# Synthese von oligovalenten Amino-*C*-Glycosiden durch Übergangsmetall-katalysierte Reaktionen von enantiomerenreinen 1,2-Oxazinen

DISSERTATION

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Disputation am: 17.12.2014

*Es ist keine Schande hinzufallen, aber es ist eine Schande liegenzubleiben.*

*(Theodor Heuss)*

*Für meine Familie und insbesondere meinen Mann,*

*die mir immer die Kraft geben wieder aufzustehen.*

Die vorliegende Arbeit wurde im Zeitraum vom Mai 2010 bis November 2014 unter Betreuung von Prof. Dr. H.-U. Reißig am Institut für Chemie und Biochemie der Freien Universität Berlin angefertigt.

Ein Teil der Ergebnisse wurde bereits veröffentlicht:

M. Kandziora, H.-U. Reissig, *Beilstein J. Org. Chem.* **2014**, *10,* 1749-1758.

M. Kandziora, H.-U. Reissig, *Eur. J. Org. Chem.* **2015**, 370-377.

M. Kandziora, E. Mucha, S. P. Zucker, H.-U. Reissig, *Synlett*, **2014**, *im Druck*.

# Abkürzungsverzeichnis

Im Text bezeichnen hochgestellte, arabische Zahlen Literaturhinweise. Verbindungsnummern sind fett gedruckt und beziehen sich, wenn vorhanden, auf die entsprechende Publikation im gleichen Kapitel.

Es wurden folgende Abkürzungen verwendet:

| | |
|---|---|
| Äq. | Äquivalente |
| Ar | Aryl |
| Arg | Arginin |
| Asn | Asparagin |
| BINAP | (2,2'-Bis(diphenyl-phosphino)-1,1'-binaphthyl) |
| *n*-BuLi | *n*-Butyllithium |
| CAN | Cer(IV)-ammoniumnitrat |
| COSY | correlated spectroscopy |
| d | Tag |
| $\delta$ | chemische Verschiebung |
| dd | Dublett von Dublett |
| DMF | *N*,*N*-Dimethylformamid |
| dr | Diastereomerenverhältnis |
| EGF | Epidermaler Wachstumsfaktor |
| ESI | electrospray ionization |
| ESL-1 | E-Selektin-Ligand-1 |
| Et | Ethyl |
| Glu | Glutaminsäure |
| h | Stunden |
| HMQC | heteronuclear multiple quantum correlation |
| HPLC | high performance liquid chromatography |
| Hz | Hertz |
| $IC_{50}$ | mittlere inhibitorische Konzentration |
| IR | Infrarot |
| *J* | Kopplungskonstante |
| konz. | konzentriert |
| Lit. | Literatur |
| m | Multiplett |
| M | Molarität |
| $m_c$ | zentriertes Multiplett |
| Me | Methyl |
| MHz | Megahertz |
| min | Minuten |
| mL | Milliliter |
| MS | Massenspektrometrie |
| *m/z* | Masse-Ladungs-Verhältnis |
| $\nu$ | Wellenzahl |
| NMR | Kernresonanzspektroskopie |
| *p* | *para* |
| Pd/C | Palladium auf Kohle |
| Ph | Phenyl |
| ppm | parts per million |
| PPTS | Pyridinium-*para*-toluolsulfonsäure |
| PSGL-1 | P-Selektin-Glycoprotein-Ligand-1 |
| q | Quartett |
| quant. | quantitativ |
| R | organischer Rest |
| RT/rt | Raumtemperatur |
| s | Singulett |
| SCR | short consensus repeat unit |
| SPR | Oberflächenplasmonen-resonanzspektroskopie |
| STD-NMR | Saturation-Transfer Difference-NMR |
| t | Triplett |
| TBS | *tert*-Butyldimethylsilyl |
| td | Triplett von Dublett |
| *tert* | tertiär |
| TFA | Trifluoressigsäure |
| THF | Tetrahydrofuran |
| TIPS | Triisopropylsilan |
| TMSE | (2-Trimethylsilyl)ethyl |
| TMSOTf | Trimethylsilyltriflat |
| Trt | Triphenylmethylgruppe |
| Tyr | Tyrosin |

# Inhaltsverzeichnis

# Abstract

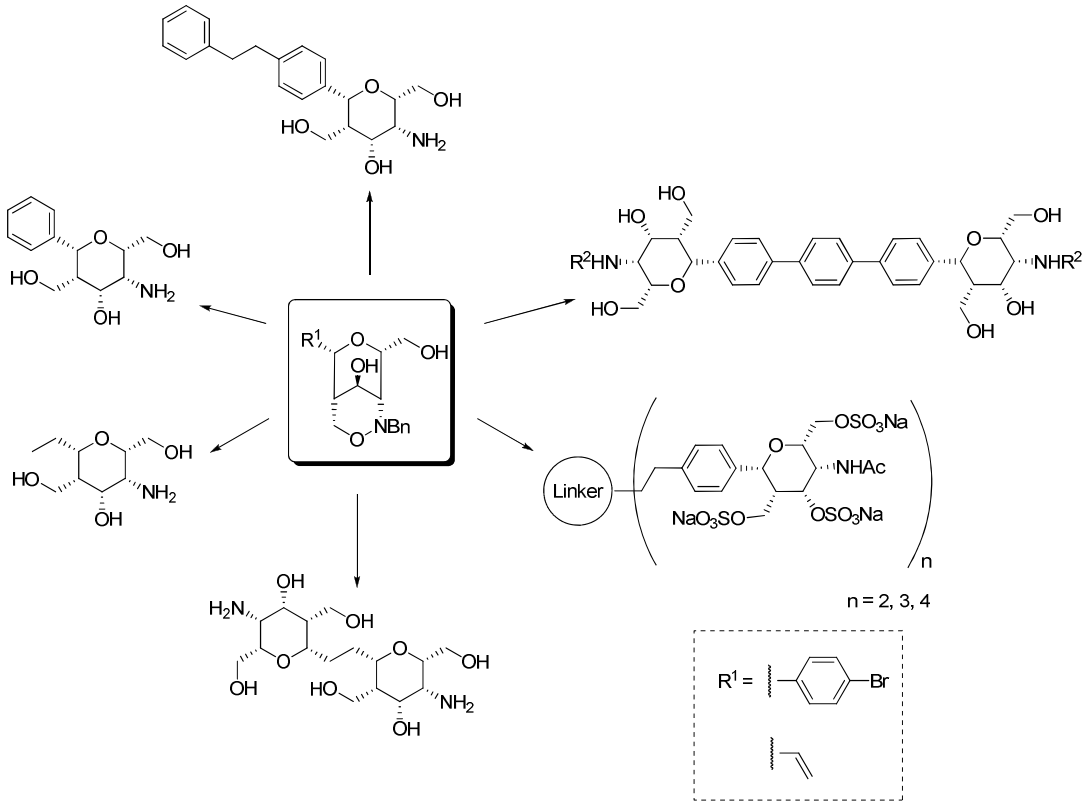
Aim of the dissertation was the development of a new approach to the synthesis of unusual mono- and oligovalent amino-*C*-glycosides. The oligovalent derivates were synthesized by substituted enantiopure bicyclic 1,2-oxazines which were connected by suitable linkers employing with different transition metal-catalyzed reactions. Subsequent reductions (like zinc in presence of acid, palladium catalyzed hydrogenolyses and samarium diiodide) convert the connected products into oligovalent amino-*C*-glycosides with D-talose configuration. Finally, these *C*-glycosides were polysulfated. The oligovalent *C*-glycosides differ in number and distance of their aminopyran units and are potential L-, P- and E-selectin inhibitors.

The key compounds, substituted 1,2-oxazines, were prepared by a stereoselective [3+3]-cyclization of aldonitrones and lithiated (2-trimethylsilyl)ethoxyallene or the introduction of new groups into the 1,3-dioxolanyl substituent of a 1,2-oxazine. The Lewis acid-induced rearrangement of these heterocycles provided the corresponding bicyclic 1,2-oxazine derivatives. After subsequent reduction of the carbonyl group, the resulting bicyclic compounds were used as building blocks for transition metal-catalyzed reactions. A *para*-bromphenyl-substituted bicyclic 1,2-oxazine could be obtained and used in Suzuki-reactions to form biphenyl aminopyran or rigid *p*-terphenyl-linked dimers. For the N-O bond cleavage zinc in the presence of acid or samarium diiodide were applied to obtain rigid *p*-terphenyl-linked amino-*C*-glycosides. Moreover this building block was used in Sonogashira reactions to synthesize functionalized mono as well as di-, tri- and tetravalent bicyclic 1,2-oxazines in excellent yields. Besides, by Glaser cross-coupling two divalent amino-*C*-glycosides could be prepared, one with a rigid and one with a flexible linker unit. Hydrogenation was used to reduce the alkyne moiety and to remove the *N*-benzyl groups, whereas samarium diiodide was employed to selectively cleave the N-O bond to obtain oligovalent carbohydrate mimetics with D-talose configuration. Some of these compounds could be polysulfated by a sulfur trioxide-*N*,*N*-dimethylformamide complex and are ready for studies of inhibitory properties towards L-, P- and E-selectin.

A vinyl- and homoallyl-substituted bicyclic 1,2-oxazine could be synthesized and “dimerized” by olefin metatheses. In case of the vinyl-substituted bicyclic 1,2-oxazine the “dimer” could be obtained in excellent yields. Its hydrogenolysis furnished the divalent *C*-aminoglycoside with D-talose configuration in good overall yield.

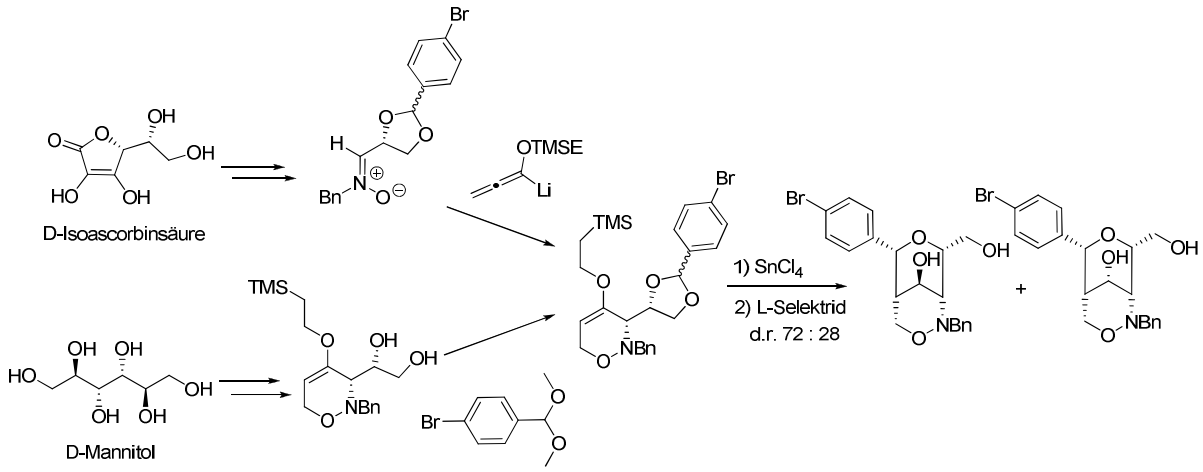
# Zusammenfassung

In der vorliegenden Arbeit wird ein Zugang zu neuartigen mono- und oligovalenten *C*-glycosidischen Kohlenhydratmimetika vorgestellt. Die oligovalenten Derivate werden durch unterschiedliche Übergangsmetall-katalysierte Reaktionen substituierter bicyclischer 1,2-Oxazine mit geeigneten Linkern verknüpft und durch verschiedene Reduktionsmittel (wie Zink mit Essigsäure, Palladium-katalysierte Hydrogenolyse und Samariumdiiodid) in oligovalente *C*-Glycoside übergeführt. Die dargestellten oligovalenten *C*-Glycoside unterscheiden sich in Anzahl, Abstand und Anordnung der Aminopyraneinheiten und sollen als potentielle L-, P- und E-Selektininhibitoren getestet werden.

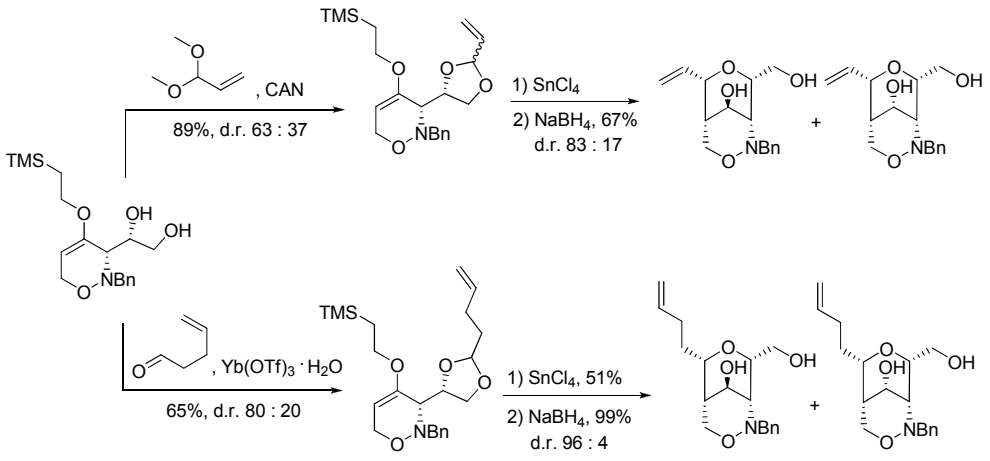


1. Darstellung der Synthesebausteine aus enantiomerenreinen Aldonitronen

Das bicyclische 1,2-Oxazin, das als Synthesebaustein für viele in dieser Arbeit dargestellten Verbindungen diente, wurde aus zwei chiralen Naturstoffen synthetisiert: aus D-Isoascorbinsäure wurde ein (*Z*)-Aldonitron mit *para*-Bromphenylsubstituenten dargestellt und in einer [3+3]-Cyclisierung mit lithiierten 2-(Trimethylsilyl)ethoxyallen zum 1,2-Oxazin in sechs Schritten und einer Gesamtausbeute von 46% übergeführt. D-Mannitol diente als Ausgangsverbindung eines literaturbekannten Diols, welches säurekatalysiert mit *para*-Bromphenyldimethylacetal zum 1,3-dioxanylsubstituierte 1,2-Oxazin umgesetzt wurde. Dieses 1,2-Oxazin konnte anschließend Lewis-Säure-induziert zu einem bicyclischen Keton umgelagert werden. Nach Reduktion des Ketons des 1,2-Oxazinons erhielt man die Zielverbindung.

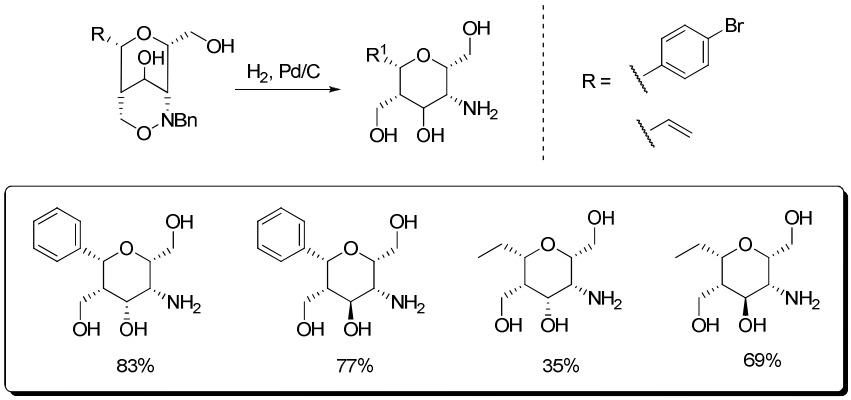



Zwei weitere Schlüsselverbindungen mit Vinyl- und Homoallylsubstituenten konnten aus dem literaturbekannten 1,2-Diol durch Lewis-Säure-Katalyse in ihre 1,3-dioxanylsubstituierten 1,2-Oxazine in guten bis sehr guten Ausbeuten übergeführt werden. Nach Lewis-Säure-induzierten Umlagerung und anschließender Reduktion des entstehenden Ketons erhielt man die vinyl- und homoallylsubstituierten, bicyclischen Produkte.



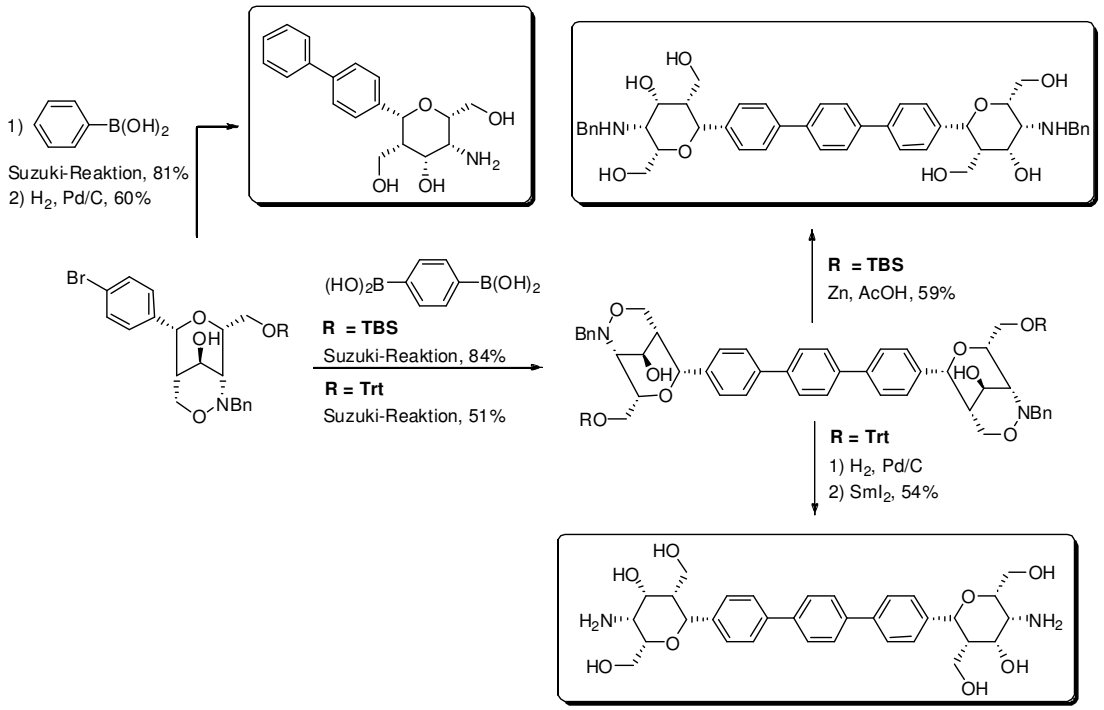

2. Hydrogenolyse von bicyclischen 1,2-Oxazinen zur Darstellung von *C*-Aminoglycosiden

Die erhaltenen bicyclischen 1,2-Oxazine wurden durch Palladium-katalysierte Hydrogenolyse in ihre Aminoglycoside mit D-Talose- bzw. D-Idose-Konfiguration in meist guten Ausbeuten übergeführt.



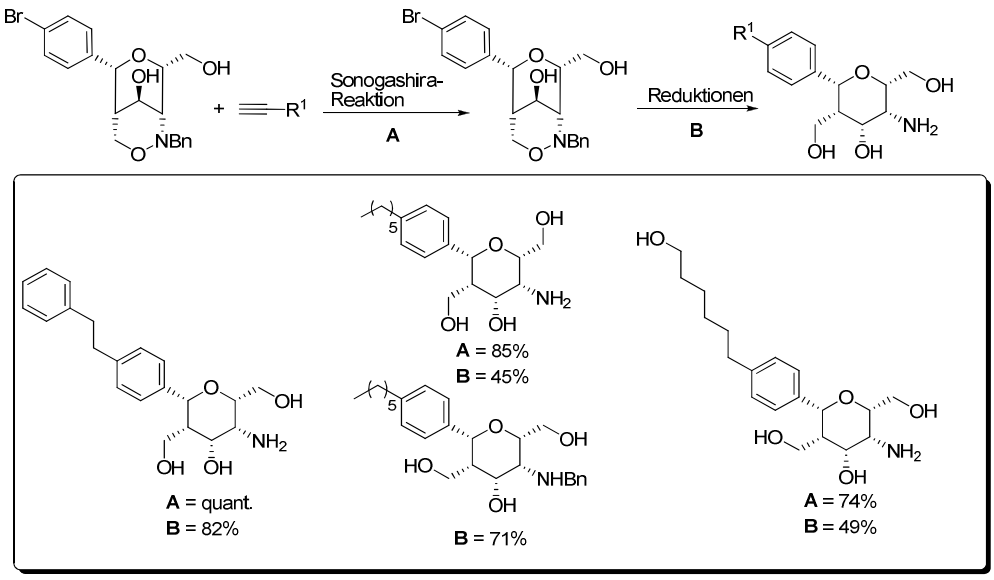

3. Synthese von *C*-Arylglycosiden durch Suzuki-Reaktionen

Der Synthesebaustein mit *para*-Bromphenylsubstituenten konnte mit geeigneten Boronsäuren für die Darstellung von mono- und divalenten *C*-Arylglycosiden mit *β*-D-Talose-Konfiguration genutzt werden. Hierfür wurde als Schlüsselschritt die Suzuki-Reaktion eingesetzt, wobei ein biphenylsubstituierter Bicyclus gebildet wurde, der nach Hydrogenolyse ein interessant funktionalisiertes Aminopyran ergab. Nach der Suzuki-Reaktion mit Benzol-1,4-diboronsäure konnten durch die Wahl des Reduktionsmittels unterschiedliche divalente, starre, *p*-terphenyl-verknüpfte *C*-Arylglycoside dargestellt werden.

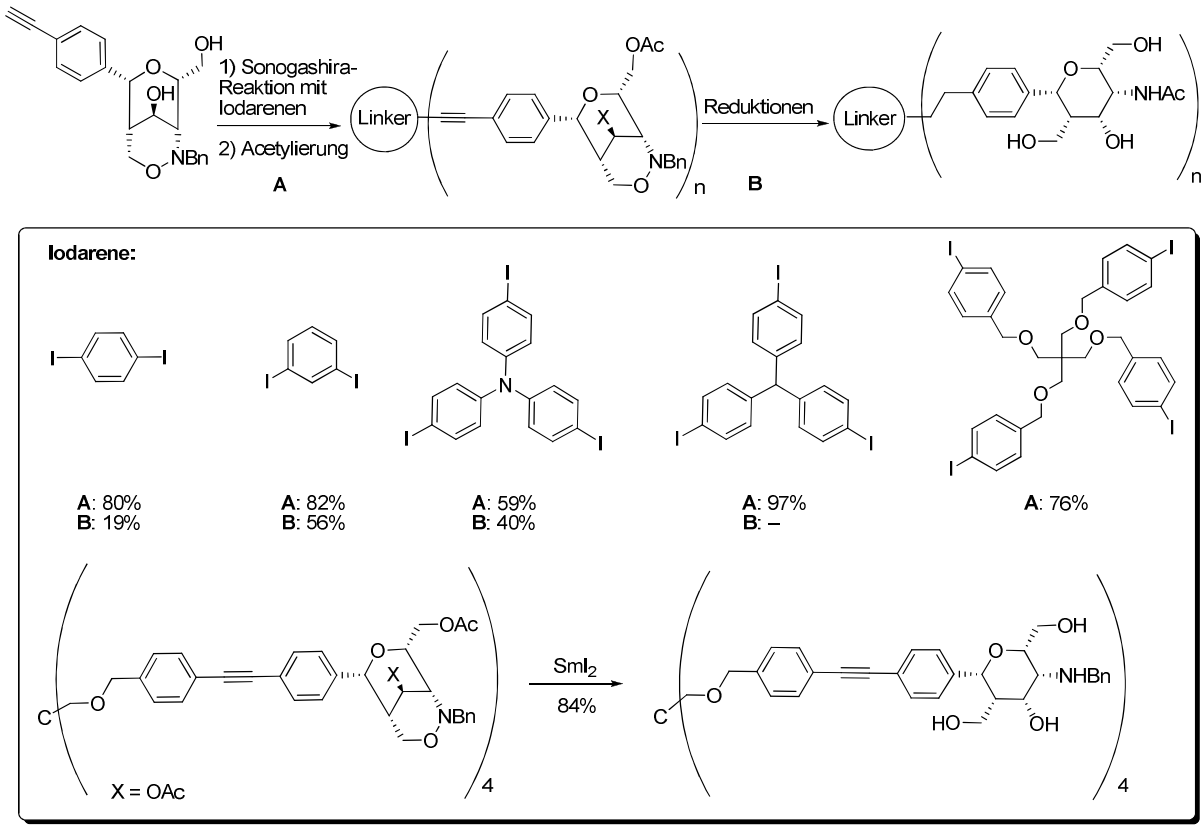



4. Darstellung von mono- und oligovalenten Kohlenhydratmimetika durch Sonogashira-Reaktionen

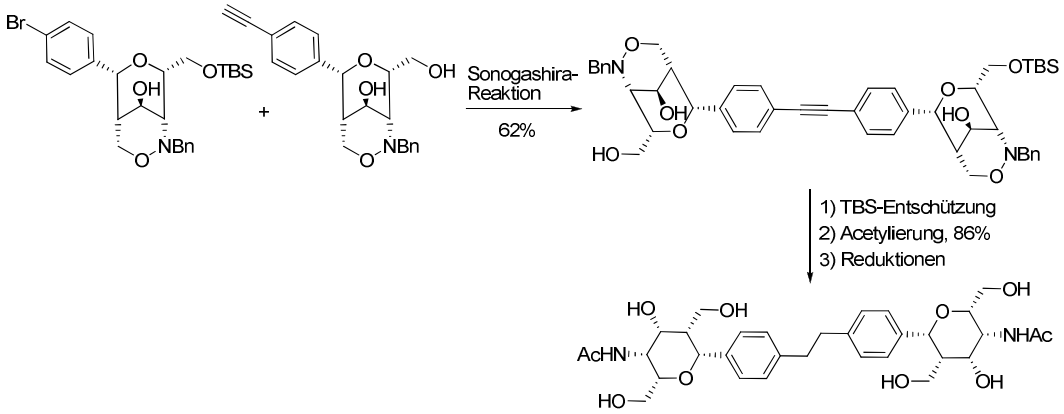
Die Sonogashira-Kupplung wurde als Schlüsselschritt zur Funktionalisierung von *para*-bromsubstituierten, bicyclischen 1,2-Oxazin verwendet. Unter Einsatz von verschieden funktionalisierten Alkinen wurden Produkte erhalten, die anschließend durch geeignete Reduktionsmittel, wie Hydrogenolyse und Samariumdiiodid, in ihre korrespondierenden Aminopyrane übergeführt wurden. Diese Aminopyrane können als *C*-Arylaminoglycoside betrachtet werden.



Die oligovalenten *C*-Glycoside, die sich in ihrer Geometrie, Linkerlänge und Anzahl an Aminopyraneinheiten unterscheiden, wurden durch Sonogashira-Reaktion von alkinsubstituierten Bicyclen und geeigneten Oligoiodarenen dargestellt und anschließend durch Reduktionen in ihre entsprechenden Aminopyrane übergeführt. Die direkte Verknüpfung des *para*-bromphenylsubstituierten bicyclischen 1,2-Oxazins mit oligovalenten Alkinlinkern konnte unter diesen Bedingungen nicht realisiert werden.

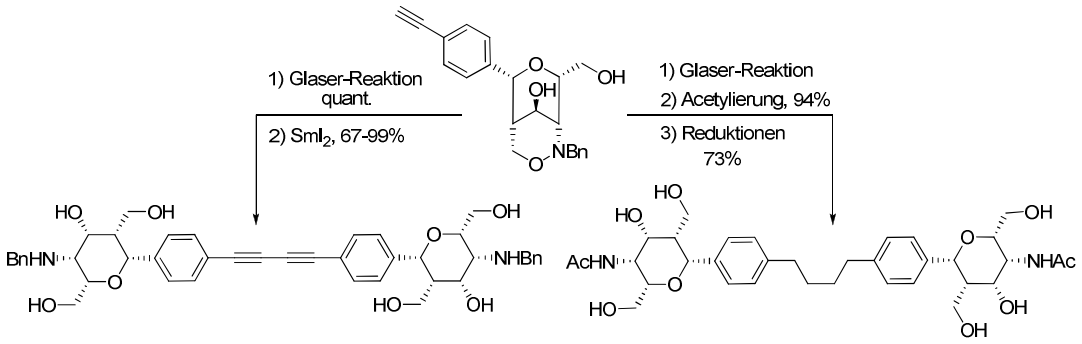



Ein weiteres Pseudodisaccharid konnte durch die Sonogashira-Reaktion und anschließender Reduktionen eines alkinylsubstituierten Bicyclus mit einem *para*-bromphenylsubstituierten, bicyclischen 1,2-Oxazin dargestellt werden.



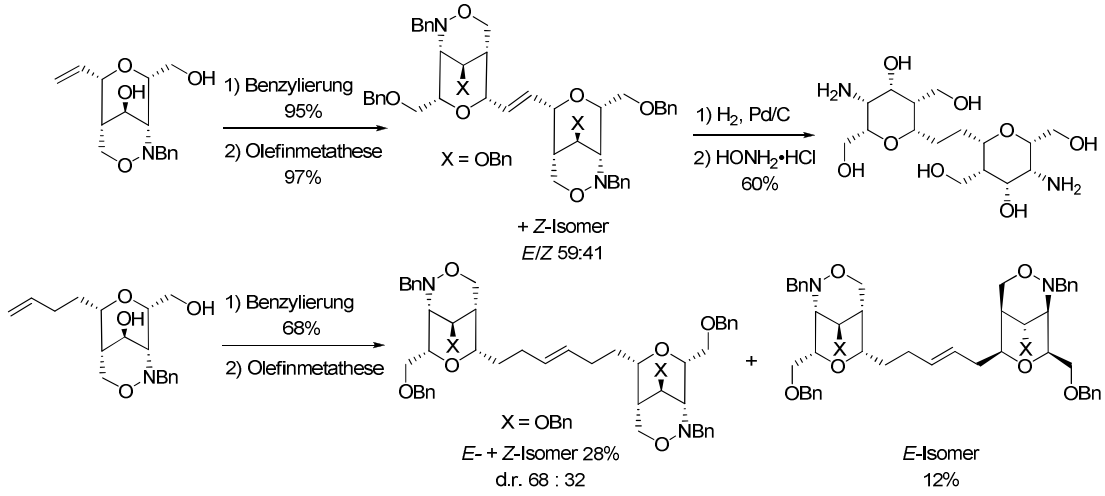
5. Synthese eines starren und flexiblen Kohlenhydratmimetikums durch Glaser-Reaktion

Weiterhin wurde zur Darstellung zweier divalenter Kohlenhydratmimetika die Glaser-Kupplung verwendet, wobei nach Reduktionsschritten zwei Produkte mit exzellenten Ausbeuten erhalten wurden. Durch direkte Reaktion mit Samariumdiiodid konnte einerseits ein besonders rigides Kohlenhydratmimetikum erhalten werden. Andererseits wurde durch Hydrogenolyse debenzyliert, die Alkineinheit reduziert und anschließend die N-O-Bindung durch Samariumdiiodid gespalten, wodurch eine flexible Verbindung entstand.



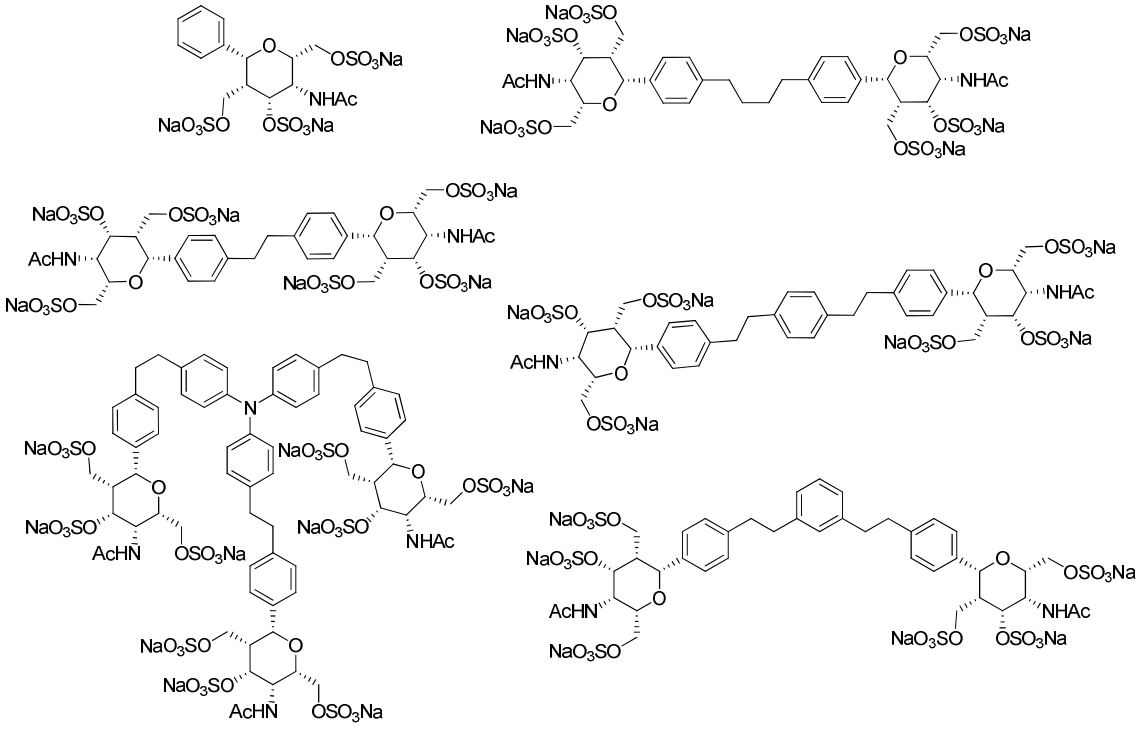

6. Olefinmetathese von alkenylsubstituierten bicyclischen 1,2-Oxazinen zu Pseudodisacchariden

Die vinyl- und homoallylsubstituierten bicyclischen 1,2-Oxazine wurden benzylgeschützt und durch Olefinmetathese „dimerisiert“, wobei für das vinylsubstituierte Derivat eine exzellente Ausbeute erhalten wurde. Durch eine anschließende Hydrogenolyse und Reaktion mit Hydroxylaminhydrochlorid konnte das Produkt in ein Pseudodisaccharid mit einem flexiblen Linker übergeführt werden. Das Produkt der Olefinmetathese des homoallylsubstituierten bicyclischen 1,2-Oxazins konnte aufgrund von Isomerisierungsprodukten, nur in einer geringen Ausbeute, isoliert werden, so dass zukünftig die Reaktionsbedingungen optimiert werden müssten.




7. Polysulfatierung der mono- und oligovalenten Kohlenhydratmimetika

Ein Teil der in der Arbeit beschriebenen mono- und oligovalenten Kohlenhydratmimetika wurden dem mit Schwefeltrioxid-*N*,*N*-dimethylformamid-Komplex polysulfatiert und der Arbeitsgruppe Dernedde/Tauber für die Testung als L-, P- und E-Selektininhibitoren zur Verfügung gestellt. Aufgrund der breiten Variabilität dieser Produkte hinsichtlich Geometrie, Linkerlänge und Anzahl an Aminopyraneinheiten sollte es damit möglich sein, nach ihrer Testung Rückschlüsse auf die Struktur-Wirkungs-Beziehung von Kohlenhydratmimetika und Selektinen zu ziehen.



# 1 Einleitung

### Bedeutung von Kohlenhydraten in der Natur

Neben Proteinen, Nukleinsäuren und Fetten gehören Kohlenhydrate zu den biologisch wichtigsten Stoffklassen.[1] Sie sind aufgrund der Vielzahl chemisch unterschiedlicher Monosaccharide und deren vielfältigen Verknüpfungsmöglichkeiten die umfangreichste und komplexeste Klasse von Biopolymere.[2] In Form von Zuckern, Stärke und anderen wichtigen Bestandteilen der Nahrung, wie Ballaststoffe, versorgen Kohlenhydrate als physiologische Energieträger humane und tierische Organismen mit Energie. In Pflanzen, die in der Photosynthese aus Kohlendioxid und Wasser unter Freisetzung von Sauerstoff Kohlenhydrate synthetisieren, fungieren sie als Gerüststoffe. Überdies sind Kohlenhydrate in biologischen Signal- und Erkennungsprozessen von herausragender Bedeutung. Auf der Außenseite der eukaryotischen Zellmembran (außer auf der Zellmembran von Pflanzen) befindet sich eine Schicht aus Polysacchariden, die als Glycocalix bezeichnet wird. Die wichtigsten am Aufbau beteiligten Zucker sind Glucose, Galactose, Fructose und Aminozucker, wie Glucosamin, Galactosamin und Neuroaminsäure. Zusätzlich ist noch Sialinsäure auf der Zellmembran gebunden, die der Zelloberfläche eine negative Ladung verleiht. Diese Polysaccharidstrukturen sind kovalent an Lipide und vor allem an Proteine gebunden und dienen unter anderem der Zellspezifizität, da sie charakteristisch für jeden Zelltyp sind.[3] Eine weitere, wichtige Funktion der Glycocalix besteht in der interzellulären Zellkommunikation. Diese findet zum Teil durch nichtkovalente Wechselwirkungen zwischen Kohlenhydrat-Liganden und Protein-Rezeptoren statt. Unter anderem sind Wechselwirkungen mit den sogenannten Zelladhäsionsmolekülen, wie z.B. Selektinen, Integrinen, Cadherinen und Mitgliedern der Immunglobulin-Superfamilie bekannt, die eine entscheidende Bedeutung bei Entzündungsreaktionen haben. Die Polysaccharide der Glycocalix wirken als Antigene und gehören zu den Blutgruppensystemen höherer Lebewesen.[4] Ergänzend spielen Kohlenhydrat-Protein-Wechselwirkungen in weiteren, biologischen Ereignissen, wie der Fertilisation und der Metastasierung, eine wichtige Rolle.[1]

## Prozesse bei Entzündungsreaktionen

Eine Entzündung ist die Reaktion des Körpers auf einen Reiz, der z.B. durch das Eindringen eines infektiösen Erregers in das Körpergewebe oder durch physikalische Faktoren, wie Temperaturänderungen oder Strahlung, verursacht wird. Als Folge eines derartigen Reizes werden im Körper eine Vielzahl von Signalen und Bindungsereignissen initiiert, um Leukozyten aus der Blutbahn an den Ort der Entzündung einzuschleusen, um so das entzündete Gewebe zu reparieren und/oder den Reiz aus dem Körper zu entfernen.[5] Der Mechanismus des Einschleusens von Leukozyten in das Gewebe findet in mehreren Schritten statt und ist in der Abbildung 1 schematisch dargestellt. Entzündetes Gewebe exprimiert eine Vielzahl von E- und P-Selektinen; diese Zelladhäsionsproteine bilden viele schwache Bindungen zu den Leukozyten aus. Zusätzlich befinden sich auf der Zellmembran des Leukozyten L-Selektine, die Bindungen zu dem Endothel ausüben. Dadurch werden die Leukozyten in ihrer Wanderungsgeschwindigkeit „abgebremst“ und fangen an, auf dem Gewebe zu “rollen“, bis weitere Zelladhäsionsproteine, die sogenannten Integrine, ausgeschüttet werden und eine feste Adhäsion zwischen Gewebe und Leukozyten eingehen. Als Folge dieses Adhäsionsprozesses werden die Leukozyten in ihrer Form abgeflacht, wodurch ihre Migration in das entzündete Gewebe stattfindet kann.[6]

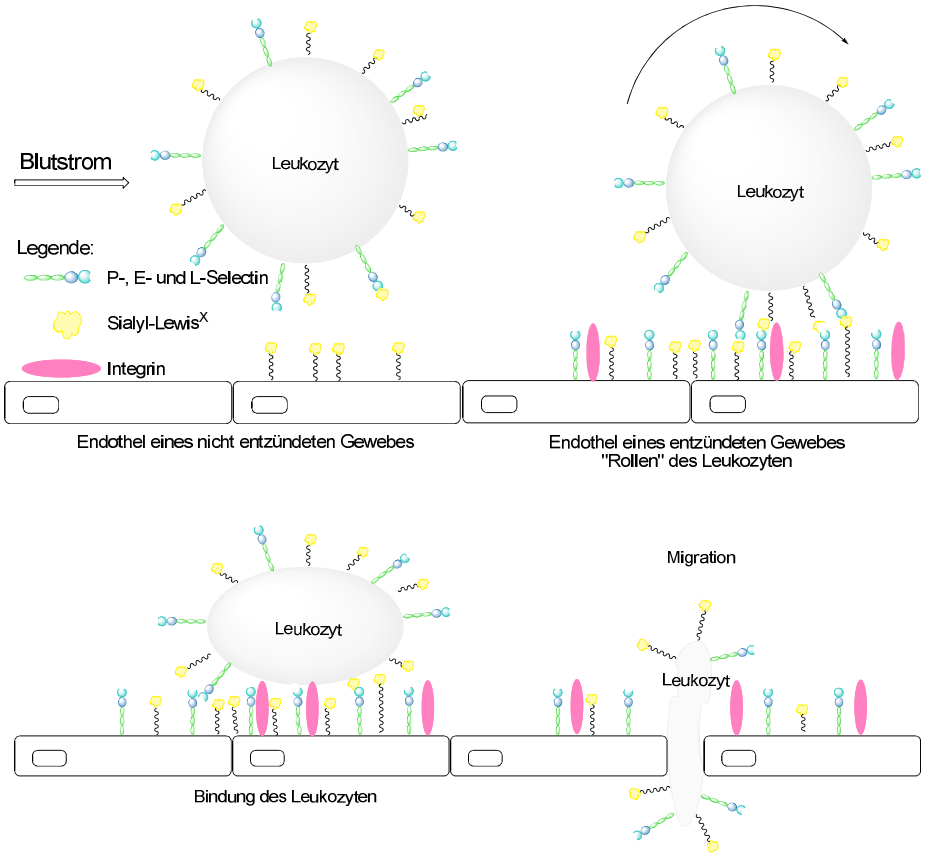



Abbildung 1: Schematische Darstellung des Leukozytenrollens auf einem entzündeten Gewebe.

Die Selektine, die für das „Rollen“ und die anschließende Adhäsion der Leukozyten verantwortlich sind, gehören zu der Klasse der Transmembranproteine und haben eine ähnliche Grundstruktur (Abbildung 2). Sie bestehen aus einer *N*-terminalen, Calcium-abhängigen Lektindomäne (die zu 60% bei allen drei Selektinen übereinstimmt)[7], einer epidermalen Wachstumsfaktor-ähnlichen (EGF) Domäne und einer sogenannten „short consensus repeat unit“, die sich, je nach Art des Selektins, in der Anzahl an Wiederholungseinheiten (zwei bis neun) unterscheidet. Außerdem haben die Selektine noch eine Transmembrandomäne und einen kurzen, cytoplasmatischen Bestandteil. L-Selektine werden auf Leukozyten, P-Selektine sowohl auf Blutplättchen (platelets) als auch auf Endothelzellen und E-Selektine auf vaskularen Endothelzellen exprimiert.[8]

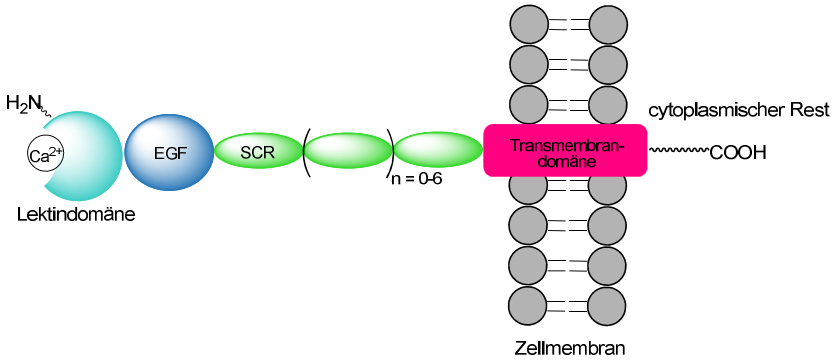



Abbildung 2: Schematischer Aufbau von Selektinen und Wechselwirkung mit der Zellmembran.

Diese Selektine weisen viele natürliche Liganden, wie PSGL-1 (P-Selektin Ligand)[9], ESL-1 (E-Selektin-Ligand)[10] und Heparansulfat[9b] auf. Alle drei Selektine binden das Tetrasaccharid Sialyl-Lewis$^X$. Wie in der Abbildung 3 angedeutet befindet sich die recht flache Bindungsstelle des Sialyl-Lewis$^X$ in der Lektindomäne der Selektine. Das Tetrasaccharid, das aus den Monosacchariden Fucose, Galactose, Sialinsäure und *N*-Acetylglucosamin aufgebaut ist, bindet an das Calciumion der Selektin sowie an deren polare Aminosäuren, wie z. B. Asparagin und Glutaminsäure.[11]

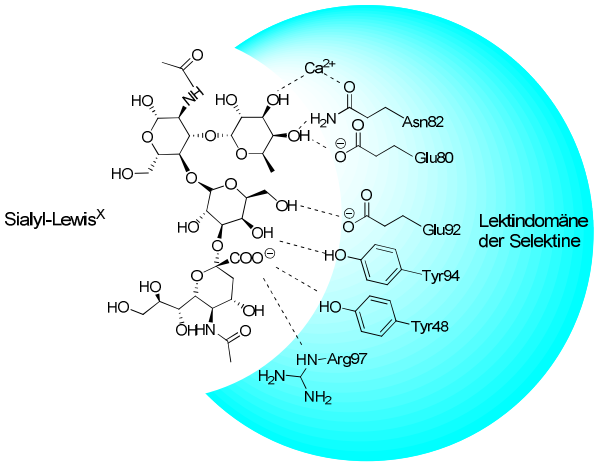



Abbildung 3: Lektin-Domäne des E-Selektins und das gebundene Tetrasaccharid Sialyl-Lewis$^X$.

