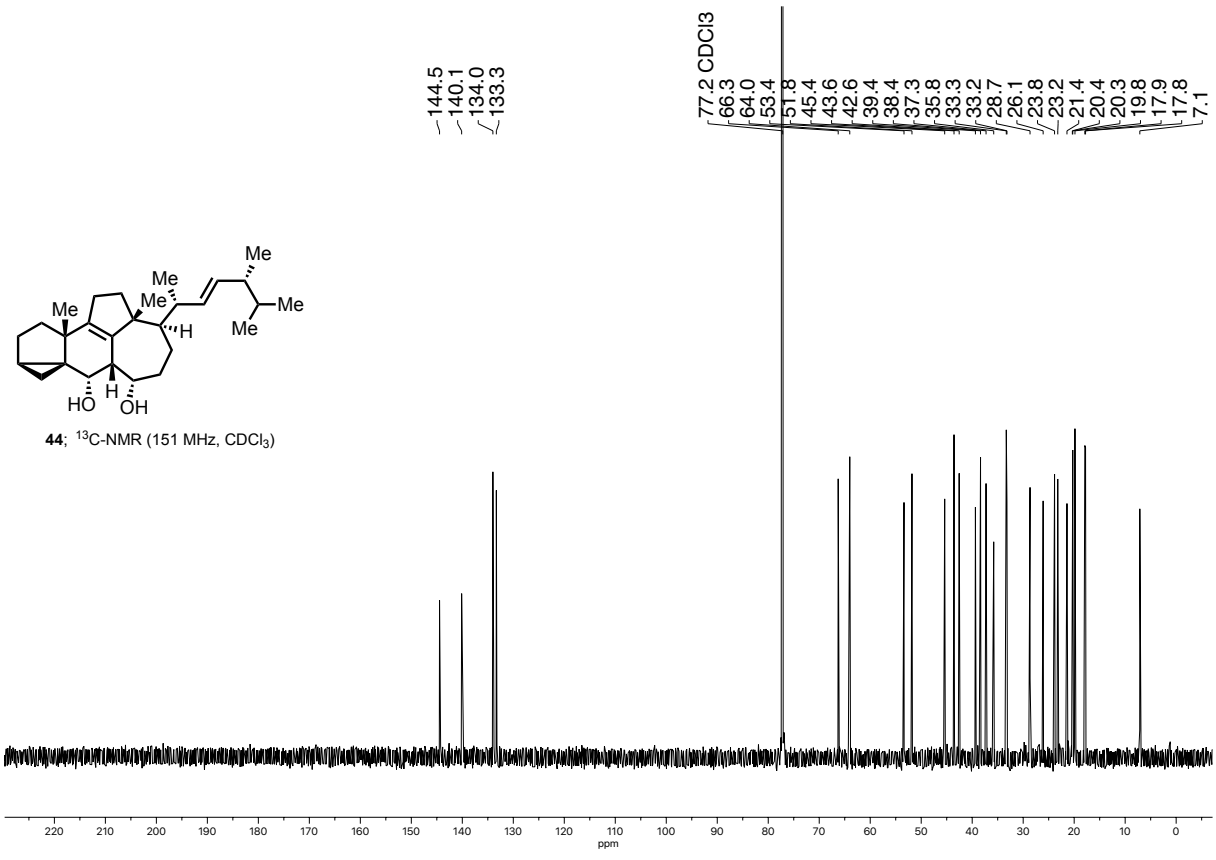
40; ^{1}H-NMR (500 MHz, $CDCl_3$)



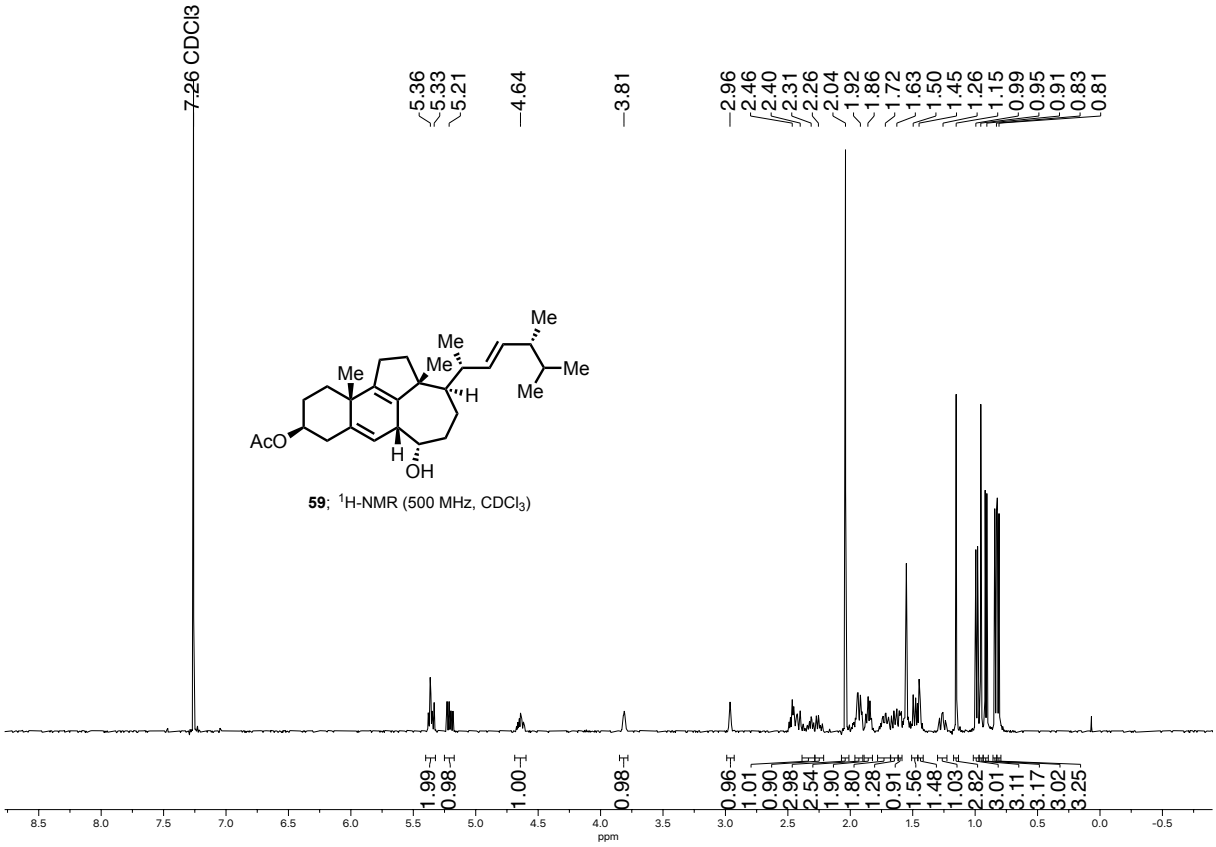
40; ^{13}C-NMR (126 MHz, $CDCl_3$)



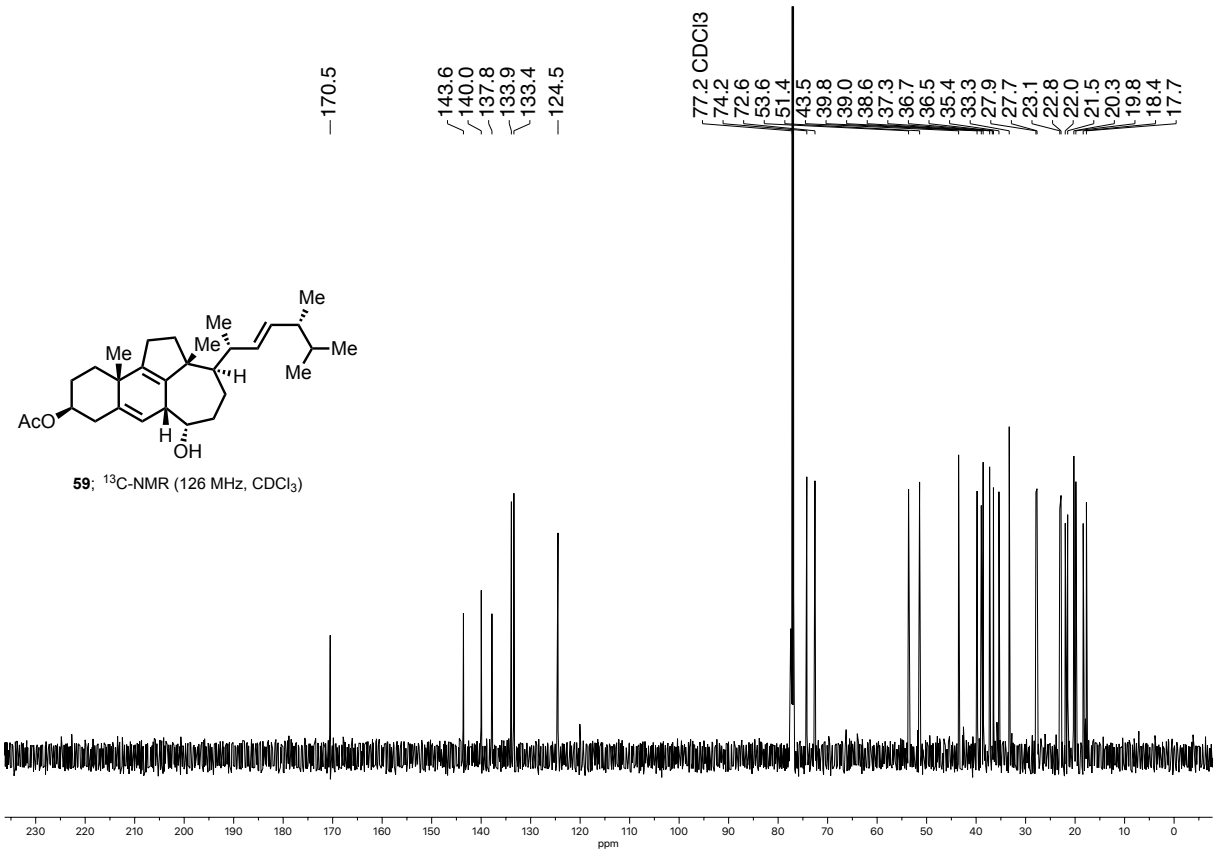
44; ^{1}H-NMR (600 MHz, $CDCl_3$)