Diese Verteidigungsstrategie des Organismus gegen zum Beispiel infektiöse Erreger kann manchmal fehlerhaft gestaltet sein. Zu einer Dysregulation oder Überexprimierung von Selektinen kann es bei Schlaganfall, Allergien, Krebs oder bei chronischen Entzündungen, wie rheumatoide Arthritis, kommen. In diesen Fällen schädigen die eintretenden Leukozyten gesundes Gewebe. Eine mögliche Strategie, um diese Schädigungen zu unterdrücken, ist mit der Inhibierung der Selektin-Ligand-Wechselwirkung und damit der Leukozytenextravasation gegeben.[12]

**Multivalenz**

Die Bindungen zwischen Kohlenhydraten und Proteinen sind gewöhnlich schwach.[13] In der Natur wird diese geringe Wechselwirkung daher meist durch eine multivalente Präsenz von Liganden kompensiert. Dieses Prinzip kann auch bei der Entwicklung von potentiellen Arzneimitteln genutzt werden, um die Bindungsstärke der Wirkstoffe zu erhöhen. Das Design von multivalenten Wirkstoffen ist oft nicht trivial, so dass eine erfolgreiche Synthese von künstlichen, multivalenten Systemen ein detailliertes Verständnis des Zusammenspiels von Entropie und Enthalpie erfordert.[14] Zudem gibt es verschiedene Arten der multivalenten Bindung, wie statistische Rückbindung, Chelatisierung, Clustering und „subsite binding“[15], auf die in dieser Arbeit nicht näher eingegangen werden soll.

Neben der spezifischen Affinität eines monovalenten Liganden zum Rezeptor besitzen bei multivalenten Wechselwirkungen der Abstand zwischen den einzelnen Liganden und deren Flexibilität den größten Einfluss auf die resultierende Bindungsstärke. Ein optimaler Linker überbrückt die Distanz zwischen den Rezeptoren, ohne Spannungen zu erzeugen, und minimiert die Abnahme des Entropiebeitrages während eines Bindungsvorganges.[16] Daraus resultiert, dass der bestmögliche Linker ein maßgeschneiderter, vorzugsweise rigider Verbinder mit optimaler Orientierung ist. Das Design von passenden Linkern ist praktisch oft schwierig, wenn die genaue Struktur des Rezeptors unbekannt ist. In diesen Fällen wählt man daher einen ausreichend flexiblen Linker, so dass der Ligand auch bei nicht optimaler Orientierung prinzipiell binden kann.[17]

**Kohlenhydratmimetika und *C*-Gycoside**

Fehlerhafte Kohlenhydrat-Ligand-Wechselwirkungen spielen bei einer Vielzahl von Krankheiten eine große Rolle.[2] Kohlenhydrate selbst eignen sich nur selten als potente Wirkstoffe, da sie meist nur eine geringe Bindungsaffinität zu ihren Liganden haben.[18] Außerdem sind sie pharmakinetisch durch ihre hohe Polarität ungünstig; sie können den Dünndarm nicht passiv passieren und sind damit auch für eine orale Applikation ungeeignet. Außerdem werden sie sehr schnell über die Niere ausgeschieden.[19] Kohlenhydratmimetika hingegen sind Verbindungen, die die bioaktiven Funktionen von Kohlenhydraten imitieren, jedoch verbesserte Eigenschaften, wie eine höhere Affinität und bessere Wirkstoff-Eigenschaften, haben können.[18, 20]

Die geringe Bindungsaffinität von Kohlenhydraten an Liganden kann durch den Mangel an hydrophoben Gruppen und elektrischen Ladungen bedingt sein. Zusätzlich weisen Zucker labile glycosidische Bindungen auf, die enzymatisch leicht gespalten werden können.[20] Eine Kohlenhydrat-Leitstruktur kann in einen Wirkstoff gewandelt werden, wenn es gelingt, hydrophile Gruppen und metabolisch angreifbare Stellen, die für die Bindungen nicht erforderlich sind, zu eliminieren oder zu reduzieren.[19] Dieses Konzept der Entwicklung von Kohlenhydratmimetika soll anhand von bereits erfolgreichen Entwicklungen von Selektininhibitoren, die in klinischen Studien getestet wurden, verdeutlicht werden (Abbildung 4). Bimosiamose (Encysive®) und Rivipansel (GlycoMimetics®, Pfizer®) sind Kohlenhydratmimetika, die sich an einer Sialyl-Lewis$^X$-Leitstruktur orientieren. In diesen Strukturen wurden die Monosaccharide des Sialyl-Lewis$^X$ entfernt, die nicht direkt zu deren Bindung an die Selektine beteiligt sind, und wurde zum Beispiel gegen hydrophobe Gruppen ausgetauscht. Um die Bindungsaffinität weiter zu steigern, sind außerdem Carboxylate und Sulfate in die Struktur eingebaut worden, was zusätzlich ionische Wechselwirkungen ermöglicht. Hervorzuheben ist die besonders einfach zu synthetisierende divalente Struktur von Bimosiamose. Wegen der wiederholenden Einheit und dem unkomplizierten Linker ist diese Substanz für die pharmazeutische Industrie besonders attraktiv.

Ein ganz anderer Syntheseansatz wurde für die Darstellung des Kohlenhydratmimetikums PSI-697 beschritten, dessen struktureller Aufbau keine offensichtlichen Merkmale der Leitstruktur des Sialyl-Lewis$^X$ aufweist. Diese Verbindung, für die ein geringes Molekulargewicht, das Vorhandensein eines unpolaren, steifen Chinolinkers und sowohl saure als auch basische Gruppen charakteristisch sind, ist oral einsetzbar und ebenfalls relativ leicht zu synthetisieren. Obwohl eine chemische Ähnlichkeit mit der Struktur des Sialyl-Lewis$^X$ nicht erkennbar ist, können die bioaktiven Merkmale des Sialyl-Lewis$^X$ durch die Auswahl der Art an funktionellen Gruppen und Struktur imitiert werden.[21]

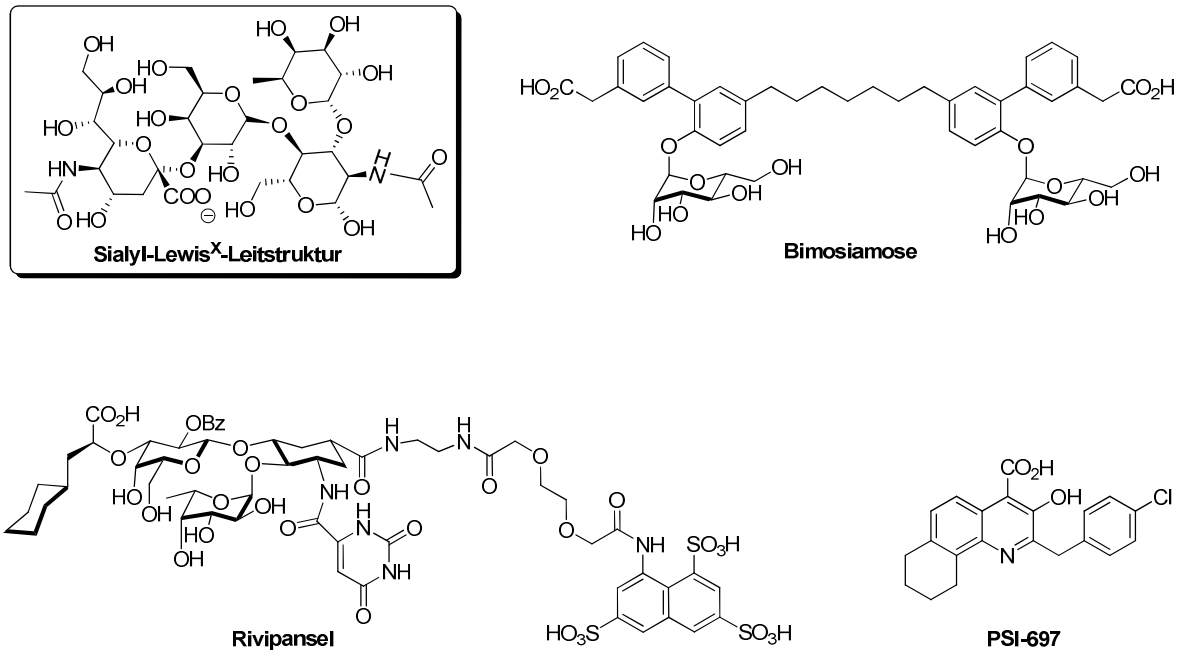



Abbildung 4: Beispiele für erfolgreiche Kohlenhydratmimetika, die als Selektininhibitoren wirken.

Die vorgestellten Beispiele verdeutlichen, dass es für die Darstellung erfolgreich einsetzbarer Kohlenhydratmimetika sehr unterschiedliche Ansätze gibt, die erfolgreich realisiert und deren Wirksamkeit nachgewiesen wurde. Weitere Konzepte zur Darstellung von Kohlenhydratmimetika wurden mit der Synthese von Pyran- oder Furanringstrukturen mit neuen, funktionellen Gruppen (z.B. Fluorsubstituenten), einer Variation der Ringgröße (z.B. 7-Ring- oder 8-Ringstrukturen) oder der Austausch eines Sauerstoffatoms eines Heterocyclus durch ein Stickstoff- (Iminozucker), Kohlenstoff- (Carbazucker) oder Schwefelatom (Thiazucker) verfolgt (Abbildung 5). Iminozucker, wie der Wirkstoff Miglustat (Zavesca®, Brazaves®) wurden bereits erfolgreich bei erblichen Stoffwechselkrankheiten wie Morbus-Gaucher-Typ 1 und Niemann-Pick-Krankheit Typ C eingesetzt.[22] Der strukturell sehr ähnliche Iminozucker Miglitol (Diastabol®) wirkt als ein Antidiabetikum, welches die α-Glucosidase hemmt und damit den Abbau von Polysacchariden verzögert.[23] Ein weiterer α-Glucosidase-Inhibitor ist unter den Handelsnamen Voglibose (BASEN®) eingeführt und stellt ein gutes Beispiel für eine Carbazuckerstruktur mit D-Glucose als Grundstruktur als wirksames Therapeutikum dar.[24]

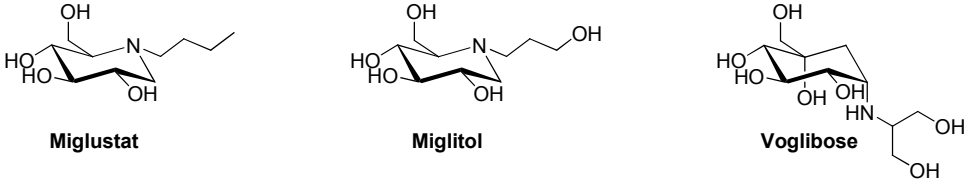
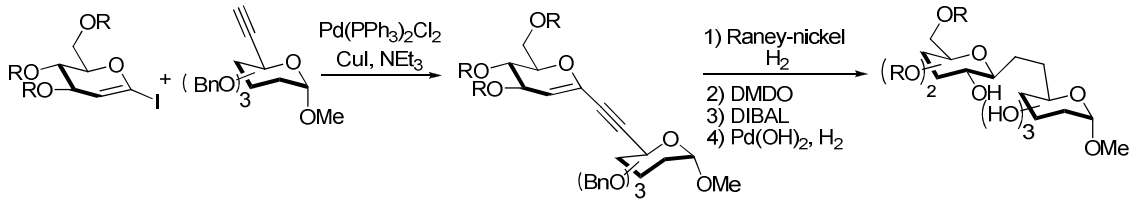



Abbildung 5: Beispiele für Kohlenhydratmimetika auf Basis von Imino- und Carbazuckern.

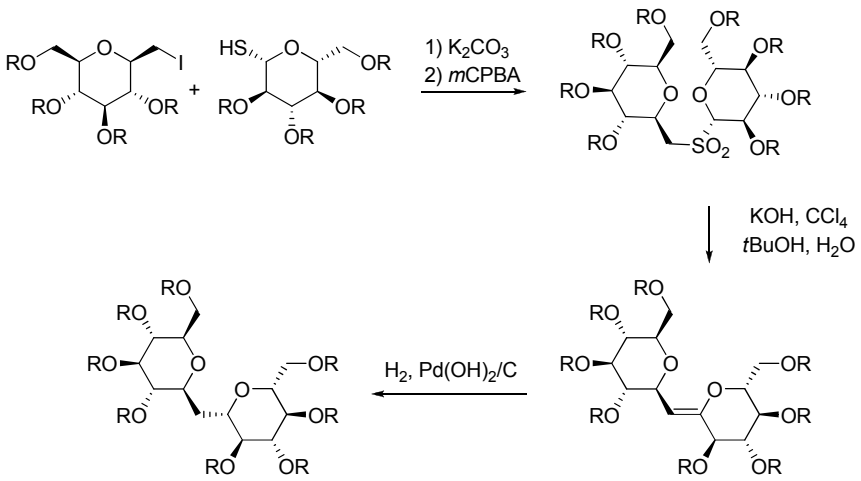
Als weitere Strategie zur Synthese von Kohlenhydratmimetika wird häufig die Verknüpfung zwischen den Zuckereinheiten modifiziert, indem Heteroatome wie Schwefel (*S*-Glycoside) und Stickstoff (*N*-Glycoside) oder Kohlenstoff (*C*-Glycoside) eingebaut werden.[20] Aufgrund ihrer hohen enzymatischen Stabilität sind *C*-Glycoside von besonderem Interesse. Es gibt eine Vielzahl an Synthesemöglichkeiten, um aus Monosacchariden *C*-Glycoside zu bilden, wie z.B. die Verknüpfung von Zuckern über Kreuz-Kupplungen.

2010 zeigten Werz et al., dass es möglich ist, 1,6-verknüpfte *C*-Glycoside durch Sonogashira-Reaktion darzustellen (Schema 1). Dafür synthetisierten sie 1-Iodglycal und alkinsubstituierte Zucker, die mittels Kupplung erfolgreich verknüpft werden konnten. Eine Vielzahl von Pseudodisacchariden konnte dargestellt werden, indem weitere oxidative und reduktive Syntheseschritte in den Herstellungsprozess integriert wurden.[25] Ebenso gelang die Darstellung von *C*-Disacchariden mittels Kreuzkupplungen durch Stille-Reaktion [26].




Schema 1: Darstellung eines Pseudodisaccharides durch Sonogashira-Reaktion.

Ein weiterer, eleganter Weg, um divalente *C*-Glycoside darzustellen, kann über eine Umlagerungsreaktion, wie zum Beispiel die Ramberg-Bäcklund-Reaktion, realisiert werden (siehe Schema 2). Durch diese Methode gelang es der Arbeitsgruppe Taylor et al., verschiedene Monosaccharide am anomeren Zentrum zu Pseudodisacchariden zu verknüpfen. Hierbei wurden zunächst zwei Zucker über eine nucleophile Substitutionreaktion zu einem *S*-Glycosid umgesetzt. Anschließend wurde der Thio-Linker zum Sulfon oxidiert und eine Ramberg-Bäcklund-Umlagerung vorgenommen. Das entstandene Olefin wurde im Anschluss zum Pseudodisaccharid reduziert.[27]



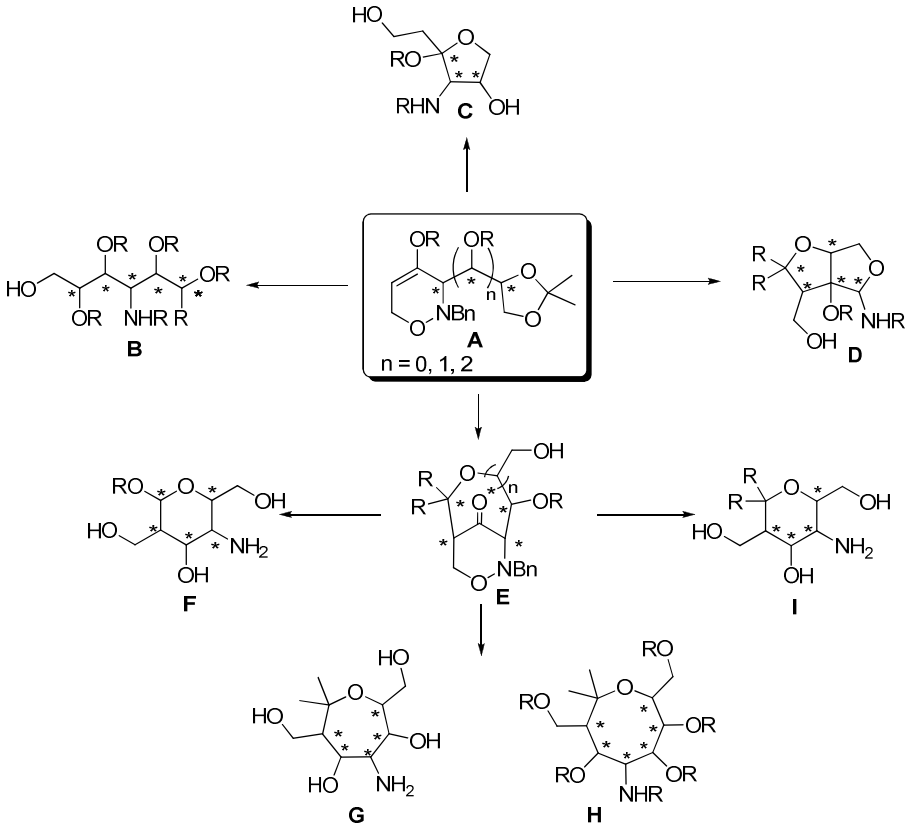

Schema 2: Synthese von Pseudodisacchariden durch Ramberg-Bäcklund-Umlagerung.

Die hohe Affinität und die verbesserten pharmakinetischen Eigenschaften von vielen Kohlenhydratmimetika verdeutlicht sehr anschaulich das hohe Potential dieses Forschungsgebietes und die Notwenigkeit, durch neue Ansätze und Konzepte die Synthese neuer Produkte zu ermöglichen und die Synthesen solcher Strukturen effektiver zu gestalten.

# 2 Arbeitshintergrund und Aufgabenstellung

## Arbeitshintergrund

Die in der Arbeitsgruppe Reißig entwickelten hochfunktionalisierten 1,2-Oxazine **A** lassen sich in eine Vielzahl interessanter Kohlenhydratmimetika umwandeln, die potentielle Wirkstoffe für die pharmazeutische Industrie sind (Schema 3). Die Synthese der 1,2-Oxazine erfolgt hierbei durch eine [3+3]-Cyclisierung von lithiierten Alkoxyallenen mit aus Kohlenhydraten dargestellten Nitronen, was einen einfachen Zugang zu den enantiomerenreinen 1,2-Oxazinen **A** bietet.[28] Diese können, wie am Beispiel des bicyclischen 1,2-Oxazins **E** belegt, Säure-induziert zu Bicyclen umgelagert werden, um anschließend durch reduktive N-O-Spaltung, dem Schlüsselschritt dieser Synthesen, in Aminopolyole übergeführt zu werden. Durch diese flexible Synthesestrategie ließen sich zahlreiche Aminozucker synthetisieren: acyclische Aminopolyole **B**,[29] Aminofurane **C**,[30] anellierte, bicyclische Furane **D**[31] sowie auch Aminopyrane **I**,[32] **F**[33] und deren höhermolekulare Analoga, wie Aminooxepan **G**[34] und Aminooxocane **H**[35].




Schema 3: Überblick zur Synthese enantiomerenreiner Kohlenhydratmimetika aus 1,2-Oxazinen **A**.

Diese hochfunktionalisierten Verbindungen weisen eine Vielzahl von Modifikationsmöglichkeiten auf, so dass sie als Ausgangsmaterialien für die Synthese von Naturstoffen oder Naturstoffanaloga genutzt werden können.

Viele der durch dieses Konzept erhaltenen Kohlenhydratmimetika wurden von der Arbeitsgruppe Schlecht durch eine Amidbindung an funktionalisierte Goldnanopartikel gebunden, dann sulfatiert und als Selektininhibitoren getestet (Abbildung 6).[36] Die biologischen Tests wurden von der Arbeitsgruppe Dernedde/Tauber vorgenommen. Zur Ermittlung der mittleren inhibitorischen Konzentration wurde ein kompetitiver Bindungsassay entwickelt und mit Oberflächenplasmonenresonanzspektroskopie (SPR) untersucht. Die getesteten Goldnanopartikel haben in der Regel einen Durchmesser von 6 nm und sind mit Mercaptoundecansäure funktionalisiert. Das nicht sulfatierte, einzelne monovalente Produkt (Abbildung 6, erstes Beispiel) zeigte keine Inhibition von L- und P-Selektin. Bei multivalenter Präsentation des Liganden am Goldnanopartikel konnte hingegen für P-Selektin ein $IC_{50}$-Wert von 10 nM erreicht werden, während keine Inhibition für L-Selektin festgestellt wurde. Letzteres lässt darauf schließen, dass diese Verbindung ein hochselektiver und effizienter Inhibitor für P-Selektin ist.

Werden die Kohlenhydratmimetika sulfatiert, konnten $IC_{50}$-Werte von 0.35 nM für L-Selektin und 0.04 nM für P-Selektin ermittelt werden. Es wurden noch weitere Kohlenhydratmimetika, wie Aminofurane oder auch acyclische Liganden getestet, wobei die acyclischen Liganden ähnlich niedrige $IC_{50}$-Werte erreichten (bis zu 0.02 nM), jedoch keine Selektivität bezüglich der Selektine aufwiesen.[36] Diese vielversprechenden, ersten Ergebnisse zeigen, dass sich Aminopyrane grundsätzlich gut als Selektininhibitoren eignen, wenngleich bisher noch wenig über die Struktur-Wirkungs-Beziehungen zum Einfluss der Art des Liganden, deren Anzahl und ihrer Anordnung und den resultierenden Bindungsselektivitäten zu Selektinen verstanden wird.

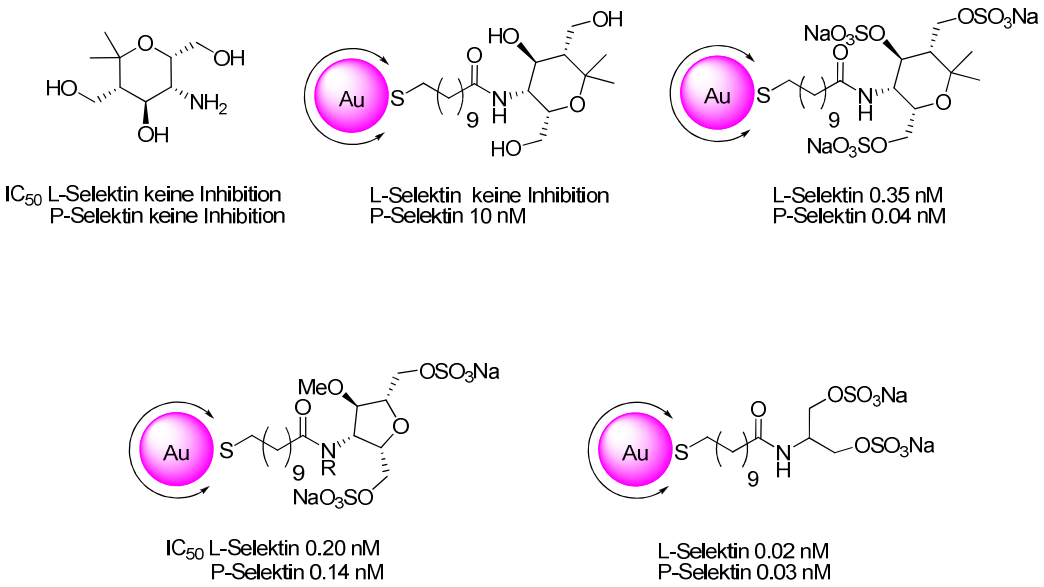
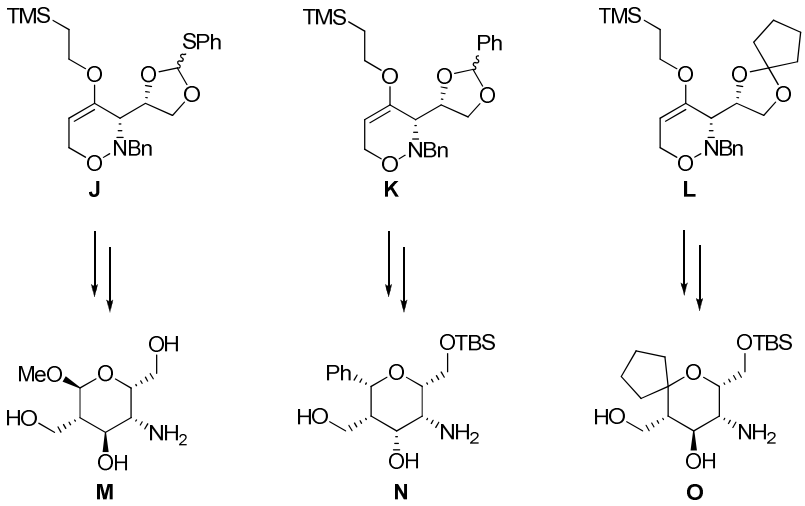



Abbildung 6: Ermittelte $IC_{50}$-Werte von terminal funktionalisierten Goldnanopartikeln gegenüber L- und P-Selektin.

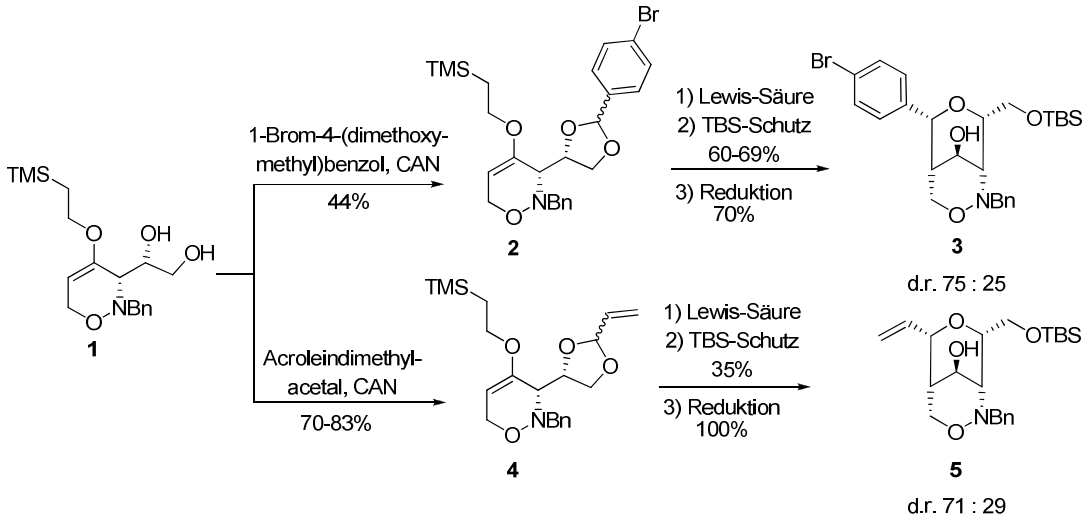
Um dieses bessere Verständnis zu erreichen, sollten in weiteren Untersuchungen Synthesen mit neuen Liganden, zum Beispiel mit hydrophoben Gruppen, synthetisiert und hinsichtlich Bindungsselektivität für Selektine charakterisiert werden.

In den Arbeiten von Pfrengle[37] und Al-Harrasi[35] wurde gezeigt, dass die Synthese der 1,2-Oxazine durch variable Bedingungen möglich ist, so dass unterschiedliche 1,3-dioxolanyl-substituierten 1,2-Oxazinen erhalten und in die entsprechenden Aminopyrane übergeführt werden können (Schema 4). Auf diesem Weg konnten *O*-methylglycosidierte Aminozucker **M** oder Aminopyrane mit Phenylsubstituenten **N** oder mit Spirocyclopentaneinheit **O** hergestellt werden.




Schema 4: Darstellung von *O*-methylglycosidierten **M**, phenyl- und spirocyclopentyl-substituierten Aminopyranen **N** und **O**.

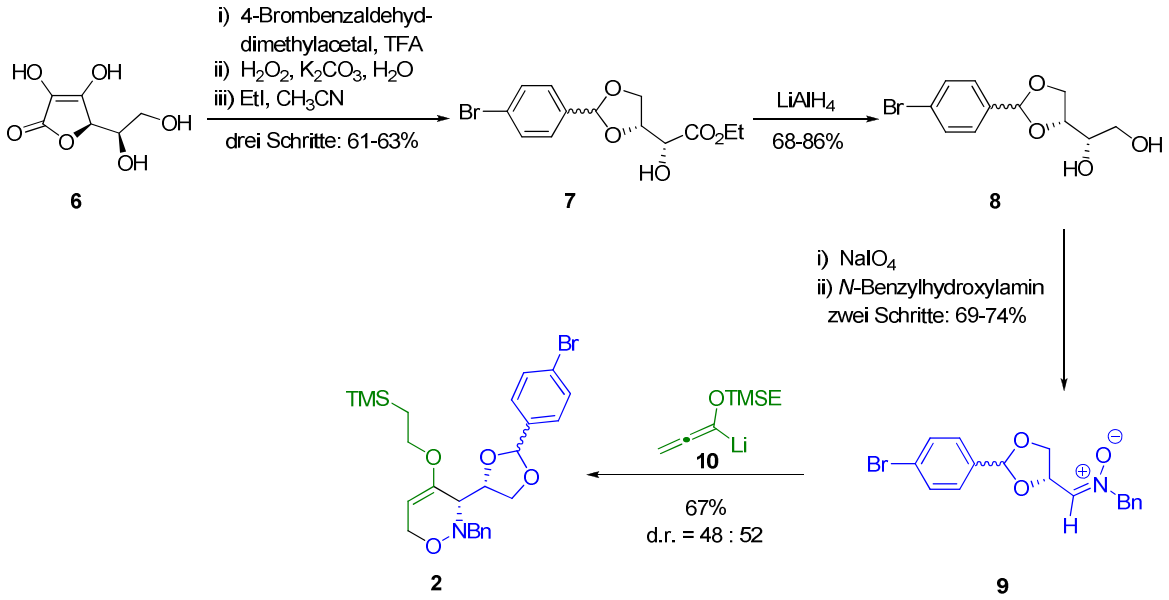
In meiner Masterarbeit gelang nach diesem Reaktionsprinzip mit der Herstellung des *para*-bromphenylsubstituierten 1,2-Oxazins **2** und des vinylsubstituierten 1,2-Oxazin **4** die Synthese von weiteren, besonders interessanten 1,3-dioxolanyl-substituierten 1,2-Oxazinen (Schema 5). Beide 1,2-Oxazine können als Vorläufer von neuen Aminopyranen angesehen werden. In Analogie zur Arbeit von Pfrengle konnte das 1,2-Diol **1** katalysiert durch Lewis-Säure in die substituierten 1,3-dioxolanyl-substituierten 1,2-Oxazinen **2** und **4** übergeführt werden, aus denen anschließend durch eine Lewis-Säure-induzierte Umlagerung die entsprechenden, enantiomerenreinen Bicyclen dargestellt wurden. Durch Schutz mit *tert*-Butyldimethylsilylchlorid und Reduktion mit Natriumborhydrid wurden die Synthesebausteine mit *para*-Bromphenylsubstituenten **3** und Vinylsubstituenten **5** hergestellt, die sich als interessante Vorläufer für Übergangsmetall-katalysierte Reaktionen wie Kreuzkupplungen und Olefinmetathesen eignen sollten.[38]




Schema 5: Synthese von neuen 1,3-dioxolanyl-substituierten 1,2-Oxazinen **2**, **4** und ihre Umlagerung zu bicyclischen 1,2-Oxazine **3** und **5**.

Weiterhin konnte das *para*-bromphenylsubstituierte 1,2-Oxazin **2** auch durch eine alternative Syntheseroute dargestellt werden (Schema 6). Entsprechend diesem Syntheseweg wird ein *para*-bromphenylsubstituiertes Nitron **9** mit guten bis sehr guten Ausbeuten in sechs Schritten dargestellt. Im ersten Schritt wird D-Isoascorbinsäure **6** mit 4-Brombenzaldehyd-dimethylacetal zur 1,3-dioxolanylsubstituierten D-Isoascorbinsäure umgesetzt. Anschließend wurde eine C-C-Bindung oxidativ mit Wasserstoffperoxid gespalten und die entstandene Carbonsäure mit Ethyliodid zum Produkt **7** verestert. Der Ester **7** wurde durch Lithiumaluminiumhydrid reduziert, das Glykol gespalten und mit *N*-Benzylhydroxylamin durch Kondensation zum (*Z*)-Nitron umgesetzt. Durch eine [3+3]-Cyclisierung mit dem lithiierten TMSE-Allen **10** wurde das 1,2-Oxazin **2** in einer guten Ausbeute von 67% isoliert. Diese alternative Syntheseroute ist länger, hat aber durchschnittlich höhere Ausbeuten. Trotzdem

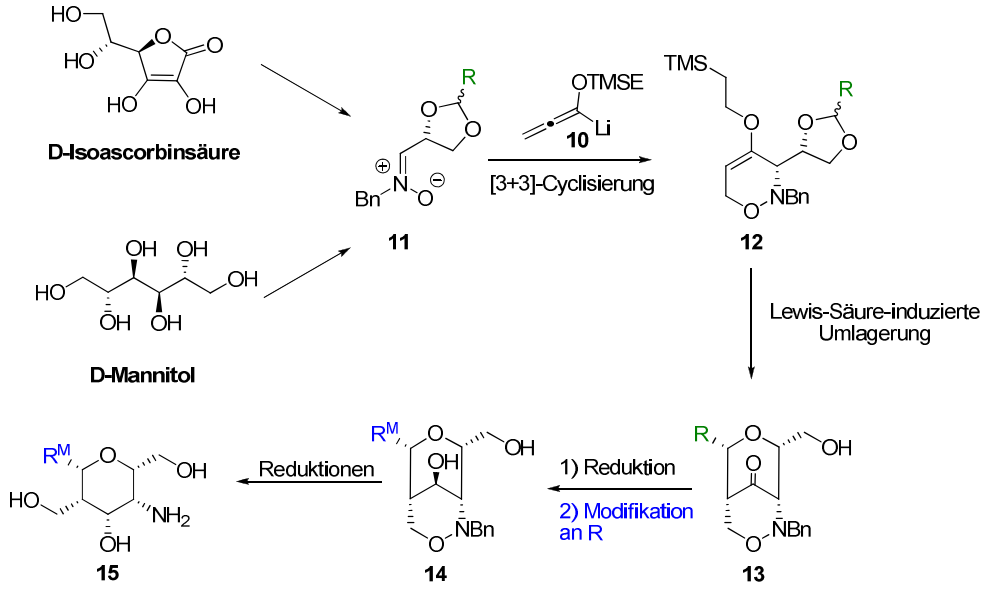
sollte die erste Syntheseroute bevorzugt werden, da diese aufgrund der geringeren Anzahl der Schritte weniger zeitaufwändig ist.




Schema 6: Alternative Syntheseroute zur Herstellung des *para*-bromphenylsubstituierten 1,2-Oxazins **2**.

## Aufgabenstellung

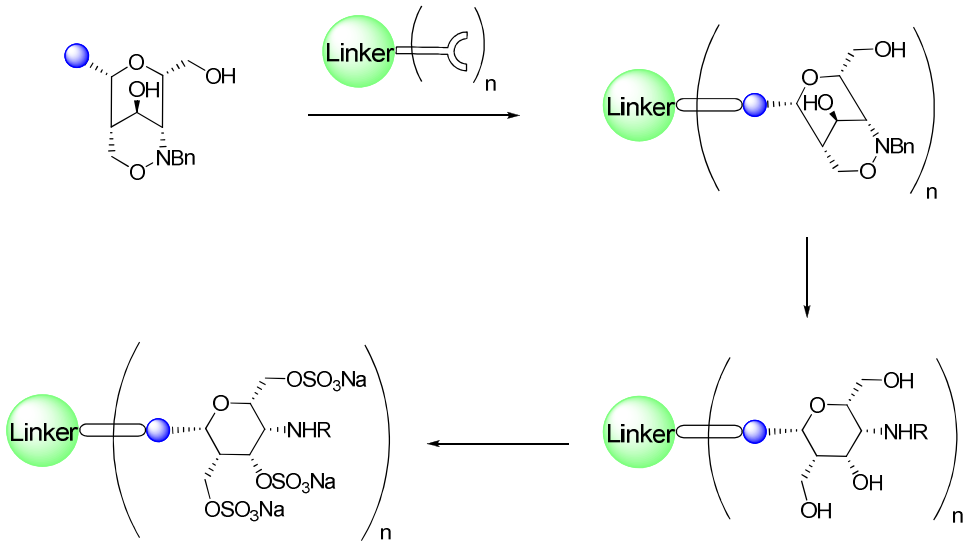
Aufbauend auf den Ergebnissen meiner Masterarbeit war es das Ziel der vorliegenden Dissertation, den Syntheseweg zur Darstellung von 1,3-dioxolanyl-substituierten 1,2-Oxazinen **12** und deren Lewis-Säure-induzierte Umlagerung zu optimieren (Schema 7). Des Weiteren sollten weitere neue 1,3-dioxolanyl-substituierte 1,2-Oxazine **12** mit neuen, funktionellen Gruppen synthetisiert werden. Anknüpfend auf den vielversprechenden Ergebnissen sollten neue interessant funktionalisierte Aminopyrane **15** dargestellt werden und der Arbeitsgruppe Schlecht zur Anbindung an Goldnanopartikel bereitgestellt, *O*-sulfatiert und anschließend von der AG Dernedde/Tauber hinsichtlich Selektinbindungsvermögen getestet werden. Des Weiteren sollten die neuen Aminopyrane **15** der AG Rademacher zur Verfügung gestellt werden, um deren Bindungsaffinität bezüglich des Lektins Langerin zu quantifizieren. Die aus der Synthese neu erhaltenen Aminopyrane **15** sollten nicht nur Modifikationen an der Aminogruppe ermöglichen, sondern auch Reaktionen an dem eingeführten Substituenten (z.B. der Vinylgruppe).




Schema 7: Darstellung von funktionalisierten Aminopyranen **15** aus 1,3-dioxolanyl-substituierten 1,2-Oxazinen **12**.

Ein besonderer Fokus der Arbeit sollte auf der Synthese von niedervalenten Konjugaten liegen (Schema 8). Um mehr Information über die Struktur-Wirkungs-Beziehung der Kohlenhydratmimetika bezüglich der Selektine zu erhalten, sollten der Grad der Valenz, die Länge und die Flexibilität der Linker variiert werden. Durch Untersuchung des Bindungsvermögens dieser neuen Konjugate mit definierter Anzahl an Aminopyranen und eindeutiger Struktur sollte es möglich sein, Schlussfolgerungen bezüglich der Wechselwirkung und zum Multivalenzeffekt zu ziehen. Zu diesem Zweck sollten die erhaltenen 1,2-Oxazinbausteine an geeignete Linker durch Übergangsmetall-katalysierte Reaktionen, wie zum Beispiel Suzuki-Kupplung, Sonogashira-Kupplung und

Olefinmetathese, gekoppelt werden. Dabei sollten einerseits starre Linker wie Phenylgruppen oder 1,3-Diine eingeführt werden, um Mimetika zu erhalten, die möglichst kleine Entropieverluste bei Selektin-Bindung verursachen. Anderseits sollten Kohlenhydratmimetika synthetisiert werden, die den gleichen Abstand wie bei den Verbindungen mit starren Linkern aufweisen, jedoch flexible aliphatische Linker besitzen. Anschließend sollten geeignete Bedingungen gefunden werden, um die oligovalenten Produkte zu *N*-debenzylieren und die N-O-Bindung zu spalten. Die hergestellten, multivalenten Kohlenhydratmimetika sollten sulfatiert werden, um die Bindungsaffinität der Produkte zu steigern. Die Arbeitsgruppe Dernedde/Tauber sollte ihre Bindungsaffinität testen und anschließend ihre Affinität bezüglich L-, P- und E-Selektin bewerten.




Schema 8: Allgemeines Schema zur Darstellung von multivalenten, sulfatierten Kohlenhydratmimetika.

# 3 Allgemeiner Teil

Das Kapitel drei der vorliegenden Arbeit unterteilt sich in vier Abschnitte. Die Abschnitte beschreiben die Synthese von mono- und oligovalenten Kohlenhydratmimetika, die durch Suzuki-Reaktion (Kapitel 3.1), Sonogashira-Reaktion (Kapitel 3.2) und Olefinmetathese (Kapitel 3.3) funktionalisiert und verknüpft wurden. Die Ergebnisse wurden im Rahmen dieser Arbeit erhalten und in chemischen Fachzeitschriften publiziert. Das Kapitel 3.4 beschreibt bisher noch unveröffentlichte Ergebnisse, wie z.B. die Synthese eines homoallylsubstituierten bicyclischen 1,2-Oxazins und die Polysulfatierung der erhaltenen Kohlenhydratmimetika.

## 3.1 Synthesis of rigid *p*-terphenyl-linked carbohydrate mimetics

Dieses Kapitel wurde in der folgenden Zeitschrift publiziert:

M. Kandziora, H.-U. Reissig, *Beilstein J. Org. Chem.* **2014**, *10,* 1749–1758.

Das Kapitel 3.1 beschreibt die Synthese von neuartigen phenylsubstituierten Aminopyranen und starren, divalenten, *p*-terphenyl-verknüpften *C*-Arylglycosiden durch Suzuki-Kreuz-Kupplung. Hierzu wurde aus *para*-bromphenylsubstituierter D-Isoascorbinsäure das entsprechende (*Z*)-Aldonitron dargestellt, welches anschließend mit lithiertem TMSE-Allen in einer [3+3]-Cyclisierung in 1,2-Oxazine übergeführt wurde. Alternativ konnte das *para*-bromphenylsubstituierte 1,2-Oxazin aus einem literaturbekannten Diol synthetisiert werden. Anschließend wurde das 1,2-Oxazin in einer Lewis-Säure-induzierten Umlagerung zu einem enantiomerenreinen bicyclischen 1,2-Oxazin übergeführt. Es konnten drei enantiomerenreine Aminopyrane dargestellt werden; zwei mit D-Talose- und eines mit D-Idose- Konfiguration. Für die Spaltung der N-O-Bindung wurden verschiedene Methoden (Hydrogenolyse, Samariumdiiodid, Zink/Essigsäure) untersucht und für jedes Substrat die optimale Methode gefunden.
Alle beschriebenen Experimente wurden im Rahmen der vorliegenden Arbeit durchgeführt.

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# Synthesis of rigid *p*-terphenyl-linked carbohydrate mimetics

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Full Research Paper

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## Abstract

An approach to β-D-2-aminotalose- and β-D-2-aminoidose-configured carbohydrate mimetics bearing a phenyl substituent is described. Unnatural divalent rigid *p*-terphenyl-linked *C*-aryl glycosides with 2.0 nm dimension are available using Suzuki cross-couplings. The key compound, a *p*-bromophenyl-substituted 1,2-oxazine, was prepared by a stereoselective [3 + 3]-cyclization of a D-isoascorbic acid-derived (*Z*)-nitrone and lithiated TMSE-allene. The Lewis acid-induced rearrangement of this heterocycle provided the corresponding bicyclic 1,2-oxazine derivative that may be regarded as internally protected amino sugar analogue. After subsequent reduction of the carbonyl group, the resulting bicyclic compound was used for Suzuki cross-couplings to form biphenyl aminopyran or *p*-terphenyl-linked dimers. Hydrogenolysis afforded new unnatural aminosugar mimetics. Zinc in the presence of acid or samarium diiodide were examined for the N–O bond cleavage in order to obtain the rigid *p*-terphenyl-linked *C*-glycosyl dimers.

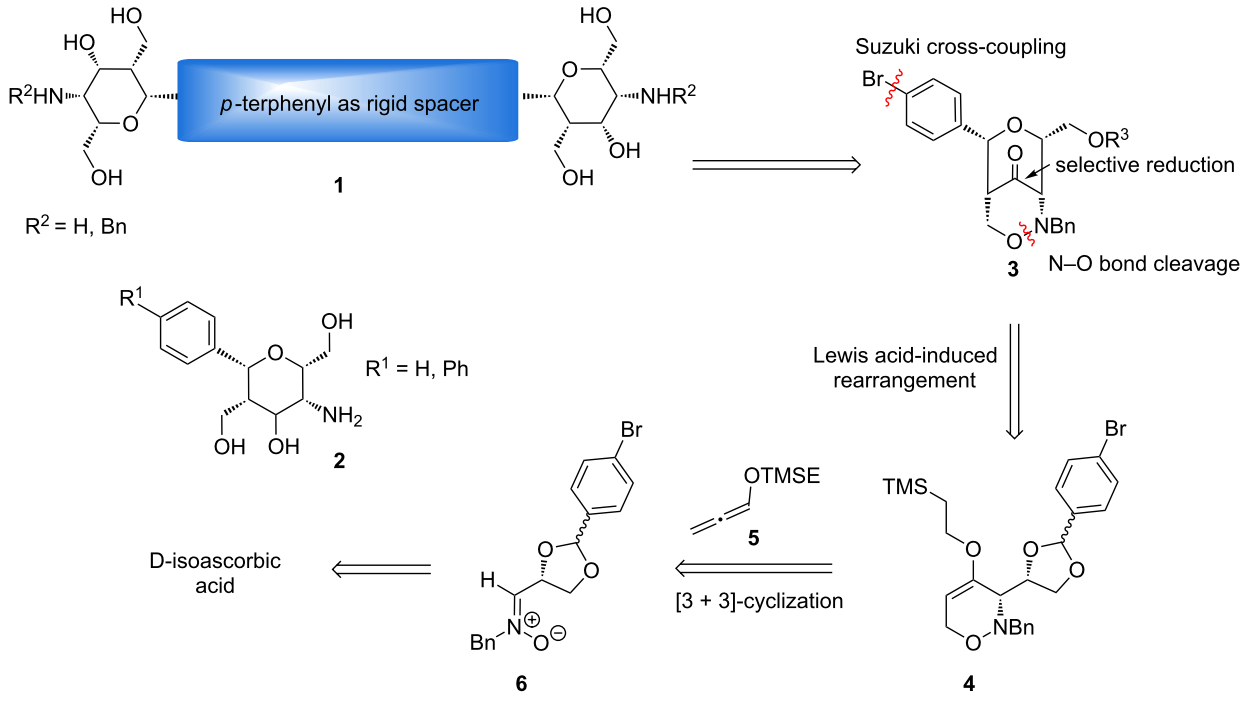
## Introduction

Carbohydrates are the class of biomolecules with the highest structural diversity [1,2]. Specific carbohydrates are responsible for cell-type specific interactions [3] and they are involved in different diseases such as cancer [4], inflammation [5], and infections [6]. However, the use of carbohydrates as drugs has been strongly limited due to the hydrolytic lability of the glycosidic bond [7] and the weak binding affinities of single molecules. With the development of artificial *C*-glycosides which possess structural and functional aspects of the corresponding carbohydrates, these disadvantages can be overcome, resulting in an improved bioavailability, higher affinities and improved selectivities [8-13]. Recent results indicate that divalent rigid carbohydrate conjugates may have even higher binding affinities and specificities than their flexible multivalent equivalents [14,15]. The rigidity of the system is supposed to improve the overall activity of the ligands by over-

coming the entropic penalty of flexible multivalent scaffolds [16].