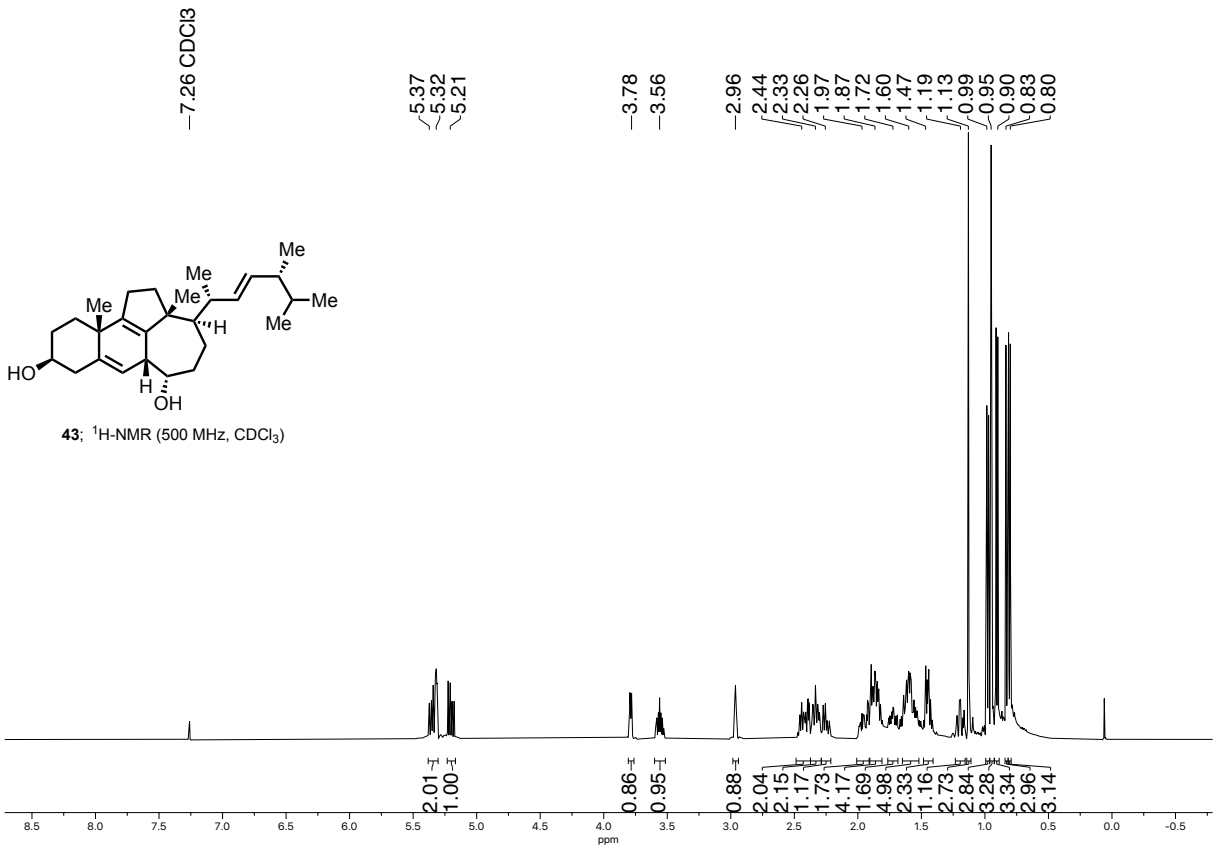
44; ^{13}C-NMR (151 MHz, $CDCl_3$)



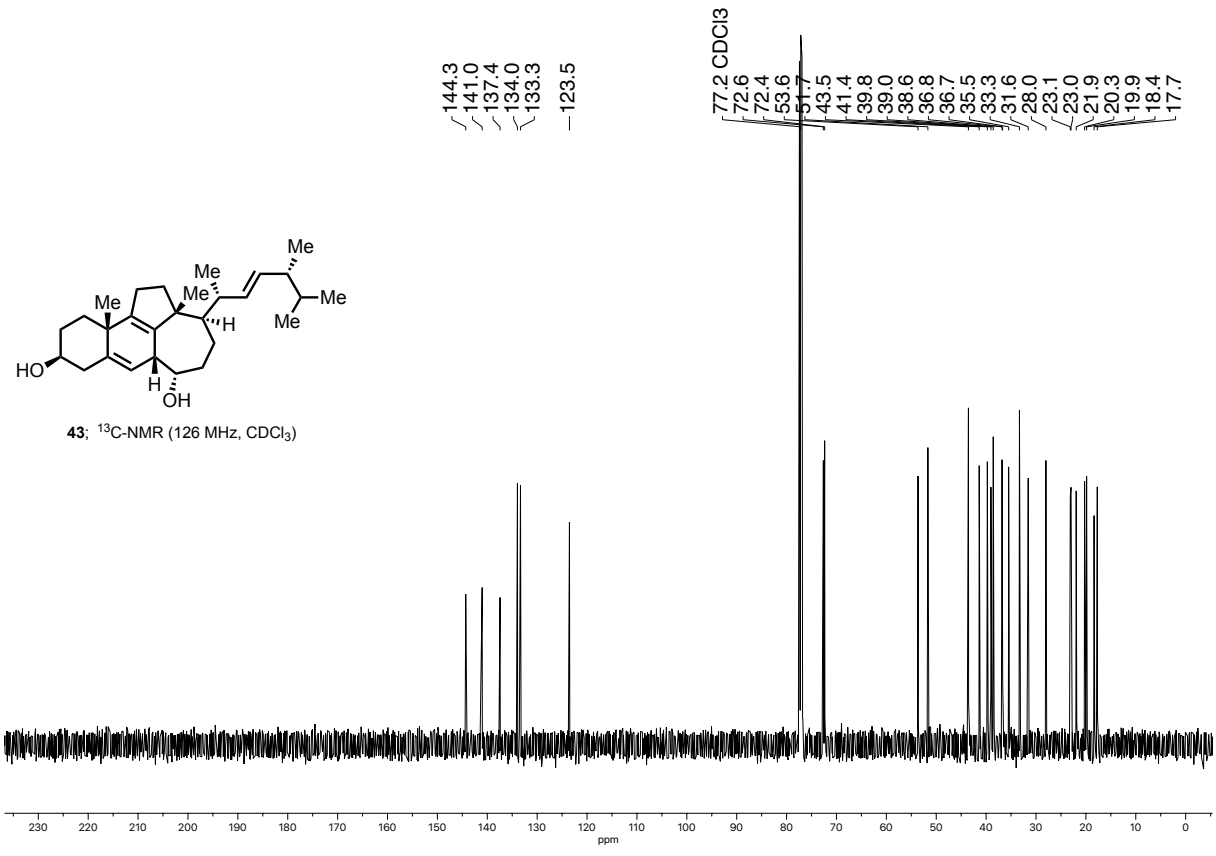
59; ^{1}H-NMR (500 MHz, $CDCl_3$)



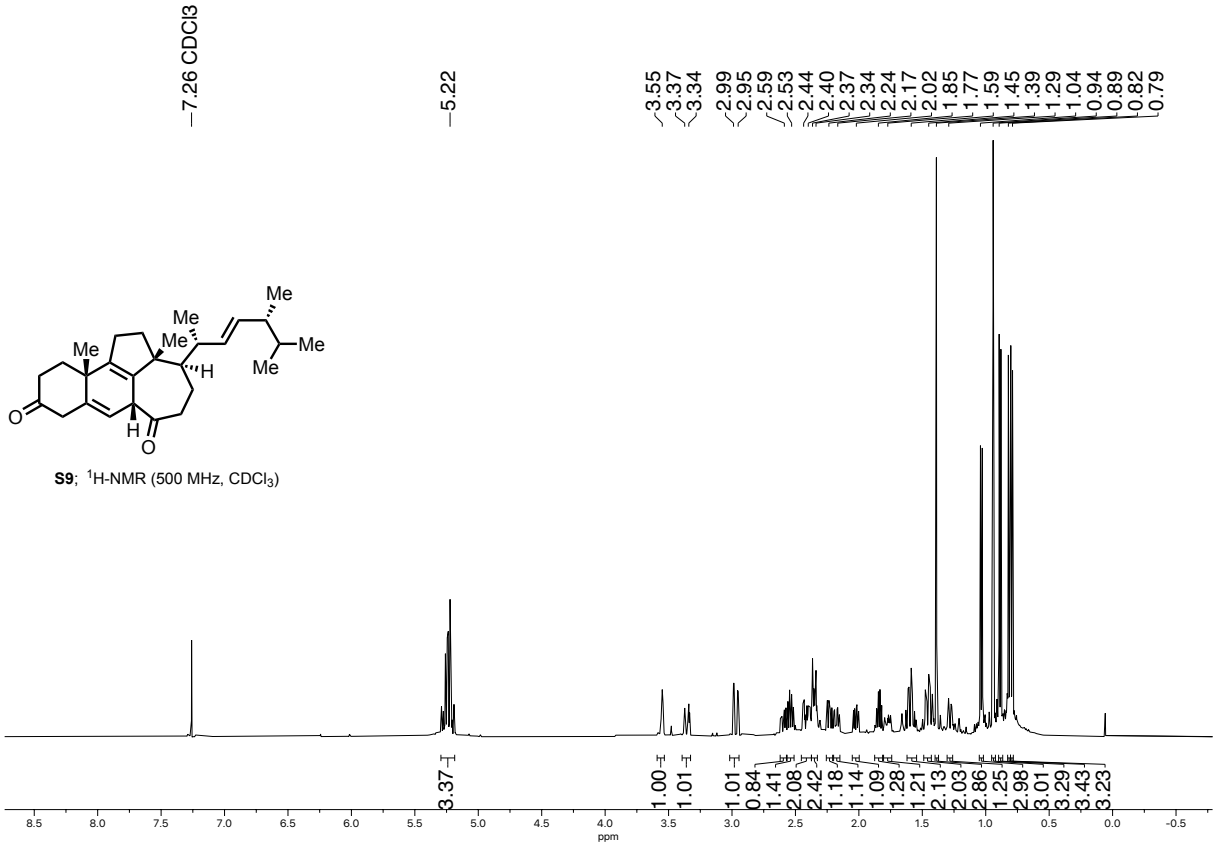
59; ^{13}C-NMR (126 MHz, $CDCl_3$)