Cross-coupling reactions are among the best methods to prepare *C*-arylglycosides, *C*-nucleosides and *C*-glycosidic oligomers when new artificial pharmacophores are approached [17]. With Suzuki cross-couplings *C*-glycoside analogues of phloriain with antidiabetic properties [18] or aryl-scaffolded dimers and trimers were successfully prepared [19]. The Suzuki cross-coupling is particularly suitable for carbohydrate chemistry due to the mild reaction conditions and its tolerance to a variety of functional groups [20]. In addition, the reactions are easy to perform and the required boronic acids exhibit exceptional stabilities to heat, air and moisture compared to other organometallic reagents [21]. Up to now there are not many examples of nanorod-like carbohydrate dimers with aryl-linked divalent glycosides. A mannopyranoside dimer was generated by a palladium-catalyzed Ullmann-type reductive homocoupling [22] and biphenyl-linked dimers were prepared by Lewis acid-catalyzed glycosidations [23]. All these examples possess an acid-labile *O*-glycosidic bond and are labile to hydrolysis and enzymes. Therefore, new approaches to the synthesis of rigid multivalent *C*-arylglycosides should be a valuable extension of compounds with potential biological activity. In order to achieve this goal we investigated the synthesis of divalent compounds of general structure **1** and their monovalent analogues **2** (Scheme 1). Structurally similar aminopyrans without aryl groups have intensively been studied as carbohydrate mimetics in our group [24,25]. When they are coupled by amide bonds to gold nanoparticle and O-sulfated these conjugates gave extremely high binding affinities towards L- and P-selectin in sub-nanomolar concentrations. These results were achieved by a multivalent presentation (ca. 1000–1200 ligands per nanoparticle) of the sulfated pyrans [26,27]. We were therefore interested to prepare inhibitors offering only a small number of ligands to get better information about structure–activity relationships and to study the influence of the flexible and rigid spacer units.

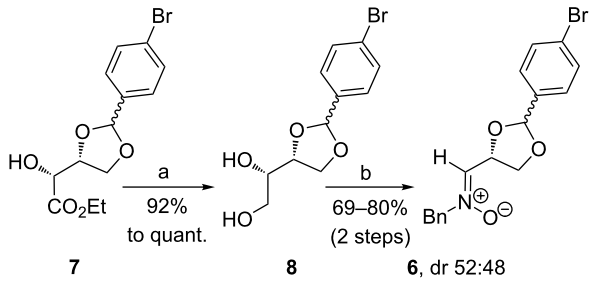
In this report we present methods for the synthesis of divalent compounds **1** with *p*-terphenyl spacers and of β-D-2-aminotalose- or β-D-2-aminoidose-configured carbohydrate mimetics **2** (Scheme 1). These novel carbohydrate mimetics represent unique structures, combining the features of *C*-aryl-glycosides and aminosugars. The *p*-bromophenyl-substituted bicyclic 1,2-oxazine derivative **3** was used as key building block for the Suzuki cross-coupling reaction to synthesize *p*-terphenyl-linked derivatives **1**. The key intermediate **3** was prepared by a Lewis acid-induced rearrangement of 3,6-dihydro-2*H*-oxazine **4**, that origins from a stereoselective [3 + 3]-cyclization of D-isoascorbic acid-derived (*Z*)-nitrone **6** and lithiated TMSE-allene **5**.




**Scheme 1:** Approach to divalent carbohydrate mimetics **1** with rigid spacer and monovalent analogues **2**.

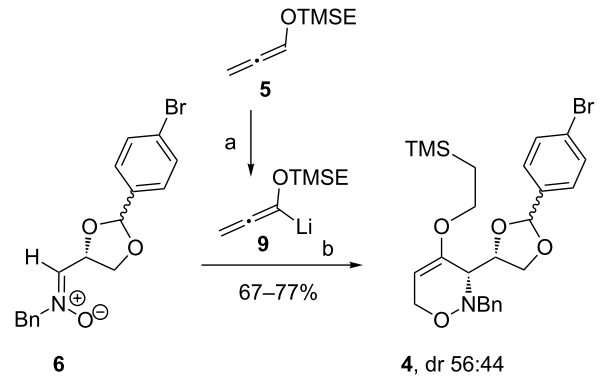
## Results and Discussion

For our synthesis of new divalent carbohydrate mimetics we required 1,2-oxazine derivatives derived from (*Z*)-nitrone **6** and lithiated alkoxyallenes. The 4-bromophenyl group should allow transition metal-promoted coupling reactions to a variety of new compounds. For this purpose the D-erythrose-configured ester **7**, easily available from D-isoascorbic acid [28], was converted into nitrone **6** in a three step procedure (Scheme 2). Its reduction with lithium aluminum hydride was performed under standard conditions providing diol **8** in excellent yield in multigram scale (up to 20 g). Attention should be paid to a possible reductive removal of the bromine substituent that can occur at higher temperature or longer reaction times as the resulting debrominated product is hard to remove from diol **8** by column chromatography. According to the protocol of Dondoni et al. [29] glycol cleavage of diol **8** afforded the corresponding aldehyde that was directly treated with *N*-benzylhydroxylamine to furnish the desired (*Z*)-nitrone **6**. All compounds in this sequence of reactions are mixtures of the two diastereomers at the dioxolane C-2 (ratios close to 1:1).



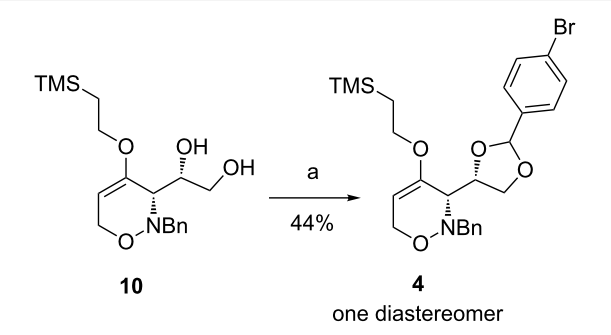

**Scheme 2:** Synthesis of (*Z*)-nitrone **6**. Conditions: a) $LiAlH_4$, THF, 1 h, rt; b) 1. $NaIO_4$, $CH_3CN/H_2O$, 1 h, rt; 2. *N*-benzylhydroxylamine, $MgSO_4$, $CH_2Cl_2$, 18 h, rt.

The preparation of *syn*-1,2-oxazine **4** was achieved in good yields ranging from 67–77% by stereocontrolled addition of lithiated (trimethylsilyl)ethoxyallene **9** to (*Z*)-nitrone **6** at −78 °C (Scheme 3). Although the formation of four stereoisomers is possible only two were observed. Due to the complexation of lithiated allene **9** to the nitrone **6** an exclusive formation of the two *syn*-1,2-oxazines **4** was observed. This result suggests that the configuration at C-2 of the dioxolane moiety has no influence on the stereochemical outcome of the reaction. The model suggested by Dondoni et al. [30] can also be employed for this process to rationalize the observed diastereoselectivity of the addition step. The subsequent [3 + 3]-cyclization to 3,6-dihydro-2*H*-1,2-oxazine **4** follows the previously reported mechanism [31]. In the presented sequence *syn*-1,2-oxazine **4** was successfully prepared in six steps with an overall yield of 46%. The diastereomers can easily be separated by column chromatography, but this turned out not to be mandatory. The next step of our anticipated sequence, the Lewis acid-induced rearrangement, converts the dioxolane C-2 carbon into an $sp^2$-hybridized carbon and hence the configuration of the precursor does not play a role for this reaction.




**Scheme 3:** [3 + 3]-Cyclization of (*Z*)-nitrone **6** with lithiated allene **9**. Conditions: a) *n*-BuLi, THF, 15 min, −40 °C; b) 1. THF, 2 h, −78 °C; 2. $H_2O$, 1 h, −78 °C → rt.

An alternative route to prepare 1,2-oxazine **4** is depicted in Scheme 4. The preparation of the 4-bromophenyl-1,3-dioxolane moiety started from diol **10** that has successfully been used earlier for the preparation of phenylthio-substituted 1,2-oxazine derivatives [32]. Compound **10** is easily accessible by a mild cleavage of the corresponding acetonide by an indium trichloride-mediated hydrolysis [33]. By using cerium ammonium nitrate as Lewis acid [34] in high concentration (13 mmol/mL) as well as an excess of 1-bromo-4-(dimethoxymethyl)benzene enabled the synthesis of *syn*-1,2-oxazine **4**. The conversion of this reaction was high (>80%) giving the two diastereomers of **4** (ca. 1:1), but only one diastereomer was isolated in pure form. The second diastereomer could hardly be separated from the excess of 1-bromo-4-(dimethoxymethyl)-benzene by column chromatography or distillation. Besides, Brønsted acids like trifluoroacetic acid, *p*-toluenesulfonic acid,




**Scheme 4:** Synthesis of 1,2-oxazine **4** by acetal formation from **10**. Conditions: a) 1-bromo-4-(dimethoxymethyl)benzene (10 equiv.), CAN, $CH_2Cl_2$, 3 d, rt.

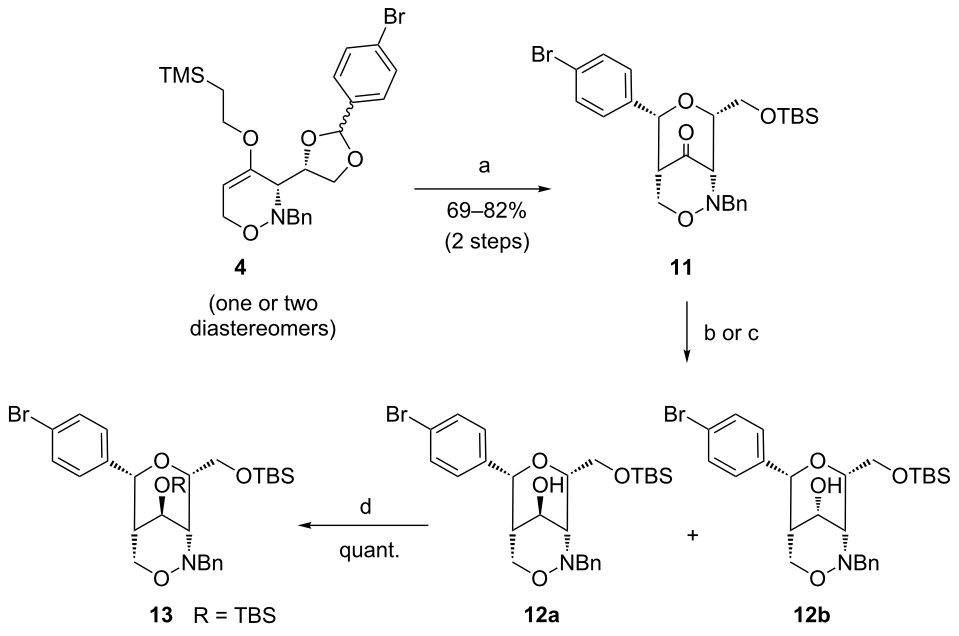
that are usually used to generate ketals, or weaker acids like pyridine/hydrogen fluoride led to a side product [35].

The Lewis acid-promoted rearrangement of 1,3-dioxolanyl-substituted 1,2-oxazines to bicyclic ketones has been described in many examples [24]. Gratifyingly, starting from 1,2-oxazine **4** with tin(IV) chloride as Lewis acidic promoter the corresponding ketone was obtained in excellent stereoselectivity. The subsequent protection of the primary hydroxy group as TBS ether under standard conditions provided **11** in very good yields of up to 82% (Scheme 5). In order to perform the Lewis acid-promoted rearrangement and the protection in one step, we also employed TBSOTf as Lewis acid for the rearrangement step [24], however, no product formation could be observed in this case. The mechanism of the rearrangement **4** → **11** can be described as an aldol-type cyclization process. The Lewis acid coordinates to the sterically less hindered oxygen atom of the dioxolane ring of **4** opening this ring and forming a carbenium ion that intramolecularly attacks the enol ether moiety. A six-membered chair-like transition state with the bulky 4-bromophenyl group in an equatorial position for this crucial step rationalizes the product configuration as shown.

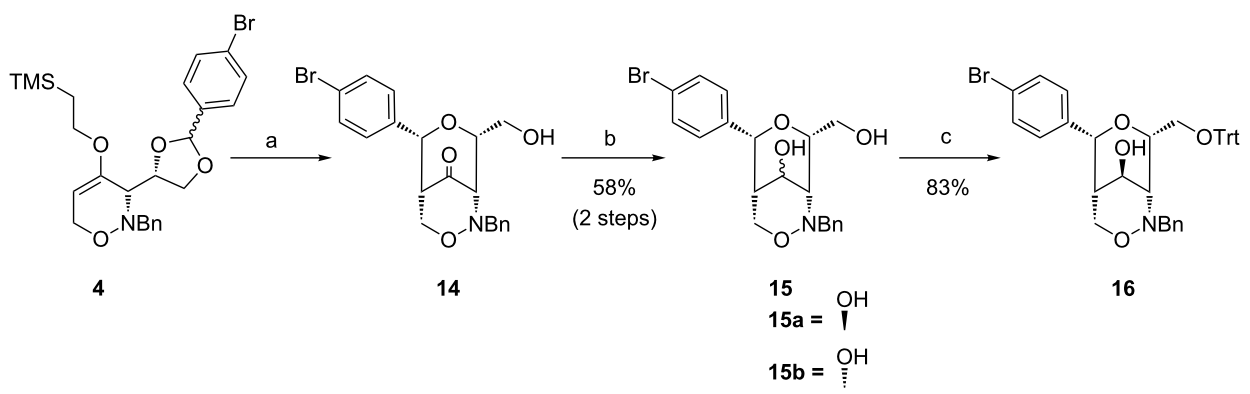
TBS-protected bicyclic ketone **11** was subsequently reduced with sodium borohydride at −40 °C to form alcohols **12a** and **12b** as 81:19 mixture of diastereomers in 72% yield (Scheme 5). In contrast, the reduction with L-selectride at −10 °C selectively furnished pure diastereomer **12a** in 73% yield. In accordance with previous observations of reductions of related phenylthio-substituted bicyclic compounds [25], a hydride attack from the side of the pyran moiety is assumed since the 1,2-oxazine side is more hindered by the bulky *N*-benzyl moiety. The secondary hydroxy group of **12a** was protected employing *t*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine in quantitative yield.

The Lewis acid-promoted rearrangement of 1,2-oxazine derivative **4** and the direct reduction of the unpurified ketone **14** furnished bicyclic diol **15** in good overall yield of 58% (Scheme 6). The reduction of unprotected ketone **14** with L-selectride was less stereoselective and provided a 72:28 mixture of **15**. The higher selectivity of the TBS-protected compound **11** may be explained by an indirect effect of the bulky TBS-group, possibly pushing the *N*-benzyl moiety to the top of the ring shielding the 1,2-oxazine side more efficiently. Separation of the two diastereomers and protection of the primary hydroxy group of **15a** with trityl chloride provided compound **16** in 83% yield. This protecting group should allow its removal together with the benzyl group during hydrogenolysis. Surprisingly, a benzyl protection under the same conditions was not possible.

Before approaching divalent compounds such as **1** we wanted to convert our building blocks into simple monocyclic carbohydrate mimetics. To prepare phenyl-substituted aminopyrans the N–O bond of bicyclic compounds **15a** and **15b** was cleaved by

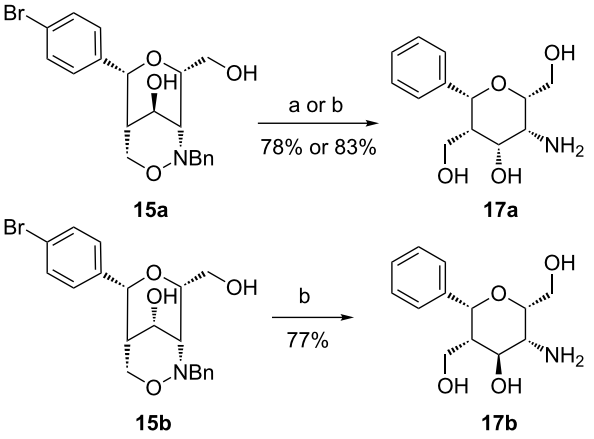



**Scheme 5:** Synthesis of bicyclic ketone **11** by Lewis acid-induced rearrangement and reduction to alcohols **12a** and **12b** and protection of **12a** to 1,2-oxazine derivative **13**. Conditions: a) 1. $SnCl_4$, $CH_3CN$, 4 h, −30 °C → rt; 2. TBSCl, imidazole, THF, 4 h, rt; b) $NaBH_4$, EtOH, 4 h, −40 °C, 72%, dr 81:19; c) L-selectride, THF, 2 h, −10 °C, 73%, only **12a**; d) TBSOTf, 2,6-lutidine, THF, 2 h, 0 °C.




**Scheme 6:** Synthesis of bicyclic diols **15** and of trityl-protected bicyclic 1,2-oxazine **16**. Conditions: a) $SnCl_4$, $CH_3CN$, 18 h, −30 °C → rt, b) 1) L-selectride, THF, 4 h, −15 °C, dr 72:28; 2) separation by column chromatography (silica gel, hexanes/EtOAc 1:1 → 1:2); c) TrtCl, DMAP, pyridine, 3 d, rt.

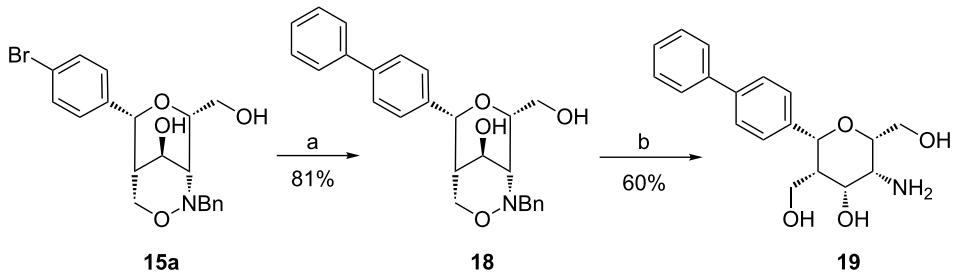
hydrogenolysis. These reactions are challenging because the resulting aminopyrans are apparently poisoning the catalyst and hence large amounts of palladium on charcoal are required for full conversion. We did not add acid to diminish catalyst poisoning since we were afraid of other side reactions of the complex product. In addition, the resulting products are very polar and difficult to purify. In our recent report [28] related compounds were reduced in methanol as solvent providing several side products and the yield of the reactions were not fully reproducible. Nevertheless, 1,2-oxazine **15a** was converted into aminopyran **17a** (Scheme 7) by hydrogenolysis under standard conditions in methanol in a yield of 78%, but this yield was not fully reproducible and the conditions were optimized. We found that isopropanol as solvent and addition of one equivalent triethylamine were more reliable and the yield of **17a** could be slightly improved. Triethylamine was added to neutralize the formed acid [36] that is generated in the first step by a very fast debromination. The debenzylation and the N–O bond cleavage occur as next steps. Under these improved conditions the isomeric bicyclic 1,2-oxazine **15b** was converted into aminopyran **17b** in a good yield of 77%. The formed aminopyrans **17a** and **17b** can be regarded as amino *C*-glycosides. Compound **17a** is related to compounds with β-D-talose configuration that are rarely found in nature, an exception being the antibiotic amino glycoside hygromycin B [37]. Aminopyran **17b** correlates to β-D-idopyranose; iduronic acid is a component of sulfated glycosamine glycans such as chrondroitin sulfate and heparan sulfate [38].



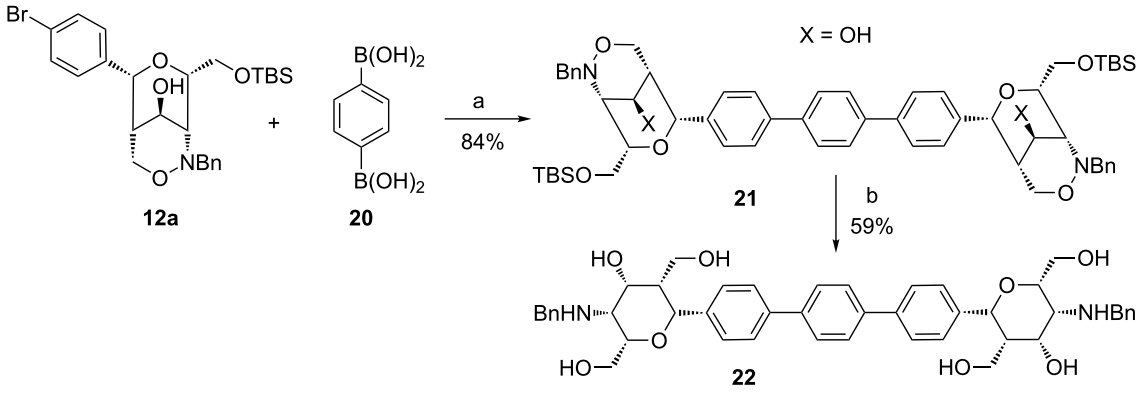

**Scheme 7:** Hydrogenolyses of bicyclic 1,2-oxazine derivatives **15a** and **15b**. Conditions: a) $H_2$, Pd/C, MeOH, EtOAc, 20 h, rt; b) $H_2$, Pd/C, iPrOH, EtOAc, $NEt_3$, 18 h, rt.

The prepared *p*-bromophenyl-substituted bicyclic 1,2-oxazine derivatives **12**, **13**, **15** and **16** provide options to perform cross-coupling reactions such as Buchwald/Hartwig, Heck, Hiyama, Kumada, Sonogashira or Stille couplings. In order to examine the conditions for Suzuki cross-couplings we subjected bicyclic compound **15a** to phenylboronic acid under standard conditions of this reaction. The desired product **18** was obtained in 81% yield (Scheme 8) and the subsequent hydrogenolysis furnished carbohydrate mimetic **19** bearing a biphenyl substituent.

The smooth transformation of bicyclic compound **15a** into a biphenyl compound by Suzuki cross-coupling encouraged us to aim the synthesis of divalent compound **21**. 1,4-Phenylenediboronic acid (**20**) was used as precursor and coupled to two equivalents of **12a** to afford the desired *p*-terphenyl compound **21** in excellent 84% yield (Scheme 9). Unfortunately, the subsequent hydrogenolysis of this compound under conditions as above led to a complex product mixture and no product could be observed. An alternative method for N–O cleavage employs elemental zinc in the presence of acid [39], conditions that should simultaneously cleave the TBS protective groups. For the conversion of **21** into **22** long reaction times were required and the high acidity led to the formation of side products.




**Scheme 8:** Suzuki cross-coupling of **15a** leading to biphenyl derivative **18** and hydrogenolysis to **19**. Conditions: a) phenylboronic acid, $Pd(PPh_3)_4$, 2 M $Na_2CO_3$ aq, THF, 70 °C, 48 h; b) $H_2$, Pd/C, iPrOH, THF, rt, 24 h.

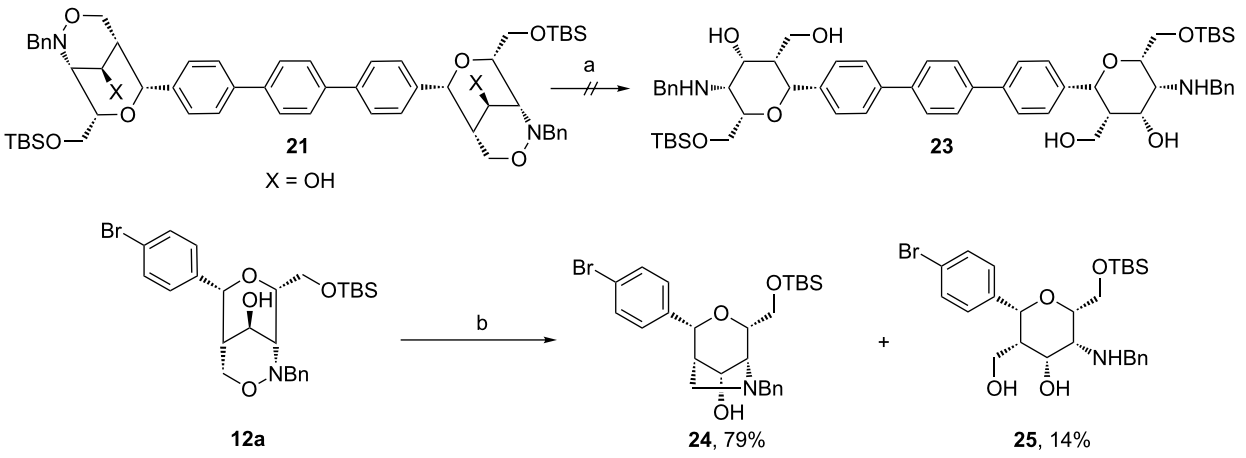



**Scheme 9:** Synthesis of *N*-benzylated *p*-terphenyl derivative **21** by Suzuki cross-coupling of **12a** with **20** and subsequent reduction with zinc. Conditions: a) $Pd(PPh_3)_4$, 2 M $Na_2CO_3$ aq, THF/DMF (8:2), 70 °C, 48 h; b) Zn, AcOH, THF, 60 °C, 18 h.

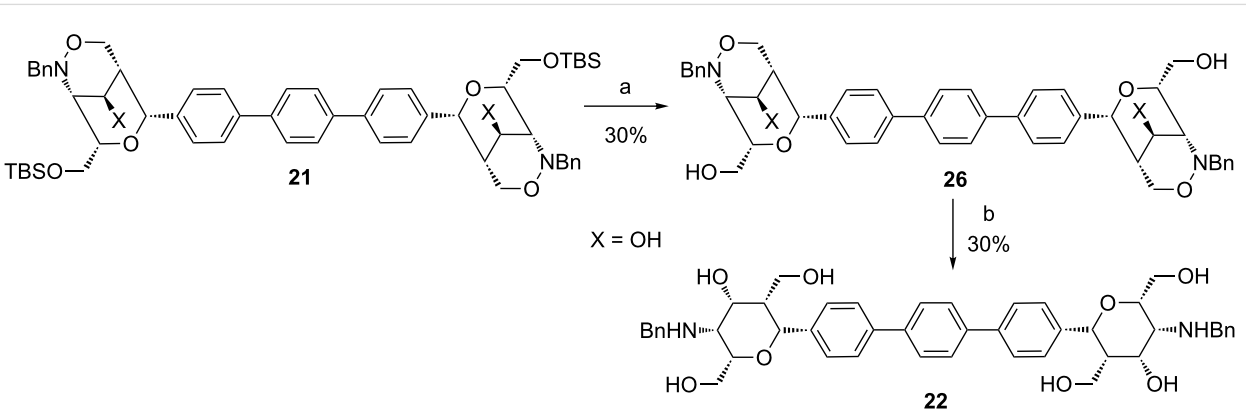
Nevertheless, the target compound **22** was isolated in a moderate yield of 59%.

As a milder alternative, samarium diiodide was examined for the N–O bond cleavage [40-45]. With this selective reagent a TBS protected aminopyran dimer **23** was expected that should be well soluble in organic solvents and therefore more suitable for subsequent transformations (Scheme 10). Disappointingly, a samarium diiodide solution converted compound **21** in a complex reaction mixture. For a better understanding of this unexpected result the reductive cleavage was examined with the simpler bicyclic 1,2-oxazine derivative **12a**. Here the unexpected bicyclic compound **24** was isolated as major product in 79% yield together with the desired aminopyran derivative **25** in 14% yield. It was observed by $^1$H NMR spectroscopy that aminopyran **25** is not stable and slowly cyclizes to **24**; after two days in $CDCl_3$ solution approximately 20% of aminopyran **25** were converted into **24**. This result indicates that the N–O bond cleavage of **12a** preceded as expected, but that the produced amino group of the pyran ring seems to be in close proximity to the C-5 hydroxy group and leads to a nucleophilic substitution under formation of the pyrrolidine moiety. This process is possibly promoted by samarium(III) which can act as Lewis acid and by the steric demanding TBS group which decreases the distance between the two functional groups. This unexpected side reaction leading to **24** indicates that in the above mentioned unclean reaction of samarium diiodide with dimer **21** similar complications may lead to the observed mixture.

To overcome these difficulties dimer **21** was deprotected with tetra-*n*-butylammonium fluoride giving the poorly soluble polyhydroxylated compound **26** (Scheme 11). Due to the amphiphilic character this compound was only soluble in pyridine that makes purification and subsequent reactions fairly difficult. The conversion of the deprotection step was high but the yield after purification was only 30%. The reduction with samarium diiodide was then performed in a methanol/tetrahydrofuran mixture in which compound **26** was scarcely soluble. Gratifyingly, after one hour reaction time and purification by column chromatography aminopyran **22** was isolated in 30% yield. Interestingly, no cyclization product similar to **24** was detected in this case.



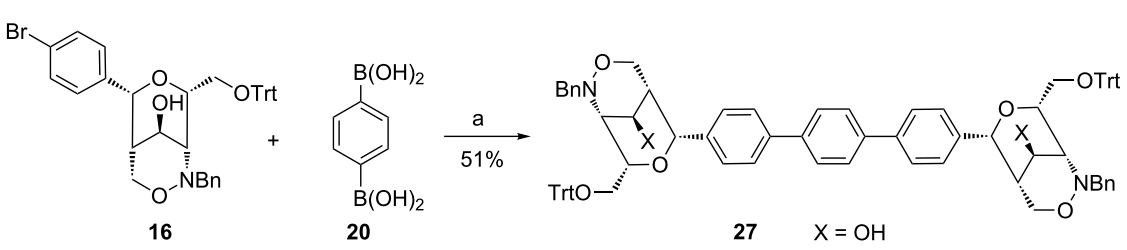

**Scheme 10:** Attempted reductive cleavage of the N–O bond of compound **21** by samarium diiodide and reaction of **12a**. Conditions: a) $SmI_2$ (0.09 M in THF), MeOH, rt, 60 min; b) $SmI_2$ (0.1 M in THF), THF, rt, 45 min.



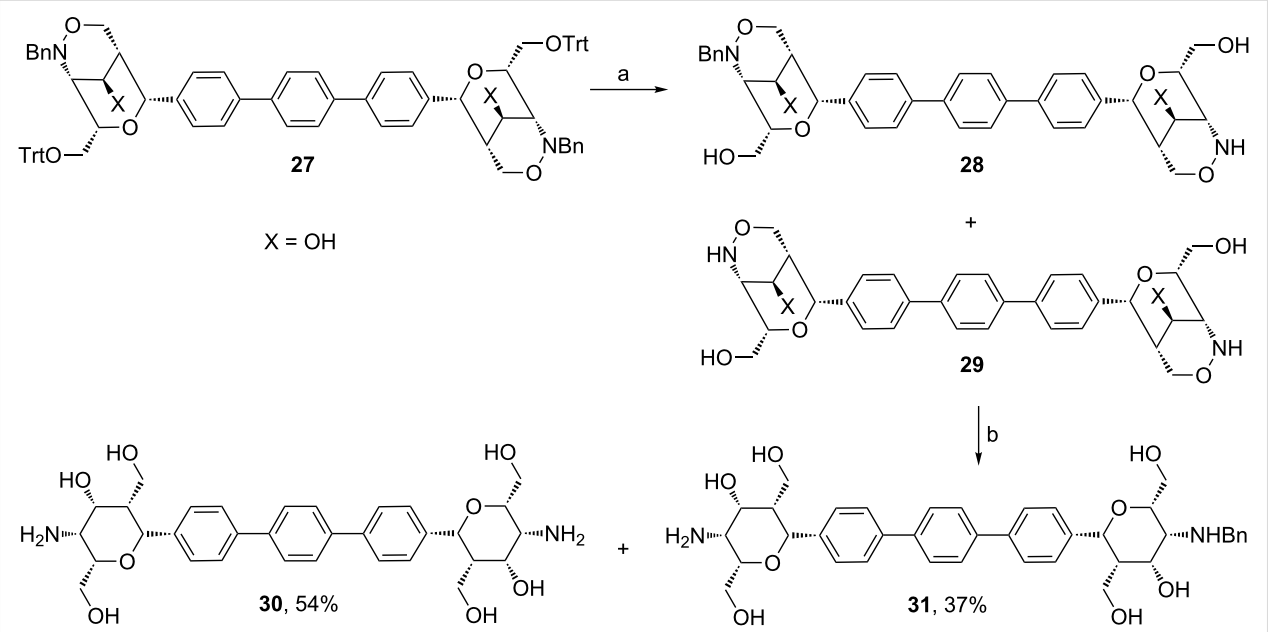

**Scheme 11:** Deprotection of compound **21** and samarium diiodide-mediated reaction of **26**. Conditions: a) TBAF, THF, rt, 2 d; b) $SmI_2$ (0.09 M in THF), MeOH, rt, 60 min.

We also investigated the Suzuki cross-coupling of bicyclic compound **16** with 1,4-phenylenediboronic acid (**20**) (Scheme 12). Although the trityl group is quite far away from the reacting bromo substituent it led to longer reaction times and slightly lower yields, but the expected product **27** was obtained in 51% yield as a well soluble compound.

The trityl protective groups enabled the deprotection of dimer **27** in one step. The *O*-trityl and *N*-benzyl groups were removed by hydrogenolysis under acidic conditions to obtain a mixture of compounds **28** and **29** (Scheme 13). As solvent a 3:2 mixture of isopropanol/hexafluoro-2-propanol was used in order to combine high polarity with product solubility and to avoid side




**Scheme 12:** Suzuki cross-coupling of compound **16**. Conditions: $Pd(PPh_3)_2Cl_2$, 2 M $Na_2CO_3$, DMF, 80 °C, 3 d.




**Scheme 13:** Hydrogenolysis of compound **27** and samarium diiodide-mediated reaction leading to compounds **30** and **31**. Conditions: a) $H_2$, Pd/C, TFA, HFIP, iPrOH, 8 h, rt; b) $SmI_2$ (0.1 M in THF), MeOH, 30 min, rt. HFIP = hexafluoro-2-propanol.

product formation [26]. The ratio of mono-benzylated **28** and fully deprotected *p*-terphenyl derivative **29** was 59:41 as confirmed by $^1$H NMR spectroscopy of the crude product. The reaction mixture was directly filtered through a pad of Celite® and the solvents were removed in vacuo to provide a crude product that was used for the subsequent samarium diiodide-mediated reduction without any purification. This reaction proceeded smoothly and furnished the very polar compounds **30** and **31**. Removal of the formed samarium salts by size exclusion chromatography provided the two divalent carbohydrate mimetics in very good overall yield. The considerably better yield in this samarium diiodide-mediated reaction is probably due to the good solubility of compounds **28** and **29** in methanol/THF.

In summary, by optimizing the protective group strategy and the reductive cleavage methods we were able to prepare the desired rigid *p*-terphenyl-linked carbohydrate mimetic **30** in twelve steps starting from D-isoascorbic acid, but in only six steps with respect to crucial intermediate **4**. The overall yields of 6% or 13% are quite respectable. The distance between the two terminal amino groups is in the range of 2.0 nm (according to optimized molecular geometry obtained by MM2 calculations performed by ChemBio3D Ultra 11.0 from ChemBioOffice 2008).

## Conclusion

We successfully established methods for the efficient preparation of phenyl-substituted aminopyrans and rigid divalent *p*-terphenyl-linked *C*-aryl glycoside using Suzuki cross-couplings as key method. Starting from the D-isoascorbic acid-derived diol **8**, which was converted into the corresponding *p*-bromophenyl-substituted (*Z*)-nitrone, a stereoselective [3 + 3]-cyclization with lithiated TMSE-allene provided the required 1,2-oxazine **4** in six steps with an overall yield of 46%. Alternatively, this 1,2-oxazine could be obtained under the formation of a 4-bromophenyl-1',3'-dioxolane moiety from diol **10** (actually derived from D-mannitol) which is a promising route to differently substituted 1,2-oxazines, introducing the dioxolane substituent at a late stage. The Lewis acid-induced rearrangement of the 1,2-oxazine **4** afforded the bicyclic ketone **11** which can be regarded as an internally protected amino sugar. After subsequent reduction of the carbonyl group the resulting bicyclic compound **12** was used as substrate for Suzuki cross-couplings to form a biphenyl-substituted aminopyran or rigid *C*-aryl dimers in good yields. These *p*-terphenyl-linked aminopyran derivatives **22**, **30** and **31** have a dimension of approximately 2.0 nm.

*p*-Bromophenyl-substituted intermediates such as **15** or **16** are also useful precursors for the synthesis of other *C*-aryl glycosides with potential biological activity. By simple hydrogenolysis of the bicyclic compounds, three new aminopyrans could be synthesized. Different methods for N–O bond cleavage like palladium-catalyzed hydrogenolysis, zinc/acid or samarium diiodide were tested. For each of the substrates the suitable method has to be found. By the N–O bond cleavage of compound **12a** with samarium diiodide an unexpected bicyclic

pyrrolidine derivative **24** was isolated. The prepared unnatural *C*-aryl glycosides could find applications in medicinal chemistry, e.g., as selectin inhibitors. After O-sulfation the biological activity of these divalent compounds will be studied together with that of related carbohydrate mimetics.

## Experimental

For general methods: See Supporting Information File 1

## Supporting Information

### Supporting Information File 1

Experimental procedures.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-182-S1.pdf]

### Supporting Information File 2

Characterization data $^{1}$H NMR and $^{13}$C NMR spectra of synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-182-S2.pdf]

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## License and Terms

# Supporting Information File 1

# for

# Synthesis of rigid *p*-terphenyl-linked carbohydrate mimetics

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## Experimental procedures

**Table of contents:**

**General information**

Reactions were generally performed under inert atmosphere (argon) in flame-dried flasks. Solvents and reagents were added by syringe. Solvents were dried using standard procedures and were purified with a MB SPS-800-dry solvent system. Triethylamine was distilled from $CaH_2$ and stored over KOH under argon atmosphere. Commercial available reagents were used as received without further purification unless otherwise stated. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck or Fluka) or by size exclusion chromatography (Sephadex™ LH-20, GE Healthcare). Unless otherwise stated, yields refer to analytical pure samples. Hydrogenolyses were performed with hydrogen from Air Liquide (Alphagaz 2). TLC-analyses were performed on silica gel coated aluminium plates purchased from Merck. Products were detected by UV-activity and by using staining reagents (Cer/molybdenum reagent, $KMnO_4$ and ninhydrine). NMR spectra were recorded on BRUKER (AV 500, AV 700) and JEOL (ECP 500) instruments. Chemical shifts (δ) are listed in parts per million (ppm) and are reported relative to solvent residual signals: $CDCl_3$ ($^1$H: δ = 7.26 ppm, $^{13}$C: δ = 77.16 ppm), $CD_3OD$ ($^1$H: δ = 3.31 ppm, $^{13}$C: δ = 49.00 ppm) or pyridine-$d^5$ ($^1$H: δ = 8.74 ppm, $^{13}$C: δ = 150.35 ppm). Integrals are in accordance with assignments; coupling constants (*J*) are given in Hz. All $^{13}$C NMR spectra are proton–decoupled. Multiplicity is indicated as follows: s (singlet), $s_{br}$ (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), m (multiplet), $m_c$ (centered multiplet). For detailed peak assignments 2D spectra were measured (COSY and HMQC). The given ratios of diastereomers were calculated by comparison of the 2'-H peaks. IR spectra were measured with a Jasco spectrometer (FT/IR-4100 with DLATGS Detector). HRMS analyses were performed with Agilent 6210

(ESI–TOF, 10 µL/min, 1.0 bar, 4 kV) and Varian/Agilent Ionspec QFT-7 (ESI–FTICR, 4 µL/min, 1.0 bar, 4 kV) instruments. Elemental analyses were carried out with instruments from PerkinElmer (CHN-Analyzer 2400) and from Elementar (Vario, Vario EL, Vario EL III). Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected.

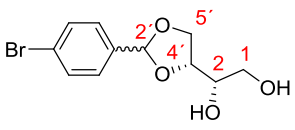
**Additional experimental procedures and analytical data**

The following compounds were prepared analogously to literature procedures: ester **1** [1], TMSE-allene **5** [2], *N*-benzylhydroxylamine [3], samarium(II) iodide [4] and 1,2-oxazine **10** [5].

**(*S*)-1-[(*R*)-2-(4´-Bromophenyl)-1´,3´-dioxolan-4-yl]ethane-1,2-diol (8)**

Under an argon atmosphere, lithium aluminum hydride (3.21 g, 84.6 mmol) was suspended in dry THF (525 mL) at 0 °C. Ester **7** (21.6 g, 65.1 mmol), dissolved in dry THF (220 mL), was dropwise added to the lithium aluminum hydride suspension. After 1 h stirring at rt, the solution was cooled to 0 °C and slowly quenched with water (30 mL). Then, 20% aq. NaOH solution (22 mL) and water (37 mL) were added and the suspension was stirred for further 4 h at rt. The suspension was filtered through a pad of Celite®. The filtrate was extracted with diethyl ether (3 x 500 mL) and the combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:3) to yield **8** (18.8 g, quant.) as a colorless solid.

The obtained two diastereomers (d.r. 52:48) were not separated.



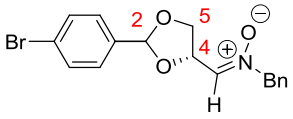

mp 81-83 °C; $[\alpha]_D^{22}$ -0.1 (*c* 1.00, $CH_3OH$); signals with * refer to the major diastereomer: $^1$H NMR (500 MHz, $CDCl_3$): δ 2.61 ($s_{br}$, 2 H, OH, OH*), 3.00, 3.06 (2 $s_{br}$, 2 H, OH, OH*), 3.62-3.67 (m, 2 H, 1-H, 1-H*), 3.74-3.86 (m, 4 H, 1-H, 1-H*, 2-H, 2-H*), 4.00 (dd, *J* = 6.6,

8.3 Hz, 1 H, 4´-H*), 4.07-4.18 (m, 4 H, 5´-H, 5´-H*), 4.20 (dd, $J$ = 6.4, 8.4 Hz, 1 H, 4´-H), 5.72 (s, 1 H, 2´-H), 5.88 (s, 1 H, 2´-H*), 7.30-7.34 (m, 4 H, Ar, Ar*), 7.49-7.52 (m, 4 H, Ar, Ar*) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 63.5, 63.6 (2 t, C-1, C-1*), 67.4, 67.5 (2 d, C-4´, C-4`*), 72.0, 72.2 (2 d, C-2, C-2*), 76.1, 76.7 (2 t, C-5´, C-5´*), 103.1, 103.3 (2 d, C-2´, C-2´*), 123.4, 123.6 (2 s, Ar, Ar*), 128.0, 128.2, 131.5, 131.6 (4 d, Ar, Ar*), 135.9, 136.8 (2 s, Ar, Ar*) ppm; IR (ATR) $\tilde{\nu}$: 3410-3035 (O-H), 3090-3030 (=C-H), 2955-2870 (C-H), 1580 (Ar), 1250 (C-O) cm$^{-1}$; ESI-TOF ($m/z$): $[M + Na]^+$ calcd. for $C_{11}H_{13}BrO_4Na$, 310.9898; found, 310.9895; $[2M + Na]^+$ calcd. for $C_{22}H_{26}Br_2O_8Na$, 600.9881; found, 600.9872; anal. calcd for $C_{11}H_{13}BrO_4$ (289.1): C, 45.70; H, 4.53; found: C, 45.53; H, 4.50.

**(*Z*)-*N*-{[(2*S*,4*S*)-2-(4-Bromophenyl)-1,3-dioxolan-4-yl]methylene}-1-phenylmethanamine oxide (6a) and (*Z*)-*N*-{[(2*R*,4*S*)-2-(4-bromophenyl)-1,3-dioxolan-4-yl]methylene}-1-phenylmethanamine oxide (6b)**

Compound **8** (17.3 g, 59.9 mmol) was dissolved in a mixture of acetonitrile and water (185 mL, 125 mL) and sodium periodate (23.1 g, 108 mmol) was added at 0 °C in small portions. The suspension was stirred for 1 h at rt and the insoluble salts were filtered off. The filtrate was extracted with dichloromethane (3 x 300 mL) and the combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was dissolved in dichloromethane (180 mL) and *N*-benzylhydroxylamine (9.30 g, 75.5 mmol) and magnesium sulfate (10.8 g) were added. The suspension was stirred over night at rt, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:1) to yield **6**

(17.3 g, 80%, d.r. 52:48) as a colorless solid. For analytical characterization small samples of pure diastereomers were obtained by a second column chromatography.




**Diastereomer 6a:**

melting range 105-109 °C; $[\alpha]_D^{22}$ -1.4 (*c* 1.20, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 3.87 (dd, *J* = 6.8, 8.5 Hz, 1 H, 5-H), 4.55 (dd, *J* = 7.3, 8.5 Hz, 1 H, 5-H), 4.89 (s, 2 H, $NCH_2$), 5.21-5.27 (m, 1 H, 4-H), 5.84 (s, 1 H, 2-H), 6.93 (d, *J* = 4.5 Hz, 1 H, N=CH), 7.29-7.32 (m, 2 H, Ar), 7.36-7.41 (m, 5 H, Ph), 7.49-7.51 (m, 2 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 68.8 (t, $NCH_2$), 69.0 (t, C-5), 72.3 (d, C-4), 103.3 (d, C-2), 123.5 (s, Ar), 128.0, 129.1, 129.3, 129.5, 131.5 ( 5 d, Ph, Ar), 131.8, 136.0 (2 s, Ar, Ph), 138.0 (d, N=CH) ppm; IR (ATR) $\tilde{\nu}$: 3080-2830 (=C-H, C-H), 1600 (C=C, C=N), 1210 (C-O) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + Na]^+$ calcd for $C_{17}H_{16}BrNO_3Na$, 384.0211; found, 384.0191; $[2M + Na]^+$ calcd for $C_{34}H_{32}Br_2N_2O_6Na$, 747.0504; found, 747.0484; anal. calcd for $C_{17}H_{16}BrNO_3$ (362.2): C, 56.37; H, 4.45; N, 3.87; found: C, 56.38; H, 4.68; N, 4.07.

**Diastereomer 6b:**

melting range 109-114 °C; $[\alpha]_D^{22}$ +7.6 (*c* 1.05, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 4.08-4.12 (m, 1 H, 5-H), 4.35 (dd, *J* = 7.9, 8.4 Hz, 1 H, 5-H), 4.85 (s, 2 H, $NCH_2$), 5.23 (td, *J* = 4.7, 7.9 Hz, 1 H, 4-H), 5.75 (s, 1 H, 2-H), 6.84 (d, *J* = 4.7 Hz, 1 H, N=CH), 7.28-7.30 (m, 2 H, Ar), 7.34-7.40 (m, 5 H, Ph), 7.47-7.49 (m, 2 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 68.9 (t, $NCH_2$), 69.3 (t, C-5), 72.5 (d, C-4), 103.5 (d, C-2), 123.5 (s, Ar), 128.0, 129.0, 129.2, 129.3, 131.5 (5 d, Ar, Ph), 131.9, 135.6 (2 s, Ar, Ph),

138.2 (d, N=CH) ppm; IR (ATR): $\tilde{\nu}$ 3070-2865 (=C-H, C-H), 1590 (C=C, C=N), 1155 (C-O) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + Na]^+$ calcd for $C_{17}H_{16}BrNO_3Na$, 384.0211; found, 384.0220; $[2M + Na]^+$ calcd for $C_{34}H_{32}Br_2N_2O_6Na$, 747.0504; found, 747.0510; anal. calcd for $C_{17}H_{16}BrNO_3$ (362.2): C, 56.37; H, 4.45; N, 3.87; found: C, 56.51; H, 4.29; N, 3.90.

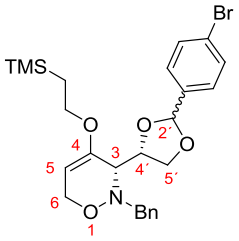
**(3*S*)-2-Benzyl-3-[(2*S*,4*S*)-2-(4-bromophenyl)-1,3-dioxolan-4-yl]-4-[2-(trimethylsilyl)-ethoxy]-3,6-dihydro-2*H*-1,2-oxazine (4a) and (3*S*)-2-benzyl-3-[(2*R*,4*S*)-2-(4-bromo-phenyl)-1,3-dioxolan-4-yl]-4-[2-(trimethylsilyl)ethoxy]-3,6-dihydro-2*H*-1,2-oxazine (4b)**

**Procedure 1:**

Under an argon atmosphere, allene **5** (86 mg, 0.55 mmol) was dissolved in THF (2 mL) and cooled to -40 °C. Then *n*-BuLi (0.22 mL, 2.5 M in THF, 0.55 mmol) was added dropwise, the solution was stirred for 10 min at -40 °C and then cooled to -78 °C. Nitrone **6** (100 mg, 0.276 mmol) was dissolved in THF (1 mL) and added dropwise to the solution of deprotonated allene. The mixture was stirred for 1.5 h at -78 °C and then quenched with water (5 mL) at -78 °C. The solution was allowed to warm up to rt and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 20:1) to yield the two diastereomers **4a** (50 mg, 35%) and **4b** (46 mg, 32%), both as colorless solids. The yields of reactions in large scale are 43-56%.

**Procedure 2:**

4-Bromobenzaldehyde dimethyl acetal (1.90 mL, 11.4 mmol) and cerium ammonium nitrate (5 mg, 0.010 mmol) were dissolved in dichloromethane (1 mL) and stirred for 15 min at rt. 1,2-Oxazine **10** (400 mg, 1.14 mmol) was added and the mixture was stirring for 3 d at rt. Sat. aq. $NaHCO_3$ solution (50 mL) was added, the layers were separated and the water layer was extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 20:1) to yield **4a** (22 mg, 4%) and **4b** (238 mg, 40%), both as colorless solids.




**Diastereomer 4a:**

mp 73-75 °C; $[\alpha]_D^{22}$ +41.0 (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 9 H, $SiMe_3$), 0.98-1.10 (m, 2 H, $Me_3SiCH_2$), 3.32 (d, *J* = 6.5 Hz, 1 H, 3-H), 3.73-3.86 (m, 2 H, $Me_3SiCH_2CH_2$), 4.08-4.20 (m, 5 H, $NCH_2$, 5´-H, 6-H), 4.41-4.45 (m, 1 H, 5´-H), 4.67-4.71 (m, 1 H, 4´-H), 4.76-4.77 (m, 1 H, 5-H), 5.85 (s, 1 H, 2´-H), 7.25-7.27 (m, 1 H, Ph), 7.30-7.33 (m, 2 H, Ph), 7.36-7.37 (m, 2 H, Ar), 7.40-7.42 (m, 2 H, Ph), 7.50-7.51 (m, 2 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ -1.4 (q, $SiMe_3$), 17.4 (t, $Me_3SiCH_2$), 58.3 (t, $NCH_2$), 63.0 (d, C-3), 63.0 (t, $Me_3SiCH_2CH_2$), 64.5 (t, C-6), 68.0 (t, C-5´), 75.3 (d, C-4´), 93.2 (d, C-5), 102.8 (d, C-2´), 123.0 (s, Ar), 127.1, 128.2, 128.2, 128.7, 131.4 (5 d, Ph, Ar), 137.6, 137.7 (2 s, Ar, Ph), 149.8 (s, C-4) ppm; IR (ATR): $\tilde{\nu}$ 3085 (=C-H), 2950-2830 (C-

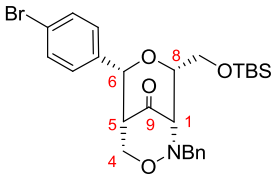
H), 1675 (C=C), 1250 (C-O) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{32}BrNO_4SiNa$, 542.1158; found, 542.1217; $[2M + Na]^+$ calcd for $C_{50}H_{64}Br_2N_2O_8Si_2Na$, 1059.2469; found, 1059.2520; anal. calcd for $C_{25}H_{32}BrNO_4Si$ (518.5): C, 57.91; H, 6.22; N, 2.70; found: C, 57.75; H, 6.15; N, 2.72.

**Diastereomer 4b:**

melting range 84-89 °C; $[\alpha]_D^{22}$ +3.2 (*c* 1.25, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 0.03 (s, 9 H, $SiMe_3$), 0.92-1.05 (m, 2 H, $Me_3Si\mathit{CH_2}$), 3.30-3.33 (m, 1 H, 3-H), 3.70-3.75 (m, 1 H, $Me_3SiCH_2\mathit{CH_2}$), 3.77-3.83 (m, 1 H, $Me_3SiCH_2\mathit{CH_2}$), 3.96 (dd, *J* = 6.6, 8.0 Hz, 1 H, 5´-H), 4.07 (t, *J* = 8.0 Hz, 1 H, 5´-H), 4.16-4.21 (m, 3 H, $NCH_2$, 6-H), 4.43-4.47 (m, 1 H, 6-H), 4.68 ($m_c$, 1 H, 4´-H), 4.74-4.76 (m, 1 H, 5-H), 5.82 (s, 1 H, 2´-H), 7.25-7.31 (m, 5 H, Ar, Ph), 7.39-7.40 (m, 2 H, Ar, Ph), 7.44-7.46 (m, 2 H, Ar) ppm; $^{13}C$ NMR (125 MHz, $CDCl_3$): δ -1.5 (q, $SiMe_3$), 17.4 (t, $Me_3Si\mathit{CH_2}$), 58.0 (t, $NCH_2$), 62.9 (d, C-3), 64.4 (t, C-6), 67.1 (t, $Me_3SiCH_2\mathit{CH_2}$), 72.0 (t, C-5´), 76.5 (d, C-4´), 93.1 (d, C-5), 102.9 (d, C-2´), 123.0 (s, Ar), 127.1, 128.2, 128.3, 128.7, 131.3 (5 d, Ar, Ph), 137.4, 137.5 (2 s, Ar, Ph), 149.5 (s, C-4) ppm; IR (ATR): $\tilde{\nu}$ 3065 (=C-H), 2950 (C-H), 1670 (C=C), 1250 (C-O) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{32}BrNO_4SiNa$, 542.1158; found, 542.1172; $[2M + Na]^+$ calcd for $C_{50}H_{64}Br_2N_2O_8Si_2Na$, 1059.2469; found, 1059.2446; anal. calcd for $C_{25}H_{32}BrNO_4Si$ (518.5): C, 57.91; H, 6.22; N, 2.70; found: C, 57.96; H, 6.32; N, 2.67.

**(1*S*,5*R*,6*R*,8*S*)-2-Benzyl-6-(4-bromophenyl)-8-[(*tert*-butyldimethylsiloxy)methyl]-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-one (11)**

1,2-Oxazine **4** (5.05 g, 9.74 mmol) was dissolved in acetonitrile (70 mL) and cooled to -30 °C. Tin(IV) chloride (7.61 g, 3.43 mL, 29.2 mmol) was added and the solution was stirred for 18 h and allowed to warm to rt. The mixture was quenched with water (60 mL) and extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was dissolved in THF (80 mL), imidazole (1.33 g, 19.5 mmol) and *tert*-butyldimethylsilyl chloride (2.20 g, 14.6 mmol) were added and the mixture was stirred for 4 h at rt. The salts were filtered off and the solvent was removed in vacuo. The crude product was extracted with diethyl ether (3 x 150 mL). The combined organic layers were dried with $Na_2SO_4$, filtered, the solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel, hexanes/EtOAc 30:1) to yield **11** (4.22 g, 82%) as a colorless oil.




$[\alpha]_D^{22}$ +120.2 (*c* 1.28, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 0.02, 0.04 (2 s, 3 H each, SiMe), 0.85 (s, 9 H, Si*t*-Bu), 2.71-2.75 (m, 1 H, 5-H), 3.54-3.56 (m, 1 H, 1-H), 3.88 (ddd, *J* = 1.5, 5.1, 7.9 Hz, 1 H, 8-H), 3.94 (dd, *J* = 5.1, 9.5 Hz, 1 H, 8-$CH_2$), 4.01 (d, *J* = 13.8 Hz, 1 H, $NCH_2$), 4.09-4.19 (m, 3 H, 8-$CH_2$, $NCH_2$, 4-H), 4.25 (dd, *J* = 5.6, 12.0 Hz, 1 H, 4-H), 4.89 (s, 1 H, 6-H), 7.25-7.36 (m, 7 H, Ar, Ph), 7.48-7.50 (m, 2 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ -5.32, -5.26 (2 q, SiMe), 18.3, 25.9 (q, s, Si*t*-Bu), 55.3 (d,

C-5), 60.5 (t, $NCH_2$), 61.4 (t, 8-$CH_2$), 67.2 (t, C-4), 70.8 (d, C-1), 81.2 (d, C-6), 81.6 (d, C-8), 122.0 (s, Ar), 127.6, 127.7, 128.6, 128.9, 131.8 (5 d, Ar, Ph), 136.3, 137.2 (2 s, Ar, Ph), 207.9 (s, C-9) ppm; IR (ATR): $\tilde{\nu}$ 3065 (=C-H), 2950-2855 (C-H), 1730 (C=O) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{26}H_{35}BrNO_4Si$, 534.1498; found, 534.1540; $[M + Na]^+$ calcd for $C_{26}H_{34}BrNO_4SiNa$, 556.1318; found, 556.1356; anal. calcd for $C_{26}H_{34}BrNO_4Si$ (532.5): C, 58.64; H, 6.44; N, 2.63; found: C, 57.97; H, 6.51; N, 2.50.

**(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-6-(4-bromophenyl)-8-[(*tert*-butyldimethylsiloxy)methyl]-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (12a) and (1*R*,5*S*,6*R*,8*S*,9*S*)-2-benzyl-6-(4-bromophenyl)-8-[(*tert*-butyldimethylsiloxy)methyl]-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (12b)**

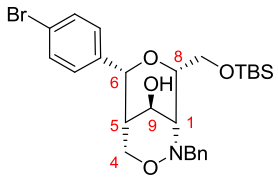
**Procedure 1:**

At 0 °C compound **11** (500 mg, 0.939 mmol) was dissolved in ethanol (14 mL), sodium borohydride (71 mg, 1.88 mmol) was added and the mixture stirred for 3 h at -40 °C. The solvent was then removed in vacuo and water (50 mL) and dichloromethane (80 mL) were added and the crude product was extracted with dichloromethane (4 x 80 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 5:1) to yield **12a** (315 mg, 63%) and **12b** (46 mg, 9%) as colorless solids.

**Procedure 2:**

Compound **11** (680 mg, 1.28 mmol) was dissolved in THF (20 mL), at -10 °C L-selectride (1.92 mL, 1 M in THF, 1.92 mmol) was added dropwise and the solution was stirred for 1 h at -10 °C. The mixture was quenched with sat. aq. $NH_4Cl$ solution (30 mL) and the aqueous layer was extracted with diethyl ether (4 x 80 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvents removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 5:1) to yield **12a** (501 mg, 73%) as a colorless solid.

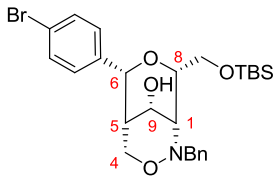
**Diastereomer 12a:**




mp 140-143 °C; $[\alpha]_D^{22}$ +25.2 (*c* 1.04, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 0.11, 0.12 (2 s, 3 H each, SiMe), 0.93 (s, 9 H, Si*t*-Bu), 2.05 ($s_{br}$, 1 H, 5-H), 3.30 ($s_{br}$, 1 H, 1-H), 3.68 (dd, $J$ = 1.3, 12.2 Hz, 1 H, 4-H), 3.76 (d, $J$ = 10.7 Hz, 1 H, OH), 3.85 (dd, $J$ = 6.9, 8.9 Hz, 1 H, 8-H), 3.98-4.07 (m, 4 H, 4-H, 9-H, 8-$CH_2$), 4.13 (AB system, $J_{AB}$ = 15.1 Hz, 1 H, $NCH_2$), 4.35 (AB system, $J_{AB}$ = 15.1 Hz, 1 H, $NCH_2$), 4.74 (s, 1 H, 6-H), 7.24-7.29 (m, 3 H, Ph), 7.32-7.36 (m, 4 H, Ar, Ph), 7.45-7.47 (m, 2 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ -5.4, -5.3 (2 q, SiMe), 18.1, 25.8 (q, s, Si*t*-Bu), 40.8 (d, C-5), 60.2 (d, C-1), 61.6 (t, $NCH_2$), 62.4 (t, 8-$CH_2$), 64.8 (t, C-4), 70.3 (d, C-8), 78.9 (d, C-6), 79.7 (d, C-9), 121.0 (s, Ar), 127.1, 127.5, 128.0, 128.3, 131.3 (5 d, Ar, Ph), 138.3 139.0 (2 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ 3555-3135 (O-H), 3095-3030 (=C-H), 2960-2855 (C-H), 1250 (C-O) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{26}H_{37}BrNO_4Si$, 534.1675; found, 534.1680;

[M + Na]$^+$ calcd for $C_{26}H_{36}BrNO_4SiNa$, 558.1474; found, 558.1481; anal. calcd for $C_{26}H_{36}BrNO_4Si$ (534.6): C, 58.42; H, 6.79; N, 2.62; found: C, 58.31; H, 5.98; N, 2.98.

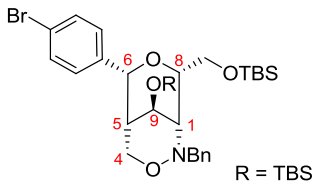
**Diastereomer 12b:**




Melting range 161-165 °C; $[\alpha]_D^{22}$ +61.7 (*c* 1.37, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 0.05, 0.07 (2 s, 3 H each, SiMe), 0.87 (s, 9 H, Si*t*-Bu), 1.85 ($s_{br}$, 1 H, 5-H), 2.98 ($s_{br}$, 1H, 1-H), 3.67 (d, *J* = 12.2 Hz, 1 H, 4-H), 3.90-4.01 (m, 4 H, 4-H, 8-$CH_2$, OH), 4.09 (t, *J* = 8.9 Hz, 1H, 8-H), 4.16 (AB system, $J_{AB}$ = 14.3 Hz, 1 H, $NCH_2$), 4.29 (AB system, $J_{AB}$ = 14.3 Hz, 1 H, $NCH_2$), 4.68 (t, *J* = 3.7 Hz, 1 H, 9-H), 5.27 (s, 1 H, 6-H), 7.23-7.36 (m, 7 H, Ar, Ph), 7.42-7.49 (m, 2 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ -5.3, -5.2 (2 q, SiMe), 18.3, 25.9 (q, s, Si*t*-Bu), 41.5 (d, C-5), 57.6 (d, C-1), 58.2 (t, $NCH_2$), 62.4 (d, C-8), 62.8 (t, 8-$CH_2$), 64.1 (d, C-9), 64.3 (t, C-4), 72.7 (d, C-6), 79.7 (d, C-9), 120.8 (s, Ar), 127.2, 127.9, 128.3, 128.6, 131.2 (5 d, Ar, Ph), 131.3, 131.6 (2 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ 3515-3340 (O-H), 3090-3030 (=C-H), 2950-2855 (C-H), 1250 (C-O) cm$^{-1}$; ESI-TOF (*m*/*z*): [M + H]$^+$ calcd for $C_{26}H_{37}BrNO_4Si$, 534.1675; found, 534.1678; [M + Na]$^+$ calcd for $C_{26}H_{36}BrNO_4SiNa$, 558.1474; found, 558.1478; anal. calcd for $C_{26}H_{36}BrNO_4Si$ (534.6): C, 58.42; H, 6.79; N, 2.62; found: C, 59.51; H, 6.69; N, 2.44.

**(1*S*,5*R*,6*R*,8*S*,9*R*)-2-Benzyl-6-(4-bromophenyl)-9-(*tert*-butyldimethylsiloxy)-8-[(*tert*-butyldimethylsiloxy)methyl]-3,7-dioxa-2-azabicyclo[3.3.1]nonane (13)**

Compound **12a** (277 mg, 0.518 mmol) was dissolved in dichloromethane (1.5 mL), 2,6-lutidine (0.11 mL, 0.932 mmol) was added and the mixture was cooled to 0 °C. *tert*-butyldimethylsilyl triflate (0.12 mL, 0.673 mmol) was added dropwise and the solution was stirred for 2 h at 0 °C. The mixture was quenched with sat. aq. $NH_4Cl$ solution (20 mL) and the aqueous layers were extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 30:1) to yield **13** (336 mg, quant.) as a colorless oil.



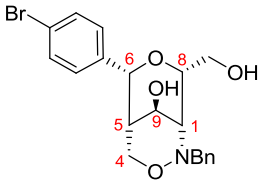

$[\alpha]_D^{22}$ +71.5 (*c* 1.12, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 0.06, 0.08, 0.17, 0.19 (4 s, 3 H each, SiMe), 0.88, 1.00 (2 s, 9 H each, Si*t*-Bu),1.65 ($m_c$, 1 H, 5 H), 3.00 ($s_{br}$, 1 H, 1-H), 3.22 (d, *J* = 11.8 Hz, 1 H, 4-H), 3.85 (ddd, *J* = 1.8, 5.1, 7.2 Hz, 1 H, 8-H), 3.92 (dd, *J* = 5.1, 9.6 Hz, 1 H, 8-$CH_2$), 4.10 ($m_c$, 1 H, 9-H), 4.11 (d, *J* = 14.7 Hz, 1 H, $NCH_2$), 4.17 (dd, *J* = 7.2, 9.6 Hz, 1 H, 8-$CH_2$), 4.47 (dt, *J* = 1.7, 11.8 Hz, 1 H, 4-H), 4.86 (d, *J* = 14.7 Hz, 1 H, $NCH_2$), 4.87 ($s_{br}$, 1 H, 6-H), 7.21-7.24 (m, 1 H, Ph), 7.29-7.32 (m, 4 H, Ph), 7.38-7.39 (m, 2 H, Ar), 7.43-7.45 (m, 2 H, Ar) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz): δ -5.13, -5.06, -4.7, -4.5 (4 q, SiMe), 18.2, 18.4 (2 s, Si*t*-Bu), 25.9, 26.1 (2 q, Si*t*-Bu), 42.4 (d, C-5), 56.0 (t, C-4), 58.7 (t, $NCH_2$), 58.8 (d, C-1), 63.3 (t, 8-$CH_2$), 70.4 (d, C-9), 79.8 (d, C-6), 80.2 (d, C-8), 121.3 (s, Ar), 127.0, 128.3, 128.3, 128.6, 131.4 (5 d, Ph, Ar), 139.4, 139.6 (2 s,

Ph, Ar) ppm; IR (ATR): $\tilde{\nu}$ 3090-3025 (=C-H), 2955-2855 (C-H), 1250 (C-O) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{32}H_{51}BrNO_4Si_2$, 648.2535; found, 648.2574; $[M + Na]^+$ calcd for $C_{32}H_{50}BrNO_4Si_2Na$, 670.2354, found, 670.2395; anal. calcd for $C_{32}H_{50}BrNO_4Si_2$ (648.8): C, 59.24; H, 7.77; N, 2.16; found: C, 59.48; H, 7.78; N, 2.16.

**(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-6-(4-bromophenyl)-8-(hydroxymethyl)-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (15a) and (1*R*,5*S*,6*R*,8*S*,9*S*)-2-benzyl-6-(4-bromophenyl)-8-(hydroxymethyl)-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (15b)**

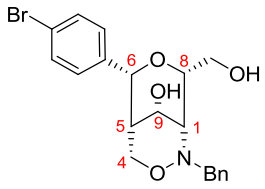
1,2-Oxazine **4** (2.00 g, 3.86 mmol) was dissolved in acetonitrile (20 mL) and cooled to −30 °C. Tin(IV) chloride (3.02 g, 1.36 mL, 11.6 mmol) was added and the solution was stirred for 18 h and allowed to warm up to rt. The mixture was quenched with water (40 mL) and the aqueous layer extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was dissolved in THF (30 mL) and cooled to -15 °C. L-selectride (4.63 mL, 1 M in THF, 4.63 mmol) was added dropwise and the solution was stirred for 1 h at -15 °C. The mixture was quenched with sat. aq. $NH_4Cl$ solution (50 mL) and the aqueous layer extracted with diethyl ether (5 x 80 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:1 → 1:2) to yield **15a** (254 mg, 16%) and **15b** (685 mg, 42%) as colorless solids.

**Diastereomer 15a:**



mp 58-60 °C; $[\alpha]_D^{22}$ +88.9 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 2.02 ($m_c$, 1 H, 5-H), 2.60 ($s_{br}$, 1 H, OH), 3.08 ($m_c$, 1 H, 1-H), 3.60 ($s_{br}$, 1 H, OH), 3.66 (dd, *J* = 2.3, 12.3 Hz, 1 H, 4-H), 3.81-3.85 (m, 2 H, 8-H, 8-$CH_2$), 4.03-4.13 (m, 3 H, 4-H, 8-$CH_2$, 9-H), 4.09 (AB system, $J_{AB}$= 14.0 Hz, 1 H, $NCH_2$), 4.29 (AB system, $J_{AB}$= 14.0 Hz, 1 H, $NCH_2$), 4.75 (s, 1 H, 6-H), 7.24-7.29 (m, 3 H, Ph), 7.33-7.34 (m, 4 H, Ar, Ph), 7.45-7.48 (m, 2 H, Ar) ppm; $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 40.8 (d, C-5), 61.3 (d, C-1), 61.6 (t, $NCH_2$), 64.0 (t, 8-$CH_2$), 64.2 (t, C-4), 70.3 (d, C-9), 79.2 (d, C-6), 79.9 (d, C-8), 121.4 (s, Ar), 127.7, 128.6, 128.7, 131.6 (4 d, Ar, Ph), 137.3, 138.9 (2 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ 3530-3210 (O-H), 2920-2850 (C-H), 1070 (C-O) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{23}BrNO_4$, 420.0810; found, 420.0807; $[M + Na]^+$ calcd for $C_{20}H_{22}BrNO_4Na$, 442.0630; found, 442.0630; anal. calcd for $C_{20}H_{22}BrNO_4$ (420.3): C, 57.15; H, 5.28; N, 3.33; found: C, 57.30; H, 5.42; N, 3.48.

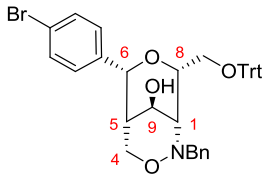
**Diastereomer 15b:**




mp 197-198 °C; $[\alpha]_D^{22}$ +125.4 (*c* 0.95, $CHCl_3$/MeOH, 9:1); $^1H$ NMR ($CDCl_3$/$CD_3OD$, 6:1, 700 MHz): δ 1.81 ($m_c$, 1 H, 5-H), 2.80 ($s_{br}$, 1 H, 1-H), 3.61 (dd, *J* = 1.4, 12.3 Hz, 1 H, 4-H), 3.79 (dd, *J* = 4.2, 11.6 Hz, 1 H, 8-$CH_2$), 3.98 (dd, *J* = 5.7, 11.6 Hz, 1 H, 8-$CH_2$), 4.02 (ddd, *J* = 1.4, 2.6, 12.3 Hz, 1 H, 4-H), 4.08 (AB system, *J* = 13.5 Hz, 1 H, $NCH_2$), 4.26 (AB system, *J* = 13.5 Hz, 1 H, $NCH_2$), 4.26 ($m_c$, 1 H, 8-H), 4.85 (t, *J* = 3.8 Hz, 1 H, 9-H), 5.25 (s, 1 H, 6-H), 7.21-7.73 (m, 1 H, Ph), 7.26-7.30 (m, 6 H, Ar, Ph), 7.40-7.41 (m, 2 H, Ar) ppm; $^{13}C$ NMR ($CDCl_3$/$CD_3OD$, 6:1, 175 MHz): δ 41.2 (d, C-5), 57.2 (t, $NCH_2$), 58.7

(d, C-1), 61.5 (d, C-9), 63.7 (t, C-4), 64.5 (t, 8-$CH_2$), 72.8 (d, C-8), 73.0 (d, C-6), 120.9 (s, Ar), 127.8, 127.9, 128.5, 128.6, 131.1 (5 d, Ar, Ph), 137.0, 140.0 (2 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ 3385 (O-H), 3085-3025 (=CH), 2920-2870 (CH), 1490 (CH) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{23}BrNO_4$, 420.0810; found, 420.0824; $[M + Na]^+$ calcd for $C_{20}H_{22}BrNO_4Na$, 442.0630; found, 442.0652; anal. calcd for $C_{20}H_{22}BrNO_4$ (420.3): C, 57.15; H, 5.28; N, 3.33; found: C, 57.52; H, 5.32; N, 3.37.

**(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-6-(4-bromophenyl)-8-(trityloxymethyl)-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (16)**



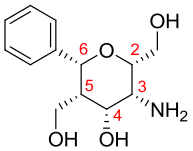

Compound **15a** (360 mg, 0.857 mmol) was dissolved in pyridine (4 mL). Trityl chloride (287 mg, 1.03 mmol) and DMAP (42 mg, 0.343 mmol) were added and the mixture was stirred for 3 d at 60 °C. The mixture was quenched with brine (10 mL) and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvents removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 4:1) to yield **16** (470 mg, 83%) as a colorless solid.

mp 94-96 °C; $[\alpha]_D^{22}$ +17.8 (*c* 1.10, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 2.01 ($s_{br}$, 1 H, 5-H), 3.30 (s, 1 H, 1-H), 3.34 (dd, *J* = 7.8, 8.8 Hz, 1 H, 8-$CH_2$), 3.60 (d, *J* = 12.2 Hz, 1 H,

4-H), 3.83 (dd, *J* = 6.3, 8.8 Hz, 1 H, 8-$CH_2$), 3.84 (AB system, *J* = 14.9 Hz, 1 H, $NCH_2$), 3.91 (AB system, *J* = 14.9 Hz, 1 H, $NCH_2$), 3.96 (dd, *J* = 4.7, 12.2 Hz, 1 H, 4-H), 4.12 ($m_c$, 2 H, 9-H, 8-H), 4.80 (s, 1 H, 6-H), 7.05-7.07 (m, 2 H, Ph, Ar), 7.22-7.28 (m, 14 H, Ph, Ar), 7.45-7.51 (m, 8 H, Ph, Ar) ppm; $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 41.1 (d, C-5), 60.7 (d, C-1), 61.2 (t, $NCH_2$), 64.1 (t, 8-$CH_2$), 64.9 (t, C-4), 70.2 (d, C-9), 78.7 (d, C-8), 79.2 (d, C-6), 87.0 (s, *C*$Ph_3$), 121.2 (s, Ar), 127.2, 127.3, 127.7, 128.0, 128.1, 128.2, 128.3, 128.7, 131.4 (9 d, Ar, Ph), 137.9, 139.2, 143.8 (3 s, Ph, Ar) ppm; IR (ATR): $\tilde{\nu}$ 3555-3300 (O-H), 3025 (=C-H), 2940-2855 (C-H), 1450 ($CH_2$) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{39}H_{37}BrNO_4$, 662.1906; found, 662.1904; $[M + Na]^+$ calcd for $C_{39}H_{36}BrNO_4Na$, 684.1725; found, 684.1721; anal. calcd for $C_{39}H_{36}BrNO_4$ (662.6): C, 70.69; H, 5.48; N, 2.11; found: C, 71.21; H, 6.59; N, 2.13.

**[(2*S*,3*R*,4*R*,5*S*,6*R*)-3-Amino-2,5-di(hydroxymethyl)-6-phenyltetrahydro-2*H*-pyran-4-ol (17a)**

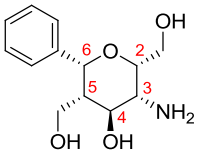
A suspension of Pd/C (10% Pd, 50 mg) and iPrOH (3 mL) was saturated with hydrogen for 15 min. Compound **15a** (50 mg, 0.119 mmol) and $NEt_3$ (12 mg, 0.119 mmol) were dissolved in EtOAc (1 mL) and added to this suspension. The mixture was stirred for 18 h under hydrogen pressure (balloon), filtered through a pad of Celite® and the solvent removed in vacuo. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 15:1) to yield **17a** (25 mg, 83%) as a colorless solid.



mp 163 °C; $[\alpha]_D^{22}$ +71.5 (*c* 0.60, $CH_3OH$); $^1H$ NMR (500 MHz, $CD_3OD$): δ 2.21 ($s_{br}$, 1 H, 5-H), 3.19 (dd, *J* = 4.2, 11.5 Hz, 1 H, 5-$CH_2$), 3.24 (d, *J* = 1.6 Hz, 1 H, 3-H), 3.59-3.64 (m, 2 H, 5-$CH_2$, 2-H), 3.71 (dd, *J* = 5.5, 11.3 Hz, 1 H, 2-$CH_2$), 3.83 (dd, *J* = 6.6, 11.3 Hz, 1 H, 2-$CH_2$), 4.27 (dd, *J* = 4.4, 5.5 Hz, 1 H, 4-H), 4.68 (d, *J* = 2.6 Hz, 1 H, 6-H), 7.21 (C part of AA´BB´C system, $J_{CB}$ = 7.5 Hz, 1 H, Ph), 7.30 (B part of AA´BB´C system, $J_{ABC}$ = 7.5 Hz, 2 H, Ph), 7.44 (A part of AA´BB´C system, $J_{AB}$ = 7.5 Hz, 2 H, Ph) ppm; $^{13}C$ NMR ($CD_3OD$, 175 MHz): δ 47.3 (d, C-5), 50.8 (d, C-3), 56.2 (t, 5-$CH_2$), 63.1 (t, 2-$CH_2$), 73.1 (d, C-4), 80.4 (d, C-2), 82.0 (d, C-6), 127.1, 127.9, 128.9, 141.6 (3 d, s, Ph) ppm; IR (ATR): $\tilde{\nu}$ 3600-3300 (O-H, N-H), 3070-3025 (=C-H), 2930-2855 (C-H) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{13}H_{20}NO_4$, 254.1392; found, 254.1408; $[M + Na]^+$ calcd for $C_{13}H_{19}NO_4Na$, 276.1212; found, 276.1223; anal. calcd for $C_{13}H_{19}NO_4$ (253.3): C, 61.64; H, 7.56; N, 5.53; C, 61.60; H, 7.65; N, 5.66.

**(2*S*,3*R*,4*S*,5*S*,6*R*)-3-Amino-2,5-di(hydroxymethyl)-6-phenyltetrahydro-2*H*-pyran-4-ol (17b)**

A suspension of Pd/C (10% Pd, 69 mg) and iPrOH (3 mL) was saturated with hydrogen for 15 min. Compound **15b** (69 mg, 0.164 mmol) and $NEt_3$ (17 mg, 0.164 mmol) were dissolved in EtOAc (1 mL) and added to this suspension. The mixture was stirred for 18 h under hydrogen pressure (balloon), then filtrated through a pad of Celite® and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 15:1) to yield **17b** (32 mg, 77%) as a colorless solid.

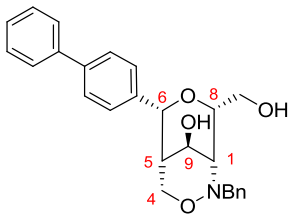



mp 185-188 °C, $[\alpha]_D^{22}$ +46.1 (*c* 1.09, $CH_3OH$); $^1H$ NMR (500 MHz, $CD_3OD$): δ 2.06 (dd, *J* = 4.2, 7.5 Hz, 1 H, 5-H), 3.39 (dd, *J* = 4.2, 11.1 Hz, 1 H, 5-$CH_2$), 3.44 (d, *J* = 4.5 Hz, 1 H, 3-H), 3.45 (dd, *J* = 2.9, 11.1 Hz, 1 H, 5-$CH_2$), 3.93 ($d_{br}$, *J* = 4.7 Hz, 2 H, 2-$CH_2$), 4.17 (td, *J* = 1.8, 4.7 Hz, 1 H, 2-H), 4.32 ($s_{br}$, 1 H, 4-H), 5.17 (d, *J* = 4.2 Hz, 1 H, 6-H), 7.26 (C part of AA´BB´C system, $J_{CB}$ = 7.3 Hz, 1 H, Ph), 7.35 (A part of AA´BB´C system, $J_{AB}$ = 7.3 Hz, 2 H, Ph), 7.43 (B part of AA´BB´C system $J_{BAC}$ = 7.3 Hz, 2 H, Ph) ppm; $^{13}C$ NMR (125 MHz, $CD_3OD$): δ 47.1 (d, C-5), 51.7 (d, C-3), 60.3 (t, 5-$CH_2$), 63.6 (t, 2-$CH_2$), 70.8 (d, C-4), 74.1 (d, C-2), 79.2 (d, C-6), 126.8, 128.1, 129.1, 141.0 (3 d, s, Ph) ppm; IR (ATR): $\tilde{\nu}$ 3435, 3245 (O-H, N-H), 3020 (=C-H), 2930-2830 (C-H) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{13}H_{20}NO_4$, 254.1392; found, 254.1394; $[M + Na]^+$ calcd for $C_{13}H_{19}NO_4Na$, 276.1212; found, 276.1206.

**(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-6-(biphenyl-4-yl)-8-(hydroxymethyl)-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (18)**

Compound **15a** (290 mg, 0.690 mmol), $Pd(PPh_3)_4$ (40 mg, 34.5 µmol) and phenylboronic acid (93 mg, 0.759 mmol) were filled in a sealed tube and flushed with argon. THF (3 mL) and 2 M $Na_2CO_3$ solution (0.69 mL) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt, water (20 mL) added and the aqueous layer extracted with ethyl acetate (3 x 80 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvents removed in vacuo. The crude product was purified by

column chromatography (silica gel, hexanes/EtOAc 1:1) to yield **18** (234 mg, 81%) as a colorless solid.

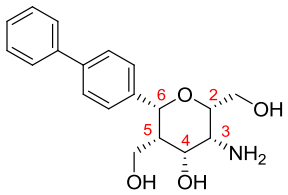



mp 173-175 °C; $[\alpha]_D^{22}$ +91.9 (*c* 1.1, $CH_3OH$); $^1H$ NMR (500 MHz, $CDCl_3$): δ 2.12 (s, 1 H, 5-H), 2.28 ($s_{br}$, 1 H, OH), 3.11 (s, 1 H, 1-H), 3.71 (d, *J* = 10.0 Hz, 1 H, OH), 3.81 (dd, *J* = 1.7, 12.1 Hz, 1 H, 4-H), 3.86-3.89 (m, 2 H, 8-H, 8-$CH_2$), 4.08-4.11 (m, 1 H, 9-H), 4.12-4.13 (m, 1 H, 4-H), 4.14 (d, *J* = 14.1 Hz, 1 H, $NCH_2$), 4.17 (dd, *J* = 8.0, 12.4 Hz, 1 H, 8-$CH_2$), 4.33 (d, *J* = 14.1 Hz, 1 H, $NCH_2$), 4.85 (s, 1 H, 6-H), 7.28-7.31 (m, 1 H, Ph), 7.34-7.39 (m, 5 H, Ph, Ar), 7.43-7.48 (m, 4 H, Ph, Ar), 7.58-7.60 (m, 4 H, Ar) ppm; $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 40.9 (d, C-5), 61.4 (d, C-1), 61.5 (t, $NCH_2$), 64.0 (t, 8-$CH_2$), 64.3 (t, C-4), 70.4 (d, C-9), 79.6 (d, C-6), 79.8 (d, C-8), 126.4, 127.1, 127.2, 127.4, 127.6, 128.6, 128.7, 128.9 (8 d, Ar, Ph), 137.4, 138.9, 140.4, 140.8 (4 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ 3610-3180 (O-H), 3090-3010 (=C-H), 2950-2850 (C-H), 1240 (C-O) $cm^{-1}$; ESI-TOF (*m*/*z*): [M + H] calcd for $C_{26}H_{28}NO_4$, 418.2013; found, 418.2015; [M + Na] calcd for $C_{26}H_{27}NO_4Na$, 440.1838; found, 440.1831; anal. calcd for $C_{26}H_{27}NO_4$ (417.5): C, 74.80; H, 6.52; N, 3.35; found: C, 74.80; H, 6.67; N, 3.73.

**(2*S*,3*R*,4*R*,5*S*,6*R*)-3-Amino-6-(biphenyl-4-yl)-2,5-di(hydroxymethyl)tetrahydro-2*H*-pyran-4-ol (19)**

A suspension of Pd/C (10% Pd, 55 mg) and iPrOH (3 mL) was saturated with hydrogen for 15 min. The bicyclic compound **18** (55 mg, 0.132 mmol) was dissolved in THF

(1 mL), and added to the suspension. The mixture was stirred for 24 h under hydrogen pressure (balloon). The mixture was then filtrated through a pad of Celite® and the solvent was removed in vacuo. The crude material was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 7:1) to yield **19** (26 mg, 60%) as a colourless solid.

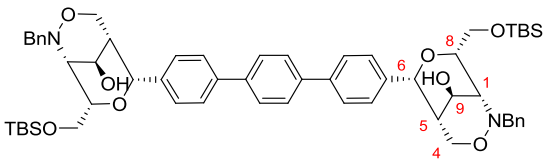



Decomposition >230 °C; $[\alpha]_D^{22}$ +44.4 (*c* 1.00, $CH_3OH/CHCl_3$, 7:3); $^1$H NMR (700 MHz, $CD_3OD/CDCl_3$, 2:1): δ 2.40 (dt, *J* = 3.0, 6.7 Hz, 1 H, 5-H), 3.40 (dd, *J* = 3.0, 11.1 Hz, 1 H, 5-$CH_2$), 3.73 (dd, *J* = 1.7, 4.5 Hz, 1 H, 3-H), 3.88-3.90 (m, 2 H, 2-H, 5-$CH_2$), 4.07 ($m_c$, 2 H, 2-$CH_2$), 4.64 (dd, *J* = 4.5, 6.7 Hz, 1 H, 4-H), 4.98 (d, *J* = 3.6 Hz, 1 H, 6-H), 7.43-7.45 (m, 1 H, Ph), 7.53-7.55 (m, 2 H, Ph), 7.63-7.64 (m, 2 H, Ar), 7.70-7.72 (m, 4 H, Ph, Ar) ppm; $^{13}$C NMR (175 MHz, $CD_3OD/CDCl_3$, 2:1): δ 45.5 (d, C-5), 51.6 (d, C-3), 55.0 (t, 5-$CH_2$), 63.1 (t, 2-$CH_2$), 69.0 (d, C-4), 76.8 (d, C-2), 81.7 (d, C-6), 127.0, 127.4, 127.6, 128.0, 129.5 (5 d, Ph), 139.0, 141.1, 141.6 (3 s, Ph, Ar) ppm; IR (ATR): $\tilde{\nu}$ 3480-3240 (O-H, N-H), 3045-3030 (=C-H), 2950-2850 (C-H) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{19}H_{24}NO_4$, 330.1705; found, 330.1713; $[M + Na]^+$ calcd for $C_{19}H_{23}NO_4Na$, 352.1525; found, 352.1518.

### *p*-Terphenyl derivative 21

Compound **12a** (400 mg, 0.748 mmol), $Pd(PPh_3)_4$ (86 mg, 74.8 µmol) and benzene-1,4-diboronic acid (59 mg, 0.36 mmol) were filled in a sealed tube and flushed with argon.

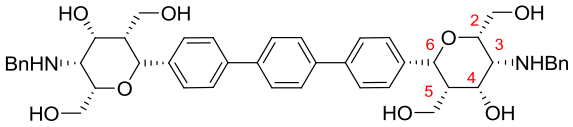
THF (2 mL), DMF (8 mL) and 2 M aq. $Na_2CO_3$ solution (1.5 mL) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt, brine (20 mL) was added and the aqueous layer extracted with ethyl acetate (3 x 80 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvents removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 3:2) to yield **21** (296 mg, 84%) as a yellow solid.




mp 163-165 °C; $[\alpha]_D^{22}$ + 55.6 (*c* 1.10, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 0.12, 0.13 (2 s, 6 H each, SiMe), 0.94 (s, 18 H, Si*t*-Bu), 2.15 ($s_{br}$, 2 H, 5-H), 3.33 (s, 2 H, 1-H), 3.80 (d, *J* = 10.9 Hz, 2 H, OH), 3.84 (dd, *J* = 1.9, 12.0 Hz, 2 H, 4-H), 3.88 (ddd, *J* = 1.0, 5.8, 9.0 Hz, 2 H, 8-H), 4.01-4.12 (m, 8 H, 8-$CH_2$, 9-H, 4-H), 4.15, 4.39 (AB system, $J_{AB}$ = 15.1 Hz, 4 H, $NCH_2$), 4.84 (s, 2 H, 6-H), 7.28-7.29 (m, 2 H, Ar), 7.33-7.38 (m, 8 H, Ph), 7.46 (AB part of AA´BB´ system, $J_{AB}$ = 8.3 Hz, 4 H, Ar), 7.61 (A´B´ part of AA´BB´ system $J_{A'B'}$= 8.3 Hz, 4 H, Ar), 7.65 (s, 4 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ -5.2, -5.1 (2 q, SiMe), 18.3, 26.0 (s, q, Si*t*-Bu), 41.2 (d, C-5), 60.6 (d, C-1), 61.9 (t, $NCH_2$), 62.6 (t, 8-$CH_2$), 65.4 (t, C-4), 70.7 (d, C-9), 79.6 (d, C-6), 79.9 (d, C-8), 126.4, 127.0, 127.3, 127.5, 128.2, 128.5 (6 d, Ar, Ph), 138.6, 139.3, 139.8, 139.8 (4 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ 3615-3155 (O-H), 3085-3030 (=C-H), 2955-2855 (C-H), 1250 (C-O) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{58}H_{77}N_2O_8Si_2$, 985.5219; found, 985.5216; $[M + Na]^+$ calcd for $C_{58}H_{76}N_2O_8Si_2Na$, 1007.5038; found, 1007.5032; anal. calcd for $C_{58}H_{76}N_2O_8Si_2$ (985.4): C, 70.69; H, 7.77; N 2.84; found, C, 70.71; H, 7.49; N, 3.25.

***p*-Terphenyl derivative 22**

Compound **21** (50 mg, 0.051 mmol) was dissolved in THF (1 mL), AcOH (1 mL) and $H_2O$ (0.1 mL). Zinc (67 mg, 1.02 mmol) was added and the mixture was heated to 60 °C for 18 h. The salts were filtered off and the solvent was removed in vacuo. The crude product was purified by column chromatography [silica gel, $CH_2Cl_2$/MeOH (7 N $NH_3$) 10:1] to yield **22** (23 mg, 59%) as a colorless solid.

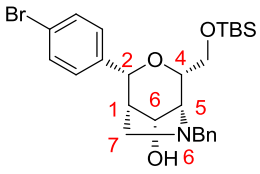



mp 135-137 °C; $[\alpha]_D^{22}$ +57.1 (*c* 1.05, $CH_3OH/C_5H_5N$, 9:1); $^1$H NMR (700 MHz, $CD_3OD$/ $CDCl_3$ 5:1): δ 2.27 ($m_c$, 2 H, 5-H), 3.16 (dd, *J* = 1.8, 3.9 Hz, 2 H, 3-H), 3.37 (dd, *J* = 4.7, 11.6 Hz, 2 H, 5-$CH_2$), 3.65 (td, *J* = 1.8, 5.2 Hz, 2 H, 2-H), 3.74 (dd, *J* = 2.8, 11.6 Hz, 2 H, 5-$CH_2$), 3.84 (dd, *J* = 4.8, 11.7 Hz, 2 H, 2-$CH_2$), 3.90 (dd, *J* = 5.2, 11.7 Hz, 2 H, 2-$CH_2$), 3.95 (d, *J* = 12.6 Hz, 2 H, $NCH_2$), 4.12 (d, *J* = 12.6 Hz, 2 H, $NCH_2$), 4.39 (dd, *J* = 3.9, 5.9 Hz, 2 H, 4-H), 4.78 ($m_c$, 2 H, 6-H), 7.25-7.27 (m, 2 H, Ar), 7.33-7.35 (m, 4 H, Ph), 7.39-7.40 (m, 4 H, Ph), 7.54 (A part of AA´BB´ system; *J* = 8.3 Hz, 4 H, Ar), 7.64 (B part of AA´BB´, *J* = 8.3 Hz, 4 H, Ar), 7.69 (s, 4 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CD_3OD/CDCl_3$ 5:1): δ 45.2 (d, C-5), 53.7 (t, $NCH_2$), 55.3 (t, 5-$CH_2$), 57.1 (d, C-3), 62.3 (t, 2-$CH_2$), 73.2 (d, C-4), 78.9 (d, C-2), 80.3 (d, C-6), 125.6, 125.6, 126.4, 127.1, 127.7 (5 d, Ph, Ar), 138.6, 138.6, 139.0, 139.1 (4 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ 3560-3080 (O-H), 3060-3025 (=C-H), 2950-2800 (C-H), 1235 (C-O) $cm^{-1}$; ESI-TOF (*m*/z): $[M + H]^+$ calcd for

$C_{46}H_{53}N_2O_8$, 761.3796; found, 761.3796; $[M + 2H]^{2+}$ calcd for $C_{46}H_{54}N_2O_8$, 381.1934; found, 381.1945.