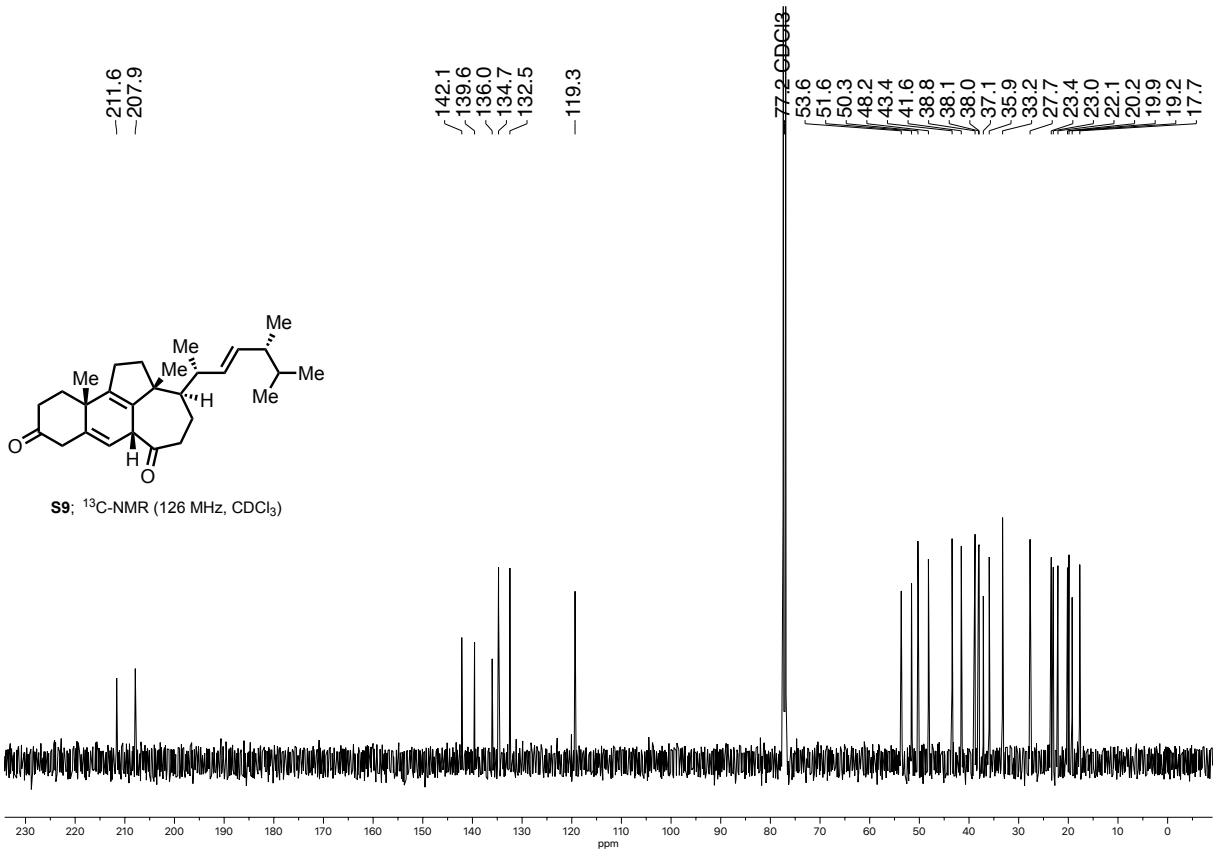
43; ^{1}H-NMR (500 MHz, $CDCl_3$)



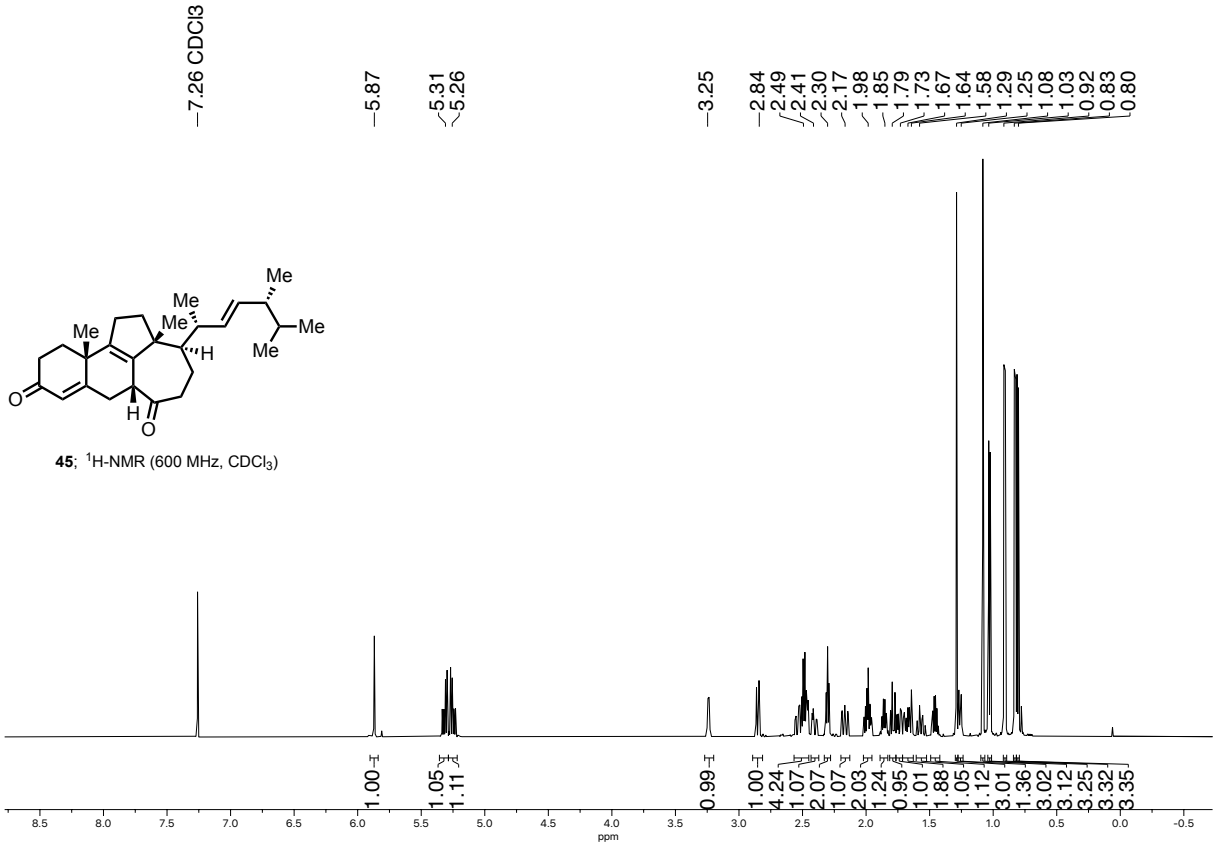
43; ^{13}C-NMR (126 MHz, $CDCl_3$)



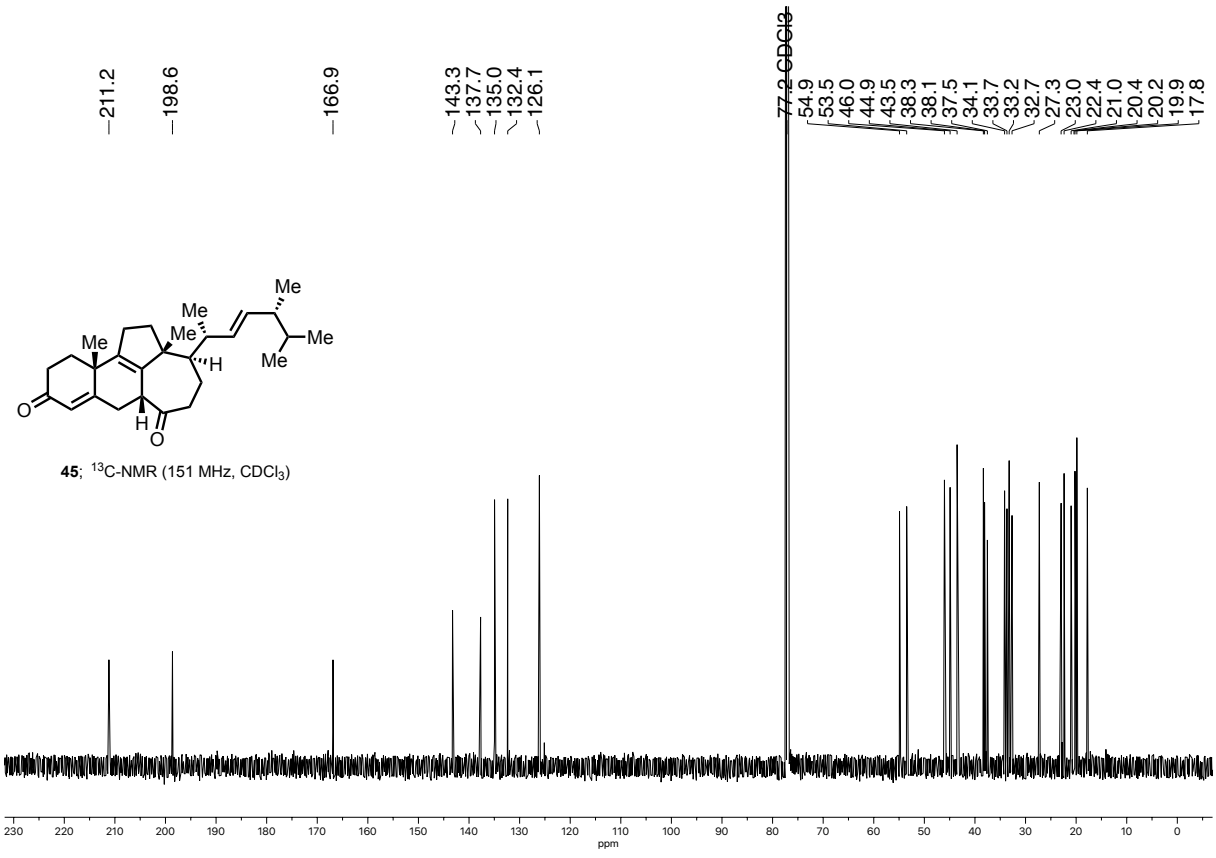
S9; ^{1}H-NMR (500 MHz, $CDCl_3$)