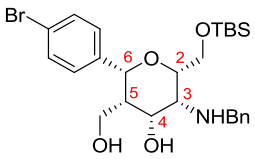
**(1*S*,2*R*,4*S*,5*R*,8*S*)-6-Benzyl-2-(4-bromophenyl)-4-[(*tert*-butyldimethylsiloxy)methyl]-3-oxa-6-azabicyclo[3.2.1]octan-8-ol (24) and (2*S*,3*R*,4*R*,5*S*,6*R*)-3-(benzylamino)-6-(4-bromophenyl)-2-[(*tert*-butyldimethylsiloxy)methyl]-5-(hydroxymethyl)tetrahydro-2*H*-pyran-4-ol (25)**

Under an argon atmosphere compound **12a** (150 mg, 0.281 mmol) was dissolved in degassed THF (2 mL), a samarium(II) iodide solution (8.12 mL, 0.1 M in THF, 0.812 mmol) was added dropwise and the solution stirred for 30 min at rt. After completion of the reaction (control by TLC), the mixture was stirred under air for 10 min, sat. aq. potassium sodium tartrate solution (20 mL) was added and the aqueous layer was extracted with ethyl acetate (5 x 80 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvents removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 2:1 → 1:1) to yield **24** (115 mg, 79%) and **25** (21 mg, 14%) as colorless solids.




mp 39-41 °C; $[\alpha]_D^{22}$ +22.3 (*c* 1.01, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 6 H, $SiMe_2$), 0.09 (s, 9 H, Si*t*-Bu), 2.20 ($s_{br}$, 1 H, OH), 2.42 (A part of ABX system, $J_{AB}$ = 5.6 Hz, 1 H, 7-H), 2.49 (B part of ABX system, $J_{AB}$ = 5.6 Hz, $J_{BX}$ = 10.0 Hz, 1 H, 1-H), 2.73 (X part of ABX system, $J_{BX}$ = 10.0 Hz, 1 H, 7-H), 3.32 (s, 1 H, 5-H), 3.55 (X part of ABX system, $J_{AX}$ = 5.3 Hz, $J_{BX}$ = 7.7 Hz, 1 H, 4-H), 3.77 (A part of ABX system $J_{AX}$ = 5.3

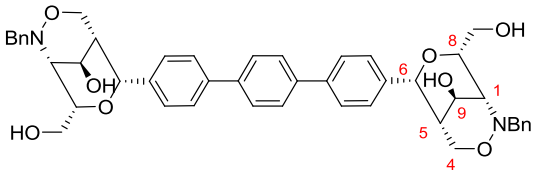
Hz, $J_{AB}$ = 9.6 Hz, 1 H, 4-$CH_2$), 3.86 (B part of AB system, $J_{BX}$ = 7.7 Hz, $J_{AB}$ = 9.6 Hz, 1 H, 4-$CH_2$), 4.01 (AB system, $J_{AB}$ = 13.4 Hz, 1 H, $NCH_2$), 4.09 (AB system, $J_{AB}$ = 13.4 Hz, 1 H, $NCH_2$), 4.20 (s, 1 H, 8-H), 4.62 (s, 1 H, 2-H), 7.20 (A part of AA´BB´ system, $J$ = 8.2 Hz, 2 H, Ar), 7.23-7.24 (m, 1 H, Ph), 7.29-7.32 (m, 2 H, Ph), 7.37-7.38 (m, 2 H, Ph), 7.43 (B part of AA´BB´ system, $J$ = 8.5 Hz, 2 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ -5.21, -5.18 (q, SiMe), 18.4, 26.1 (s, q, Si*t*-Bu), 50.0 (t, C-7), 50.2 (d, C-1), 62.0 (t, $NCH_2$), 63.0 (t, 4-$CH_2$), 65.3 (d, C-5), 78.4 (d, C-2), 78.7 (d, C-8), 80.1 (d, C-4), 121.0 (s, Ar), 126.9, 127.7, 128.4, 128.5, 131.3 (5 d, Ph, Ar), 139.9, 140.7 (2 s, Ph, Ar) ppm; IR (ATR): $\tilde{\nu}$ 3570-3150 (O-H), 3090-3030 (=C-H), 2950-2855 (C-H) cm$^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{26}H_{37}BrNO_3Si$, 518.1726; found, 518.1738; anal. calcd for $C_{26}H_{36}BrNO_3Si$ (518.6): C, 60.22; H, 7.00; N, 2.70; found: C, 60.42; H, 7.15; N, 2.75.




mp 46-48 °C; $[\alpha]_D^{22}$ +56.1 (*c* 1.00, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD$): δ 0.07 (s, 6 H, $SiMe_2$), 0.88 (s, 9 H, Si*t*-Bu), 2.16 (ddd, $J$ = 2.0, 3.6, 9.8 Hz, 1 H, 5-H), 3.14 (dd, $J$ = 4.0, 11.5 Hz, 1 H, 5-$CH_2$), 3.23 ($m_c$, 1 H, 3-H), 3.61 (td, $J$ = 1.8, 4.7 Hz, 1 H, 2-H), 3.79 (dd, $J$ = 2.0, 11.5 Hz, 1 H, 5-$CH_2$), 3.93 (d, $J$ = 12.7 Hz, 1 H, $NCH_2$), 3.97 ($m_c$, 2 H, 2-$CH_2$), 4.25 (d, $J$ = 12.7 Hz, 1 H, $NCH_2$), 4.41 (dd, $J$ = 3.6, 6.1 Hz, 1 H, 4-H), 4.75 (d, $J$ = 3.6 Hz, 1 H, 6-H), 7.28-7.31 (m, 1 H, Ph), 7.34-7.36 (m, 2 H, Ph), 7.39-7.40 (m, 4 H, Ph, Ar), 7.48 (d, $J$ = 8.5 Hz, 2 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CD_3OD$): δ -5.34, -5.28 (q, SiMe), 19.2, 26.3 (s, q, Si*t*-Bu), 47.4 (d, C-5), 55.6 (t, $NCH_2$), 56.1 (t, 5-$CH_2$), 59.3 (d, C-3), 65.5 (t, 2-$CH_2$), 75.3 (d, C-4), 79.9 (d, C-2), 82.1 (d, C-6), 121.5 (s, Ar), 128.4, 129.3, 129.6, 129.7, 131.9 (5 d, Ph, Ar), 132.1, 140.9 (2 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ 3555-3080 (O-H,

N-H), 3060-3030 (=C-H), 2930-2855 (C-H) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{26}H_{39}BrNO_4Si$, 536.1826; found, 536.1847.

### *p*-Terphenyl derivative 26

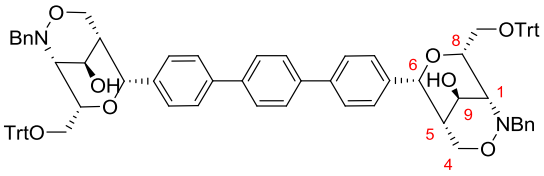



Compound **21** (209 mg, 0.212 mmol) was dissolved in THF (3 mL) and stirred with TBAF (0.86 mL, 1 M in THF, 0.858 mmol) for 2 d at rt. The resulting brownish precipitate was filtered off and washed with dichloromethane (100 mL) and methanol (100 mL) until the solid was colorless. The product was dried in vacuo to yield **23** (48 mg, 30%) as a colorless solid.

mp 247-249 °C; $[\alpha]_D^{22}$ +150.3 (*c* 0.33, $C_5H_5N$); $^1$H NMR (500 MHz, $C_5D_5N$): δ 2.25 (s, 2 H, 5-H), 3.60 (s, 2 H, 1-H), 3.71 (d, *J* = 11.6 Hz, 2 H, 4-H), 4.32 (td, *J* = 1.0, 5.8 Hz, 2 H, 8-H), 4.53 ($s_{br}$, 2 H, 9-H), 4.54 (dd, *J* = 5.8, 10.9 Hz, 2 H, 8-$CH_2$), 4.63 (dd, *J* = 6.1, 10.9 Hz, 2 H, 8-$CH_2$), 4.67 (d, *J* = 14.6 Hz, 2 H, $NCH_2$), 4.80 (dd, *J* = 2.2, 11.6 Hz, 2 H, 4-H), 5.13 (d, *J* = 14.6 Hz, 2 H, $NCH_2$), 5.17 (s, 2 H, 6-H), 7.27 (C part of AA´´BB´´C system, $J_{CB}$ = 7.4 Hz, 2 H, Ph), 7.36 (A part of AA´´BB´´C system, $J_{AB}$ = 7.4 Hz, 4 H, Ph), 7.67 (B part of AA´´BB´´C system, $J_{ABC}$ = 7.4 Hz, 4 H, Ph), 7.79 (s, 8 H, Ar), 7.81 (s, 4 H, Ar) ppm; $^{13}$C NMR (125 MHz, $C_5D_5N$): δ 42.8 (d, C-5), 59.5 (t, C-4), 60.4 (t, $NCH_2$), 61.2 (d, C-1), 64.4 (t, 8-$CH_2$), 70.1 (d, C-9), 80.8 (d, C-6), 81.7 (d, C-8), 127.4, 127.6, 128.0, 128.3, 129.0, 129.7 (6 d, Ar, Ph) 140.1, 140.5, 141.1, 141.6 (4 s, Ph, Ar) ppm; IR (ATR): $\tilde{\nu}$ 3500-3275 (O-H), 3030 (=C-H), 2920-2855 (C-H), 1255 (C-O) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{46}H_{49}N_2O_8$, 757.3489; found, 757.3488;

[M + Na]$^+$ calcd for $C_{46}H_{48}N_2O_8Na$, 779.3308; found, 779.3318; anal. calcd for $C_{46}H_{48}N_2O_8$ (756.9): C, 73.00; H, 6.39; N, 3.70; found: C, 69.73; H, 7.46; N, 3.41.

**_p_-Terphenyl derivative 27**




Compound **16** (300 mg, 0.453 mmol), $Pd(PPh_3)_2Cl_2$ (32 mg, 45.3 µmol) and benzene-1,4-diboronic acid (37 mg, 0.222 mmol) were filled in a sealed tube and flushed with argon. DMF (4 mL) and 2 M $Na_2CO_3$ solution (0.9 mL) were added and the mixture was stirred for 3 d at 80 °C. The solution was cooled to rt, brine (20 mL) was added and the aqueous layer extracted with ethyl acetate (80 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvents removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 2:1) to yield **27** (140 mg, 51%) as a yellow solid.

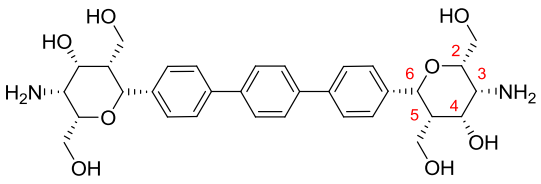
mp 144-146 °C; $[\alpha]_D^{22}$ -18.5 (*c* 1.00, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ 2.11 ($s_{br}$, 2 H, 5-H), 3.33 ($s_{br}$, 2 H, 1-H), 3.37 (dd, *J* = 7.8, 8.8 Hz, 2 H, 8-$CH_2$), 3.74 (d, *J* = 12.0 Hz, 2 H, 4-H), 3.81 (d, *J* = 10.5 Hz, 2 H, OH), 3.85-3.87 (m, 2 H, 8-$CH_2$), 3.86, 3.93 (AB system, $J_{AB}$ = 14.9 Hz, 4 H, $NCH_2$), 4.00 (dd, *J* = 5.0, 12.0 Hz, 2 H, 4-H), 4.12-4.16 (m, 4 H, 9-H, 8-H), 4.90 (s, 2 H, 6-H), 7.07-7.08 (m, 4 H, Ph), 7.21-7.28 (m, 8 H, Ph), 7.31-7.33 (m, 10 H, Ph), 7.45 (A part of AA´BB´ system, $J_{AB}$ = 8.3 Hz, 4 H, Ar), 7.50-7.51 (m, 10 H, Ph), 7.60 (B part of AA´BB´ system, $J_{AB}$ = 8.3 Hz, 4 H, Ar), 7.64 (s, 4 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ 41.1 (d, C-5), 61.0 (d, C-1), 61.3 (t, $NCH_2$), 64.3 (t, 8-$CH_2$), 65.3 (t, C-4), 70.5 (d, C-8), 78.8 (d, C-9), 79.7 (d, C-6), 87.1 (s, *C*$Ph_3$), 126.5,

127.0, 127.2, 127.3, 127.5, 128.1, 128.2, 128.4, 128.8 (9 d, Ar, Ph), 138.1, 139.3, 139.8, 139.9, 143.9 (5 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ 3605-3140 (O-H), 3086-3030 (=C-H), 2955-2850 (C-H); ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{84}H_{77}N_2O_8$, 1241.5680; found, 1241.5668; $[M + Na]^+$ calcd for $C_{84}H_{76}N_2O_8Na$, 1263.5533; found, 1263.5485; anal. calcd $C_{84}H_{76}N_2O_8$ (1241.5): C, 81.26; H, 6.17; N, 2.26; found: C, 81.17; H, 6.26; N, 2.28.

**_p_-Terphenyl derivatives 30 and 31:**

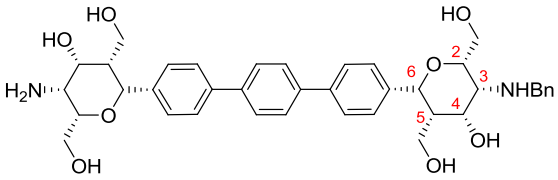
A suspension of Pd/C (10% Pd, 200 mg) and iPrOH (3 mL) was saturated with hydrogen for 15 min. Compound **27** (100 mg, 80.5 µmol) and TFA (23 mg, 0.02 mL, 0.201 mmol) were dissolved in hexafluoro-2-propanol (2 mL) and added to the suspension. The mixture was stirred for 8 h under hydrogen pressure (balloon), then filtered through Celite® and the solvents were removed in vacuo. Under an argon atmosphere the crude product was dissolved in degassed MeOH (1 mL) and a samarium(II) iodide solution (0.1 M in THF, 4.83 mL, 0.483 mmol) was added dropwise. The mixture was stirred for 30 min at rt and then for another 10 min in the presence of air. A size exclusion chromatography (Sephadex™ LH-20, $CH_3OH$) of the mixture and subsequent purification by thin-layer chromatography (silica gel, $CH_2Cl_2$:MeOH, 7N $NH_3$) afforded **30** (25 mg, 54%) and **31** (20 mg, 37%) as a yellow solid.

**_p_-Terphenyl derivatives 30**



Decomposition >200 °C; $[\alpha]_D^{22}$ +13.5 (*c* 0.40, $CH_3OH$); $^1H$ NMR (700 MHz, $CD_3OD$): δ 2.33 ($m_c$, 2 H, 5-H), 3.28 (dd, *J* = 2.8, 11.0 Hz, 2 H, 5-$CH_2$), 3.66 (dd, *J* = 1.6, 4.6 Hz, 2 H, 3-H), 3.80 (dd, *J* = 1.5, 11.0 Hz, 2 H, 5-$CH_2$), 3.85 (X part of ABX system with additional *J* = 1.6 Hz, $J_{AX}$ = $J_{BX}$ = 4.7 Hz, 2 H, 2-H), 3.95 (A part of ABX system, $J_{AX}$ = 4.7, $J_{AB}$ = 12.0 Hz, 2 H, 2-$CH_2$), 3.98 (B part ABX system, $J_{BX}$ = 4.7, $J_{AB}$ = 12.0 Hz, 2 H, 2-$CH_2$), 4.46 ($s_{br}$, 2 H, NH), 4.59 (dd, *J* = 4.6, 6.6 Hz, 2 H, 4-H), 4.94 (d, *J* = 3.6 Hz, 2 H, 6-H), 7.58 (A part of AA´BB´ system, $J_{AB}$ = 8.2 Hz, 4 H, Ar), 7.69 (B part of AA´BB´ system, $J_{AB}$ = 8.2 Hz, 4 H, Ar), 7.73 (s, 4 H, Ar) ppm; $^{13}C$ NMR (175 MHz, $CD_3OD$): δ 46.0 (d, C-5), 52.0 (d, C-3), 55.2 (t, 5-$CH_2$), 63.4 (t, 2-$CH_2$), 69.1 (d, C-4), 77.1 (d, C-2), 82.0 (d, C-6), 127.5, 127.6, 128.3 (3 d, Ar), 139.9, 140.7, 141.0 (3 s, Ar) ppm; IR (ATR): $\tilde{\nu}$ 3570-3475 (O-H, N-H), 3095-3020 (=C-H), 2960-2930 (C-H), 1240 (C-O) $cm^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{32}H_{41}N_2O_8$, 581.2863; found, 581.2882; [M + 2H] calcd for $C_{32}H_{42}N_2O_8$, 291.1471; found 291.1475.

### *p*-Terphenyl derivatives 31




mp 154-156 °C; $[\alpha]_D^{22}$ +100.9 (*c* 1.00, $CH_3OH$); $^1H$ NMR (700 MHz, $CD_3OD$): δ 2.32 ($s_{br}$, 1 H, 5-H), 2.37 ($s_{br}$, 1 H, 5´-H), 3.28-3.29 (m, 2 H, 5-$CH_2$, 5´-$CH_2$), 3.62 ($s_{br}$, 1 H, 3-H), 3.69-3.71 (m, 2 H, 2-H, 3´-H), 3.80 (d, *J* = 10.4 Hz, 1 H, 5-$CH_2$), 3.84 ($m_c$, 1 H, 2´-H), 3.88 (dd, *J* = 2.2, 10.8 Hz, 1 H, 5´-$CH_2$), 3.94 (dd, *J* = 4.8, 11.8 Hz, 1 H, 2´-$CH_2$), 3.97-4.00 (m, 2 H, 2-$CH_2$, 2´-$CH_2$), 4.07 (dd, *J* = 3.3, 12.2 Hz, 1 H, 2-$CH_2$), 4.33 (d, *J* = 12.7 Hz, 1 H, $NCH_2$), 4.57 (d, $m_c$, *J* = 12.7 Hz, 2 H, $NCH_2$, 4-H), 4.67 (dd, *J* = 4.1, 6.7 Hz, 1 H,

4´-H), 4.93 (d, *J* = 3.3 Hz, 1 H, 6-H), 4.96 (d, *J* = 3.9 Hz, 1 H, 6´-H), 7.41-7.46 (m, 3 H, Ph), 7.49-7.50 (m, 2 H, Ph), 7.56-7.59 (m, 4 H, Ar), 7.68-7.70 (m, 4 H, Ar), 7.74 (s, 4 H, Ar); $^{13}$C NMR (175 MHz, $CD_3OD$): δ 46.1 (d, C-5), 46.5 (d, C-5´), 51.9 (d, C-3), 53.9 (t, $NCH_2$), 55.3 (t, 5-$CH_2$), 55.9 (t, 5´-$CH_2$), 59.8 (d, C-3´), 63.4 (t, 2´-$CH_2$), 65.1 (t, 2-$CH_2$), 69.5 (d, C-4), 72.3 (d, C-4´), 77.3 (d, C-2), 77.4 (d, C-2´), 81.9 (d, C-6), 82.4 (d, C-6´), 127.5, 127.6, 127.7, 128.3, 130.0,130.2, 130.4 (7 d, Ar, Ph), 139.9, 140.0, 140.7, 141.0 (4 s, Ph, Ar); IR (ATR): $\tilde{\nu}$ 3605-3430 (O-H), 3090-3030 (=C-H), 2950-2880 (C-H), 1255 (C-O) cm$^{-1}$; ESI-TOF (*m*/*z*): $[M + H]^+$ calcd for $C_{39}H_{47}N_2O_8$, 671.3327; found, 671.3357; $[M + 2H]^{2+}$ calcd for $C_{78}H_{93}N_4O_{16}$, 336.1706; found 336.1713.

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## 3.2 Preparation of Multivalent Carbohydrate Mimetics Based on Enantiopure 1,2-Oxazines by Sonogashira Couplings and Subsequent Reductive Ring Openings

Dieses Kapitel wurde in der folgenden Zeitschrift publiziert:

M. Kandziora, H.-U. Reissig, *Eur. J. Org. Chem.* **2015**, 370-377.

Das Kapitel 3.2 beschreibt die Synthese von funktionalisierten enantiomerenreinen Kohlenhydratmimetika und ihrer oligomeren Analoga. Die Synthese des für ihre Darstellung benötigten *para*-bromphenylsubstituierten bicyclischen 1,2-Oxazins wurde im Kapitel 3.1 beschrieben. Die Sonogashira-Kupplung wurde als Schlüsselschritt zur Funktionalisierung und Verknüpfung der Kohlenhydratmimetika verwendet. Es ist gelungen, vier außergewöhnlich funktionalisierte Aryl-*C*-glycoside mit D-Talose-Konfiguration und einer Aminogruppe zu erhalten. Die oligovalenten *C*-Glycoside, die sich in ihrer Geometrie, der Linkerlänge und der Anzahl an Aminopyran-Einheiten unterscheiden, wurden durch Sonogashira-Reaktionen von alkinylsubstituierten Bicyclen und geeigneten Oligoiodarenen dargestellt. Des Weiteren wurde zur Darstellung zweier divalenter Kohlenhydratmimetika die Glaser-Kupplung verwendet. Anschließend wurden die erhaltenen, oligovalenten Produkte durch Hydrogenolyse debenzyliert, die Alkineinheiten reduziert und die N-O-Bindung durch Samariumdiiodid gespalten.

Alle beschriebenen Experimente wurden im Rahmen der vorliegenden Arbeit durchgeführt.

DOI: 10.1002/ejoc.201403186

# Preparation of Multivalent Carbohydrate Mimetics Based on Enantiopure 1,2-Oxazines by Sonogashira Coupling and Subsequent Reductive Ring-Opening

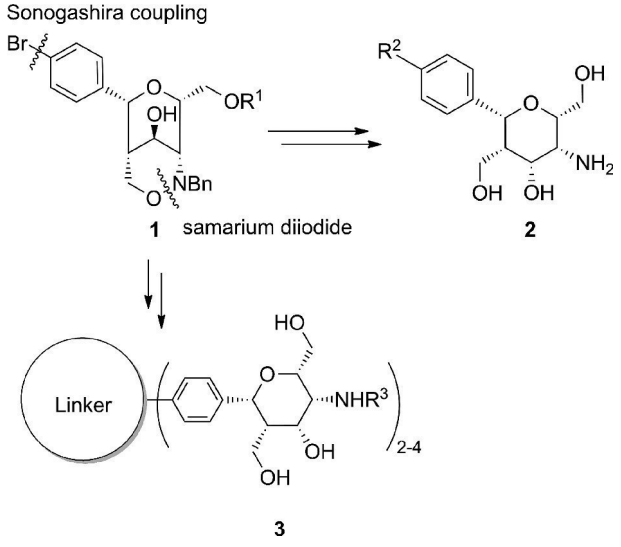
Maja Kandziora[a] and Hans-Ulrich Reissig*[a]

**Keywords:** Oxygen heterocycles / Cross coupling / Hydrogenation / Carbohydrates / Samarium diiodide

A modular approach to aryl *C*-glycosides and their multivalent analogues is presented. Sonogashira coupling reactions connected the key compounds, enantiopure bicyclic 1,2-oxazine derivatives bearing *p*-bromophenyl substituents, with alkynes. Subsequent hydrogenolyses or a combination of hydrogenolysis and samarium diiodide mediated reductions converted the coupling products into new unnatural amino carbohydrate mimetics with a D-talose configuration. By Glaser coupling reactions we obtained products with a 1,3-diyne linker and divalent compounds derived therefrom. Through Sonogashira reactions of compound **8** with several iodobenzene derivatives, di-, tri-, and tetravalent compounds were prepared in high yields. The subsequent reductive processes converted the 1,2-oxazine moieties into the corresponding aminopyrans. Severe purification problems were solved in most cases by following the appropriate strategies as an apt sequence of steps or by acetylation of the intermediates.

## Introduction

A well-established strategy to obtain potent carbohydrate-related drugs (often called carbohydrate mimetics) involves the synthesis and use of *C*-glycosides.[1] These compounds often show remarkable stability towards enzymatic and chemical degradation.[2] In addition, better oral bioavailability can be achieved by reducing the hydrophilicity of natural glycosides, for example, by employing carbohydrate derivatives with alkyl chains.[3] Frequently, aryl *C*-glycosides favor binding to a potential receptor for entropic reasons because of their higher rigidity compared with their more flexible aliphatic analogues.[4] The binding affinity can be further increased by using carbohydrate mimetics bearing additional functional groups that induce changes in physical properties, such as charge or higher hydrophobicity.[5] Our group recently reported on an approach to enantiopure bicyclic 1,2-oxazine derivatives such as the *p*-bromophenyl-substituted compound **1** (Scheme 1), which can be regarded as an internally protected *C*-glycoside precursor. This bicyclic compound offers various options for a number of chemical transformations, for example, cross-coupling reactions. Bicyclic compound **1** was efficiently prepared by a diastereoselective [3+3] cyclization of a D-isoascorbic acid derived (*Z*)-nitrone and lithiated 2-(trimethylsilyl)ethoxyallene to provide the 1,2-oxazine skeleton. A subsequent Lewis acid induced rearrangement of this primary product and stereoselective reduction afforded the corresponding bicyclic 1,2-oxazine derivative **1**.[6]




Scheme 1. Approach to *C*-glycosides **2** and multivalent analogues **3** from enantiopure bicyclic 1,2-oxazine derivative **1**.

Structurally similar aminopyrans such as **2** have been broadly studied as carbohydrate mimetics by our group.[7] *O*-Sulfated aminopyrans connected by amide bonds to gold nanoparticles show extremely high binding affinities towards L- and P-selectin even in subnanomolar concentrations. These impressive results were obtained by the multivalent[8] presentation of sulfated pyran moieties (ca. 1000–1200 ligands per nanoparticle).[9] These sialyl Lewis X ana-

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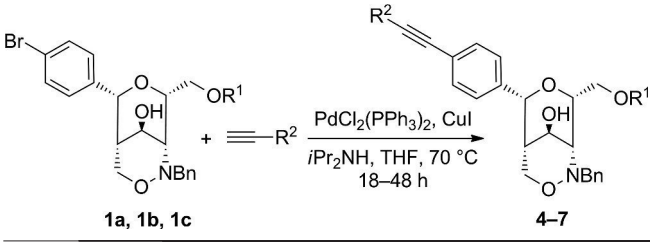
logues can be considered as potential drug candidates for chronic inflammations such as asthma. To gain more information on the structure–activity relationships and on the influence of length and flexibility of their spacer unit, we were interested in preparing related potential inhibitors offering only a small and defined number of ligands (Scheme 1). For this purpose we employed Sonogashira coupling reactions to attach the bicyclic 1,2-oxazine **1** to readily available alkynes. New monovalent aryl *C*-glycosides of the type **2** or di-, tri-, or tetravalent carbohydrate mimetics **3** could be prepared. Owing to the mild reaction conditions, high efficacy, and good functional group tolerance,[10] Sonogashira coupling reactions are frequently used for the construction of multivalent systems from ligands and suitable scaffolds,[11] and as well for the construction of multivalent glycoconjugates.[12] Alternatively, the oxidative Glaser–Hay coupling reaction[13] has been used to prepare divalent carbohydrate mimetics linked by a 1,3-diyne unit.

## Results and Discussion

### Synthesis of Monovalent Model Compounds

For the synthesis of carbohydrate mimetics and their multivalent derivatives we used *p*-bromophenyl-substituted bicyclic 1,2-oxazine **1a** and its protected derivatives **1b** and **1c** as key starting materials, the syntheses of which have been recently published.[6b] These enantiopure compounds can be obtained after a few straightforward steps from D-isoascorbic acid and lithiated 2-(trimethylsilyl)ethoxyallene.[6a] First, we investigated the influence of protecting groups at the primary hydroxy moiety on the Sonogashira reaction with (triisopropylsilyl)acetylene as the coupling partner (Table 1).

Table 1. Sonogashira reactions of *p*-bromophenyl-substituted compounds **1a**–**c** with (triisopropylsilyl)acetylene and other monosubstituted alkynes.

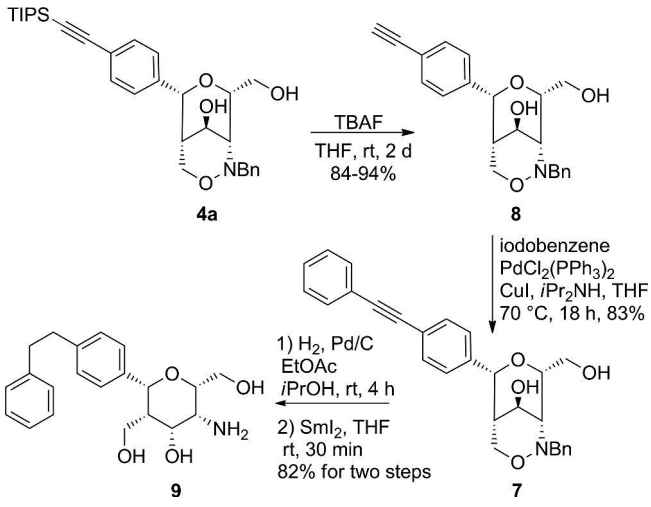



| Entry | $R^1$ | Precursor | $R^2$ | Yield [%][a] | Product |
|---|---|---|---|---|---|
| 1 | H | **1a** | TIPS | quant. | **4a** |
| 2 | TBS | **1b** | TIPS | 96 | **4b** |
| 3 | Trt | **1c** | TIPS | 0 | – |
| 4 | H | **1a** | Bu | 85 | **5** |
| 5 | H | **1a** | $(CH_2)_4OH$ | 74 | **6** |
| 6 | H | **1a** | Ph | 86 | **7** |

[a] Yield of the purified compound.

The best yields were achieved with the unprotected 1,2-oxazine derivative **1a**, which provided the expected coupling product **4a** in quantitative yield (Table 1, entry 1). The *tert*-butyldimethylsilyl-protected compound **1b** also efficiently furnished the desired product **4b** (entry 2, 96% yield). To our surprise, the trityl-protected compound **1c** did not react at all under these conditions and a high quantity of starting material **1c** was re-isolated (entry 3). Possibly, the bulky protecting group of **1c** strongly shields the *p*-bromophenyl substituent, but we did not face such problems in related Suzuki reactions of compound **1c** with boronic acids and the expected products were obtained in good yields.[6b] For our further investigations we used the unprotected compound **1a** and coupled it with commercially available aliphatic and aromatic alkynes to prepare the bicyclic *p*-alkynylphenyl-substituted compounds **5**–**7** in good yields ranging from 74 to 86% (entries 4–6). These results demonstrate that Sonogashira reactions of bicyclic 1,2-oxazine **1a** allow the synthesis of a series of monovalent carbohydrate mimetics bearing alkyl, ω-hydroxyalkyl, or phenyl groups on the alkyne moiety.

To provide an alternative access to the diaryl-substituted alkyne **7**, TIPS-protected alkyne **4a** was treated with fluoride. Four equivalents of TBAF and a reaction time of 2 days were required for full conversion of **4a** and the corresponding monosubstituted alkyne **8** was obtained in up to 94% yield (Scheme 2). Compound **8** was then subjected to a Sonogashira coupling reaction with iodobenzene to afford the desired compound **7** in 83% yield. Hence, both approaches to this compound (Table 1, entry 6 and Scheme 2) are comparably efficient. Compound **7** was converted into deprotected carbohydrate mimetic **9** in an overall yield of 82% by hydrogenolysis and subsequent N–O bond cleavage with samarium diiodide.[14] These reductive processes (alkyne reduction, *N*-debenzylation, and N–O bond cleavage) were also attempted in just one step by performing the hydrogenolysis for a longer time, but these conditions gave lower yields as several side-products were formed due to partial reductions. Possibly, amino alcohol **9** poisons the

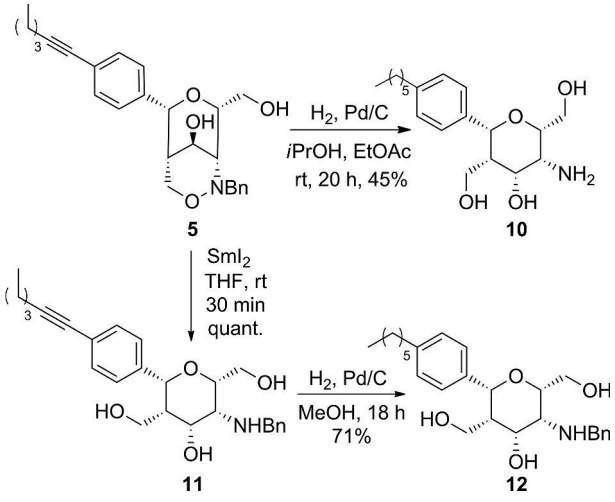



Scheme 2. Conversion of triisopropylsilyl-protected alkyne **4a** into aryl *C*-glycoside **9**.

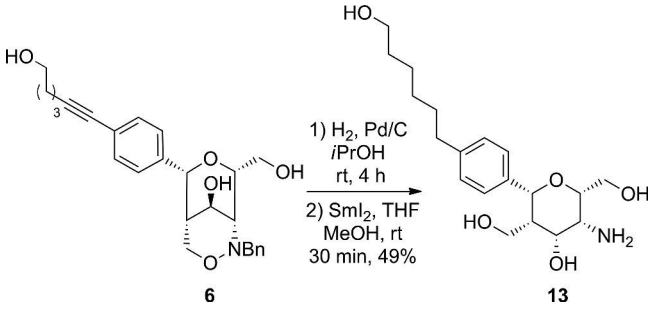
palladium catalyst and hence a larger amount of palladium may be needed for full conversion. The resulting aryl *C*-glycoside **9** bearing hydrophilic and hydrophobic moieties may be used for further modification due to the amino group, which allows amide bond formation, reductive amination, or diazo transfer to form azides.[15]

As mentioned above, hydrogenolysis may allow the execution of the three reductive steps in one operation. The expected fully reduced product **10** was isolated in a moderate 45% yield by applying these conditions to compound **5** (Scheme 3). In this example, we also examined the reductive cleavage of the N–O bond with samarium diiodide as the first step, which quantitatively provided compound **11**. This intermediate is sufficiently lipophilic to allow the removal of samarium salts by extraction with potassium sodium tartrate solution and thus the easy purification of product **11**. The subsequent hydrogenation of the alkyne moiety furnished compound **12** in 71% yield. Under the applied conditions, no *N*-debenzylation leading to compound **10** was observed. As noted in many examples examined by our group, *N*-debenzylation of 1,2-oxazine derivatives (with a still intact N–O bond) occurs fairly quickly by palladium-catalyzed hydrogenolysis,[16] whereas the reductive removal of *N*-benzyl groups after N–O bond cleavage is apparently an unfavorable and slow process.




Scheme 3. Syntheses of (*p*-hexylphenyl)-substituted aminopyrans **10** and **12** by reductive transformations.

The two-step procedure leading to compound **9** (Scheme 2) was also applied to the coupling product **6** (Scheme 4). After a short-period hydrogenolysis, the resulting intermediate was treated with samarium diiodide. In this case, the removal of samarium salts was not possible by extraction with potassium sodium tartrate solution due to the high polarity of aminopyran **13** bearing an additional terminal hydroxy group. However, size exclusion chromatography was successfully employed for the removal of the inorganic salts. Subsequent preparative TLC with a mixture of dichloromethane and ammonia in methanol allowed the final purification to provide compound **13** in a moderate overall yield.

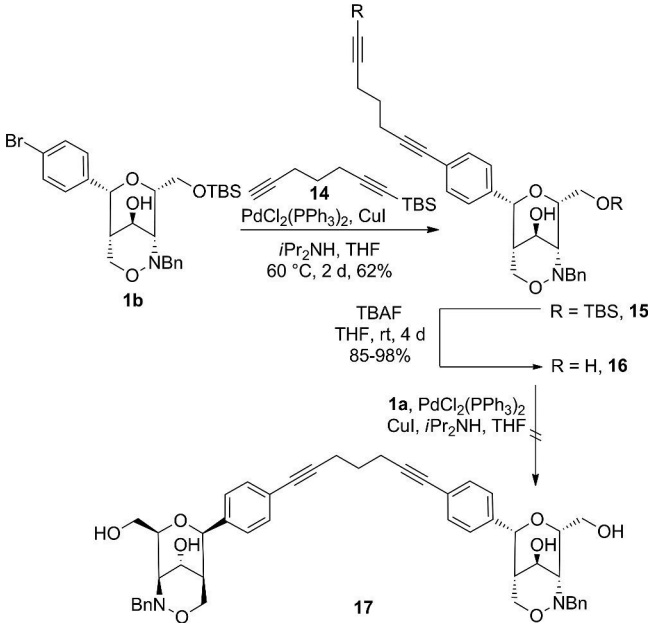



Scheme 4. Conversion of bicyclic 1,2-oxazine derivative **6** into (ω-hydroxyhexylphenyl)-substituted aryl *C*-glycoside **13**.

The aminopyrans **9**, **10**, **12**, and **13** can be considered as branched *C*-glycosides with D-talose configuration.

## Synthesis of Divalent Carbohydrate Mimetics

Having established reasonably efficient methods for the synthesis of four different monovalent carbohydrate mimetics, we examined compounds with two terminal alkyne moieties in the Sonogashira coupling reactions. We used 2.2 equiv. of precursor **1b** under the established conditions, but also examined the effect of different bases, temperatures, and copper-free conditions.[17] Unfortunately, the expected divalent products could not be detected, and even the corresponding monocoupling products could not be isolated. At the moment we have no rationale for this unexpected failure. We hence attempted a stepwise method to obtain a divalent compound (Scheme 5). The TBS-mono-



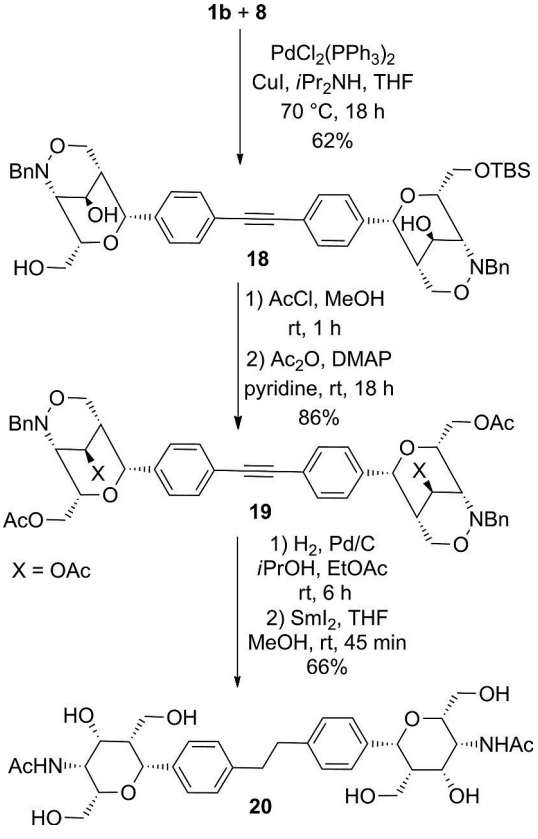

Scheme 5. Attempted three-step synthesis of divalent carbohydrate mimetic **17** by successive Sonogashira reactions.

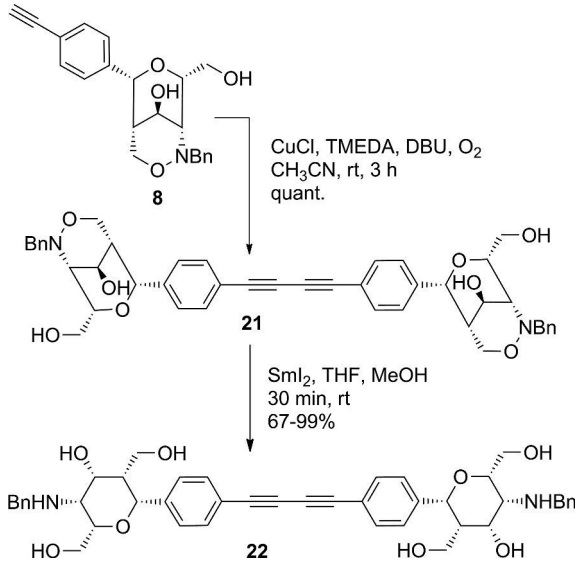
protected dialkyne **14** was prepared according to the literature[18] and its Sonogashira reaction with TBS-protected compound **1b** afforded the desired compound **15** in 62% yield. The silyl groups were removed with TBAF to give **16** in yields of 85–98%. Compound **16** was then subjected to a second Sonogashira coupling reaction. However, again, the expected product **17** was not obtained and the starting material **16** was re-isolated.

We also investigated the Sonogashira coupling of **1b** and alkyne **8** to obtain a divalent carbohydrate mimetic with an alternative linker unit (Scheme 6). In this case the desired divalent compound **18** was isolated in 62% yield. The TBS-protected compound **1b** was used to obtain a product that is soluble and allows easier purification. If the unprotected precursor **1a** was coupled to **8** the resulting symmetric divalent compound was barely soluble, even in pyridine, and the inseparable Glaser homocoupling product **21** (for the structure of **21**, see Scheme 7) was formed as a side-product. After purification of **18**, the TBS group was cleaved under mild conditions with catalytic amounts of acetic chloride in methanol (generating dry HCl).[19] The resulting poorly soluble compound was treated directly with acetic anhydride under standard conditions to give the protected divalent bicyclic compound **19** in 86% yield over two steps. Subsequent palladium-catalyzed hydrogenation led to saturation of the triple bond and removal of the *N*-benzyl groups. The final cleavage of the N–O bonds with samarium diiodide was performed in THF/methanol. Under these Lewis acidic reaction conditions the acetyl groups migrated from the hydroxy groups to the amino substituents and the remaining OAc moieties were cleaved by transesterification to the solvent thereby making additional deprotection steps unnecessary. The divalent carbohydrate mimetic **20** with a C-2 linker between the two phenyl groups was finally isolated in 66% yield.

With alkyne **8** in hand we also examined its Glaser reaction with a view to obtaining a divalent compound containing a C-4 linker (Scheme 7). The oxidative homocoupling could be put into praxis under the conditions published by Beifuss et al.[20] to deliver the rigid and polar compound **21** in quantitative yield. This product is barely soluble even in pyridine, but its samarium diiodide promoted reaction in a methanol/THF mixture was successful in furnishing up to 99% of the divalent carbohydrate mimetic **22**. This rigid and amphiphilic compound was soluble in only methanol/pyridine. We also attempted the hydrogenolysis of the unprotected homocoupling compound **21** under the standard conditions, but no conversion was observed. No suitable solvent was found to dissolve the starting material.



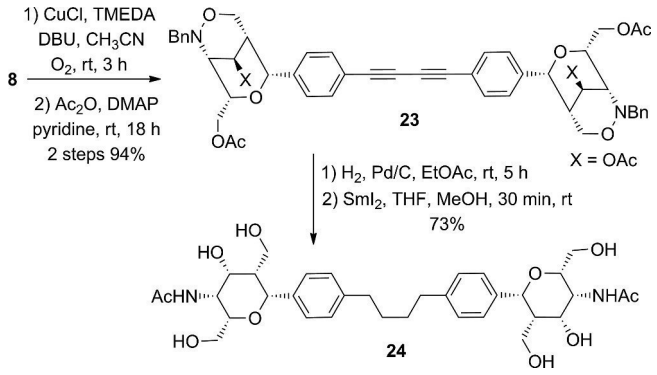

Scheme 6. Five-step synthesis of divalent carbohydrate mimetic **20** containing a 1,2-diphenylethane linker.




Scheme 7. Glaser homocoupling reaction of 1,2-oxazine derivative **8** to provide dialkyne derivative **21** and subsequent samarium diiodide promoted reaction to yield **22** bearing a 1,4-diphenyl-1,3-butadiyne linker.

Alternatively, we prepared the related dialkyne **23** by Glaser coupling of **8** and subsequent protection of the hydroxy groups with acetyl groups, thereby increasing the solubility of the product in organic solvents (Scheme 8). Protected homocoupling product **23** was isolated in 94% yield over two steps. After palladium-catalyzed hydrogenation and *N*-debenzylation followed by N–O bond cleavage with samarium diiodide, the divalent carbohydrate mimetic **24** was obtained in a satisfactory 73% yield.

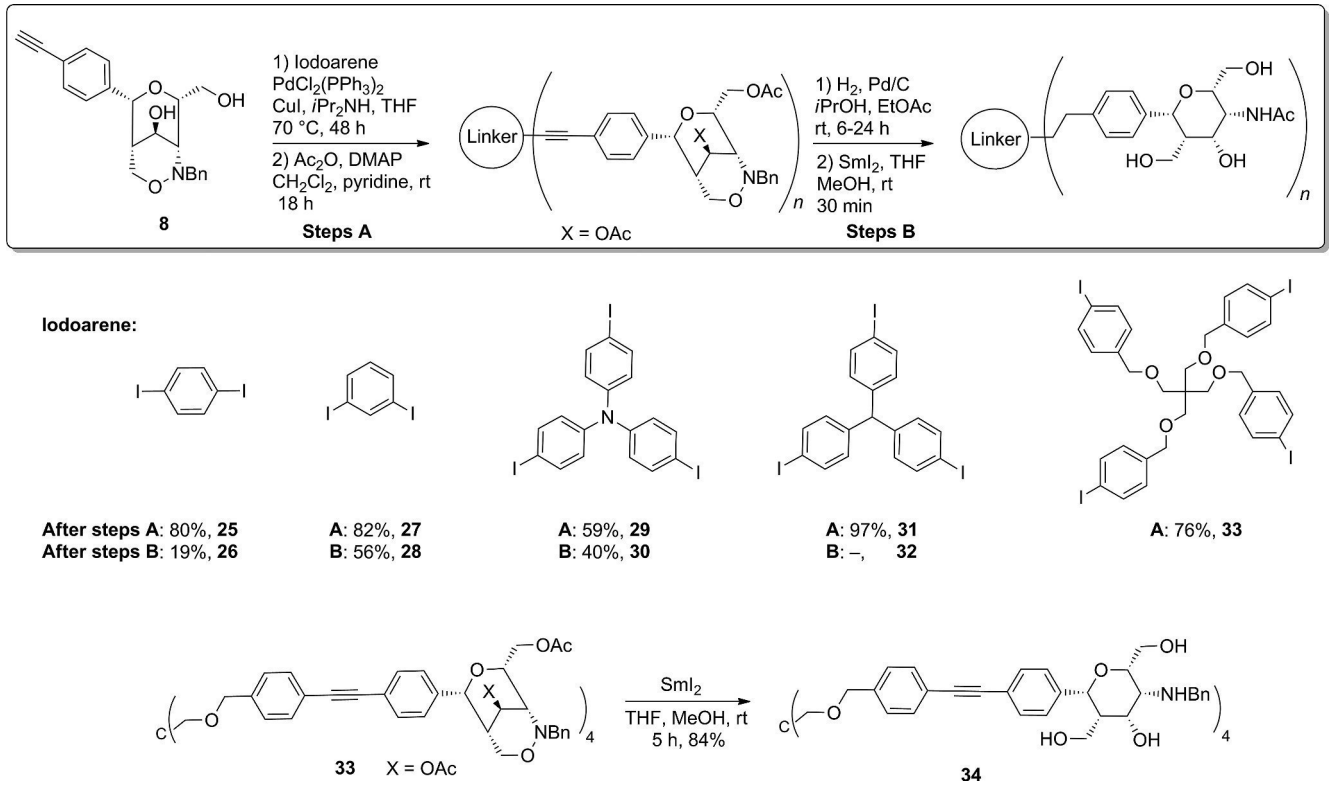



Scheme 8. Glaser homocoupling reaction of **8** and direct *O*-acetylation to give **23** and subsequent reductive conversion into divalent carbohydrate mimetic **24** bearing a 1,4-diphenylbutane linker.

### Synthesis of Other Oligovalent Carbohydrate Mimetics

We finally prepared other oligovalent carbohydrate mimetics (mainly with rigid central units) that should allow structure–activity relationship studies of these compounds (Scheme 9). After our disappointing finding that Sonogashira reactions of dialkynes with *p*-bromophenyl-substituted compounds **1a** and **1b** failed, we investigated the coupling reactions of a series of oligovalent iodo-substituted arenes with alkynyl-substituted compound **8**. Gratifyingly, we obtained the desired di-, tri-, and even tetravalent compounds in high yields (Scheme 9, steps A). All the resulting coupling products were directly *O*-acetylated to increase their solubility. We selected 1,3- and 1,4-diiodobenzene in order to have different arrangements of the aminopyran moieties in the final products. These coupling reactions and acetyl protections proceeded in good yields over two steps (**25**, 80%; **27**, 82%). Tris(4-iodophenyl)amine and -methane were selected as precursors for the central unit to form trivalent compounds **29** and **31** in 59 and 97% yields, respectively. Starting from the literature-known pentaerythrite-derived tetraalkyne,[21] we also prepared tetravalent compound **33** in 76% yield.

The oligovalent compounds obtained could then be converted into the corresponding carbohydrate mimetics. Again, hydrogenation was used for alkyne reduction as well as *N*-debenzylation and the samarium diiodide promoted reaction was employed for the N–O bond cleavage (Scheme 9, steps B). After the hydrogenation step (full conversion was ascertained by ESI-TOF) the crude products were filtered through a pad of Celite® and directly used for the $SmI_2$-mediated step. The hydrogenolysis of compounds **25**, **27**, and **31** required approximately 6 hours for full conversion, whereas the triaryl-linked compound **29** needed 24 h; possibly the central nitrogen atom deactivates the palladium catalyst. Because we feared an undesired cleavage of the *O*-benzyl-substituted linker, tetravalent compound **33** was not *N*-debenzylated by hydrogenolysis. Steps B were performed for compounds **25** and **27** to furnish products **26** and **28**, respectively, in overall yields of 19 and 56%. Incompletely converted compounds were isolated as side-products, for example, products containing a still intact




Scheme 9. Synthesis of oligovalent carbohydrate mimetics **26**, **28**, **30**, and **34** by Sonogashira coupling of different iodoarenes with compound **8** and subsequent hydrogenolysis and samarium diiodide promoted N–O bond cleavage.

N–O bond. Triarylamine-linked compound **30** was obtained from **29** in 40% yield as a readily soluble compound. In contrast, trivalent compound **31** afforded a product mixture that, after N–O bond cleavage, was only soluble in DMSO and could not be purified. Analysis by ESI-TOF showed the presence of a mixture of partially acetylated compounds. We tried to unify this trivalent compound by full acetylation, but obtained an even more complex mixture of inseparable products. We finally studied the conversion of tetravalent compound **33**. Its samarium diiodide promoted reduction required a significantly longer reaction time than the structurally quite similar 1,2-oxazine derivative **11**. To our surprise, no acetyl group transfer to the amino substituent occurred. Compound **34** was isolated in very good 84% yield. It was necessary to purify the highly polar compounds **26**, **28**, **30**, and **34** by desalting with size exclusion chromatography and subsequent reversed-phase HPLC.

## Conclusions

In this account we have presented methods for the synthesis of enantiopure carbohydrate mimetics and their oligovalent analogues by Sonogashira coupling reactions as the key step. In general, the applied key reactions are efficient, but occasionally low solubility causes severe problems in reactivity and also during purification. Starting from readily available precursors **1**, we successfully established routes for the efficient preparation of four differently substituted branched aryl *C*-glycosides with the D-talose configuration. These *C*-glycosides bear an amino group that should allow further modifications. To study the structure–activity relationship of lectin-binding oligovalent carbohydrate mimetics, compounds with different linker length, geometry, and number of aminopyran moieties were prepared. Surprisingly, Sonogashira reactions of precursors **1a** and **1b** with bis-alkynes failed, even by a stepwise route with a TBS-monoprotected bis-alkyne. However, two amphiphilic divalent carbohydrate mimetics could be prepared by Glaser cross-coupling, one with a rigid and one with a flexible linker unit. Di-, tri-, and even tetravalent compounds were isolated in high yields by Sonogashira couplings of *p*-ethynylphenyl-substituted 1,2-oxazine **8** with iodobenzene derivatives. Hydrogenation was used to saturate the triple bonds and to remove the *N*-benzyl groups whereas samarium diiodide was employed to selectively cleave the N–O bond. Future investigations will convert the prepared oligovalent aryl *C*-glycosides into their *O*-sulfated derivatives and the selectin inhibitor properties of these compounds will be compared with those of related carbohydrate mimetics.

## Experimental Section

**General:** Reactions were generally performed under argon in flame-dried flasks. Solvents and reagents were added through a syringe. Solvents were dried by using standard procedures and purified with an MB SPS-800-dry solvent system. Commercially available reagents were used as received without further purification unless stated otherwise. The products were purified by flash chromatography on silica gel (230–400 mesh, Macherey–Nagel), size exclusion chromatography (Sephadex™ LH-20, GE Healthcare), and RP-HPLC (Gemini®-NX C18 Phenomenex). Unless stated otherwise, the yields refer to analytically pure samples. Hydrogenolyses were performed with hydrogen from Air Liquide (Alphagaz 2). TLC analyses were performed with silica gel coated aluminum plates purchased from VWR. Products were detected by UV activity and by using staining reagents (cerium/molybdenum reagent, $KMnO_4$ and ninhydrin). NMR spectra were recorded with Bruker (AV 500, AV 700) and JEOL (ECP 500) spectrometers. Chemical shifts ($\delta$) are given in parts per million (ppm) and are reported relative to solvent residual signals: $CDCl_3$ ($^1$H: $\delta$ = 7.26 ppm; $^{13}$C: $\delta$ = 77.2 ppm), $CD_3OD$ ($^1$H: $\delta$ = 3.31 ppm; $^{13}$C: $\delta$ = 49.0 ppm), or [$D_5$] pyridine ($^1$H: $\delta$ = 8.74 ppm; $^{13}$C: $\delta$ = 150.4 ppm). Integrals are in accordance with assignments; coupling constants ($J$) are given in Hz. All $^{13}$C NMR spectra are proton-decoupled. Multiplicities are indicated as follows: s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), m (multiplet), and $m_c$ (centered multiplet). 2D NMR spectra were recorded (COSY and HMQC) for detailed peak assignments. IR spectra were recorded with a Jasco spectrometer (FT/IR-4100 with DLATGS Detector). HRMS analyses were performed with an Agilent 6210 (ESI–TOF, 10 μL/min, 1.0 bar, 4 kV) and Varian/Agilent Ionspec QFT-7 (ESI–FTICR, 4 μL/min, 1.0 bar, 4 kV) spectrometers. Elemental analyses were carried out with instruments from Elementar (Vario EL, Vario EL III). Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected.

### Typical Experimental Procedures

**(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-8-(hydroxymethyl)-6-{4-[(triisopropylsilyl)ethynyl]phenyl}-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (4a):** Compound **1a** (3.00 g, 7.14 mmol), [$PdCl_2(PPh_3)_2$] (250 mg, 357 μmol), and CuI (68 mg, 357 μmol) were added to a sealed tube, which was flushed with argon. Degassed THF (43 mL), $i$Pr$_2$NH (16 mL), and (triisopropylsilyl)acetylene (1.95 g, 10.7 mmol) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to room temp., water (40 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 80 mL). The combined organic layers were dried with $Na_2SO_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1) to yield **4a** (4.13 g, quant.) as a colorless solid. M.p. 61–63 °C. $[\alpha]_D^{22}$ = +82.7 ($c$ = 1.03, $CH_3OH$). $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ = 1.12 (br. s, 21 H, $i$Pr), 1.89 (br. s, 1 H, 5-H), 3.06 (s, 1 H, 1-H), 3.23 (d, $J$ = 11.7 Hz, 1 H, 4-H), 3.80, 3.86, 3.98 (ABX system, $J_{AB}$ = 4.9, $J_{AX}$ = 6.0, $J_{BX}$ = 11.0 Hz, 3 H, 8-H, 8-$CH_2$), 4.08 ($m_c$, 1 H, 9-H), 4.22 (d, $J$ = 14.1 Hz, 1 H, $NCH_2$), 4.37 (d, $J$ = 11.7 Hz, 1 H, 4-H), 4.60 (d, $J$ = 14.1 Hz, 1 H, $NCH_2$), 4.84 (br. s, 1 H, 6-H), 7.17–7.20 (m, 1 H, Ph), 7.25–7.28 (m, 2 H, Ph), 7.34–7.35 (m, 2 H, Ph), 7.40 (br. s, 4 H, Ar) ppm. $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ = 12.5 (d, $i$Pr), 19.1 (q, $i$Pr), 42.2 (d, C-5), 59.0 (t, C-4), 60.4 (t, $NCH_2$), 60.8 (d, C-1), 64.5 (t, 8-$CH_2$), 69.9 (d, C-9), 80.69, 80.71 (2 d, C-6, C-8), 90.5, 108.6 (2 s, C≡C), 123.3 (s, Ar), 127.2, 128.0, 129.1, 129.9, 132.6 (5 d, Ar, Ph), 140.3, 142.5 (2 s, Ar, Ph) ppm. IR (ATR): $\tilde{\nu}$ = 3625–3155 (O–H), 3085–3060 (=C–H), 2940–2865 (C–H), 2155 (C≡C), 1460 (C–H), 1240 (C–O) cm$^{-1}$. HRMS (ESI-TOF): calcd. for $C_{31}H_{44}NO_4Si$ [M + H]$^+$ 522.3040; found 522.3036; calcd. for $C_{31}H_{43}NNaO_4Si$ [M + Na]$^+$ 544.2859; found 544.2853. $C_{31}H_{43}NO_4Si$ (521.8): calcd. C 71.36, H 8.31, N 2.68; found C 71.30, H 8.32, N 2.70.

**(2*S*,3*R*,4*R*,5*S*,6*R*)-[3-Amino-4-hydroxy-6-(4-phenethylphenyl)tetrahydro-2*H*-pyran-2,5-diyl]dimethanol (9):** A suspension of Pd/C (10% Pd, 24 mg) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. Compound **7** (24 mg, 54 μmol) was dissolved in ethyl acetate (1 mL) and added to this suspension. The mixture was stirred for 4 h under hydrogen (balloon), filtered through a pad of Celite®, and the solvent was removed in vacuo. The crude product was dissolved in degassed MeOH (1 mL) under argon and a samarium(II) iodide solution (0.1 M in THF, 1.63 mL, 0.163 mmol) was added dropwise. The mixture was stirred for 30 min at room temp. and for a further 10 min in the presence of air. Size exclusion chromatography (Sephadex™ LH-20, $CH_3OH$) and subsequent purification by TLC (silica gel, $CH_2Cl_2$/MeOH, 10:1) yielded **9** (16 mg, 82%) as a colorless solid. Decomposition >180 °C. $[\alpha]_D^{22}$ = +14.2 (*c* = 0.50, $CH_3OH$). $^1H$ NMR (700 MHz, $CD_3OD$): $\delta$ = 2.24 ($m_c$, 1 H, 5-H), 2.93 (s, 4 H, $CH_2$), 3.22 (dd, *J* = 2.7, 10.8 Hz, 1 H, 5-$CH_2$), 3.62 (dd, *J* = 1.4, 4.9 Hz, 1 H, 3-H), 3.76 (br. d, *J* = 10.8 Hz, 1 H, 5-$CH_2$), 3.80, 3.92, 3.96 (XAB system, $J_{AX}$ = 4.9, $J_{BX}$ = 4.6, $J_{AB}$ = 11.9 Hz, 3 H, 2-H, 2-$CH_2$), 4.54 (dd, *J* = 4.9, 6.5 Hz, 1 H, 4-H), 4.84 (d, *J* = 3.2 Hz, 1 H, 6-H), 7.16–7.19 (m, 5 H, Ar, Ph), 7.24–7.26 (m, 2 H, Ph), 7.36–7.38 (m, 2 H, Ar) ppm. $^{13}C$ NMR (175 MHz, $CD_3OD$): $\delta$ = 38.7, 39.0 (2 t, $CH_2$), 46.2 (d, C-5), 51.9 (d, C-3), 55.2 (t, 5-$CH_2$), 63.3 (t, 2-$CH_2$), 69.3 (d, C-4), 77.2 (d, C-2), 82.2 (d, C-6), 126.87, 126.89, 129.2, 129.3, 129.6 (5 d, Ar, Ph), 138.1, 142.0, 143.0 (3 s, Ar, Ph) ppm. IR (Film): $\tilde{\nu}$ = 3620–3110 (O–H, N–H), 3085–3055 (=C–H), 2955–2850 (C–H), 1465 (C–H), 1265 (C–O) $cm^{-1}$. HRMS (ESI-TOF): calcd. for $C_{21}H_{28}NO_4$ $[M + H]^+$ 358.2018; found 358.2007; calcd. for $C_{21}H_{27}NNaO_4$ $[M + Na]^+$ 380.1838; found 380.1818.

**(2*S*,3*R*,4*R*,5*S*,6*R*)-[3-Amino-6-(4-hexylphenyl)-4-hydroxytetrahydro-2*H*-pyran-2,5-diyl]dimethanol (10):** A suspension of Pd/C (10% Pd, 25 mg) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. Compound **5** (25 mg, 59 μmol) was dissolved in ethyl acetate (1 mL) and added to this suspension. The mixture was stirred for 20 h under hydrogen (balloon), filtered through a pad of Celite®, and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH, 7:1) to yield **10** (9 mg, 45%) as a colorless solid. M.p. 120–122 °C. $[\alpha]_D^{22}$ = +27.6 (*c* = 0.90, $CH_3OH$). $^1H$ NMR (700 MHz, $CD_3OD$): $\delta$ = 0.92 (t, 3 H, 6′-H), 1.31–1.38 (m, 6 H, 5′-H, 4′-H, 3′-H), 1.63 ($m_c$, 2 H, 2′-H), 2.23–2.25 (m, 1 H, 5-H), 2.63 (t, *J* = 7.5 Hz, 2 H, 1′-H), 3.23 (dd, *J* = 2.8, 10.8 Hz, 1 H, 5-$CH_2$), 3.62 (dd, *J* = 1.7, 4.6 Hz, 1 H, 3-H), 3.76 (dd, *J* = 1.6, 10.8 Hz, 1 H, 5-$CH_2$), 3.80, 3.92, 3.96 (XAB system, $J_{BX}$ = 4.7, $J_{AX}$ = 4.9, $J_{AB}$ = 11.9 Hz, 3 H, 2-H, 2-$CH_2$), 4.54 (dd, *J* = 4.6, 7.0 Hz, 1 H, 4-H), 4.84 (d, *J* = 3.7 Hz, 1 H, 6-H), 7.19, 7.38 (2 d, *J* = 8.0 Hz, 4 H, Ar) ppm. $^{13}C$ NMR (175 MHz, $CD_3OD$): $\delta$ = 14.4 (t, C-6′), 23.7, 30.0 (2 t, C-5′, C-4′), 32.7 (t, C-2′), 32.9 (t, C-3′), 36.6 (t, C-1′), 46.1 (d, C-5), 52.0 (d, C-3), 55.2 (t, 5-$CH_2$), 63.3 (t, 2-$CH_2$), 69.2 (d, C-4), 77.1 (d, C-2), 82.2 (d, C-6), 126.9, 129.1 (2 d, Ar), 137.9, 143.0 (2 s, Ar) ppm. IR (ATR): $\tilde{\nu}$ = 3675–3295 (O–H, N–H), 3065–3005 (=C–H), 2955–2855 (C–H), 1465 (C–H) $cm^{-1}$. HRMS (ESI-TOF): calcd. for $C_{19}H_{32}NO_4$ $[M + H]^+$ 338.2326; found 338.2325; calcd. for $C_{19}H_{31}NNaO_4$ $[M + Na]^+$ 360.2145; found 360.2127.

**Synthesis of Dimer 21:** Compound **8** (50 mg, 137 μmol) was dissolved in acetonitrile (1.5 mL) and tetramethylethylenediamine (TMEDA; 0.04 mL, 30 mg, 239 μmol), 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU; 20 μL, 21 mg, 137 μmol), and copper(I) chloride (1 mg, 27 μmol) were added. The solution was stirred for 3 h at room temp. under oxygen. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/methanol, 10:1) to yield **21** (50 mg, quant.) as a colorless solid. M.p. 175–178 °C. $[\alpha]_D^{22}$ = +28.7 (*c* = 0.23, $C_5H_5N$). $^1H$ NMR (700 MHz, $CD_3OD/C_5D_5N$, 1:1): $\delta$ = 2.20 ($m_c$, 2 H, 5-H), 3.50 (d, *J* = 11.4 Hz, 2 H, 4-H), 3.54 ($m_c$, 2 H, 1-H), 4.26, 4.45, 4.54 (XAB system, $J_{AX}$ = 5.6, $J_{BX}$ = 6.1, $J_{AB}$ = 10.9 Hz, 6 H, 8-H, 8-$CH_2$), 4.49 (t, *J* = 3.0 Hz, 2 H, 9-H), 4.63 (d, *J* = 14.5 Hz, 2 H, $NCH_2$), 4.75 (dd, *J* = 1.6, 11.4 Hz, 2 H, 4-H), 5.08 (d, *J* = 14.5 Hz, 2 H, $NCH_2$), 5.12 (s, 2 H, 6-H), 7.31–7.33 (m, 6 H, Ph), 7.39–7.41 (m, 4 H, Ph, Ar), 7.66–7.67 (m, 8 H, Ar) ppm. $^{13}C$ NMR (175 MHz, $CD_3OD/C_5D_5N$, 1:1): $\delta$ = 42.3 (d, C-5), 59.0 (t, C-4), 60.1 (t, $NCH_2$), 64.1 (t, 8-$CH_2$), 69.7 (d, C-9), 74.9 (s, C≡C), 80.3 (d, C-6), 81.4 (d, C-8), 82.8 (s, C≡C), 120.7 (s, Ar), 123.8, 127.4, 128.9, 129.6, 133.0 (5 d, Ar, Ph), 140.8, 143.9 (2 s, Ar, Ph) ppm. IR (ATR): $\tilde{\nu}$ = 3545–3410 (O–H), 3090–3030 (=C–H), 2920–2855 (C–H), 2350, 2145 (C≡C), 1450 (C–H), 1260 (C–O) $cm^{-1}$. HRMS (ESI-TOF): calcd. for $C_{44}H_{45}N_2O_8$ $[M + H]^+$ 729.3176; found 729.3208; calcd. for $C_{44}H_{44}N_2NaO_8$ $[M + Na]^+$ 751.2995; found 751.3028.

**Synthesis of Dimer 27:** Compound **8** (400 mg, 1.09 mmol), $[PdCl_2(PPh_3)_2]$ (38 mg, 55 μmol), and CuI (10 mg, 55 μmol) were added to a sealed tube and flushed with argon. Degassed THF (10 mL), $iPr_2NH$ (2.5 mL), and 1,3-diiodobenzene (180 mg, 546 μmol) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to room temp. and filtered through silica gel ($CH_2Cl_2$/MeOH, 10:1). The solvent was removed in vacuo and the solid dissolved in a $CH_2Cl_2$/pyridine mixture (5 mL/1 mL). DMAP (213 mg, 1.75 mmol) and acetic anhydride (334 mg, 309 μL, 3.27 mmol) were added and the solution was stirred at room temp. for 18 h. Water (10 mL) was added to the mixture and the aqueous layer was extracted with dichloromethane (5 × 20 mL). The combined organic layers were dried with $Na_2SO_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1) to yield **27** (433 mg, 82%) as a colorless solid. M.p. 94–96 °C. $[\alpha]_D^{22}$ = +117.5 (*c* = 0.98, $CHCl_3$). $^1H$ NMR (700 MHz, $CDCl_3$): $\delta$ = 2.00 (s, 6 H, Ac), 2.05 (br. s, 2 H, 5-H), 2.28 (s, 6 H, Ac), 3.13 (s, 2 H, 1-H), 3.43 (d, *J* = 12.2 Hz, 2 H, 4-H), 4.12–4.16 (m, 2 H, 8-H), 4.35, 4.49 (AB system, $J_{AB}$ = 13.4 Hz, 4 H, $NCH_2$), 4.35 ($m_c$, 2 H, 4-H), 4.49–4.52 (m, 4 H, 8-$CH_2$), 5.07 (s, 2 H, 6-H), 5.19 (br. t, *J* = 2.6 Hz, 2 H, 9-H), 7.28–7.30 (m, 2 H, Ph), 7.33–7.38 (m, 9 H, Ph, Ar), 7.45, 7.53 (2 d, *J* = 8.1 Hz, 8 H, Ar), 7.49–7.50 (m, 2 H, Ar), 7.71 ($m_c$, 1 H, Ar) ppm. $^{13}C$ NMR (175 MHz, $CDCl_3$): $\delta$ = 21.0, 21.6 (2 q, Ac), 38.6 (d, C-5), 55.1 (d, C-1), 57.6 (t, C-4), 58.5 (t, $NCH_2$), 64.9 (t, 8-$CH_2$), 71.0 (d, C-9), 77.0 (d, C-8), 79.7 (d, C-6), 88.8, 89.9 (2 s, C≡C), 122.4, 123.7 (2 s, Ar), 126.4, 127.6, 128.6, 126.8, 131.4, 131.7, 134.8 (7 d, Ar), 137.7, 139.8 (2 s, Ar), 170.2, 170.8 (2 s, Ac) ppm; one d for Ph/Ar could not be detected. IR (ATR): $\tilde{\nu}$ = 3020 (=C–H), 2920–2850 (C–H), 2340, 2330 (C≡C), 1740 (C=O), 1465 (C–H), 1235 (C–O) $cm^{-1}$. HRMS (ESI-TOF): calcd. for $C_{58}H_{57}N_2O_{12}$ $[M + H]^+$ 973.3912; found 973.3879; calcd. for $C_{58}H_{56}N_2NaO_{12}$ $[M + Na]^+$ 995.3725; found 995.3713. $C_{58}H_{56}N_2O_{12}$ (973.1): calcd. C 71.59, H 5.80, N 2.88; found C 71.61, H 5.93, N 2.88.

**Synthesis of Dimer 28:** A suspension of Pd/C (10% Pd, 72 mg) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. Compound **27** (72 mg, 74 μmol) was dissolved in ethyl acetate (1.5 mL) and added to this suspension. The mixture was stirred for 6 h under hydrogen (balloon), filtered through a pad of Celite®, and the solvent was removed in vacuo. The crude product was dissolved in degassed MeOH (1 mL) under argon and a samarium(II) iodide solution (0.1 M in THF, 4.44 mL, 444 μmol) was added dropwise. The mixture was stirred for 30 min at room temp. and for a further 10 min in the presence of air. Size exclusion chromatography (Sephadex™ LH-20, $CH_3OH$) and subsequent purification by RP-HPLC (Gemini®-NX, MeOH/$H_2O$, 1:1 to 8:2) yielded **28** (30 mg, 56%) as a colorless solid. M.p. 104–106 °C. $[\alpha]_D^{22}$ = +10.4 (*c* = 1.15,

$CH_3OH$). $^1H$ NMR (700 MHz, $CD_3OD$): $\delta$ = 2.04 (s, 6 H, Ac), 2.19 ($m_c$, 2 H, 5-H), 2.86 ($m_c$, 8 H, $CH_2$), 3.36 (dd, $J$ = 3.9, 11.3 Hz, 2 H, 5-$CH_2$), 3.58, 3.67, 3.72 (XAB system, $J_{BX}$ = 5.7, $J_{AB}$ = 6.9, $J_{AX}$ = 11.6 Hz, 6 H, 2-$CH_2$, 2-H), 3.68 (dd, $J$ = 3.0, 11.3 Hz, 2 H, 5-$CH_2$), 4.27 (dd, $J$ = 1.5, 4.7 Hz, 2 H, 3-H), 4.38 (dd, $J$ = 4.7, 6.4 Hz, 2 H, 4-H), 4.74 (d, $J$ = 3.4 Hz, 2 H, 6-H), 6.88 ($m_c$, 1 H, Ar), 6.95–6.97 (m, 2 H, Ar), 7.12 ($m_c$, 1 H, Ar), 7.14, 7.35 (2 d, $J$ = 8.1 Hz, 8 H, Ar) ppm. $^{13}C$ NMR (175 MHz, $CD_3OD$): $\delta$ = 22.9 (q, Ac), 38.9 (t, $CH_2$), 39.1 (t, $CH_2$), 46.8 (d, C-5), 49.9 (d, C-3), 56.5 (t, 5-$CH_2$), 62.8 (t, 2-$CH_2$), 71.5 (d, C-4), 81.1 (d, C-2), 81.8 (d, C-6), 126.8, 127.1, 129.2, 129.4, 130.1 (5 d, Ar), 138.7, 141.8, 142.8 (3 s, Ar), 174.4 (s, Ac) ppm. IR (ATR): $\tilde{\nu}$ = 3595–3120 (O–H, N–H), 3075–3035 (=C–H), 2960–2850 (C–H), 1740 (C=O), 1465 (C–H), 1260 (C–O) $cm^{-1}$. HRMS (ESI-TOF): calcd. for $C_{32}H_{44}N_2NaO_{10}$ $[M + Na]^+$ 639.2894; found 639.2877; calcd. for $C_{32}H_{44}KN_2O_{10}$ $[M + K]^+$ 655.2633; found 655.2676.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures for all experiments and analytical data of all new compounds, and copies of all $^1H$ and $^{13}C$ NMR spectra.

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# ***SUPPORTING INFORMATION***

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***Title:*** Preparation of Multivalent Carbohydrate Mimetics Based on Enantiopure 1,2-Oxazines by Sonogashira Coupling and Subsequent Reductive Ring-Opening

***Author(s):*** Maja Kandziora and Hans-Ulrich Reissig*

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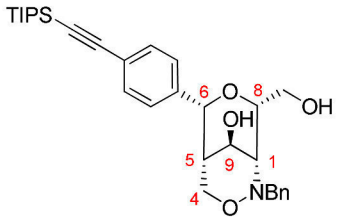
**General information**

Reactions were generally performed under inert atmosphere (argon) in flame-dried flasks. Solvents and reagents were added by syringe. Solvents were dried using standard procedures and were purified with a MB SPS-800-dry solvent system. Commercial available reagents were used as received without further purification unless otherwise stated. Products were purified by flash chromatography on silica gel (230–400 mesh, MACHERY-NAGEL), by size exclusion chromatography (Sephadex™ LH-20, GE Healthcare) and by RP-HPLC (Gemini®-NX C18 Phenomenex). Unless otherwise stated, yields refer to analytical pure samples. Hydrogenolyses were performed with hydrogen from Air Liquide (Alphagaz 2). TLC-analyses were performed on silica gel coated aluminium plates purchased from Merck. Products were detected by UV-activity and by using staining reagents (Cer/molybdenum reagent, $KMnO_4$ and ninhydrine). NMR spectra were recorded on BRUKER (AV 500, AV 700) and JEOL (ECP 500) instruments. Chemical shifts (δ) are listed in parts per million (ppm) and are reported relative to solvent residual signals: $CDCl_3$ ($^1$H: δ = 7.26 ppm, $^{13}$C: δ = 77.2 ppm), $CD_3OD$ ($^1$H: δ = 3.31 ppm, $^{13}$C: δ = 49.0 ppm) or pyridine-d$^5$ ($^1$H: δ = 8.74 ppm, $^{13}$C: δ = 150.4 ppm). Integrals are in accordance with assignments; coupling constants (*J*) are given in Hz. All $^{13}$C NMR spectra are proton-decoupled. Multiplicity is indicated as follows: s (singlet), $s_{br}$ (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), m (multiplet), $m_c$ (centered multiplet). For detailed peak assignments 2D spectra were measured (COSY and HMQC). IR spectra were measured with a Jasco spectrometer (FT/IR-4100 with DLATGS Detector). HRMS analyses were performed with Agilent 6210 (ESI–TOF, 10 µL/min, 1.0 bar, 4 kV) and Varian/Agilent Ionspec QFT-7 (ESI–FTICR, 4 µL/min, 1.0 bar, 4kV) instruments. Elemental analyses were carried out with instruments from Elementar (Vario EL, Vario EL III). Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected.

The following compounds were prepared analogously to literature procedures: **1a**[1], **1b**[1], **14**[2], 4,4'-(2,2-bis((4-iodobenzyloxy)methyl)propane-1,3-diyl)bis(oxy)bis(methylene)bis(iodo-benzene)[3].

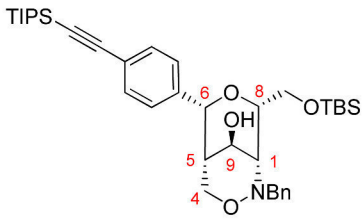
**(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-8-(hydroxymethyl)-6-{4-[(triisopropylsilyl)ethynyl]phenyl}-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (4a)**




Compound **1a** (3.00 g, 7.14 mmol), $PdCl_2(PPh_3)_2$ (250 mg, 357 µmol) and CuI (68 mg, 357 µmol) were filled in a sealed tube and flushed with argon. Degassed THF (43 mL), $i Pr_2NH$ (16 mL) and (triisopropylsilyl)acetylene (1.95 g, 10.7 mmol) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt, water (40 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 80 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:1) to yield **4a** (4.13 g, quant.) as a colorless solid.

m.p. 61-63 °C; $[\alpha]_D^{22}$ = +82.7 (*c* = 1.03, $CH_3OH$); $^1$H NMR (500 MHz, $CD_3OD$): δ = 1.12 ($s_{br}$, 21 H, *i*-Pr), 1.89 ($s_{br}$, 1 H, 5-H), 3.06 (s, 1 H, 1-H), 3.23 (d, *J* = 11.7 Hz, 1 H, 4-H), 3.80, 3.86, 3.98 (ABX system, $J_{AB}$ = 4.9 Hz, $J_{AX}$ = 6.0 Hz, $J_{BX}$ = 11.0 Hz, 3 H, 8-H, 8-$CH_2$), 4.08 ($m_c$, 1 H, 9-H), 4.22 (d, *J* = 14.1 Hz, 1 H, $NCH_2$), 4.37 (d, *J* = 11.7 Hz, 1 H, 4-H), 4.60 (d, *J* = 14.1 Hz, 1 H, $NCH_2$), 4.84 ($s_{br}$, 1 H, 6-H), 7.17-7.20 (m, 1 H, Ph), 7.25-7.28 (m, 2 H, Ph), 7.34-7.35 (m, 2 H, Ph), 7.40 ($s_{br}$, 4 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CD_3OD$): δ = 12.5 (d, *i*-Pr), 19.1 (q, *i*-Pr), 42.2 (d, C-5), 59.0 (t, C-4), 60.4 (t, $NCH_2$), 60.8 (d, C-1), 64.5 (t, 8-$CH_2$), 69.9 (d, C-9), 80.69, 80.71 (2 d, C-6, C-8), 90.5, 108.6 (2 s, C≡C), 123.3 (s, Ar), 127.2, 128.0, 129.1, 129.9, 132.6 (5 d, Ar, Ph), 140.3, 142.5 (s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ = 3625-3155 (O-H), 3085-3060 (=C-H), 2940-2865 (C-H), 2155 (C≡C), 1460 (C-H), 1240 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{31}H_{44}NO_4Si$ [*M* + H]$^+$: 522.3040; found: 522.3036; calcd for $C_{31}H_{43}NNaO_4Si$ [*M* + Na]$^+$: 544.2859; found: 544.2853; elemental analysis calcd (%) for $C_{31}H_{43}NO_4Si$ (521.8): C, 71.36; H, 8.31; N, 2.68; found: C, 71.30; H, 8.32; N, 2.70.

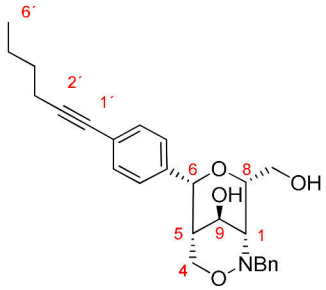
**(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-8-[(*tert*-butyldimethylsiloxy)methyl]-6-{4-[(triisopropylsilyl)-ethynyl]phenyl}-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (4b)**




Bicyclic compound **1b** (695 mg, 1.30 mmol), $PdCl_2(PPh_3)_2$ (46 mg, 65 µmol) and CuI (12 mg, 65 µmol) were filled in a sealed tube and flushed with argon. THF (10 mL), $i Pr_2NH$ (3 mL) and (triisopropylsilyl)acetylene (0.44 mL, 356 mg, 1.95 mmol) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt and water (10 mL) was added. The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried with $NaSO_4$, filtered and the solvent was removed in vacuo. The crude material was purified by column chromatography (silica gel, hexanes/EtOAc 30:1) to yield **4b** (796 mg, 96%) as a colorless solid.

m.p. 103 °C; $[\alpha]_D^{22}$ = +51.9 (*c* = 0.92, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ = 0.11 (s, 3 H, SiMe), 0.12 (s, 3 H, SiMe), 0.93 (s, 9 H, Si*t*-Bu), 1.14 (s, 21 H, *i*-Pr), 2.08 ($s_{br}$, 1 H, 5-H), 3.30 ($s_{br}$, 1 H, 1-H), 3.70 (dd, *J* = 1.9, 12.1 Hz, 1 H, 4-H), 3.76 (d, *J* = 10.4 Hz, 1 H, 8-H), 3.85 ($m_c$, 1 H, 8-$CH_2$), 3.96-4.07 (m, 4 H, 4-H, 8-$CH_2$, 9-H, OH), 4.13, 4.35 (AB system, $J_{AB}$ = 15.1 Hz, 1 H, $NCH_2$), 4.77 (s, 1 H, 6-H), 7.26-7.29 (m, 1 H, Ph), 7.31, 7.46 (AA´BB´ system, $J_{AB}$ = 8.2 Hz, 4 H, Ar), 7.34-7.36 (m, 4 H, Ph), ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = -5.3, -5.2 (q, SiMe), 11.4 (d, *i*-Pr), 18.3 (q, *i*-Pr), 18.8, 26.2 (q, s, Si*t*-Bu), 41.1 (d, C-5), 60.6 (d, C-1), 61.9 (t, $NCH_2$), 62.7 (t, 8-$CH_2$), 65.1 (t, C-4), 70.6 (d, C-9), 79.4 (d, C-6), 79.9 (d, C-8), 90.6, 107.0 (2 s, C≡C), 122.6 (s, Ar), 125.7, 127.3, 128.2, 128.5, 132.1 (5 d, Ar), 138.5, 140.4 (2 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ = 3515-3460 (O-H), 3090-3030 (=C-H), 2960-2865 (C-H), 2150 (C≡C), 1460 (CH), 1250 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{37}H_{58}NO_4Si_2$ [*M* + H]$^+$: 636.3899, found: 636.3874, calcd for $C_{37}H_{57}NNaO_4Si_2$ [*M* + Na]$^+$: 658.3718; found: 658.3689.

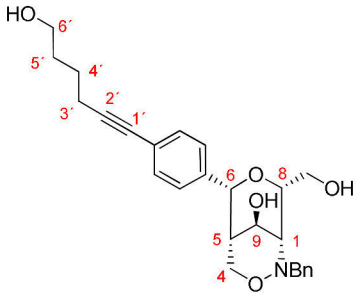
**(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-6-[4-(hex-1-ynyl)phenyl]-8-(hydroxymethyl)-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (5)**




Compound **1a** (100 mg, 0.238 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 9 µmol) and CuI (2 mg, 9 µmol) were filled in a sealed tube and flushed with argon. Degassed DMF (3 mL), *i*$Pr_2NH$ (0.4 mL) and 1-hexyne (23 mg, 0.032 mL, 281 µmol) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt, brine (10 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:1) to yield **5** (85 mg, 85%) as a colorless solid.

m.p. 136 °C; $[\alpha]_D^{22}$ = +103.6 (*c* = 1.00, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.4 Hz, 3 H, 6´-H), 1.45-1.50 (m, 2 H, 5´-H), 1.57-1.61 (m, 2 H, 4´-H), 2.04 (s, 1 H, 5-H), 2.40 (t, *J* = 7.1 Hz, 2 H, 3´-H), 2.66 ($s_{br}$, 1 H, OH), 3.08 (s, 1 H, 1-H), 3.63 ($s_{br}$, 1-H, OH), 3.69 (dd, *J* = 1.7, 12.1 Hz, 1 H, 4-H), 3.84 ($m_c$, 2 H, 8-H, 8-$CH_2$), 4.03-4.08 (m, 2 H, 4-H, 9-H), 4.09, 4.29 (AB system, $J_{AB}$ = 14.0 Hz, 2 H, $NCH_2$), 4.11-4.15 (m, 1 H, 8-$CH_2$), 4.77 (s, 1 H, 6-H), 7.27-7.30 (m, 3 H, Ar, Ph), 7.32-7.34 (m, 4 H, Ph), 7.37-7.38 (m, 2 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 13.8 (q, C-6´), 19.2 (t, C-3´), 22.2 (t, C-5´), 30.9 (t, C-4´), 40.9 (d, C-5), 61.4 (d, C-1), 61.6 (t, $NCH_2$), 64.0 (t, 8-$CH_2$), 64.3 (t, C-4), 70.4 (d, C-9), 79.5 (d, C-6), 79.8 (d, C-8), 80.4, 90.7 (2 s, C≡C), 123.3 (s, Ar), 125.7, 127.7, 128.6, 128.7, 131.6 (5 d, Ar, Ph), 137.4, 139.1 (2 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ = 3635-3150 (O-H), 3030 (=C-H), 2955-2870 (C-H), 2230 (C≡C), 1455 (C-H), 1240 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{32}NO_4$ $[M + H]^+$: 422.2326, found: 422.2340; calcd for $C_{26}H_{31}NNaO_4$ $[M + Na]^+$: 444.2145, found, 444.2158; elemental analysis calcd (%) for $C_{26}H_{31}NO_4$ (421.2): C, 74.08; H, 7.41; N, 3.32; C, 73.86; H, 7.41; N, 3.60.

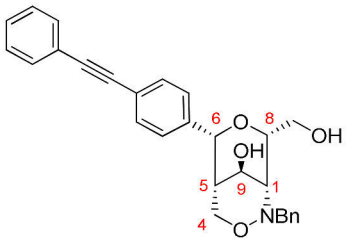
**(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-6-[4-(6-hydroxyhex-1-ynyl)phenyl]-8-(hydroxymethyl)-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (6)**




Compound **1a** (240 mg, 0.571 mmol), $PdCl_2(PPh_3)_2$ (40 mg, 57 µmol) and CuI (11 mg, 57 µmol) were filled in a sealed tube and flushed with argon. Degassed DMF (4 mL), $i$Pr$_2$NH (1.3 mL) and hex-5-yn-1-ol (84 mg, 0.095 mL, 0.86 mmol) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt, water (5 mL) and brine (5 mL) were added and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:1) to yield **6** (185 mg, 74%) as a colorless solid.

m.p. 51-53 °C; $[\alpha]_D^{22}$ = +96.6 ($c$ = 0.10, $CHCl_3$); $^1$H NMR (500 MHz, $CD_3OD$): δ = 1.65-1.76 (m, 4 H, 4´-H, 5´-H), 1.94 (s, 1 H, 5-H), 2.46 (t, $J$ = 6.5 Hz, 2 H, 3´-H), 3.11 (s, 1 H, 1-H), 3.29 (d, $J$ = 11.8 Hz, 1 H, 4-H), 3.63 (t, $J$ = 6.2 Hz, 2 H, 6´-H), 3.85, 3.90, 4.01 (ABX system, $J_{AB}$ = 5.1 Hz, $J_{AX}$ = 6.0 Hz, $J_{BX}$ = 11.0 Hz, 3 H, 8-H, 8-$CH_2$), 4.14 ($m_c$, 1 H, 9-H), 4.27 (d, $J$ = 14.1 Hz, 1 H, $NCH_2$), 4.41 (dd, $J$ = 2.2, 11.8 Hz, 1 H, 4-H), 4.64 (d, $J$ = 14.1 Hz, 1 H, $NCH_2$), 4.92 (s, 1 H, 6-H), 7.22-7.25 (m, 1 H, Ph), 7.30-7.32 (m, 8 H, Ar, Ph) ppm; $^{13}$C NMR (125 MHz, $CD_3OD$): δ = 19.8 (t, C-3´), 25.3 (t, C-4´), 32.8 (t, C-5´), 42.3 (d, C-5), 59.1 (t, C-4), 60.4 (t, $NCH_2$), 60.9 (d, C-1), 62.5 (t, C-6´), 64.6 (t, 8-$CH_2$), 70.0 (d, C-9), 80.8 (2 d, C-6, C-8), 81.7, 90.5 (2 s, C≡C), 124.2 (s, Ar), 127.1, 128.0, 129.1, 129.9, 132.2 (5 d, Ar, Ph), 140.3, 141.4 (2 s, Ar) ppm; IR (ATR): $\tilde{\nu}$ = 3610-3110 (O-H), 3060-3030 (=C-H), 2935-2855 (C-H), 2230 (C≡C), 1455 (C-H), 1245 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{32}NO_5$ [$M$ + H]$^+$: 438.2280, found: 438.2280, calcd for $C_{26}H_{31}NNaO_5$ [$M$ + Na]$^+$: 460.2094, found: 460.2088; elemental analysis calcd (%) for $C_{26}H_{31}NO_5$ (437.2): C, 71.37; H, 7.14; N, 3.20; C, 71.72; H, 7.25; N, 3.66.

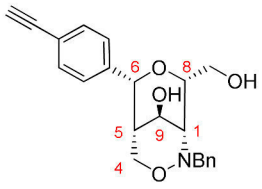
**(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-8-(hydroxymethyl)-6-[4-(phenylethynyl)phenyl]-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (7)**




Compound **1a** (30 mg, 71 µmol), $PdCl_2(PPh_3)_2$ (3 mg, 4 µmol) and CuI (1 mg, 4 µmol) were filled in a sealed tube and flushed with argon. Degassed THF (1 mL), *i*$Pr_2NH$ (0.16 mL) and phenylacetylene (8.7 mg, 85 µmol) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt, water (3 mL) was added and the aqueous layer was extracted with ethyl acetate (5 x 5 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:2) to yield **7** (27 mg, 86%) as a colorless solid.

m.p. 174-177 °C; $[\alpha]_D^{22}$ = +92.2 (*c* = 1.10, $CHCl_3$); $^1$H NMR (500 MHz, $CD_2Cl_2$): δ = 2.07 ($s_{br}$, 1 H, 5-H), 2.52 ($s_{br}$, 1 H, OH), 3.12 ($m_c$, 1 H, 1-H), 3.49 ($d_{br}$, *J* = 9.9 Hz, 1 H, OH), 3.63 (dd, *J* = 2.2, 12.1 Hz, 1 H, 4-H), 3.84-3.89 (m, 2 H, 8-$CH_2$, 8-H), 4.06 (dd, *J* = 2.2, 12.1 Hz, 1 H, 4-H), 4.07- 4.15 (m, 2 H, 8-$CH_2$, 9-H), 4.12, 4.25 (AB system, $J_{AB}$ = 14.3 Hz, 2 H, $NCH_2$), 4.85 (s, 1 H, 6-H), 7.25-7.29 (m, 1 H, Ph), 7.32-7.37 (m, 7 H, Ar, Ph), 7.40-7.41 (m, 2 H, Ar) 7.52-7.54 (m, 4 H, Ar, Ph) ppm; $^{13}$C NMR (125 MHz, $CD_2Cl_2$): δ = 41.4 (d, C-5), 61.9 (t, $NCH_2$), 62.3 (d, C-1), 64.4 (t, C-4), 64.5 (t, 8-$CH_2$), 70.7 (d, C-9), 79.8 (d, C-6), 80.4 (d, C-8), 89.6, 89.8 (2 s, C≡C), 122.7, 123.7 (2 s, Ar, Ph), 126.5, 127.9, 128.89, 128.91, 129.0, 129.1, 132.0, 132.1 (8 d, Ar, Ph), 138.5, 141.0 (2 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ = 3600-3405 (O-H), 3140-3030 (=C-H), 2925-2855 (C-H), 2350, 2220 (C≡C), 1455 (C-H) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{28}H_{28}NO_4$ [*M* + H]$^+$: 442.2018; found: 442.2028; calcd for $C_{28}H_{27}NNaO_4$ [*M* + Na]$^+$: 464.1832; found: 464.1839; elemental analysis calcd (%) for $C_{28}H_{27}NO_4 + H_2O$ (459.5): C, 73.18; H, 6.36; N, 3.05; C, 73.78; H, 6.38; N, 3.15.

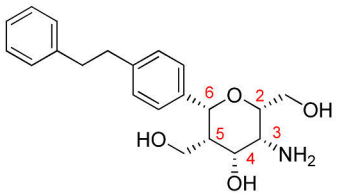
**(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-6-(4-ethynylphenyl)-8-(hydroxymethyl)-3,7-dioxa-2-azabicyclo-[3.3.1]nonan-9-ol (8)**




Bicyclic compound **4a** (711 mg, 1.36 mmol) was dissolved in THF (8 mL) and tetra-*n*-butylammonium fluoride (1 M in THF, 2.73 mL, 2.73 mmol) was added. The solution was stirred for two days at rt and then quenched with water (20 mL). The aqueous layer was extracted with ethyl acetate (5 x 20 mL). The combined organic layers were dried with $NaSO_4$, filtered and the solvent was removed in vacuo. The crude material was purified by column chromatography (silica gel, hexanes/EtOAc 1:2) to yield **8** (417 mg, 84%) as a colorless solid.

m.p. 163-165 °C; $[\alpha]_D^{22}$ = +35.6 (*c* = 0.62, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3/CD_3OD$, 2:1): δ = 2.43 ($m_c$, 1 H, 5-H), 3.58 ($s_{br}$, 1 H, 1-H), 3.65 ($m_c$, 1 H, C≡C-H), 3.91 (d, *J* = 12.0 Hz, 1 H, 4-H), 4.31, 4.34, 4.53 (ABX system, $J_{AB}$ = 4.7 Hz, $J_{AX}$ = 5.9 Hz, $J_{BX}$ = 11.2 Hz, 3 H, 8-H, 8-$CH_2$), 4.56 ($m_c$, 1 H, 9-H), 4.78 ($m_c$, 1 H, 4-H), 4.79, 4.93 (AB system, $J_{AB}$ = 14.0 Hz, 2 H, $NCH_2$), 5.36 (s, 1 H, 6-H), 7.71-7.73 (m, 1 H, Ph), 7.78-7.80 (m, 2 H, Ph), 7.83-7.84 (m, 2 H, Ph), 7.87-7.88 (m, 2 H, Ar), 7.93-7.94 (m, 2 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CDCl_3/CD_3OD$, 2:1): δ = 40.5 (d, C-5), 59.57, 59.61 (2 t, $NCH_2$, C-4), 59.7 (d, C-1), 63.4 (t, 8-$CH_2$), 68.8 (d, C-9), 77.0 (d, C≡C-H), 79.0 (d, C-8), 79.3 (d, C-6), 83.1 (s, C≡C-H), 120.9 (s, Ar), 125.7, 127.0, 128.0, 128.4, 131.7 (5 d, Ph, Ar), 138.0, 140.7 (2 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ = 3575-3080 (O-H), 3080-3025 (=C-H), 2980-2835 (C-H), 2100 (C≡C), 1460 (C-H), 1250 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{24}NO_4$ [*M* + H]$^+$: 366.1700; found: 366.1708; calcd for $C_{22}H_{23}NNaO_4$ [*M* + Na]$^+$: 388.1519; found: 388.1527; elemental analysis calcd (%) for $C_{22}H_{23}NO_4$ (365.4): C, 72.31; H, 6.34; N, 3.83; found: C, 72.41; H, 6.35; N, 3.90.