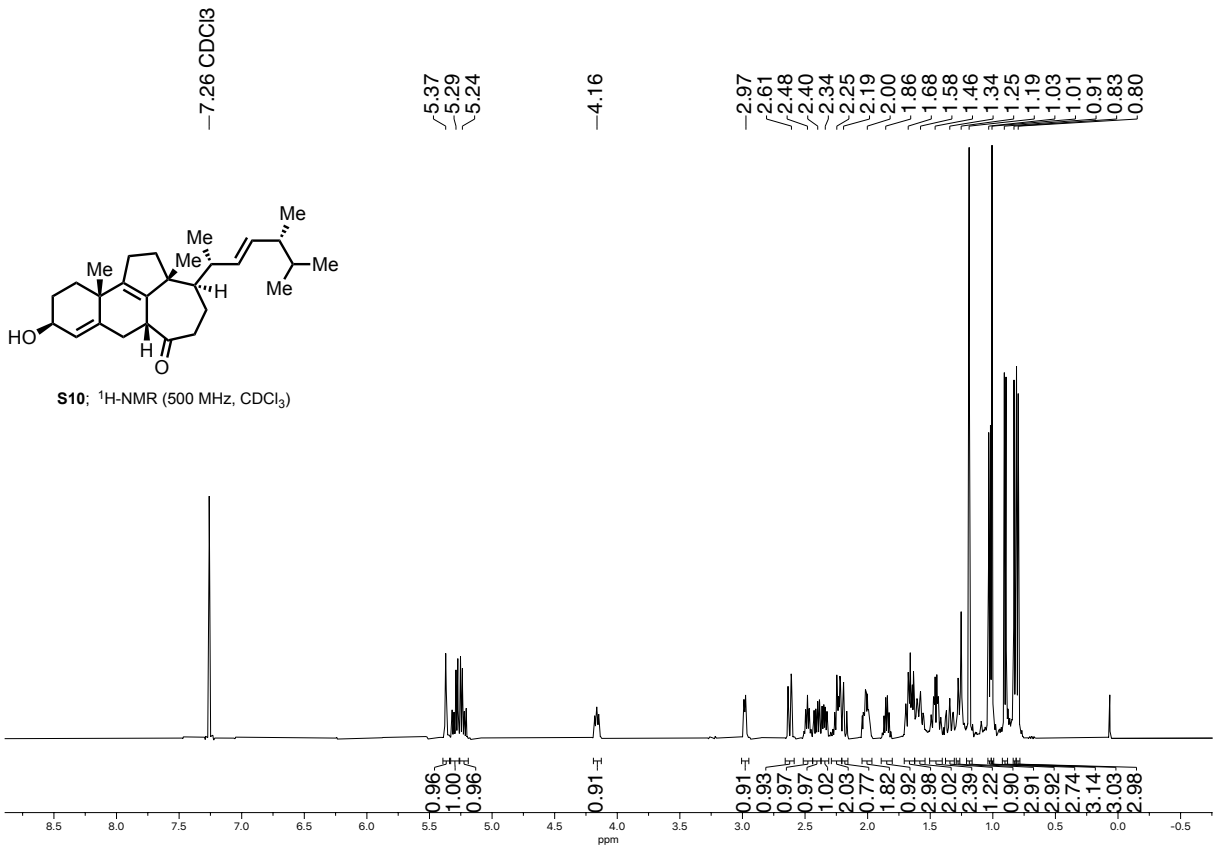
S9; ^{13}C-NMR (126 MHz, $CDCl_3$)



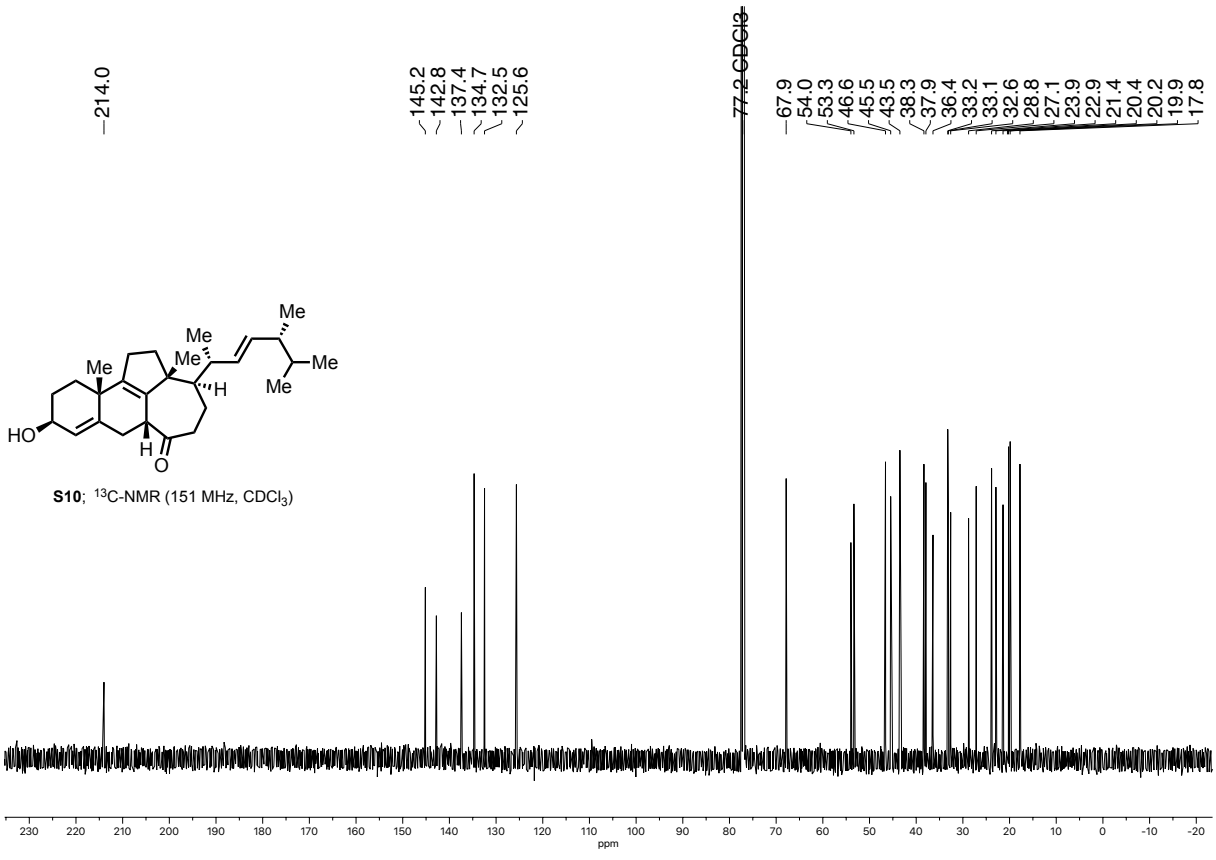
45; ^{1}H-NMR (600 MHz, $CDCl_3$)



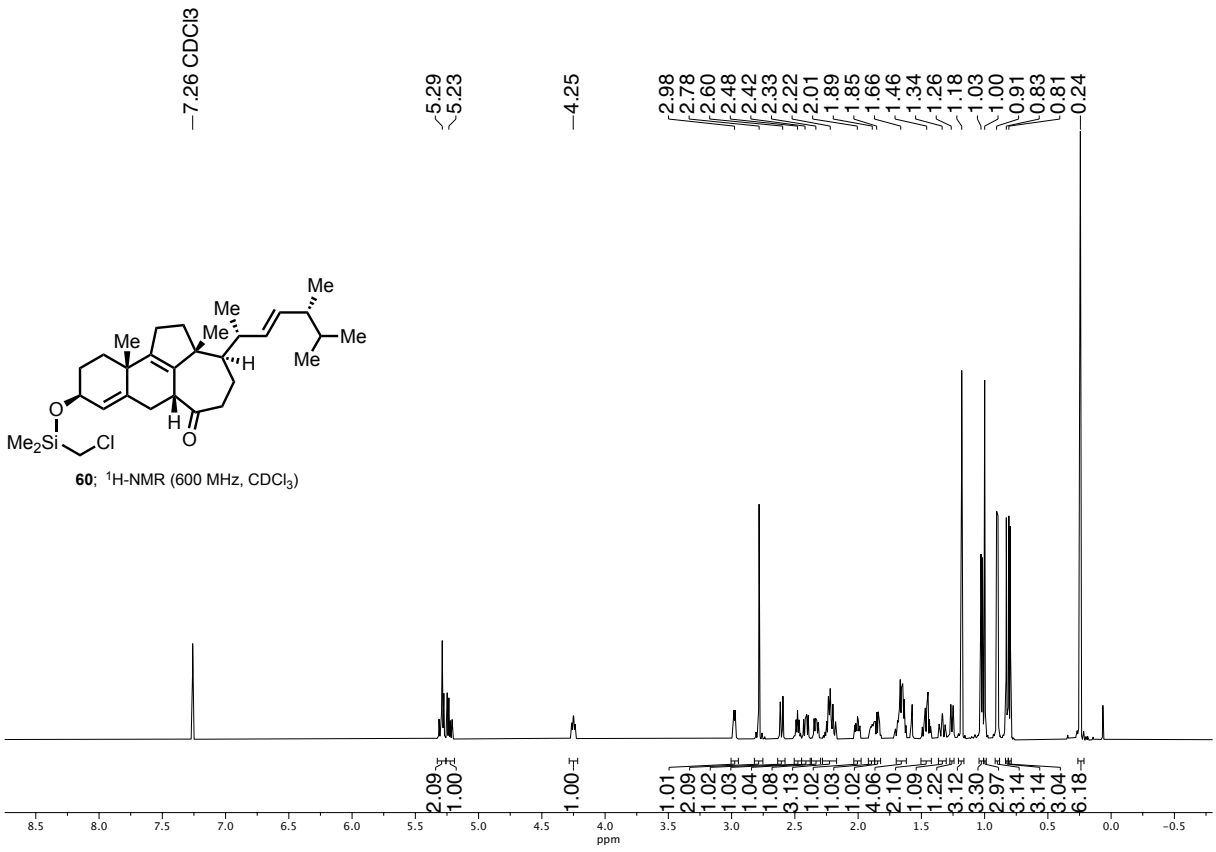
45; ^{13}C-NMR (151 MHz, $CDCl_3$)