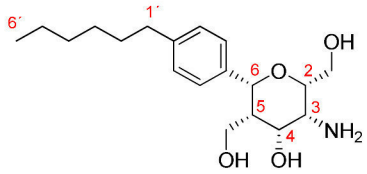
**(2*S*,3*R*,4*R*,5*S*,6*R*)-[3-Amino-4-hydroxy-6-(4-phenethylphenyl)tetrahydro-2*H*-pyran-2,5-diyl]dimethanol (9)**




A suspension of Pd/C (10% Pd, 24 mg) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. Compound **7** (24 mg, 54 µmol) was dissolved in ethyl acetate (1 mL) and added to this suspension. The mixture was stirred for 4 h under hydrogen atmosphere (balloon), filtered through a pad of Celite® and the solvent was removed in vacuo. Under an argon atmosphere the crude product was dissolved in degassed MeOH (1 mL) and a samarium(II) iodide solution (0.1 M in THF, 1.63 mL, 0.163 mmol) was added drop wise. The mixture was stirred for 30 min at rt and for further 10 min in the presence of air. Size exclusion chromatography (Sephadex™ LH-20, $CH_3OH$) and subsequent purification by thin-layer chromatography (silica gel, $CH_2Cl_2$/MeOH, 10:1) yielded **9** (9 mg, 46%) as a colorless solid.

Decomposition >180 °C; $[\alpha]_D^{22}$ = +14.2 (*c* = 0.50, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD$): δ = 2.24 ($m_c$, 1 H, 5-H), 2.93 (s, 4 H, $CH_2$), 3.22 (dd, *J* = 2.7, 10.8 Hz, 1 H, 5-$CH_2$), 3.62 (dd, *J* = 1.4, 4.9 Hz, 1 H, 3-H), 3.76 ($d_{br}$, *J* = 10.8 Hz, 1 H, 5-$CH_2$), 3.80, 3.92, 3.96 (XAB system, $J_{AX}$ = 4.9 Hz, $J_{BX}$ = 4.6 Hz, $J_{AB}$ = 11.9 Hz, 3 H, 2-H, 2-$CH_2$), 4.54 (dd, *J* = 4.9, 6.5 Hz, 1 H, 4-H), 4.84 (d, *J* = 3.2 Hz, 1 H, 6-H), 7.16-7.19 (m, 5 H, Ar, Ph), 7.24-7.26 (m, 2 H, Ph), 7.36-7.38 (m, 2 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CD_3OD$): δ = 38.7, 39.0 (t, $CH_2$), 46.2 (d, C-5), 51.9 (d, C-3), 55.2 (t, 5-$CH_2$), 63.3 (t, 2-$CH_2$), 69.3 (d, C-4), 77.2 (d, C-2), 82.2 (d, C-6), 126.87, 126.89, 129.2, 129.3, 129.6 (5 d, Ar, Ph), 138.1, 142.0, 143.0 (3 s, Ar, Ph) ppm; IR (Film): $\tilde{\nu}$ = 3620-3110 (O-H, N-H), 3085-3055 (=C-H), 2955-2850 (C-H), 1465 (C-H),1265 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{28}NO_4$ $[M + H]^+$: 358.2018, found: 358.2007, calcd for $C_{21}H_{27}NNaO_4$ $[M + Na]^+$: 380.1838, found: 380.1818.

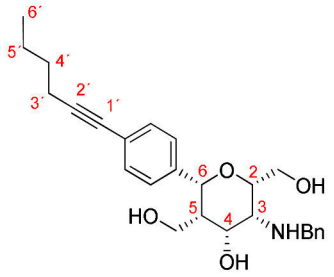
**(2*S*,3*R*,4*R*,5*S*,6*R*)-[3-Amino-6-(4-hexylphenyl)-4-hydroxytetrahydro-2*H*-pyran-2,5-diyl]-dimethanol (10)**




A suspension of Pd/C (10% Pd, 25 mg) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. Compound **5** (25 mg, 59 µmol) was dissolved in ethyl acetate (1 mL) and added to this suspension. The mixture was stirred for 20 h under hydrogen atmosphere (balloon), filtered through a pad of Celite® and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 7:1) to yield **10** (9 mg, 45%) as a colorless solid.

m.p. 120-122 °C; $[\alpha]_D^{22}$ = +27.6 (*c* = 0.90, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD$): δ = 0.92 (t, 3 H, 6´-H), 1.31-1.38 (m, 6 H, 5´-H, 4´-H, 3´-H), 1.63 (dt, *J* = 7.5, 15.4 Hz, 2 H, 2´-H), 2.23-2.25 (m, 1 H, 5-H), 2.63 (t, *J* = 7.5 Hz, 2 H, 1´-H), 3.23 (dd, *J* = 2.8, 10.8 Hz, 1 H, 5-$CH_2$), 3.62 (dd, *J* = 1.7, 4.6 Hz, 1 H, 3-H), 3.76 (dd, *J* = 1.6, 10.8 Hz, 1 H, 5-$CH_2$), 3.80, 3.92, 3.96 (XAB system, $J_{BX}$ = 4.7 Hz, $J_{AX}$ = 4.9 Hz, $J_{AB}$ = 11.9 Hz, 3 H, 2-H, 2-$CH_2$), 4.54 (dd, *J* = 4.6, 7.0 Hz, 1 H, 4-H), 4.84 (d, *J* = 3.7 Hz, 1 H, 6-H), 7.19, 7.38 (AA´BB´ system, $J_{AB}$ = 8.0 Hz, 4 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CD_3OD$): δ = 14.4 (t, 6´-H), 23.7, 30.0 (2 t, 5´-H, 4´-H), 32.7 (t, 2´-H), 32.9 (t, 3´-H), 36.6 (t, 1´-H), 46.1 (d, 5-H), 52.0 (d, 3-H), 55.2 (t, 5-$CH_2$), 63.3 (t, 2-$CH_2$), 69.2 (d, C-4), 77.1 (d, C-2), 82.2 (d, C-6), 126.9, 129.1 (2 d, Ar), 137.9, 143.0 (2 s, Ar) ppm; IR (ATR): $\tilde{\nu}$ = 3675-3295 (O-H, N-H), 3065-3005 (=C-H), 2955-2855 (C-H), 1465 (C-H) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{32}NO_4$ $[M + H]^+$: 338.2326; found: 338.2325; calcd for $C_{19}H_{31}NNaO_4$ $[M + Na]^+$: 360.2145; found: 360.2127.

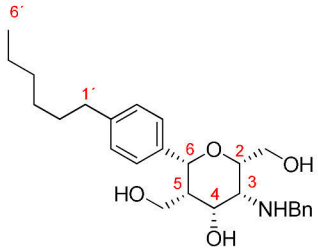
**(2*S*,3*R*,4*R*,5*S*,6*R*)-{3-(Benzylamino)-6-[4-(hex-1-ynyl)phenyl]-4-hydroxytetrahydro-2*H*-pyran-2,5-diyl}dimethanol (11)**




Under an argon atmosphere the compound **5** (30 mg, 71 µmol) was dissolved in degassed THF (1 mL) and a samarium(II) iodide solution (0.1 M in THF, 2.13 mL, 213 µmol) was added drop wise. The mixture was stirred for 30 min at rt and for further 10 min in the presence of air. Sat. potassium sodium tartrate solution (5 mL) was added and the aqueous layer was extracted with dichloromethane (5 x 10 mL). The combined organic layers were dried with $NaSO_4$, filtered and the solvent was removed in vacuo. The crude material was purified by thin-layer chromatography (silica gel, $CH_2Cl_2$/MeOH, 10:1) to yield **11** (19 mg, 63%) as a colorless solid.

m.p. 62-65 °C; $[\alpha]_D^{22}$ = +82.5 (*c* = 1.03, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD/C_5D_5N$ 5:1): δ = 0.90 (t, *J* = 7.3 Hz, 3 H, 6´-H), 1.41-1.46 (m, 2 H, 5´-H), 1.50-1.54 (m, 2 H, 4´-H), 2.24 ($m_c$, 1 H, 5-H), 2.35 (t, *J* = 7.0 Hz, 2 H, 3´-H), 3.14 (dd, *J* = 2.9, 10.9 Hz, 1 H, 5-$CH_2$), 3.54 (d, *J* = 2.9 Hz, 1 H, 3-H), 3.60, 3.89, 3.96 (XAB system, $J_{AX}$ = 3.2 Hz, $J_{BX}$ = 3.6 Hz, $J_{AB}$ = 12.1 Hz, 3 H, 2-H, 2-$CH_2$), 3.78 (dd, *J* = 2.4, 10.9 Hz, 1 H, 5-$CH_2$), 4.21, 4.45 (d, *J* = 12.7 Hz, 2 H, $NCH_2$), 4.54 (dd, *J* = 4.1, 6.8 Hz, 1 H, 4-H), 4.79 (d, *J* = 4.0 Hz, 1 H, 6-H), 7.28-7.43 (m, 9 H, Ph, Ar) ppm; $^{13}$C NMR (175 MHz, $CD_3OD/C_5D_5N$ 5:1): δ = 14.0 (q, C-6´), 19.7 (t, C-3´), 23.0 (t, C-5´), 32.0 (t, C-4´), 46.4 (d, C-5), 54.0 (t, $NCH_2$), 55.9 (t, 5-$CH_2$), 59.6 (d, C-3), 64.9 (t, 2-$CH_2$), 72.6 (d, C-4), 77.7 (d, C-2), 81.5 (s, C-1´), 82.2 (d, C-6), 90.8 (s, C-2´), 124.3 (s, Ar), 127.0, 129.7, 130.1, 130.3, 132.1 (5 d, Ar, Ph), 138.1, 140.3 (2 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ = 3650-3280 (O-H, N-H), 3090-3035 (=C-H), 2955-2855 (C-H), 2230 (C≡C), 1455 (C-H) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{34}NO_4$ [*M* + H]$^+$: 424.2488, found: 424.2473.

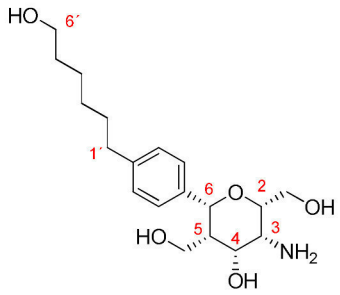
**(2*S*,3*R*,4*R*,5*S*,6*R*)-[3-(Benzylamino)-6-(4-hexylphenyl)-4-hydroxytetrahydro-2*H*-pyran-2,5-diyl]dimethanol (12)**




A suspension of Pd/C (10% Pd, 18 mg) and MeOH (3 mL) was saturated with hydrogen for 15 min. Compound **11** (18 mg, 43 µmol) was dissolved in ethyl acetate (0.5 mL) and added to this suspension. The mixture was stirred for 18 h under hydrogen atmosphere (balloon), filtered through a pad of Celite® and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 7:1) to yield **12** (13 mg, 71%) as a colorless solid.

m.p. 55-57 °C; $[\alpha]_D^{22}$= +58.7 (*c* = 1.20, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD$): δ = 0.91 ($m_c$, 3 H, 6´-H), 1.31-1.35 (m, 6 H, 3´-H, 4´-H, 5´-H), 1.62 ($m_c$, 2 H, 2´-H), 2.23 ($s_{br}$, 1 H, 5-H), 2.61 (t, *J* = 7.6 Hz, 2 H, 1´-H), 3.26 (dd, *J* = 3.6, 11.2 Hz, 1 H, 5-$CH_2$), 3.39 ($s_{br}$, 1 H, 3-H), 3.63 (td, *J* = 1.3, 4.0 Hz, 1 H, 2-H), 3.75 (dd, *J* = 2.6, 11.2 Hz, 1 H, 5-$CH_2$), 3.91 ($m_c$, 2 H, 2-$CH_2$), 4.12, 4.33 (d, *J* = 12.7 Hz, 2 H, $NCH_2$), 4.49 (dd, *J* = 3.6, 5.9 Hz, 1 H, 4-H), 4.77 (d, *J* = 3.6 Hz, 1 H, 6-H), 7.15-7.17 (m, 2 H, Ar), 7.35-7.36 (m, 3 H, Ar, Ph), 7.38-7.40 (m, 2 H, Ph), 7.43-7.44 (m, 2 H, Ph) ppm; $^{13}$C NMR (175 MHz, $CD_3OD$): δ = 14.4 (q, 6´-H), 23.7 (t, C-5´), 30.0 (t, C-4´), 30.8 (t, C-3´), 32.9 (t, C-2´), 36.6 (t, C-1´), 47.0 (d, C-5), 54.7 (t, $NCH_2$), 56.3 (t, 5-$CH_2$), 59.3 (d, C-3), 64.6 (t, 2-$CH_2$), 73.8 (d, C-4), 79.1 (d, C-2), 82.6 (d, C-6), 127.0, 129.0, 129.1, 129.9, 130.0 (5 d, Ar, Ph), 138.3, 142.8 (2 s, Ar, Ph) ppm; one singlet for Ph/Ar could not be detected; IR (ATR): $\tilde{\nu}$ = 3685-3295 (O-H, N-H), 3060-3025 (=C-H), 2955-2855 (C-H), 1455 (C-H) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{38}NO_4$ [*M* + H]$^+$: 428.2801, found: 428.2779.

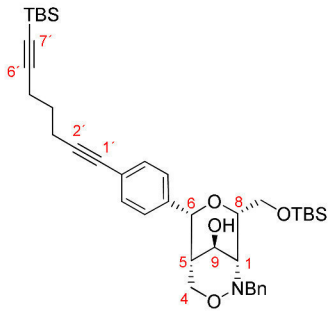
**(2*S*,3*R*,4*R*,5*S*,6*R*)-{3-Amino-4-hydroxy-6-[4-(6-hydroxyhexyl)phenyl]tetrahydro-2*H*-pyran-2,5-diyl}dimethanol (13)**




A suspension of Pd/C (10% Pd, 40 mg) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. Compound **6** (40 mg, 91 µmol) was dissolved in *i*PrOH (1 mL) and added to this suspension. The mixture was stirred for 4 h under hydrogen atmosphere (balloon), filtered through a pad of Celite® and the solvent was removed in vacuo. Under an argon atmosphere the crude product was dissolved in degassed MeOH (2 mL) and a samarium(II) iodide solution (0.1 M in THF, 2.74 mL, 274 µmol) was added drop wise. The mixture was stirred for 30 min at rt and for further 10 min in the presence of air. Size exclusion chromatography (Sephadex™ LH-20, $CH_3OH$) and subsequent purification by thin-layer chromatography (silica gel, $CH_2Cl_2$/MeOH 7N $NH_3$, 7:1) yielded **13** (18 mg, 56%) as a colorless solid.

m.p. 68-70 °C; $[\alpha]_D^{22}$ = +43.8 (*c* = 0.60, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD$): δ = 1.34-1.42 (m, 4 H, 3´-H, 4´-H), 1.53 ($m_c$, 2 H, 2´-H), 1.64 ($m_c$, 2 H, 5´-H), 2.13 ($m_c$, 1 H, 5-H), 2.61 (t, *J* = 7.6 Hz, 2 H, 1´-H), 3.25 (dd, *J* = 4.4, 11.6 Hz, 1 H, 5-$CH_2$), 3.27, 3.74, 3.85 (XAB system, $J_{AX}$ = 5.5 Hz, $J_{BX}$ = 6.6 Hz, $J_{AB}$ = 11.6 Hz, 3 H, 2-H, 2-$CH_2$), 3.54 (t, *J* = 6.7 Hz, 2 H, 6´-H), 3.63-3.65 (m, 2 H, 3-H, 5-$CH_2$), 4.29 (dd, *J* = 4.3, 5.8 Hz, 1 H, 4-H), 4.67 (d, *J* = 3.1 Hz, 1 H, 6-H), 7.16, 7.36 (AA´BB´ system, $J_{AB}$ = 8.1 Hz, 4 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CD_3OD$): δ = 26.8 (t, C-3´), 30.1 (t, C-4´), 32.7 (t, C-5´), 33.6 (t, C-2´), 36.5 (t, C-1´), 47.2 (d, C-5), 50.8 (d, C-2), 56.2 (t, 5-$CH_2$), 62.9 (t, C-6´), 63.1 (t, 2-$CH_2$), 72.9 (d, C-4), 80.2 (d, C-3), 82.0 (d, C-6), 127.0, 128.9 (2 d, Ar), 138.7, 142.5 (2 s, Ar) ppm; IR (ATR): $\tilde{\nu}$ = 3600-3265 (O-H, N-H), 3040-3020 (=C-H), 2925-2855 (C-H), 1415 (CH) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{32}NO_5$ [*M* + H]$^+$: 354.2280, found: 354.2297; calcd for $C_{19}H_{31}NNaO_5$ [*M* + Na]$^+$: 367.2100, found 367.2116.

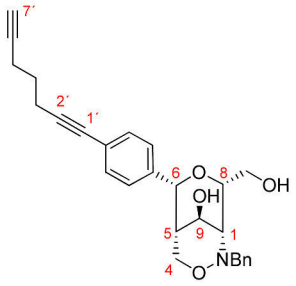
**(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-6-{4-[7-(*tert*-butyldimethylsilyl)hepta-1,6-diynyl]phenyl}-8-[(*tert*-butyldimethylsiloxy)methyl]-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (15)**




Compound **1b** (50 mg, 94 µmol), $PdCl_2(PPh_3)_2$ (4 mg, 5 µmol) and CuI (1 mg, 5 µmol) were filled in a sealed tube and flushed with argon. Degassed THF (1 mL), *i*$Pr_2NH$ (0.2 mL) and dialkyne **14** (29 mg, 140 µmol) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt, water (5 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 15:1) to yield **15** (20 mg, 62%) as a brown oil.

$[\alpha]_D^{22}$= -23.0 (*c* = 0.10, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ = 0.08 (s, 6 H, $SiMe_2$), 0.09 (s, 3 H, SiMe), 0.10 (s, 3 H, SiMe), 0.91 (s, 9 H, Si*t*-Bu), 0.93 (s, 9 H, Si*t*-Bu), 1.81 (quint., *J* = 7.1 Hz, 2 H, 4´-H), 2.07 ($s_{br}$, 1 H, 5-H), 2.40 (t, *J* = 7.1 Hz, 2 H, 5´-H), 2.52 (t, *J* = 7.1 Hz, 2 H, 3´-H), 3.29 ($s_{br}$, 1 H, 1-H), 3.69 (d, *J* = 12.0 Hz, 1 H, 4-H), 3.83 (dd, *J* = 6.7, 7.9 Hz, 1 H, 8-H), 3.96-4.07 (m, 5 H, 4-H, 8-$CH_2$, 9-H, OH), 4.11, 4.34 (AB system, $J_{AB}$ = 15.1 Hz, 2 H, $NCH_2$), 4.76 (s, 1 H, 6-H), 7.25-7.29 (m, 3 H, Ar), 7.31-7.37 (m, 6 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = -5.3, -5.2, -4.3 (3 q, SiMe), 16.7, 18.3 (2 s, Si*t*-Bu), 18.7 (t, C-3´), 19.3 (t, C-5´), 26.0, 26.2 (2 q, Si*t*-Bu), 28.0 (t, C-4´), 41.1 (d, C-5), 60.5 (d, C-1), 61.9 (t, $NCH_2$), 62.6 (t, 8-$CH_2$), 65.2 (t, C-4), 70.6 (d, C-9), 79.8 (d, C-6), 81.0 (d, C-8), 83.4, 89.3, 100.0, 107.0 (4 s, C≡C), 122.9 (s, Ar), 125.8, 127.3, 128.2, 128.5, 131.6 (5 d, Ar, Ph), 138.6, 139.6 (2 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ = 3585-3165 (O-H), 3065-3030 (=C-H), 2960-2855 (C-H), 2365, 2345 (C≡C), 1465 (C-H), 1260 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{39}H_{58}NO_4Si_2$ [*M* + H]$^+$: 660.3904, found: 660.3905.

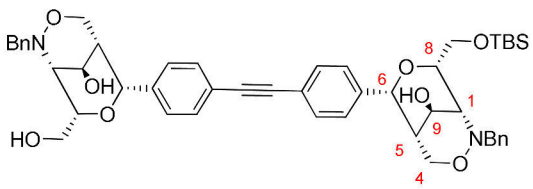
**(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-6-[4-(hepta-1,6-diynyl)phenyl]-8-(hydroxymethyl)-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (16)**




Bicyclic compound **15** (34 mg, 52 µmol) was dissolved in THF (1 mL) and tetra-*n*-butylammonium fluoride (1 M in THF, 0.312 mL, 312 µmol) was added. The solution was stirred for four days at rt and then quenched with water (5 mL). The aqueous layer was extracted with ethyl acetate (5 x 10 mL). The combined organic layers were dried with $NaSO_4$, filtered and the solvent was removed in vacuo. The crude material was purified by column chromatography (silica gel, EtOAc) to yield **16** (22 mg, 98%) as a colorless solid.

m.p. 68-69 °C; $[\alpha]_D^{22}$ = +32.9 (*c* = 0.20, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 1.83 (quint., *J* = 7.0 Hz, 2 H, 4´-H), 1.98 (t, *J* = 2.6 Hz, 1 H, 7´-H), 2.06 ($s_{br}$, 1 H, 5-H), 2.38 (dt, *J* = 2.6, 7.0 Hz, 2 H, 5´-H), 2.45 ($s_{br}$, 1 H, OH), 2.54 (t, *J* = 7.0 Hz, 2 H, 3´-H), 3.10 ($s_{br}$, 1 H, 1-H), 3.59 (d, *J* = 9.9 Hz, 1 H, 9-H), 3.70 (dd, *J* = 2.2, 12.2 Hz, 1 H, 4-H), 3.83-3.87 (m, 2 H, 8-$CH_2$, 8-H), 4.04 (ddd, *J* = 0.7, 5.2, 12.2 Hz, 1 H, 4-H), 4.09 (d, *J* = 14.0 Hz, 1 H, $NCH_2$), 4.13 (dd, *J* = 5.8, 10.1 Hz, 1 H, 8-$CH_2$), 4.30 (d, *J* = 14.0 Hz, 1 H, $NCH_2$), 4.79 (s, 1 H, 6-H), 7.27-7.29 (m, 1 H, Ph), 7.30, 7.38 (AA´BB´ system, $J_{AB}$ = 8.2 Hz, 4 H, Ar), 7.34 (m, 4 H, Ph) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 17.8 (t, C-5´), 18.6 (t, C-3´), 27.8 (t, C-4´), 40.9 (d, C-5), 61.5 (d, C-1), 61.7 (t, $NCH_2$), 64.1 (t, 8-$CH_2$), 64.5 (t, C-4), 69.0 (d, C-7´), 70.5 (d, C-9), 79.5 (d, C-6), 79.9 (d, C-8), 81.1, 83.7, 89.3 (3 s, C≡C), 123.0 (s, Ar), 125.8, 127.7, 128.6, 128.7, 131.7 (5 d, Ar), 137.3, 139.4 (2 s, Ar) ppm; IR (ATR): $\tilde{\nu}$ = 3575-3105 (O-H), 3020 (=C-H), 2920-2855 (C-H), 2360 (C≡C), 1470 (C-H) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{27}H_{30}NO_4$ [*M* + H]$^+$: 432.2175; found: 432.2159; calcd for $C_{27}H_{29}NNaO_4$ [*M* + Na]$^+$: 454.1994; found: 454.1980.

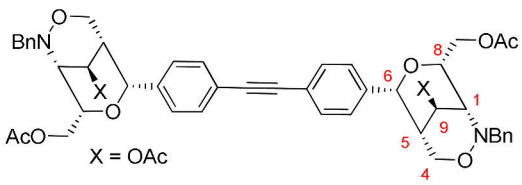
**Dimer 18:**




Compound **1b** (220 mg, 411 µmol), $PdCl_2(PPh_3)_2$ (14 mg, 21 µmol) and CuI (4 mg, 21µmol) were filled in a sealed tube and flushed with argon. Degassed THF (4 mL), *i*$Pr_2NH$ (0.63 mL) and alkyne **8** (100 mg, 274 µmol) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt, water (5 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:1) to yield **18** (138 mg, 62%) as a colorless solid.

m.p. 220-222 °C; $[\alpha]_D^{22}$ = +184.1 (*c* = 0.64, $C_5H_5N$); assignments of NMR signals to each bicyclic unit is possible, but both units may be interchanged; $^1$H NMR (700 MHz, $C_5D_5N$): δ = 0.15 (s, 3 H, SiMe), 0.17 (s, 3 H, SiMe), 0.94 (s, 9 H, *t*-Bu), 2.18, 2.19 (2 $m_c$, 2 H, 5-H, 5´-H), 3.47 (s, 1 H, 1-H), 3.56 (s, 1 H, 1´-H), 3.56 (d, *J* = 11.8 Hz, 1 H, 4-H), 3.59 (d, *J* = 11.8 Hz, 1 H, 4´-H), 4.12, 4.25, 4.45 (ABX system, $J_{AB}$ = 5.7 Hz, $J_{AX}$ = 7.2 Hz, $J_{XB}$ = 9.7 Hz, 3 H, 8-H, 8-$CH_2$), 4.27 (ddd, *J* = 1.6, 5.9, 6.1 Hz, 1 H, 8´-H), 4.48 ($m_c$, 3 H, 9-H, 9´-H, 8´-$CH_2$), 4.59 (dd, *J* = 6.1, 10.9 Hz, 1 H, 8´-$CH_2$), 4.62 (d, *J* = 14.7 Hz, 1 H, $NCH_2$), 4.65 (d, *J* = 14.6 Hz, 1 H, $NCH_2$´), 4.77 ($m_c$, 2 H, 4´-H), 5.08 (d, *J* = 14.7 Hz, 1 H, $NCH_2$), 5.09 (s, 2 H, 6-H, 6´-H), 5.13 (d, *J* = 14.6 Hz, 1 H, $NCH_2$´), 6.79 ($s_{br}$, 1 H, OH), 6.87 ($s_{br}$, 1 H, OH), 7.24-7.31 (m, 2 H, Ar), 7.33-7.35 (m, 2 H, Ar), 7.39-7.41 (m, 2 H, Ar), 7.51-7.54 (m, 1 H, Ar), 7.64-7.72 (m, 11 H, Ar), ppm; $^{13}$C NMR (175 MHz, $C_5D_5N$,): δ = -4.7 (q, SiMe), -4.6 (q, SiMe), 26.6 (q, *t*-Bu), 42.6 (d, C-5, C-5´), 59.0 (t, C-4, C-4´), 59.4 (d, C-1, C-1´), 60.2 (t, $NCH_2$, $NCH_2$´), 64.3, 64.5 (2 t, 8-$CH_2$, 8´-$CH_2$), 80.5, 80.6 (2 d, C-6, C-6´), 81.0, 81.7 (2 d, C-9, C-9´), 90.4, 90.5 (2 s, C≡C), 122.7, 122.8 (2 s, Ar, Ph), 123.7, 124.3, 127.5, 127.6, 129.0, 129.4, 129.5, 129.6, 132.2, 132.3 (10 d, Ar, Ph), 136.3, 141.0, 142.6, 142.8 (4 s, Ph, Ar) ppm; IR (ATR): $\tilde{\nu}$ = 3595-3125 (O-H), 3060-3030 (=C-H), 2925-2860 (C-H), 1450 (C-H) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{48}H_{59}N_2O_8Si$ [*M* + H]$^+$: 819.4035; found: 819.4025; calcd for $C_{48}H_{58}N_2NaO_8Si$ [*M* + Na]$^+$: 841.3855; found: 841.3843; elemental analysis calcd (%) for $C_{48}H_{58}N_2O_8Si$ (819.1): C, 70.39; H, 7.14; N, 3.42; found: C, 70.67; H, 7.20; N, 3.50.

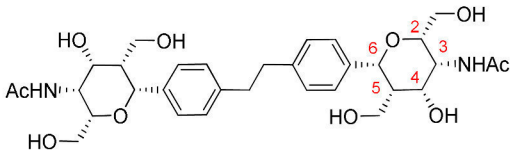
**Dimer 19:**




Compound **18** (60 mg, 73 µmol) was dissolved in methanol (2 mL) and one drop of acetyl chloride was added. The solution was stirred at rt for 1 h. The solvent was then removed in vacuo and the crude was dissolved in pyridine (1 mL). Acetic anhydride (45 mg, 42 µL, 439 µmol) and DMAP (14 mg, 117 µmol) were added and the solution was stirred for 10 h at rt. Water (10 mL) was added to the mixture and the aqueous layer was extracted with dichloromethane (5 x 15 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:1) to yield **19** (55 mg, 86%) as a colorless solid.

m.p. 92-94°C; $[\alpha]_D^{22}$= +114.2 (*c* = 0.99, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.90 (s, 6 H, Ac), 1.94 ($s_{br}$, 2 H, 5-H), 2.18 (s, 6 H, Ac), 3.02 (s, 2 H, 1-H), 3.32 (d, *J* = 12.0 Hz, 2 H, 4-H), 4.02 (dt, *J* = 1.5, 6.0 Hz, 2 H, 8-H), 4.24, 4.39 (AB system, $J_{AB}$ = 13.2 Hz, 4 H, $NCH_2$), 4.39 ($m_c$, 2 H, 4-H), 4.40-4.42 (m, 4 H, 8-$CH_2$), 4.96 (s, 2 H, 6-H), 5.08 ($t_{br}$, *J* = 2.8 Hz, 2 H, 9-H), 7.16-7.20 (m, 2 H, Ph), 7.23-7.28 (m, 8 H, Ph), 7.33, 7.42 (AA´BB´ system, $J_{AB}$ = 8.3 Hz, 8 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 21.0, 21.6 (2 q, Ac), 38.6 (d, C-5), 55.1 (d, C-1), 57.5 (t, C-4), 58.4 (t, $NCH_2$), 64.9 (t, 8-$CH_2$), 71.0 (d, C-9), 77.0 (d, C-8), 79.6 (d, C-6), 89.4 (s, C≡C), 122.5 (s, Ar), 126.3, 127.6, 128.6, 128.8, 131.7 (5 d, Ar, Ph), 137.7, 139.6 (2 s, Ar, Ph), 170.2, 170.8 (2 s, Ac) ppm; IR (ATR): $\tilde{\nu}$ = 3020 (=C-H), 2955-2850 (C-H), 1735 (C=O), 1465 (C-H), 1230 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{50}H_{53}N_2O_{12}$ [*M* + H]$^+$: 873.3599; found: 873.3608; calcd for $C_{50}H_{52}N_2NaO_{12}$ [*M* + Na]$^+$: 895.3412; found: 895.3432.

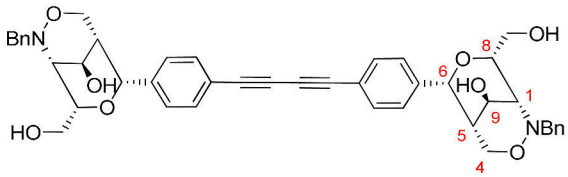
**Dimer 20:**




A suspension of Pd/C (10% Pd, 54 mg) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. Compound **19** (54 mg, 62 µmol) were dissolved in ethyl acetate (2 mL) and added to this suspension. The mixture was stirred for 6 h under hydrogen atmosphere (balloon), filtered through a pad of Celite® and the solvent was removed in vacuo. Under an argon atmosphere the crude product was dissolved in degassed MeOH (1 mL) and a samarium(II) iodide solution (0.1 M in THF, 3.71 mL, 371 µmol) was added drop wise. The mixture was stirred for 30 min at rt and for further 10 min in the presence of air. Size exclusion chromatography (Sephadex™ LH-20, $CH_3OH$) yielded **20** (25 mg, 66%) as a colorless solid.

Decomposition > 260 °C; $[\alpha]_D^{22}$ = +49.8 (*c* = 0.90, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD/CDCl_3$, 2:1): δ = 2.14 (s, 6 H, NAc), 2.29 ($m_c$, 2 H, 5-H), 3.01 (s, 4 H, $CH_2$), 3.44 (dd, *J* = 4.1, 11.5 Hz, 2 H, 5-$CH_2$), 3.66, 3.77, 3.81 (XAB system, $J_{BX}$ = 6.1 Hz, $J_{AB}$ = 6.9 Hz, $J_{AX}$ = 11.5 Hz, 6 H, 2-$CH_2$, 2-H), 3.76 ($m_c$, 2 H, 5-$CH_2$), 4.36 (dd, *J* = 1.8, 4.8 Hz, 2 H, 3-H), 4.47 (dd, *J* = 4.8, 6.3 Hz, 2 H, 4-H), 4.82 (d, *J* = 3.4 Hz, 2 H, 6-H), 7.22, 7.39 (AA´BB´ system, $J_{AB}$ = 8.0 Hz, 8 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CD_3OD/CDCl_3$, 2:1): δ = 22.9 (q, NAc), 38.4 (t, $CH_2$), 46.2 (d, C-5), 49.5 (d, C-3), 56.4 (t, 5-$CH_2$), 62.3 (t, 2-$CH_2$), 71.1 (d, C-4), 80.7 (d, C-2), 81.4 (d, C-6), 126.3, 129.1 (2 d, Ar), 138.0, 141.4 (2 s, Ar), 174.2 (s, C=O) ppm; IR (ATR): $\tilde{\nu}$ = 3595-3120 (O-H, N-H), 3075-3035 (=C-H), 2960-2850 (C-H), 1740 (NAc), 1465 (C-H), 1260 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{32}H_{44}N_2NaO_{10}$ [*M* + Na]$^+$: 639.2894; found: 639.2877; calcd for $C_{32}H_{44}KN_2O_{10}$ [*M* + K]$^+$: 655.2633; found: 655.2676.

**Dimer 21:**




Compound **8** (50 mg, 137 µmol) was dissolved in acetonitrile (1.5 mL) and tetramethylethylenediamine (0.04 mL, 30 mg, 239 µmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (20 µL, 21 mg, 137 µmol) and copper(I) chloride (1 mg, 27 µmol) were added. The solution was stirred for 3 h at rt under oxygen atmosphere. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/methanol 10:1) to yield **21** (50 mg, quant.) as a colorless solid.

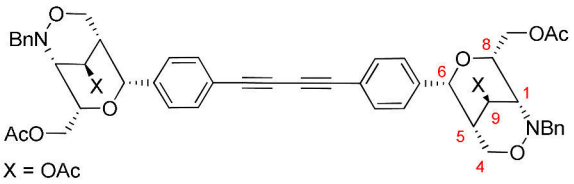
m.p. 175-178 °C; $[\alpha]_D^{22}$= +28.7 (*c* = 0.23, $C_5H_5N$); $^1$H NMR (700 MHz, $CD_3OD/C_5D_5N$, 1:1): δ = 2.20 ($m_c$, 2 H, 5-H), 3.50 (d, *J* = 11.4 Hz, 2 H, 4-H), 3.54 ($m_c$, 2 H, 1-H), 4.26, 4.45, 4.54 (XAB system, $J_{AX}$ = 5.6 Hz, $J_{BX}$ = 6.1 Hz, $J_{AB}$= 10.9 Hz, 6 H, 8-H, 8-$CH_2$), 4.49 (t, *J* = 3.0 Hz, 2 H, 9-H), 4.63 (d, *J* = 14.5 Hz, 2 H, $NCH_2$), 4.75 (dd, *J* = 1.6, 11.4 Hz, 2 H, 4-H), 5.08 (d, *J* = 14.5 Hz, 2 H, $NCH_2$), 5.12 (s, 2 H, 6-H), 7.31-7.33 (m, 6 H, Ph), 7.39-7.41 (m, 4 H, Ph, Ar), 7.66-7.67 (m, 8 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CD_3OD/C_5D_5N$, 1:1): δ = 42.3 (d, C-5), 59.0 (t, C-4), 60.1 (t, $NCH_2$), 64.1 (t, 8-$CH_2$), 69.7 (d, C-9), 74.9 (s, C≡C), 80.3 (d, C-6), 81.4 (d, C-8), 82.8 (s, C≡C), 120.7 (s, Ar), 123.8, 127.4, 128.9, 129.6, 133.0 (5 d, Ar, Ph), 140.8, 143.9 (2 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ = 3545-3410 (O-H), 3090-3030 (=C-H), 2920-2855 (C-H), 2350, 2145 (C≡C), 1450 (C-H), 1260 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{44}H_{45}N_2O_8$ [*M* + H]$^+$: 729.3176; found: 729.3208; calcd for $C_{44}H_{44}N_2NaO_8$ [*M* + Na]$^+$: 751.2995; found: 751.3028.

**Dimer 22:**


Dimer **21** (50 mg, 69 µmol) was dissolved in methanol (1 mL) and a samarium(II) iodide solution (0.09 M in THF, 4.57 mL, 412 µmol) was added. The solution was stirred for 30 min at rt. Sat. potassium sodium tartrate solution (10 mL) was added and the mixture was stirred for further 2 h at rt. The aqueous layer was extracted with dichloromethane (5 x 15 mL) and the combined organic layers were dried with $NaSO_4$, filtered and the solvent was removed in vacuo. The crude material was purified by column chromatography (silica gel, $CH_2Cl_2$/$CH_3OH$ 7 N $NH_3$, 20:1) to yield **22** (50 mg, 99%) as a colorless solid.

Decomposition > 215 °C; $[\alpha]_D^{22}$= +67.8 (*c* = 0.36, $C_5H_5N$); $^1$H NMR (400 MHz, $CD_3OD$): δ = 2.43 ($m_c$, 2 H, 5-H), 3.40 (dd, *J* = 3.8, 11.3 Hz, 2 H, 5-$CH_2$), 3.53 ($m_c$, 2 H, 3-H), 3.80 ($m_c$, 2 H, 2-H), 3.91 (dd, *J* = 2.1, 11.3 Hz, 2 H, 5-$CH_2$), 4.06 ($m_c$, 4 H, 2-$CH_2$), 4.22, 4.41 (AB system, $J_{AB}$ = 12.6 Hz, 4 H, $NCH_2$), 4.61 ($s_{br}$, 2 H, 4-H), 4.96 ($s_{br}$, 2 H, 6-H), 7.47-7.48 (m, 2 H, Ph), 7.52-7.54 (m, 4 H, Ar, Ph), 7.56-7.57 (m, 4 H, Ar, Ph), 7.62-7.67 (m, 8 H, Ar, Ph) ppm; $^{13}$C NMR (175 MHz, $CD_3OD$): δ = 46.6 (d, C-5), 54.9 (t, $NCH_2$), 56.5 (t, 5-$CH_2$), 59.1 (d, C-3), 64.3 (t, 2-$CH_2$), 73.9 (d, C-4), 74.3 (s, C≡C), 79.5 (d, C-2), 81.8 (d, C-6), 82.2 (s, C≡C), 121.4 (s, Ar), 127.2, 128.7, 129.7, 133.0 (4 d, Ar, Ph), 139.0, 142.7 (2 s, Ar, Ph) ppm; one d for Ar or Ph could not be detected; IR (ATR): $\tilde{\nu}$ = 3675-3180 (O-H, N-H), 3080-3030 (=C-H), 2970-2865 (C-H), 2140 (C≡C), 1455 (C-H), 1230 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{44}H_{49}N_2O_8$ [*M* + H]$^+$: 733.3489; found: 733.3490; calcd for $C_{44}H_{48}N_2NaO_8$ [*M* + Na]$^+$: 755.3308; found: 755.3343.

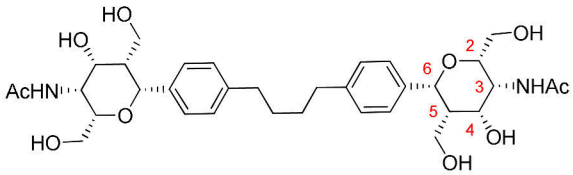
**Dimer 23:**




Compound **8** (100 mg, 274 µmol) was dissolved in acetonitrile (3 mL) and tetramethylethylenediamine (0.07 mL, 56 mg, 239 µmol), copper(I) chloride (~1 mg, 55 µmol) and diazabicycloundecene (0.04 mL, 42 mg, 274 µmol) were added. The solution was stirred for 18 h at rt under air. The crude product was filtered through silica gel ($CH_2Cl_2$/$CH_3OH$, 10:1) and the solvent was removed in vacuo. The compound was dissolved in pyridine (2 mL), acetic anhydride (0.08 mL, 84 mg, 821 µmol) and DMAP (27 mg, 219 µmol) were added and the solution was stirred for 18 h at rt. Water (5 mL) and dichloromethane (10 mL) were added to the mixture and the aqueous layer was extracted with dichloromethane (5 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 2:1) to yield **23** (115 mg, 94%) as a colorless solid.

m.p. 91-93 °C; $[\alpha]_D^{22}$ = +136.2 (*c* = 0.96, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.95 (s, 6 H, Ac), 2.00 ($s_{br}$, 2 H, 5-H), 2.24 (s, 6 H, Ac), 3.08 ($s_{br}$, 2 H, 1-H), 3.34 (d, *J* = 12.1 Hz, 2 H, 4-H), 4.07-4.09 (m, 2 H, 8-H), 4.28-4.31 (m, 2 H, 4-H), 4.30, 4.45 (AB system, $J_{AB}$ = 13.4 Hz, 4 H, $NCH_2$), 4.47 ($m_c$, 4 H, 8-$CH_2$), 5.01 ($s_{br}$, 2 H, 6-H), 5.14 (t, *J* = 2.9 Hz, 2 H, 9-H), 7.22-7.25 (m, 2 H, Ph), 7.29-7.34 (m, 8 H, Ph), 7.39, 7.48 (AA´BB´ system, $J_{AB}$ = 8.3 Hz, 8 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 20.9 (q, Ac), 21.5 (q, Ac), 38.4 (d, C-5), 55.0 (d, C-1), 57.4 (t, C-4), 58.3 (t, $NCH_2$), 64.8 (t, 8-$CH_2$), 70.8 (d, C-9), 74.0 (s, C≡C), 76.9 (d, C-8), 79.4 (d, C-6), 81.5 (s, C≡C), 121.0 (s, Ar), 126.4, 127.5, 128.5, 128.7, 132.5 (5 d, Ar), 137.6, 140.7 (2 s, Ar, Ph), 170.1, 170.7 (2 s, Ac) ppm; IR (ATR): $\tilde{\nu}$ = 3065 (=C-H), 2960-2850 (C-H), 1740 (C=O), 1465 (C-H) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{52}H_{53}N_2O_{12}$ [*M* + H]$^+$: 897.3599, found: 879.3612, calcd for $C_{52}H_{52}N_2NaO_{12}$ [*M* + Na]$^+$: 919.3418, found: 919.3431.

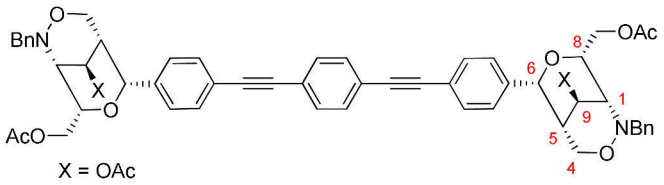
**Dimer 24:**




A suspension of Pd/C (10% Pd, 57 mg) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. Compound **23** (57 mg, 64 µmol) were dissolved in ethyl acetate (1 mL) and added to this suspension. The mixture was stirred for 6 h under hydrogen atmosphere (balloon), filtered through a pad of Celite® and the solvent removed in vacuo. Under an argon atmosphere the crude product was dissolved in degassed MeOH (1 mL) and a samarium(II) iodide solution (0.1 M in THF, 3.81 mL, 381 µmol) was added drop wise. The mixture was stirred for 30 min at rt and then for another 10 min in the presence of air. A size exclusion chromatography (Sephadex™ LH-20, $CH_3OH$) of the mixture and subsequent purification by RP-HPLC (Gemini®-NX, MeOH:$H_2O$ 7:3) afforded **24** (30 mg, 73%) as a colorless solid.

m.p. 81-83 °C; $[\alpha]_D^{22}$= +145.0 (*c* = 0.77, $CH_3OH/C_5H_5N$, 5:1); $^1$H NMR (700 MHz, $CD_3OD/C_5D_5N$, 6:1): δ = 1.24 ($m_c$, 4 H, $CH_2$), 1.63 (s, 6 H, Ac), 1.91 ($m_c$, 2 H, 5-H), 2.22 ($m_c$, 4 H, $CH_2$), 3.10 (dd, *J* = 3.8, 11.2 Hz, 2 H, 5-$CH_2$), 3.36-3.39 (m, 2 H, 2-$CH_2$), 3.44-3.37 (m, 2 H, 2-$CH_2$), 3.45 (s, 2 H, 3-H), 3.53 (dd, *J* = 2.5, 11.2 Hz, 2 H, 5-$CH_2$), 4.11-4.14 (m, 4 H, 2-H, 4-H), 4.40 (d, *J* = 3.5 Hz, 2 H, 6-H), 6.77, 7.05 (AA´BB´ system, $J_{AB}$ = 8.0 Hz, 8 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CD_3OD/C_5D_5N$, 6:1): δ = 23.2 (q, Ac), 31.9 (t, $CH_2$), 36.2 (t, $CH_2$), 46.5 (d, C-5), 49.7 (d, C-4), 56.2 (t, 5-$CH_2$), 62.6 (t, 2-$CH_2$), 71.0 (d, C-2), 81.1 (d, C-3), 81.7 (d, C-6), 126.8, 128.9 (2 d, Ar), 138.4, 142.1 (2 s, Ar), 173.6 (s, Ac) ppm; IR (ATR): $\tilde{\nu}$ = 3575-3130 (O-H, N-H), 3085-3015 (=C-H), 2970-2855 (CH), 1740 (C=O), 1440 (C-H), 1230 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{34}H_{49}N_2O_{10}$ [*M* + H]$^+$: 645.3387; found: 645.3406; calcd for $C_{34}H_{48}N_2NaO_{10}$ [*M* + Na]$^+$: 667.3207; found: 667.3238.