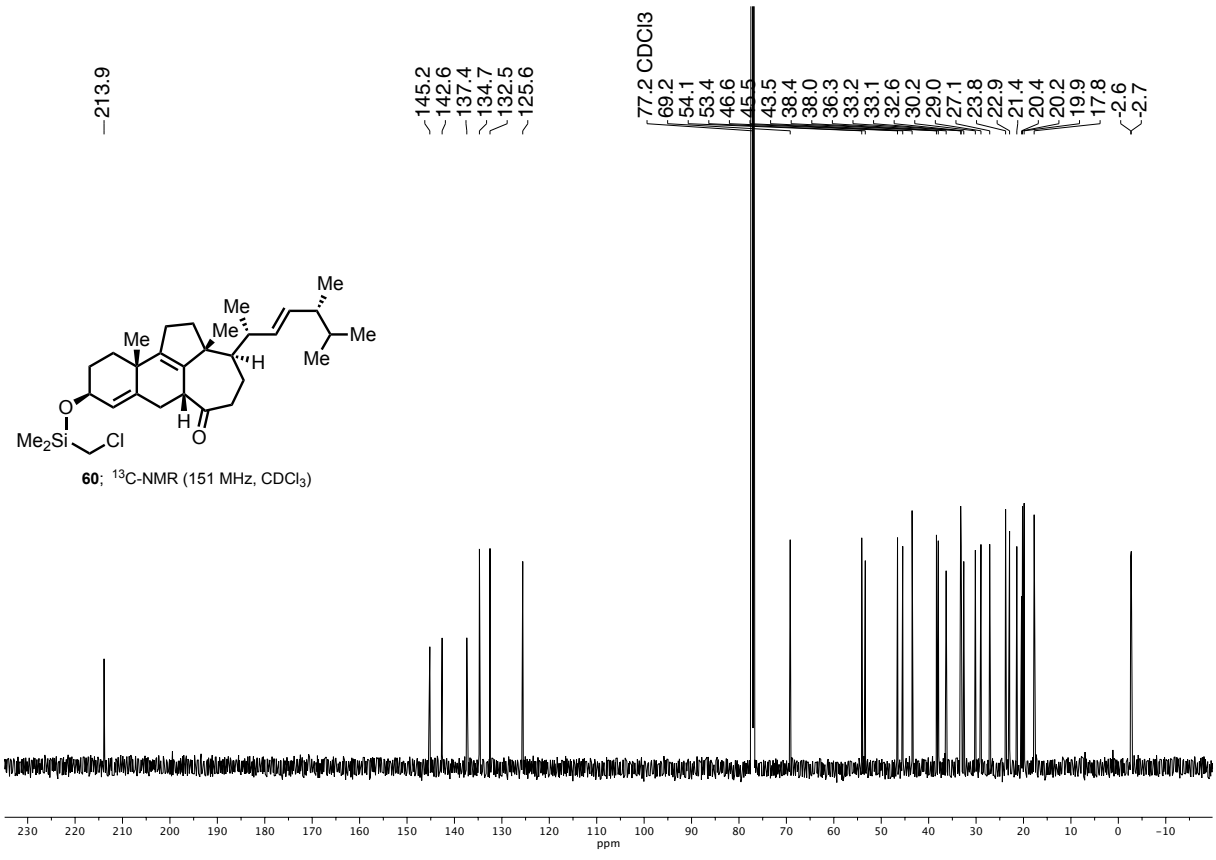
S10; ^{1}H-NMR (500 MHz, $CDCl_3$)



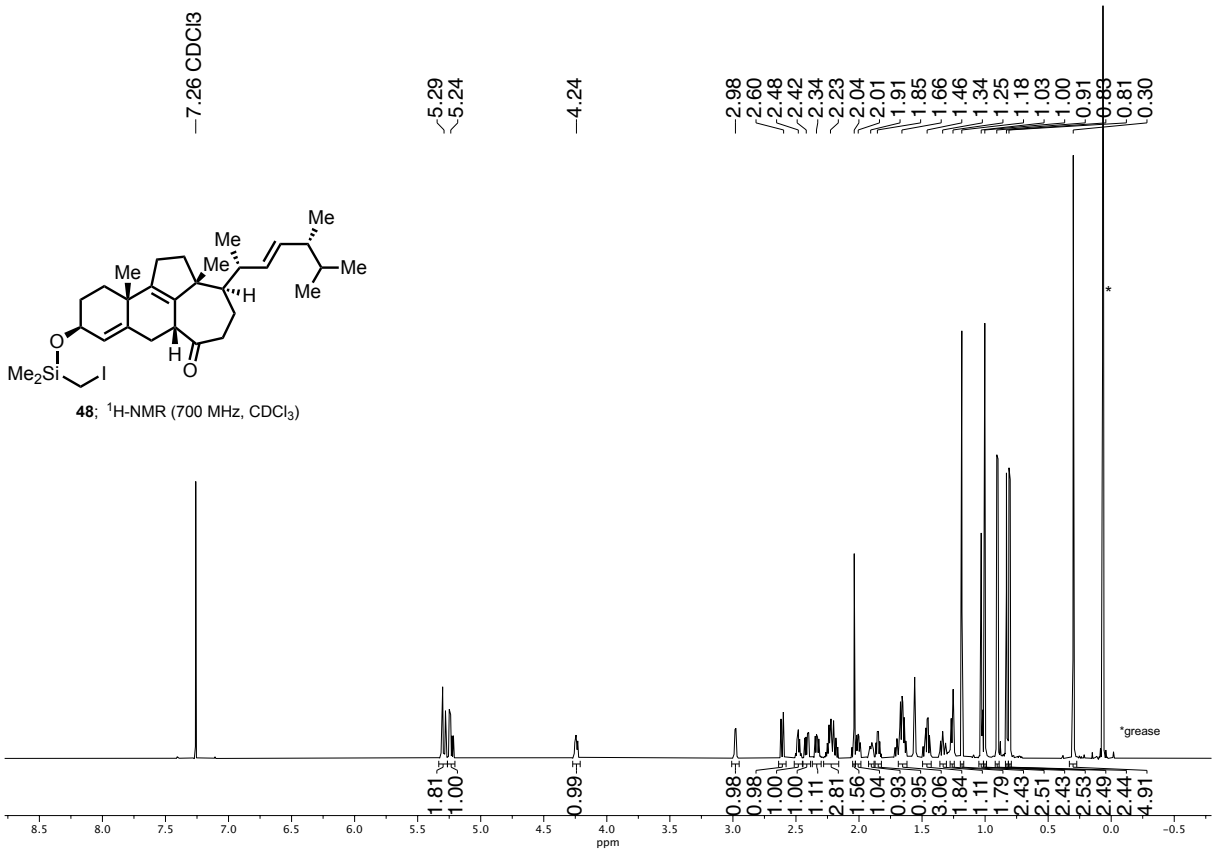
S10; ^{13}C-NMR (151 MHz, $CDCl_3$)



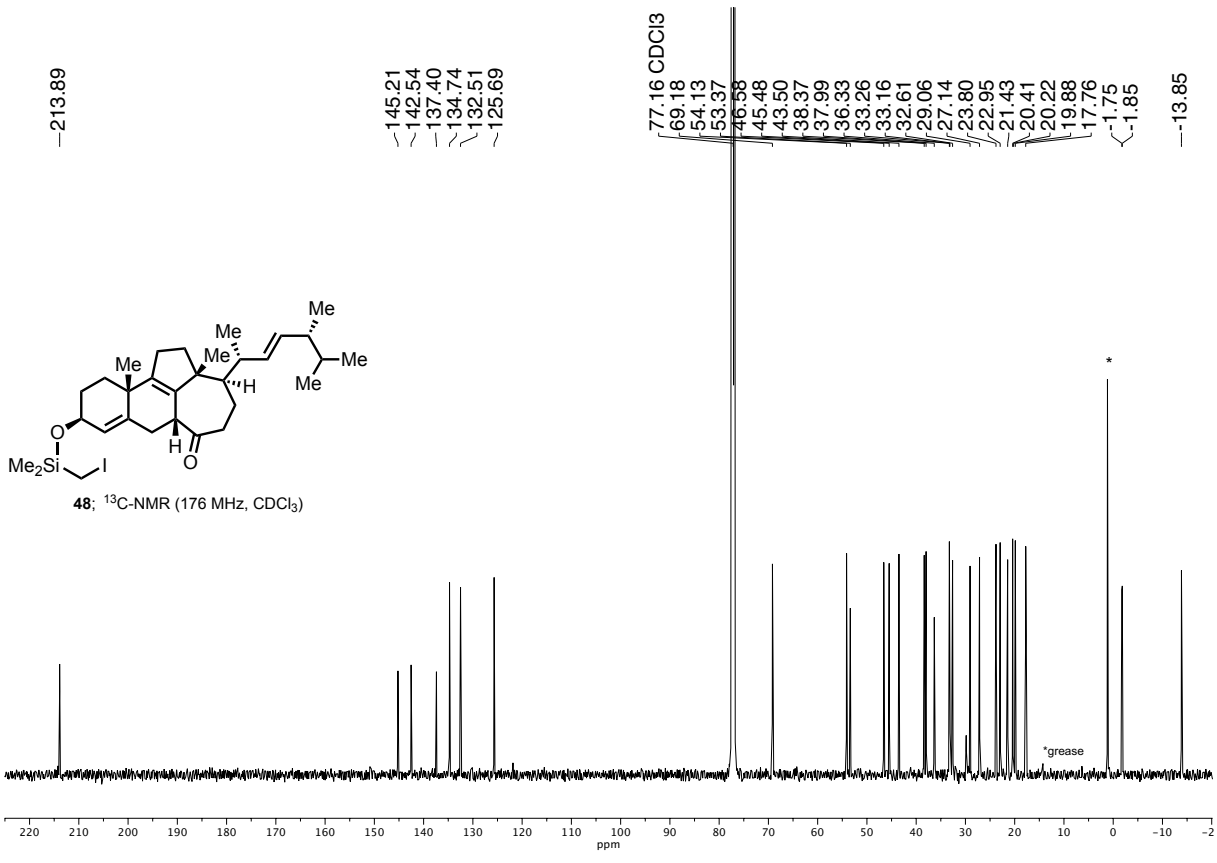
60; ^{1}H-NMR (600 MHz, $CDCl_3$)



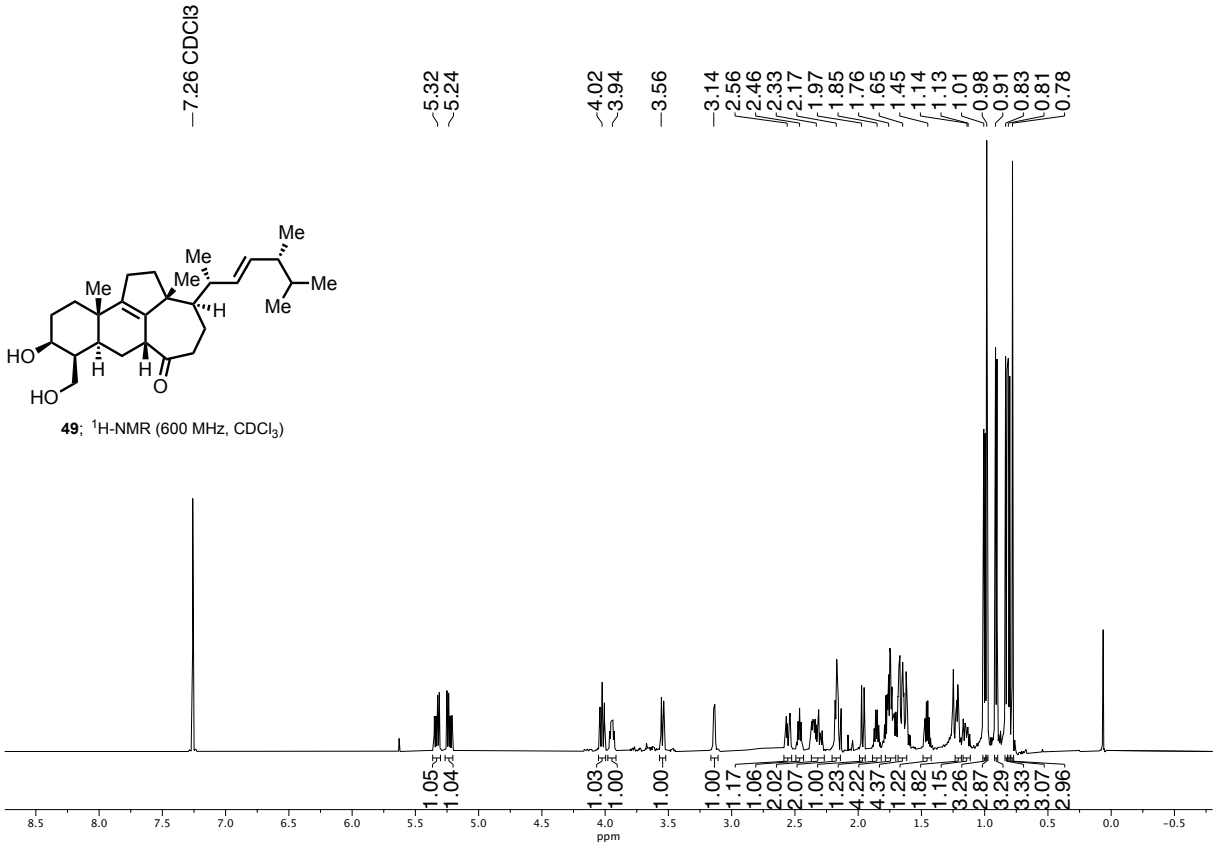
60; ^{13}C-NMR (151 MHz, $CDCl_3$)



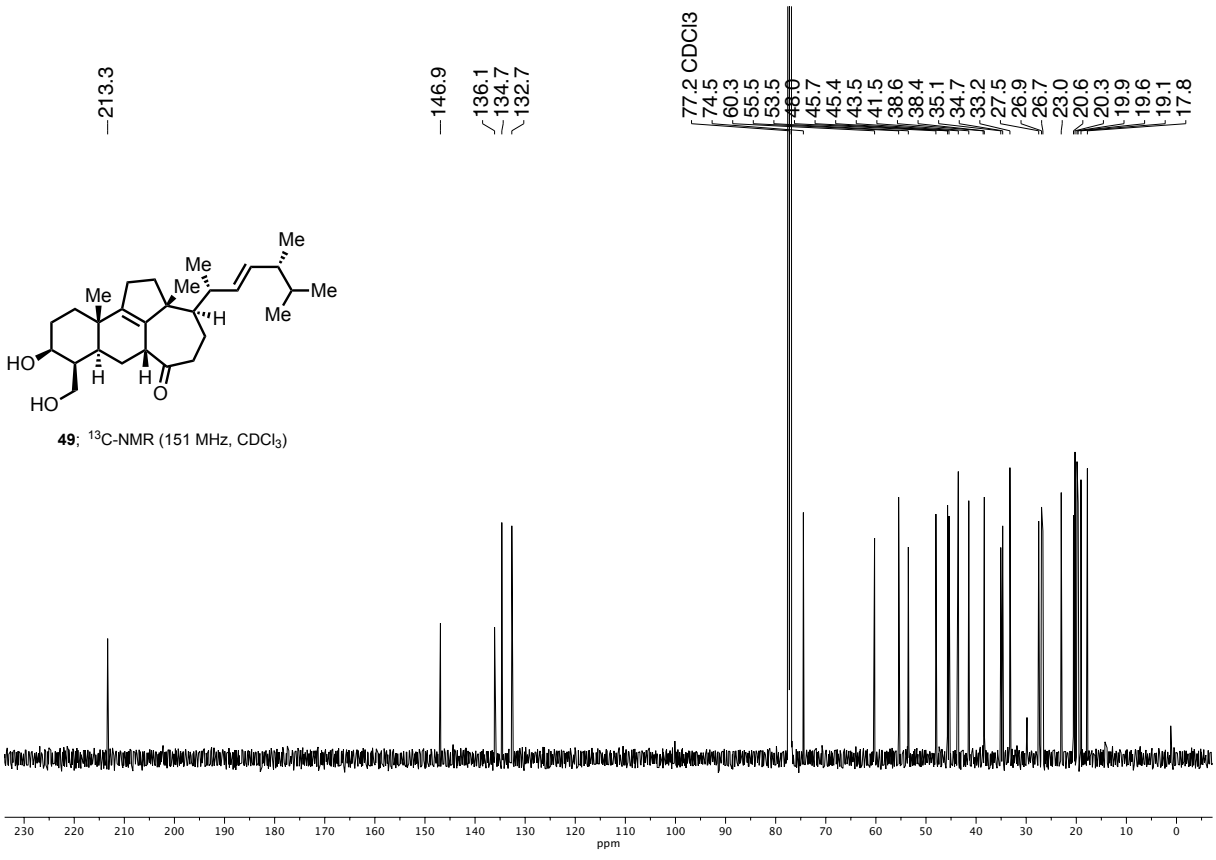
48; ^{1}H-NMR (700 MHz, $CDCl_3$)



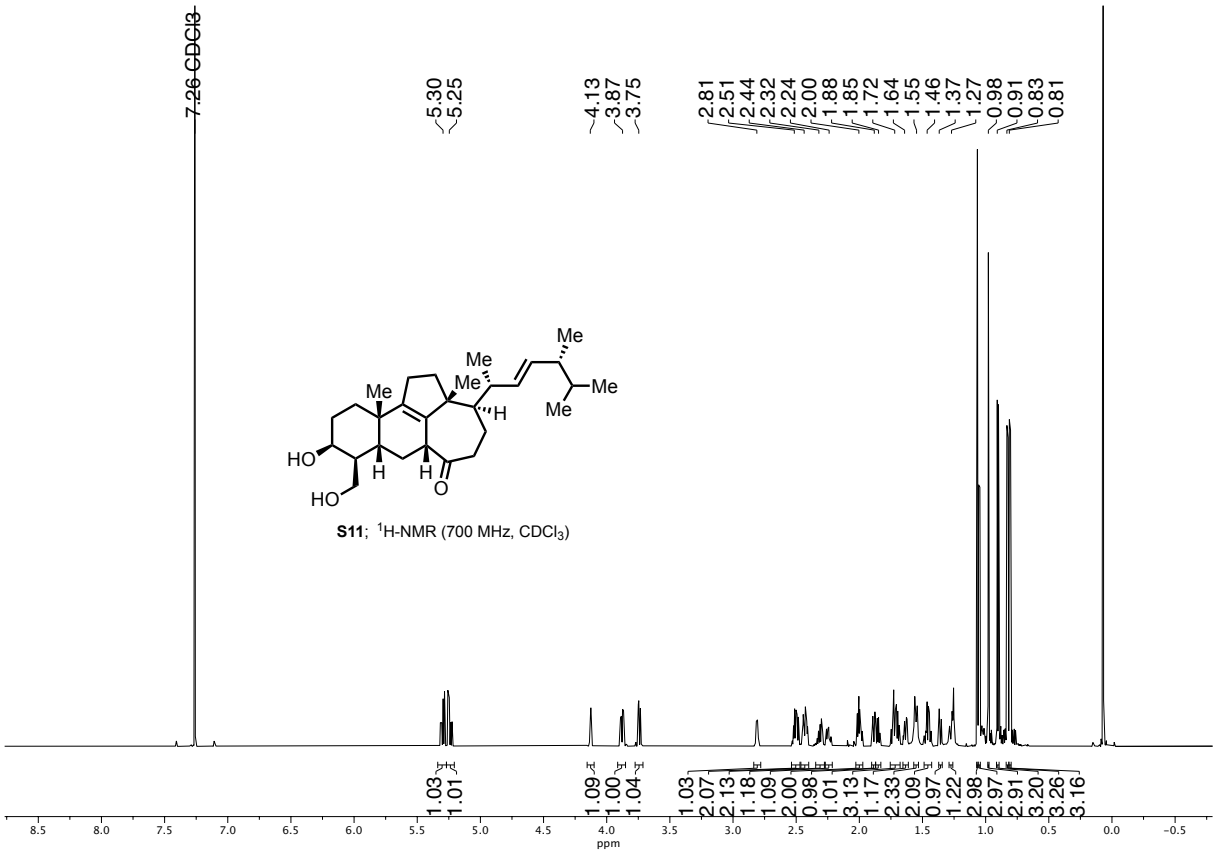
48; ^{13}C-NMR (176 MHz, $CDCl_3$)



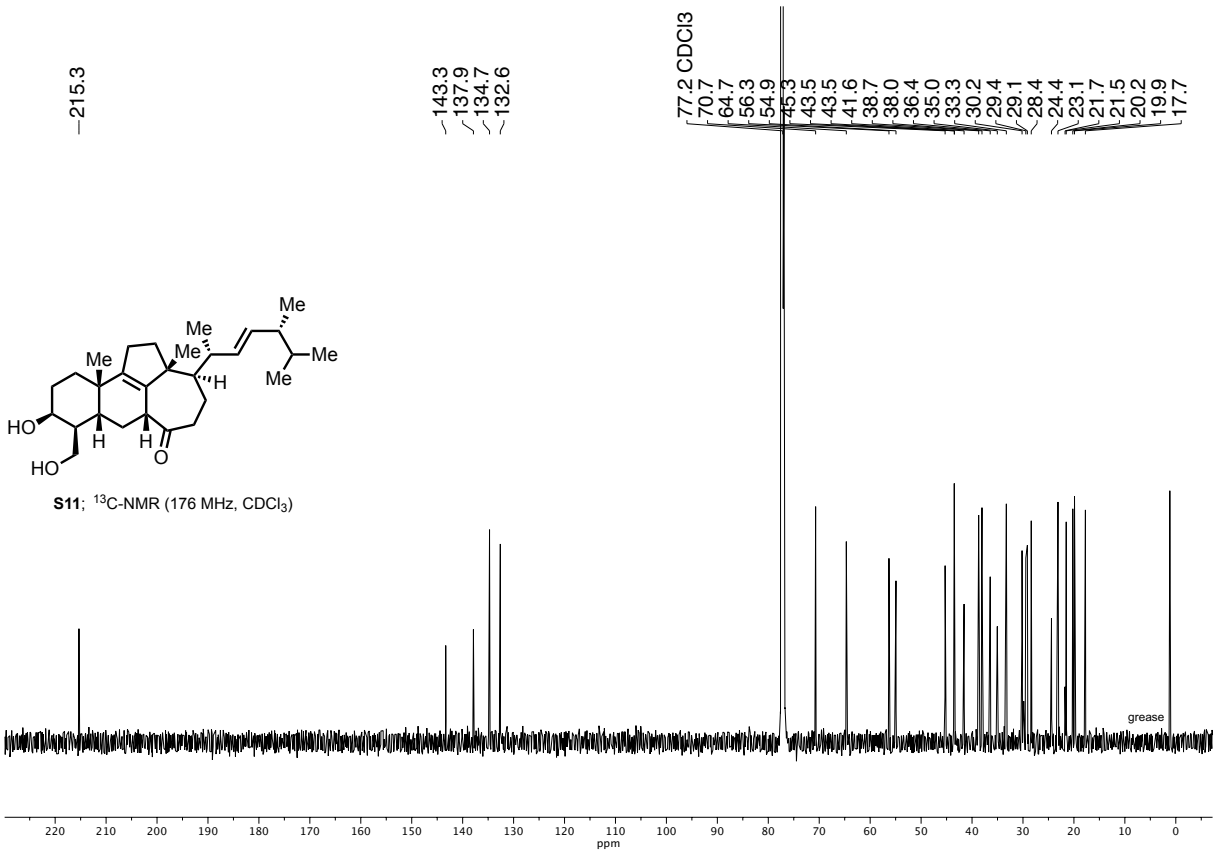
49; ^{1}H-NMR (600 MHz, $CDCl_3$)



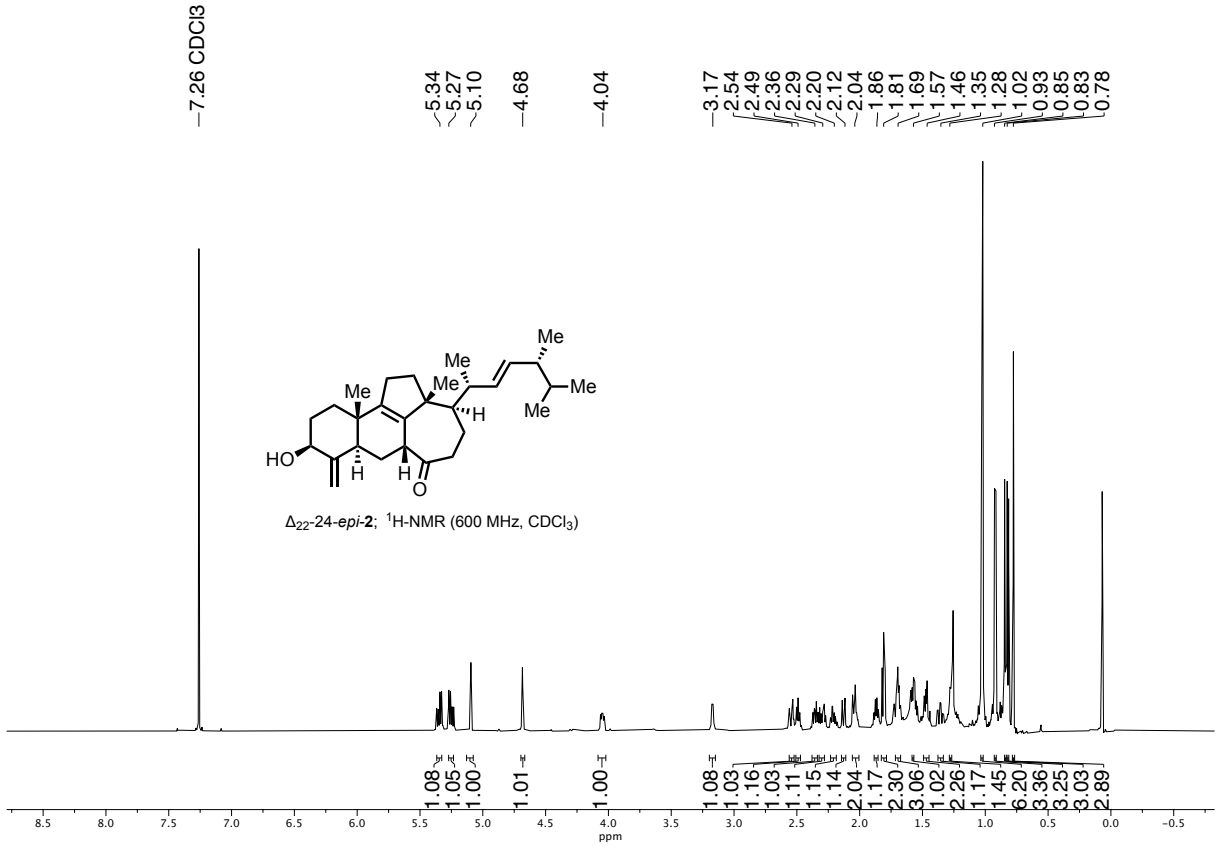
49; ^{13}C-NMR (151 MHz, $CDCl_3$)



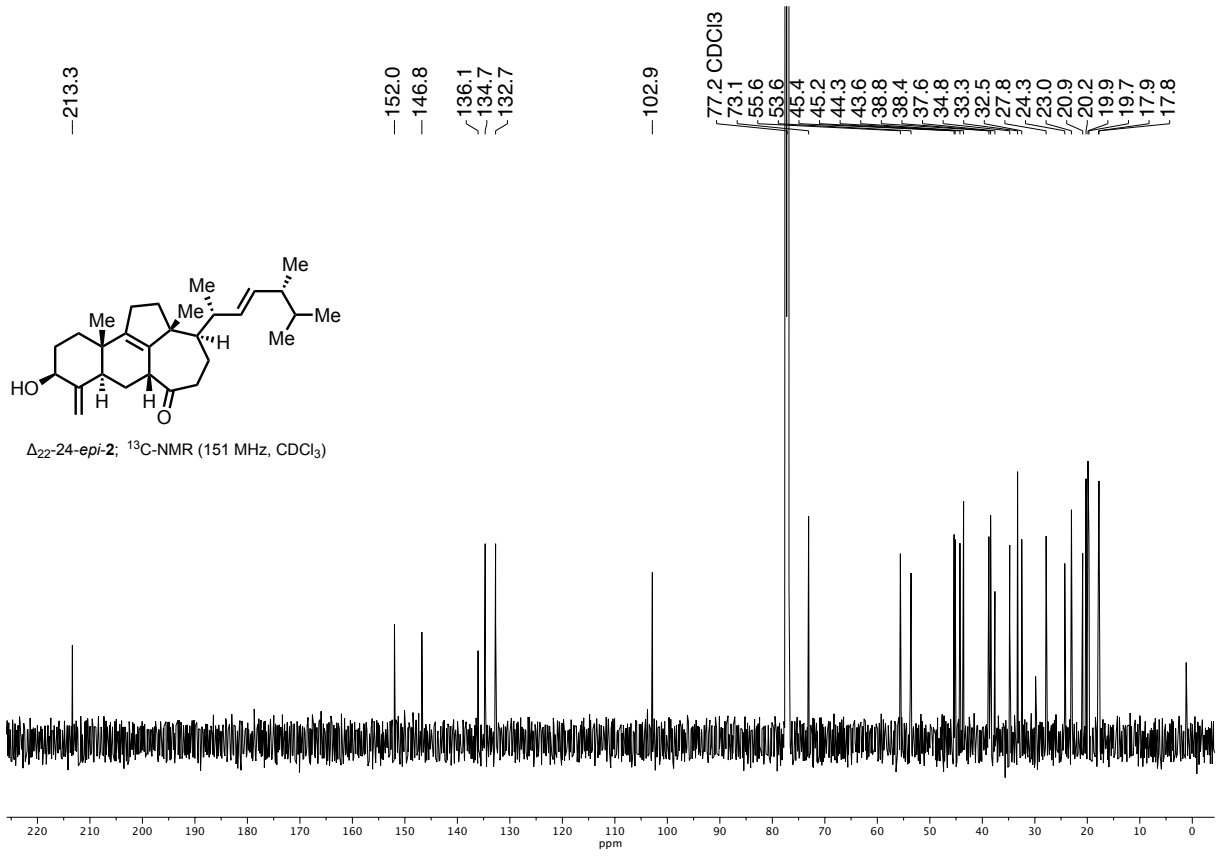
S11; ^{1}H-NMR (700 MHz, $CDCl_3$)



S11; ^{13}C-NMR (176 MHz, $CDCl_3$)



Δ_{22}-24-*epi*-**2**; ^{1}H-NMR (600 MHz, $CDCl_3$)



Δ_{22}-24-*epi*-**2**; ^{13}C-NMR (151 MHz, $CDCl_3$)

5 X-Ray Crystallographic Data

Periconiastone A (**5**)

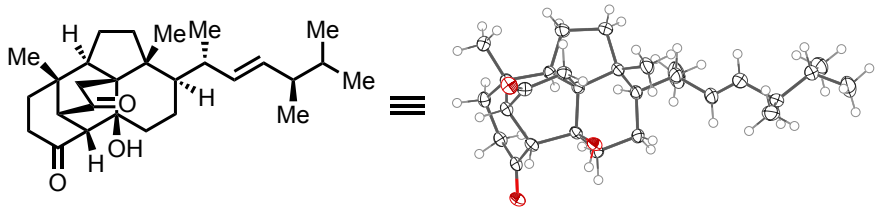


Table S3. Crystal data and structure refinement for **5**.

Identification code	FD1845F1
Empirical formula	$C_{28}H_{42}O_3$
Formula weight	426.61
Temperature/K	100 (2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	11.87605 (9)
b/Å	7.20073(5)
c/Å	15.10530 (11)
α/°	90
β/°	110.4521(4)
γ/°	90
Volume/Å^3	1210.322(16)
Z	2
ρ_{calc} g/cm^3	1.171
μ/mm^{-1}	0.571
F(000)	468.0
Crystal size/mm^3	0.370 × 0.205 × 0.096
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	5.85 to 68.46
Index ranges	–14 ≤ h ≤ 14, –8 ≤ k ≤ 8, –18 ≤ l ≤ 18
Reflections collected	29387
Independent reflections	4380 [R_{int} = 0.0643, R_{sigma} = 0.0382]
Data/restraints/parameters	4380/1/287
Goodness-of-fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.0365, wR_2 = 0.0878
Final R indexes [all data]	R_1 = 0.0403, wR_2 = 0.0900
Largest diff. peak/hole / e Å^{-3}	0.40/–0.15
Flack parameter	0.03(9)

(22*E*)-6,14-Dioxo-13(14→8),14(8→7)di*abeo*-5α(H)-ergosta-7,9(11),22-trien-3β-yl acetate (**9**)

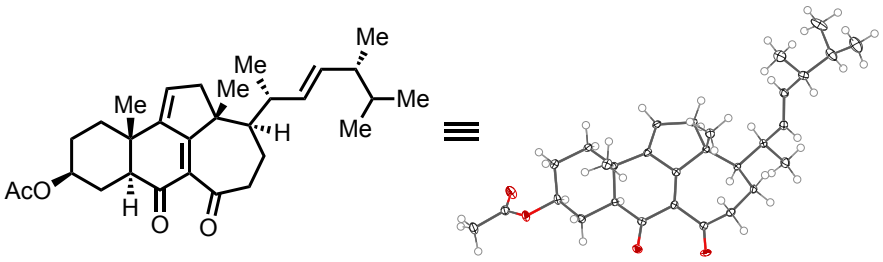


Table S4. Crystal data and structure refinement for **9**.

Identification code	fd_321_4_a
Empirical formula	$C_{30}H_{42}O_4$
Formula weight	466.63
Temperature/K	99.99
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.4425(5)
b/Å	17.0502(10)
c/Å	18.1656(10)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2614.9(3)
Z	4
ρ_{calc} g/cm^3	1.185
μ/mm^{-1}	0.077
F(000)	1016.0
Crystal size/mm^3	0.4 × 0.12 × 0.1
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.48 to 56.644
Index ranges	–11 ≤ h ≤ 11, –22 ≤ k ≤ 22, –24 ≤ l ≤ 24
Reflections collected	33915
Independent reflections	6504 [R_{int} = 0.0783, R_{sigma} = 0.0544]
Data/restraints/parameters	6504/0/314
Goodness-of-fit on F^2	0.887
Final R indexes [I>=2σ (I)]	R_1 = 0.0470, wR_2 = 0.1152
Final R indexes [all data]	R_1 = 0.0632, wR_2 = 0.1259
Largest diff. peak/hole / e Å^{-3}	0.31/–0.29
Flack parameter	–0.2(5)

(22*E*)-6,14-Dioxo-5α,9α-endoperoxide-13(14→8),14(8→7)di*abeo*-ergosta-7,22-dien-3β-yl acetate (**10**)

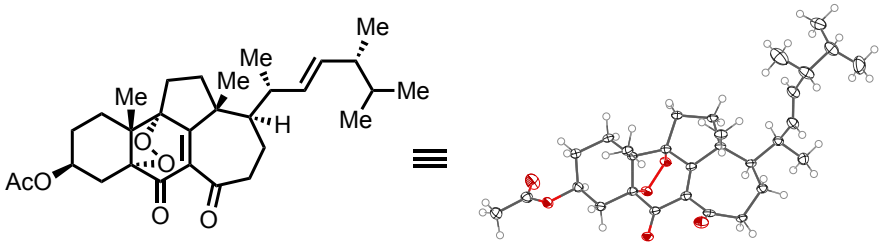


Table S5. Crystal data and structure refinement for **10**.

Identification code	fd321_3_a
Empirical formula	$C_{30}H_{42}O_6$
Formula weight	498.63
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1$
a/Å	10.296
b/Å	8.273
c/Å	16.108
α/°	90
β/°	96.82
γ/°	90
Volume/Å^3	1362.4
Z	2
ρ_{calc} g/cm^3	1.216
μ/mm^{-1}	0.668
F(000)	540.0
Crystal size/mm^3	0.5 × 0.08 × 0.02
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	5.526 to 159.246
Index ranges	–13 ≤ h ≤ 13, –9 ≤ k ≤ 10, –20 ≤ l ≤ 20
Reflections collected	40217
Independent reflections	5773 [R_{int} = 0.0463, R_{sigma} = 0.0291]
Data/restraints/parameters	5773/1/332
Goodness-of-fit on F^2	1.098
Final R indexes [I>=2σ (I)]	R_1 = 0.0376, wR_2 = 0.1220
Final R indexes [all data]	R_1 = 0.0391, wR_2 = 0.1241
Largest diff. peak/hole / e Å^{-3}	0.28/–0.26
Flack parameter	0.12(5)

References

(1) F. L. Duecker, R. C. Heinze, M. Mueller, S. Zhang, P. Heretsch, Synthesis oft he Alleged Structures of Fortisterol and Herbarulide and Structural Revision of Herbarulide. *Org. Lett.*, **2020**, *22*, 1585–1588.

(2) R. C. Heinze, D. Lentz, P. Heretsch, Synthesis of Strophasterol A Guided by a Proposed Biosynthesis and Innate Reactivity. *Angew. Chem., Int. Ed.* **2016**, *55*, 11656–11659.

(3) F. L. Duecker, R. C. Heinze, P. Heretsch, Synthesis of Swinhoeisterol A, Dankasterone A and B, and Periconiastone A by Radical Framework Reconstruction. *J. Am. Chem. Soc.* **2020**, *142*, 104–108.

(4) J. Gong, P. Sun, N. Jiang, R. Riccio, G. Lauro, G. Bifulco, T.-J- Li, W. H. Gerwick, W. Zhang, New Steroids with a Rearranged Skeleton as (h)P300 Inhibitors from the Sponge *Theonella swinhoei*. *Org. Lett.* **2014**, *16*, 2224–2227.