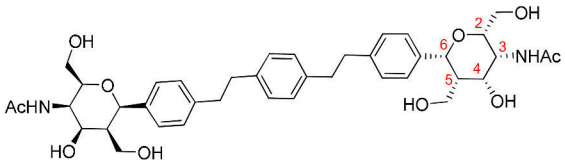
**Dimer 25:**




Compound **8** (250 mg, 684 µmol), $PdCl_2(PPh_3)_2$ (24 mg, 34 µmol) and CuI (7 mg, 34 µmol) were filled in a sealed tube and flushed with argon. Degassed THF (6 mL), *i*$Pr_2NH$ (1.7 mL) and 1,4-diiodobenzene (102 mg, 308 µmol) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt and filtered through silica gel ($CH_2Cl_2$/MeOH 10:1). The solvent was removed in vacuo and the solid was dissolved in a $CH_2Cl_2$/pyridine mixture (15 mL/1 mL). DMAP (120 mg, 985 µmol), acetic anhydride (190 mg, 176 µL, 1.85 mmol) were added and the solution was stirred at rt for 18 h. Water (10 mL) was added to the mixture and the aqueous layer was extracted with dichloromethane (5 x 20 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:1) to yield **25** (240 mg, 80%) as a colorless solid.

m.p. 100-103 °C; $[\alpha]_D^{22}$ = +134.6 (*c* = 1.00, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 1.98, 2.26 (2 s, 12 H, Ac), 2.03 ($m_c$, 2 H, 5-H), 3.11 (s, 2 H, 1-H), 3.40 (d, *J* = 12.0 Hz, 2 H, 4-H), 4.10 ($m_c$, 2 H, 8-H), 4.33 ($m_c$, 2 H, 4-H), 4.33, 4.47 (AB system, $J_{AB}$ = 13.3 Hz, 2 H, $NCH_2$), 4.49, 4.50 (AB part of ABX system, $J_{AX/BX}$ = 4.2 Hz, $J_{AB}$ = 11.2 Hz, 4 H, 8-$CH_2$), 5.04 ($s_{br}$, 2 H, 6-H), 5.17 (t, *J* = 2.5 Hz, 2 H, 9-H), 7.25-7.28 (m, 2 H, Ph), 7.32-7.36 (m, 8 H, Ph), 7.43, 7.51 (AA´BB´, $J_{AB}$ = 8.2 Hz, 8 H, Ar), 7.50 (s, 4 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 21.1, 21.6 (2 q, Ac), 38.6 (d, C-5), 55.2 (d, C-1), 57.7 (t, C-4), 58.5 (t, $NCH_2$), 64.9 (t, 8-$CH_2$), 71.0 (d, C-9), 79.7 (d, C-6), 89.4, 91.2 (2 s, C≡C), 122.4, 123.2 (s, Ar, Ph), 126.4, 127.6, 128.6, 128.9, 131.6, 131.7 (6 d, Ar), 137.7, 139.8 (2 s, Ar, Ph), 170.1, 170.8 (2 s, Ac) ppm; IR (ATR): $\tilde{\nu}$ = 3030-3015 (=C-H), 2925-2855 (C-H), 1740 (C=O), 1455 (C-H), 1230 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{58}H_{57}N_2O_{12}$ $[M + H]^+$: 973.3912; found: 973.3908; calcd for $C_{58}H_{56}N_2NaO_{12}$ $[M + Na]^+$: 995.3725; found: 995.3725.

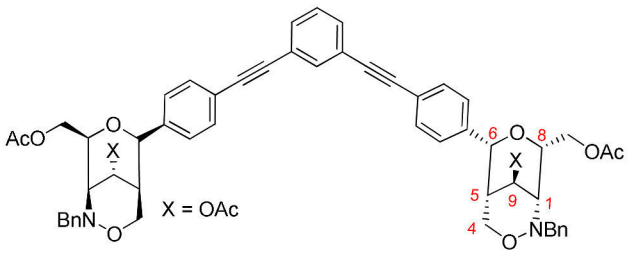
**Dimer 26:**




A suspension of Pd/C (10% Pd, 221 mg) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. Compound **25** (221 mg, 227 µmol) was dissolved in ethyl acetate (5 mL) and added to this suspension. The mixture was stirred for 6 h under hydrogen atmosphere (balloon), filtered through a pad of Celite® and the solvent was removed in vacuo. Under an argon atmosphere the crude product was dissolved in degassed MeOH (1 mL) and a samarium(II) iodide solution (0.1 M in THF, 13.6 mL, 1.36 mmol) was added drop wise. The mixture was stirred for 30 min at rt and for further 10 min in the presence of air. Size exclusion chromatography (Sephadex™ LH-20, $CH_3OH$) and subsequent purification by RP-HPLC (Gemini®-NX, MeOH:$H_2O$ 6:4 -> 7:3) afforded **26** (31 mg, 19%) as a colorless solid.

m.p. 120-123 °C; $[\alpha]_D^{22}$ = +65.3 (*c* = 1.20, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD$): δ = 2.04 (s, 6 H, Ac), 2.20 ($m_c$, 2 H, 5-H), 2.86-2.92 (m, 8 H, $CH_2$), 3.36 (dd, *J* = 4.0, 11.3 Hz, 2 H, 5-$CH_2$), 3.59, 3.69, 3.74 (XAB system, $J_{BX}$ = 5.6 Hz, $J_{AB}$ = 6.9 Hz, $J_{AX}$ = 11.6 Hz, 6 H, 2-H, 2-$CH_2$), 3.68 (dd, *J* = 4.5, 11.3 Hz, 2 H, 5-$CH_2$), 4.28 (dd, *J* = 1.8, 4.9 Hz, 2 H, 3-H), 4.39 (dd, *J* = 4.9, 6.4 Hz, 2 H, 4-H), 4.75 (d, *J* = 3.6 Hz, 2 H, 6-H), 7.04 (s, 4 H, Ar), 7.15, 7.35 (AA´BB´ system, $J_{AB}$ = 7.9 Hz, 8 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CD_3OD$): δ = 22.9 (q, Ac), 38.7 (t, $CH_2$), 38.8 (t, $CH_2$), 46.8 (d, C-5), 49.9 (d, C-3), 56.5 (t, 5-$CH_2$), 62.9 (t, 2-$CH_2$), 71.5 (d, C-4), 81.2 (d, C-2), 81.8 (d, C-6), 126.7, 129.3, 129.5 (3 d, Ar), 138.6, 140.4, 141.9 (3 s, Ar), 174.4 (s, Ac) ppm; IR (ATR): $\tilde{\nu}$ = 3650-3100 (O-H, N-H), 3085-3010 (=C-H), 2955-2855 (C-H), 2360, 2345 (C≡C), 1650 (C=O), 1420 (C-H) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{40}H_{53}N_2O_{10}$ [*M* + H]$^+$: 721.3700; found: 721.3672; calcd for $C_{40}H_{52}N_2NaO_{10}$ [*M* + Na]$^+$: 743.3514; found: 743.3492.

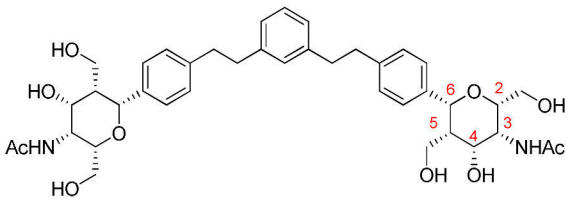
**Dimer 27:**




Compound **8** (400 mg, 1.09 mmol), $PdCl_2(PPh_3)_2$ (38 mg, 55 µmol) and CuI (10 mg, 55 µmol) were filled in a sealed tube and flushed with argon. Degassed THF (10 mL), *i*$Pr_2NH$ (2.5 mL) and 1,3-diiodobenzene (180 mg, 546 µmol) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt and filtered through silica gel ($CH_2Cl_2$/MeOH 10:1). The solvent was removed in vacuo and the solid was dissolved in a $CH_2Cl_2$/pyridine mixture (5 mL/1 mL). DMAP (213 mg, 1.75 mmol), acetic anhydride (334 mg, 309 µL, 3.27 mmol) were added and the solution was stirred at rt for 18 h. Water (10 mL) was added to the mixture and the aqueous layer was extracted with dichloromethane (5 x 20 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:1) to yield **27** (433 mg, 82%) as a colorless solid.

m.p. 94-96 °C; $[\alpha]_D^{22}$ = +117.5 (*c* = 0.98, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 2.00 (s, 6 H, Ac), 2.05 ($s_{br}$, 2 H, 5-H), 2.28 (s, 6 H, Ac), 3.13 (s, 2 H, 1-H), 3.43 (d, *J* = 12.2 Hz, 2 H, 4-H), 4.12-4.16 (m, 2 H, 8-H), 4.35, 4.49 (AB system, $J_{AB}$ = 13.4 Hz, 4 H, $NCH_2$), 4.35 ($m_c$, 2 H, 4-H), 4.49-4.52 (m, 4 H, 8-$CH_2$), 5.07 (s, 2 H, 6-H), 5.19 ($t_{br}$, *J* = 2.6 Hz, 2 H, 9-H), 7.28-7.30 (m, 2 H, Ph), 7.33-7.38 (m, 9 H, Ph, Ar), 7.45, 7.53 (AA´BB´ system, $J_{AB}$ = 8.1 Hz, 8 H, Ar), 7.49-7.50 (m, 2 H, Ar), 7.71 ($m_c$, 1 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 21.0, 21.6 (2 q, Ac), 38.6 (d, C-5), 55.1 (d, C-1), 57.6 (t, C-4), 58.5 (t, $NCH_2$), 64.9 (t, 8-$CH_2$), 71.0 (d, C-9), 77.0 (d, C-8), 79.7 (d, C-6), 88.8, 89.9 (2 s, C≡C), 122.4, 123.7 (2 s, Ar), 126.4, 127.6, 128.6, 126.8, 131.4, 131.7, 134.8 (7 d, Ar), 137.7, 139.8 (2 s, Ar), 170.2, 170.8 (2 s, Ac) ppm; one d for Ph/Ar could not be detected; IR (ATR): $\tilde{\nu}$ = 3020 (=C-H), 2920-2850 (C-H), 2340, 2330 (C≡C), 1740 (C=O), 1465 (C-H), 1235 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{58}H_{57}N_2O_{12}$ [*M* + H]$^+$: 973.3912; found: 973.3879; calcd for $C_{58}H_{56}N_2NaO_{12}$ [*M* + Na]$^+$: 995.3725; found: 995.3713; elemental analysis calcd (%) for $C_{58}H_{56}N_2O_{12}$ (973.1): C, 71.59; H, 5.80; N, 2.88; found: C, 71.61; H, 5.93; N, 2.88.

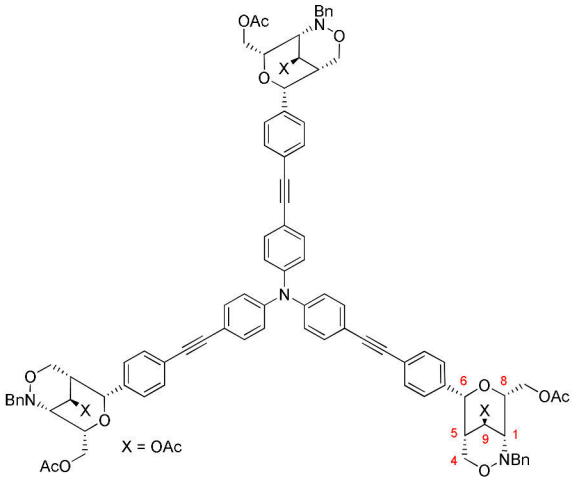
**Dimer 28:**




A suspension of Pd/C (10% Pd, 72 mg) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. Compound **27** (72 mg, 74 µmol) was dissolved in ethyl acetate (1.5 mL) and added to this suspension. The mixture was stirred for 6 h under hydrogen atmosphere (balloon), filtered through a pad of Celite® and the solvent was removed in vacuo. Under an argon atmosphere the crude product was dissolved in degassed MeOH (1 mL) and a samarium(II) iodide solution (0.1 M in THF, 4.44 mL, 444 µmol) was added drop wise. The mixture was stirred for 30 min at rt and for further 10 min in the presence of air. Size exclusion chromatography (Sephadex™ LH-20, $CH_3OH$) and subsequent purification by RP-HPLC (Gemini®-NX, MeOH:$H_2O$, 1:1 to 8:2) to yield **28** (30 mg, 56%) as a colorless solid.

m.p. 104-106 °C; $[\alpha]_D^{22}$ = +10.4 (*c* = 1.15, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD$): δ = 2.04 (s, 6 H, Ac), 2.19 ($m_c$, 2 H, 5-H), 2.86 ($m_c$, 8 H, $CH_2$), 3.36 (dd, *J* = 3.9, 11.3 Hz, 2 H, 5-$CH_2$), 3.58, 3.67, 3.72 (XAB system, $J_{BX}$ = 5.7 Hz, $J_{AB}$ = 6.9 Hz, $J_{AX}$ = 11.6 Hz, 2 H, 2-$CH_2$, 2-H), 3.68 (dd, *J* = 3.0, 11.3 Hz, 2 H, 5-$CH_2$), 4.27 (dd, *J* = 1.5, 4.7 Hz, 2 H, 3-H), 4.38 (dd, *J* = 4.7, 6.4 Hz, 2 H, 4-H), 4.74 (d, *J* = 3.4 Hz, 2 H, 6-H), 6.88 ($m_c$, 1 H, Ar), 6.95-6.97 (m, 2 H, Ar), 7.12 ($m_c$, 1 H, Ar), 7.14, 7.35 (AA´BB´ system, $J_{AB}$ = 8.1 Hz, 8 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CD_3OD$): δ = 22.9 (q, Ac), 38.9 (t, $CH_2$), 39.1 (t, $CH_2$), 46.8 (d, C-5), 49.9 (d, C-3), 56.5 (t, 5-$CH_2$), 62.8 (t, 2-$CH_2$), 71.5 (d, C-4), 81.1 (d, C-2), 81.8 (d, C-6), 126.8, 127.1, 129.2, 129.4, 130.1 (5 d, Ar), 138.7, 141.8, 142.8 (3 s, Ar), 174.4 (s, Ac) ppm; IR (ATR): $\tilde{\nu}$ = 3595-3120 (O-H, N-H), 3075-3035 (=C-H), 2960-2850 (C-H), 1740 (C=O), 1465 (C-H), 1260 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{32}H_{44}N_2NaO_{10}$ [*M* + Na]$^+$: 639.2894; found: 639.2877; calcd for $C_{32}H_{44}KN_2O_{10}$ [*M* + K]$^+$: 655.2633; found: 655.2676.

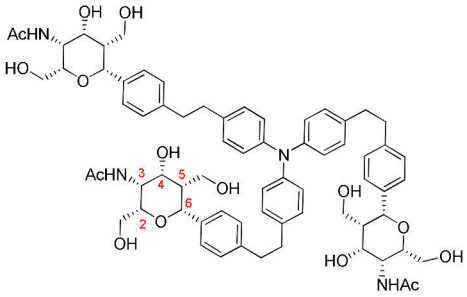
**Trimer 29:**




Compound **8** (50 mg, 137 µmol), $PdCl_2(PPh_3)_2$ (14 mg, 21 µmol) and CuI (4 mg, 21 µmol) were filled in a sealed tube and flushed with argon. Degassed THF (1 mL), *i*$Pr_2NH$ (1 mL) and tris(4-iodophenyl)amine (28 mg, 46 µmol) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt, the solids were filtered off and washed with ethyl acetate (3 x 10 mL). The crude product was dissolved in a $CH_2Cl_2$/pyridine mixture (1 mL/1 mL). DMAP (60 mg, 493 µmol), acetic anhydride (42 mg, 39 µL, 419 µmol) were added and the solution was stirred at rt for 18 h. Water (5 mL) was added to the mixture and the aqueous layer was extracted with dichloromethane (5 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:1) to yield **29** (43 mg, 59%) as a yellow solid.

m.p. 128-130 °C; $[\alpha]_D^{22}$ = +112.0 (*c* = 1.05, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 1.98 (s, 9 H, Ac), 2.02 ($m_c$, 3 H, 5-H), 2.26 (s, 9 H, Ac), 3.11 ($s_{br}$, 3 H, 1-H), 3.42 (d, *J* = 11.9 Hz, 3 H, 4-H), 4.10 (dt, *J* = 1.8, 6.0 Hz, 3 H, 8-H), 4.33 ($m_c$, 3 H, 4-H), 4.33, 4.47 (AB system, $J_{AB}$ = 13.5 Hz, 6 H, $NCH_2$), 4.49, 5.51 (AB part of ABX system, $J_{AX/BX}$ = 6.0 Hz, $J_{AB}$ = 11.1 Hz, 6 H, 8-$CH_2$), 5.04 (s, 3 H, 6-H), 5.17 (t, *J* = 2.6 Hz, 3 H, 9-H), 7.07, 7.41 (AA´BB´ system, $J_{AB}$ = 8.7 Hz, 12 H, Ar), 7.25-7.28 (m, 3 H, Ph), 7.32-7.36 (m, 12 H, Ph), 7.42, 7.50 (AA´BB´ system, $J_{AB}$ = 8.4 Hz, 12 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 21.0 (q, Ac), 21.5 (q, Ac), 38.6 (d, C-5), 55.1 (d, C-1), 57.5 (t, C-4), 58.4 (t, $NCH_2$), 64.8 (t, 8-$CH_2$), 71.0 (d, C-9), 77.1 (d, C-8), 79.6 (d, C-6), 89.2, 89.4 (2 s, C≡C), 118.0, 122.7 (2 s, Ar), 124.1, 126.3, 127.5, 128.5, 128.8, 131.5, 132.9 (7 d, Ar, Ph), 137.7, 139.4, 146.8 (3 s, Ar), 170.1, 170.8 (2 s, Ac) ppm; IR (ATR): $\tilde{\nu}$ = 3090-3030 (=C-H), 2925-2855 (C-H), 2210 (C≡C), 1740 (C=O), 1450 (C-H), 1240 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{96}H_{91}N_4O_{18}$ $[M + H]^+$: 1587.6328; found: 1587.6301; calcd for $C_{96}H_{90}N_4NaO_{18}$ $[M + Na]^+$: 1610.6181; found: 1610.6164.

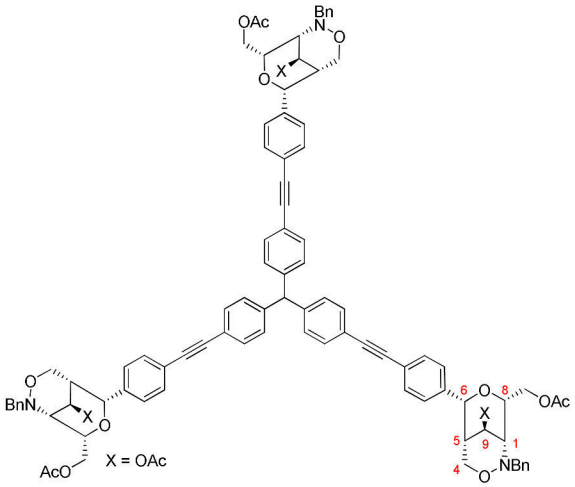
**Trimer 30:**



A suspension of Pd/C (10% Pd, 105 mg) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. Compound **29** (70 mg, 44 µmol) was dissolved in ethyl acetate (1 mL) and added to this suspension. The mixture was stirred for 24 h under hydrogen atmosphere (balloon), filtered through a pad of Celite® and the solvent was removed in vacuo. Under an argon atmosphere the crude product was dissolved in degassed MeOH (1 mL) and a samarium(II) iodide solution (0.1 M in THF, 3.97 mL, 397 mmol) was added drop wise. The mixture was stirred for 30 min at rt and for further 10 min in the presence of air. Size exclusion chromatography (Sephadex™ LH-20, $CH_3OH$) and subsequent purification by RP-HPLC (Gemini®-NX, MeOH/$H_2O$ 8:2) yielded **30** (21 mg, 40%) as a colorless solid.

m.p. 138-140 °C; $[\alpha]_D^{22}$ = +32.7 (*c* = 0.30, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD$): δ = 2.03 (s, 9 H, Ac), 2.20 ($m_c$, 3 H, 5-H), 2.84-2.96 (m, 12 H, $CH_2$), 3.35 ($m_c$, 3 H, 5-$CH_2$), 3.59, 3.69, 3.74 (XAB system, $J_{BX}$ = 5.6 Hz, $J_{AB}$ = 7.5 Hz, $J_{AX}$ = 11.6 Hz, 9 H, 2-$CH_2$, 2-H), 3.68 ($m_c$, 3 H, 5-$CH_2$), 4.28 (dd, *J* = 1.7, 4.8 Hz, 3 H, 3-H), 4.40 (dd, *J* = 4.8, 6.3 Hz, 3 H, 4-H), 4.76 (d, *J* = 3.3 Hz, 3 H, 6-H), 6.88, 7.04 (AA´BB´ system, $J_{AB}$ = 8.4 Hz, 12 H, Ar), 7.18, 7.36 (AA´BB´ system, $J_{AB}$ = 8.0 Hz, 12 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CD_3OD$): δ = 22.9 (q, Ac), 38.4 (t, $CH_2$), 38.8 (t, $CH_2$), 46.9 (d, C-5), 50.0 (d, C-3), 56.5 (t, 5-$CH_2$), 62.9 (t, 2-$CH_2$), 71.5 (d, C-4), 81.2 (d, C-2), 81.8 (d, C-6), 124.9, 126.7, 129.3, 130.4 (4 d, Ar), 137.3, 138.7, 141.8, 147.4 (4 s, Ar), 174.4 (s, Ac) ppm; IR (ATR): $\tilde{\nu}$ = 3600-3130 (O-H, N-H), 3075-3050 (=C-H), 2925-2855 (C-H), 1735 (C=O), 1465 (CH), 1265 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{69}H_{85}N_4O_{15}$ [*M* + H]$^+$: 1209.6011; found: 1209.6061; calcd for $C_{69}H_{84}N_4NaO_{15}$ [*M* + Na]$^+$: 1231.5831; found: 1231.5853.

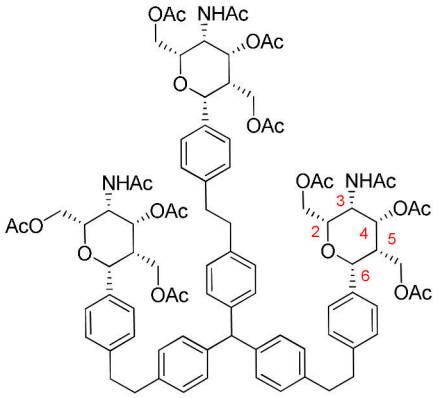
**Trimer 31:**




Compound **8** (310 mg, 849 µmol), $PdCl_2(PPh_3)_2$ (27 mg, 39 µmol), CuI (7 mg, 39 µmol) and tris(4-iodophenyl)methane (160 mg, 257 µmol) were filled in a sealed tube and flushed with argon. Degassed THF (10 mL) und *i*$Pr_2NH$ (4 mL) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt, the solids were filtered off and washed with ethyl acetate (3 x 80 mL). The crude product was dissolved in a $CH_2Cl_2$/pyridine mixture (2 mL/2 mL), acetic anhydride (0.22 mL, 236 mg, 2.32 mmol) and DMAP (151 mg, 1.23 mmol) were added. The mixture was stirred at rt for 18 h. Water (20 mL) was added to the mixture and the aqueous layer was extracted with dichloromethane (5 x 20 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:2) to yield **31** (395 mg, 97%) as a colorless solid.

m.p. 130-132 °C; $[\alpha]_D^{22}$ = +103.1 (*c* = 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.97 (s, 9 H, Ac), 2.02 ($s_{br}$, 3 H, 5-H), 2.26 (s, 9 H, Ac), 3.10 ($s_{br}$, 3 H, 1-H), 3.40 (d, *J* = 11.9 Hz, 3 H, 4-H), 4.10 ($m_c$, 3 H, 8-H), 4.33, 4.47 (AB system, $J_{AB}$ = 14.3 Hz, 6 H, $NCH_2$), 4.33 ($m_c$, 3 H, 4-H), 4.47-4.50 (m, 6 H, 8-$CH_2$), 5.03 ($s_{br}$, 3 H, 6-H), 5.16 ($s_{br}$, 3 H, 9-H), 5.54 ($s_{br}$, 1 H, $HCAr_3$), 7.08, 7.46 (AA´BB´ system, $J_{AB}$ = 8.1 Hz, 12 H, Ar), 7.25-7.27 (m, 3 H, Ph), 7.31-7.36 (m, 12 H, Ph), 7.42, 7.50 (AA´BB´ system, $J_{AB}$ = 8.2 Hz, 12 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 20.9, 21.5 (2 q, Ac), 38.4 (d, C-5), 54.9 (d, C-1), 56.3 (d, $HCAr_3$), 57.4 (t, C-4), 58.3 (t, $NCH_2$), 64.7 (t, 8-$CH_2$), 70.8 (d, C-9), 76.8 (d, C-8), 79.5 (d, C-6), 89.3, 89.4 (2 s, C≡C), 121.6, 122.5 (2 s, Ar), 126.2, 127.5, 128.5, 128.7, 129.4, 131.6, 131.7 (7 d, Ar, Ph), 137.6, 139.5, 143.3 (3 s, Ar, Ph), 170.0, 170.7 (2 s, Ac) ppm; IR (ATR): $\tilde{\nu}$ = 3085-3030 (=C-H), 2960-2870 (C-H), 1230 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{97}H_{92}N_3O_{18}$ [*M* + H]$^+$: 1587.6409; found: 1587.6414; calcd for $C_{97}H_{93}N_3O_{18}$ [*M* + 2H]$^{2+}$: 794.3244; found: 794.3242; elemental analysis calcd (%) for $C_{97}H_{91}N_3O_{18}$ (1586.8): C, 73.42; H, 5.78; N, 2.65; found: C, 73.27; H, 5.87; N, 2.69.

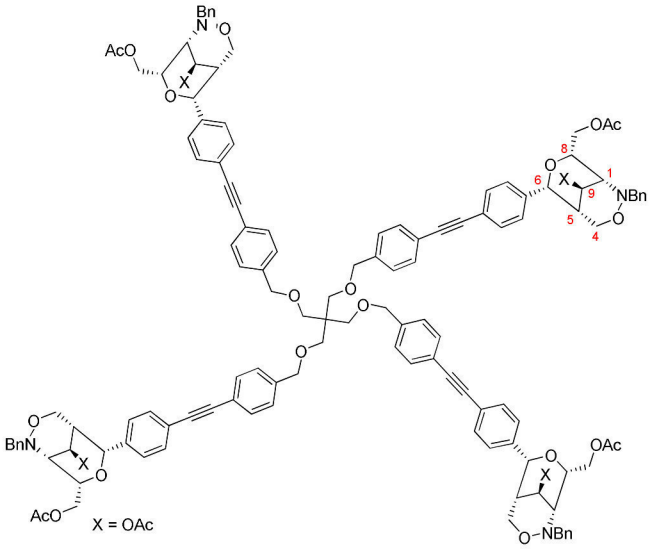
**Trimer 32:**




A suspension of Pd/C (10% Pd, 255 mg) and *i*PrOH (10 mL) was saturated with hydrogen for 15 min. Compound **31** (170 mg, 107 µmol) was dissolved in ethyl acetate (3 mL) and added to this suspension. The mixture was stirred for 6 h under hydrogen atmosphere (balloon), filtered through a pad of Celite® and the solvent was removed in vacuo. Under an argon atmosphere the crude product was dissolved in degassed methanol (1 mL) and a samarium(II) iodide solution (0.1 M in THF, 9.64mL, 964 µmol) was added drop wise. The mixture was stirred for 30 min at rt and for further 10 min in the presence of air. The obtained solid was filtered off and washed with dichloromethane (3 x 10 mL) and methanol (3 x 10 mL) and then dissolved in a $CH_2Cl_2$/pyridine mixture (2 mL/ 2mL). Acetic anhydride (182 µL, 197 mg, 1.93 mmol) and DMAP (125 mg, 1.03 mmol) were added. The mixture was stirred at rt for 18 h. Water (5 mL) was added to the mixture and the aqueous layer was extracted with dichloromethane (5 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was subjected to column chromatography (silica gel, $CH_2Cl_2$:MeOH 15:1) to yield a mixture of compounds containing **32** and a numerous other unknown products.

HRMS (ESI-TOF): m/z calcd for $C_{88}H_{104}N_3O_{24}$ $[M + H]^+$: 1586.7010, found: 1586.6995.

**Tetramer 33:**

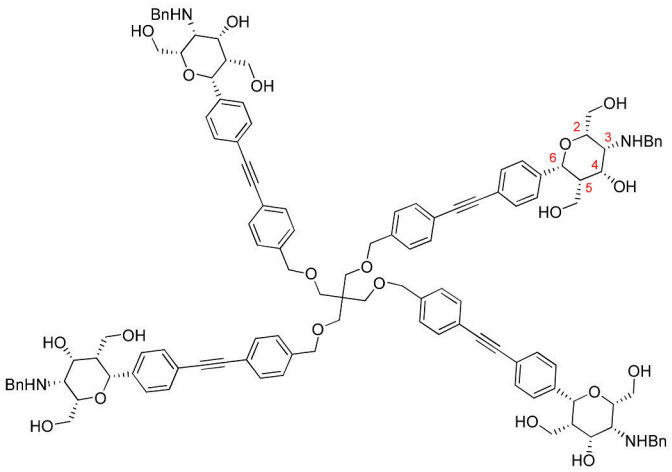



Compound **8** (110 mg, 301 µmol), $PdCl_2(PPh_3)_2$ (11 mg, 15 µmol) and CuI (3 mg, 15 µmol) were filled in a sealed tube and flushed with argon. Degassed THF (3 mL), *i*$Pr_2NH$ (0.7 mL) and 4,4'-(2,2-bis((4-iodobenzyloxy)methyl)propane-1,3-diyl)bis(oxy)bis(methylene)bis(iodobenzene) (50 mg, 50 µmol) were added and the mixture was stirred for 48 h at 70 °C. The solution was cooled to rt, the solids were filtered off and washed with ethyl acetate (3 x 10 mL). The obtained solid was dissolved in a $CH_2Cl_2$/pyridine mixture (1 mL/2 mL), DMAP (39 mg, 320 µmol) and acetic anhydride (61 mg, 56 µL, 600 µmol) were added. The mixture was stirred at rt for 18 h. Water (5 mL) was added to the mixture and the aqueous layer was extracted with dichloromethane (5 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was recrystallized (EtOAc/$CH_3OH$ 1:3) to yield **33** (87 mg, 76%) as a colorless solid.

m.p. 109-111 °C; $[\alpha]_D^{22}$ = +127.3 (*c* = 1.00, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 2.01 (s, 12 H, Ac), 2.04 ($m_c$, 4 H, 5-H), 2.28 (s, 12 H, Ac), 3.12 ($s_{br}$, 4 H, 1-H), 3.43 (d, *J* = 11.7 Hz, 4 H, 4-H), 3.60 (s, 8 H, $CCH_2O$), 4.13 (dt, *J* = 1.8, 6.0 Hz, 4 H, 8-H), 4.36 ($d_{br}$, *J* = 13.3 Hz, 8 H, 4-H, $NCH_2$), 4.49-4.55 (m, 20 H, $NCH_2$, 8-$CH_2$, $OCH_2Ar$), 5.05 (s, 4 H, 6-H), 5.19 (t, *J* = 2.6 Hz, 4 H, 9-H), 7.27, 7.50 (AA´BB´ system, $J_{AB}$ = 8.2 Hz, 16 H, Ar), 7.28-7.29 (m, 4 H, Ph), 7.34-7.38 (m, 16 H, Ph), 7.42, 7.52 (AA´BB´ system, $J_{AB}$ = 8.2 Hz, 16 H, Ar) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 21.0, 21.5 (2 q, Ac), 29.8 [s, $C(CH_2)_4$], 38.6 (d, C-5), 55.1 (d, C-1), 57.5 (t, C-4), 58.4 (t, $NCH_2$), 64.8 (t, 8-$CH_2$), 69.5 (t, $CCH_2O$), 71.0 (d, C-9), 73.0 (t, $OCH_2Ar$), 76.9 (d, C-8), 79.6 (d, C-6), 89.2, 89.6 (s, C≡C), 122.3, 122.7 (2 s, Ar, Ph), 126.3, 127.3, 127.5, 128.5, 128.8, 131.6, 131.7 (7 d, Ar, Ph), 137.8, 139.2, 139.5 (3 s, Ar, Ph), 170.1, 170.8 (2 s, Ac) ppm; IR (ATR): $\tilde{\nu}$ = 3060-3025 (=C-H), 2925-2870 (C-H), 2365, 2340 (C≡C), 1740 (C=O), 1455 (C-H), 1230 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{137}H_{137}N_4O_{28}$ [*M*

+ H]$^+$: 2286.9453, found: 2286.9473, calcd for $C_{137}H_{136}N_4NaO_{28}$ [*M* + Na]$^+$ 2308.9272, found: 2308.9315; elemental analysis calcd (%) for $C_{137}H_{136}N_4O_{28}$ (2286.6): C, 71.96; H, 6.00; N, 2.45; C, 71.84; H, 6.18; N, 2.57.

**Tetramer 34:**




Under an argon atmosphere the compound **33** (87 mg, 38 µmol) was dissolved in degassed THF (1 mL) and a samarium(II) iodide solution (0.1 M in THF, 4.56 mL, 456 µmol) was added drop wise. The mixture was stirred for 5 h at rt and for further 10 min in the presence of air. Size exclusion chromatography (Sephadex$^{TM}$ LH-20, $CH_3OH$) and subsequent purification by RP-HPLC (Gemini®-NX, MeOH:$H_2O$, 7:3) yielded **34** (68 mg, 84%) as a colorless solid.

m.p. 183-185 °C; $[\alpha]_D^{22}$ = +78.4 (*c* = 1.05, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD$): δ = 2.38 ($m_c$, 4 H, 5-H), 3.13 (dd, *J* = 2.0, 10.7 Hz, 4 H, 5-$CH_2$), 3.55 ($m_c$, 8 H, $OCH_2$), 3.80, 4.03, 4.13 (XAB system, $J_{AX}$ = 2.0 Hz, $J_{BX}$ = 2.8 Hz, $J_{AB}$ = 12.3 Hz, 12 H, 2-H, 2-$CH_2$), 3.87-3.88 (m, 8 H, 3-H, 5-$CH_2$), 4.46 (d, *J* = 12.8 Hz, 4 H, $NCH_2$), 4.50 (s, 8 H, $OCH_2$), 4.71 (d, *J* = 12.8 Hz, 4 H, $NCH_2$), 4.82 (dd, *J* = 4.1, 7.1 Hz, 4 H, 4-H), 5.02 (d, *J* = 4.0 Hz, 4 H, 6-H), 7.26-7.27 (m, 8 H, Ar), 7.43-7.45 (m, 15 H, Ar, Ph), 7.46-7.50 (m, 21 H, Ar, Ph), 7.52-7.53 (m, 8 H, Ar, Ph) ppm; $^{13}$C NMR (175 MHz, $CD_3OD$): δ = 45.8 (d, C-5), 46.7 [s, $C(CH_2)_4$], 53.3 (t, $NCH_2$), 55.6 (t, 5-$CH_2$), 60.0 (d, C-3), 65.4 (t, 2-$CH_2$), 70.0 (t, $OCH_2$), 71.1 (d, C-4), 73.8 (t, $OCH_2$), 75.9 (d, C-2), 82.0 (d, C-6), 90.0, 90.2 (2 s, C≡C), 123,48, 123.53 (2 s, Ar), 127.3, 128.7, 130.4, 130.5, 130.6, 132.3, 132.5 (7 d, Ar, Ph), 133.9, 140.5, 140.9 (3 s, Ar, Ph) ppm; IR (ATR): $\tilde{\nu}$ = 3635-3155 (O-H, N-H), 3095-3030 (=C-H), 2990-2855 (C-H), 2350, 2325 (C≡C), 1460 (C-H), 1240 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{121}H_{130}N_4O_{20}$ [*M* + 2H]$^{2+}$: 979.9656; found: 979.9627; calcd for $C_{121}H_{131}N_4O_{20}$ [*M* + 3H]$^{3+}$: 653.6463; found: 653.6447.

## 3.3 Syntheses of Mono- and Divalent *C*-Aminoglycosides Based on 1,2-Oxazine Chemistry and on Olefin-Metathesis

Dieses Kapitel wurde in der folgenden Zeitschrift zur Publikation akzeptiert:

M. Kandziora, E. Mucha, S. P. Zucker, H.-U. Reissig, *Synlett* **2014**, *im Druck.*

Das Kapitel 3.3 beschreibt einen neuen Zugang zu mono- und divalenten *C*-Aminoglycosiden. Basierend auf einem literaturbekannten 1,2-Diol wurden ein vinyl- und ein homoallyl-1,3-dioxolanylsubstituiertes 1,2-Oxazin durch Lewis-Säure-Katalyse dargestellt. Durch Lewis-Säure-induzierte Umlagerung des vinylsubstituierten 1,2-Oxazins und anschließende Reduktion des entstandenen bicyclischen 1,2-Oxazinons wurden zwei enantiomerenreine, bicyclische Diole synthetisiert. Nach Hydrogenolyse entstanden 3-Amino-substituierte-*C*-glycoside, die eine *β*-D-Talose- bzw. *β*-D-Idose-Konfiguration aufweisen. Das vinylsubstituierte bicyclische 1,2-Oxazin konnte nach Benzylierung und anschließender Selbst-Kreuzmetathese in exzellenter Ausbeute „dimerisiert“ werden. Das erhaltene Produkt ergab nach Hydrogenolyse und Reaktion mit Hydroxylaminhydrochlorid ein neues interessantes divalentes *C*-Aminoglycosid.

Die Verbindung **3** wurde erstmals von Frau Sina Zucker im Rahmen eines Forschungspraktikums dargestellt und die Verbindungen **5**, **10** und **12** wurden von Herrn Eike Mucha im Rahmen seiner Bachelorarbeit synthetisiert.

Synlett M. Kandziora et al. Letter

# Syntheses of Mono- and Divalent *C*-Aminoglycosides Using 1,2-Oxazine Chemistry and Olefin Metathesis

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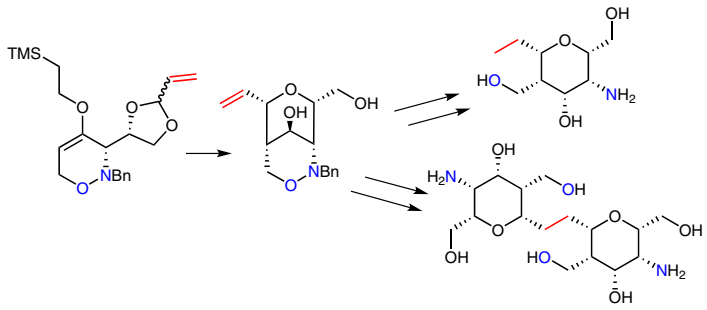


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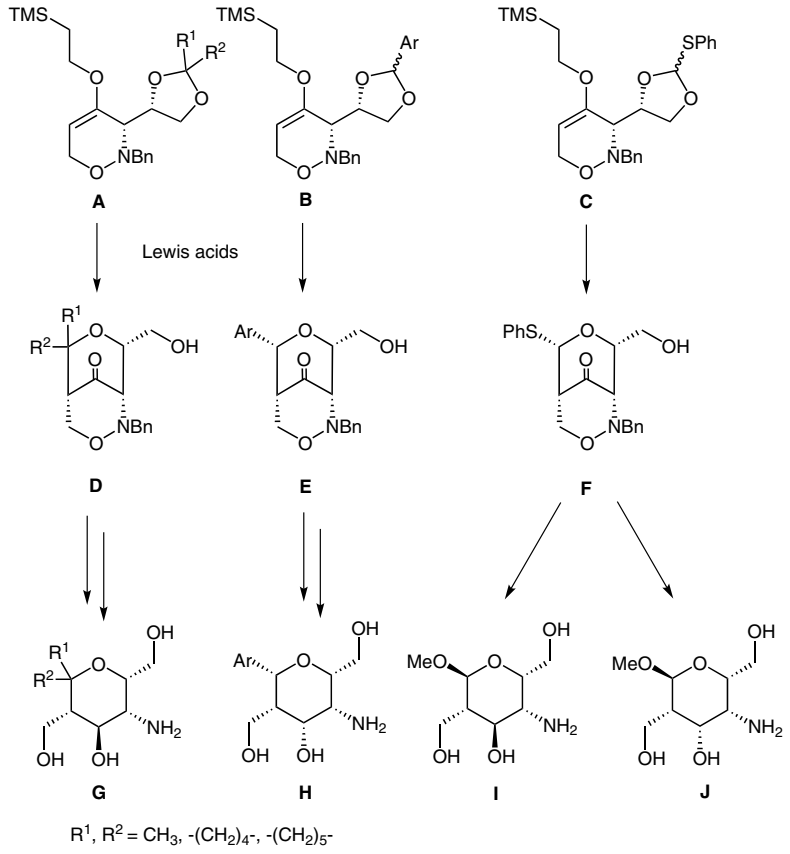
**Abstract** An approach to mono- and divalent *C*-aminoglycosides starting from a new enantiopure 1,2-oxazine derivative is described. The introduction of a vinyl group into the 1,3-dioxolanyl substituent of a 1,2-oxazine allowed the Lewis acid promoted preparation of a vinyl-substituted bicyclic 1,2-oxazinone. After reduction of the carbonyl group, exhaustive hydrogenolysis provided branched *C*-aminoglycosides either with β-D-talose or β-D-idose configuration. The vinyl group of the protected rearrangement product **8** also allowed a self-metathesis with Grubbs II catalyst providing a 'dimeric' compound as an *E*/*Z* mixture. Its hydrogenolysis furnished the divalent *C*-aminoglycoside in good overall yield.

**Key words** 1,2-oxazine, pyran, *C*-glycoside, amino sugar, olefin metathesis, hydrogenation

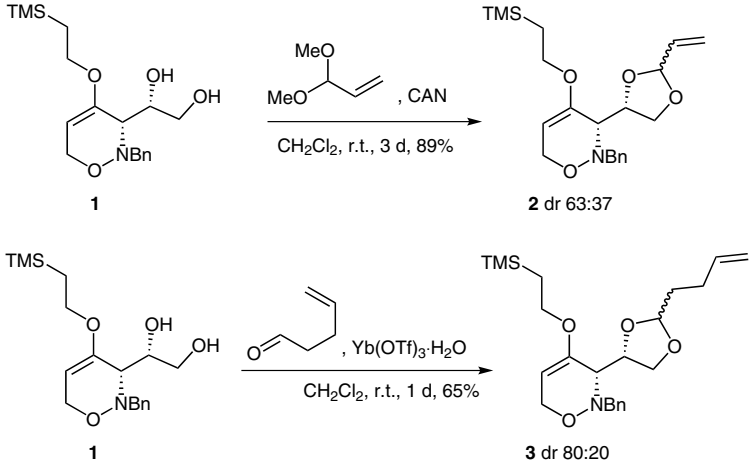
Amino sugars and their derivatives have gained increasing interest due to their widespread biological activity and other properties.[1] Aminoglycosides belong to the most potent antibiotics known for more than five decades. However, the emergence and rapid spread of aminoglycoside-resistant pathogens limit their intensive clinical use.[2] As consequence of this trend, new methods for the synthesis of unnatural amino sugar derivatives with improved antibacterial properties are required.[3] One approach towards new unnatural C-2-branched 4-amino carbohydrate derivatives involves a *de novo* strategy employing enantiopure 1,3-dioxolanyl-substituted 1,2-oxazines **A**, **B** and **C** (Scheme 1) that are easily accessible by [3+3] cyclizations of lithiated alkoxyallenes and carbohydrate-derived nitrones.[4] The Lewis acid induced rearrangements of these 1,2-oxazines lead to the corresponding bicyclic 1,2-oxazine intermediates **D**, **E** or **F** in a highly stereoselective fashion. After reduction of the carbonyl group and the crucial reductive N–O bond cleavage, 4-aminopyrans **G**, **H**, **I** or **J** are obtained. Compounds **G**[5] and **H**[6] can be regarded as *C*-glycosides of amino sugars. The two diastereomeric methoxy-substituted amino sugars **I** and **J** are accessible from **F** by stereodivergent routes. Compounds **I** and **J** are 4-amino D-idose and D-talose derivatives with branching at C-2.[7] All compounds are available with excellent diastereoselectivities and in both enantiomeric forms depending on the configuration of the enantiopure precursor nitrone.[8]

In this report we describe the successful synthesis of a new (2-vinyl-1,3-dioxolan-4-yl)-substituted 1,2-oxazine and its transformation into the corresponding *C*-glycosidic aminopyrans. In addition, we report the synthesis of a divalent *C*-aminoglycoside employing a cross-metathesis as crucial reaction.

The preparation of (2-vinyl-1,3-dioxolan-4-yl)-substituted 1,2-oxazine **2** started from diol **1** that is easily accessible by the mild cleavage of the corresponding acetonide employing indium trichloride and water.[9] With cerium ammonium nitrate as Lewis acid[10] and an excess of acrolein dimethyl acetal (high concentrations are advantageous) diol **1** was converted into the desired vinyl-substituted dioxolane derivative **2** in excellent 89% yield (dr 63:37; Scheme 2). Unfortunately, these conditions were not suitable for the synthesis of (2-but-3′-enyl-1,3-dioxolan-4-yl)-substituted 1,2-oxazine **3**. We examined Lewis acids such as zinc triflate, ytterbium(III) triflate hydrate, scandium(III) triflate or boron trifluoride diethyl etherate to achieve the acetal formation of **1** and used either pent-4-enal or the corresponding dimethyl acetal. The best yield could be achieved with the aldehyde as precursor and $Yb(OTf)_3$ hydrate as Lewis acid giving compound **3** in 65% yield (dr 80:20; Scheme 2). Other weak acids like pyridine/hydrogen fluoride or Brønsted acids such as trifluoroacetic acid and *p*-toluenesulfonic acid led to an undesired side product.[11] The diastereomers of **2** and **3** could be separated by chromatography, but no configurational assignments were attempted. The subsequent Lewis acid mediated rearrangements are stereoconvergent processes via oxocarbenium ions and hence diastereomeric mixtures of **2** or **3**, respectively, were used for these reactions (see Scheme 3).

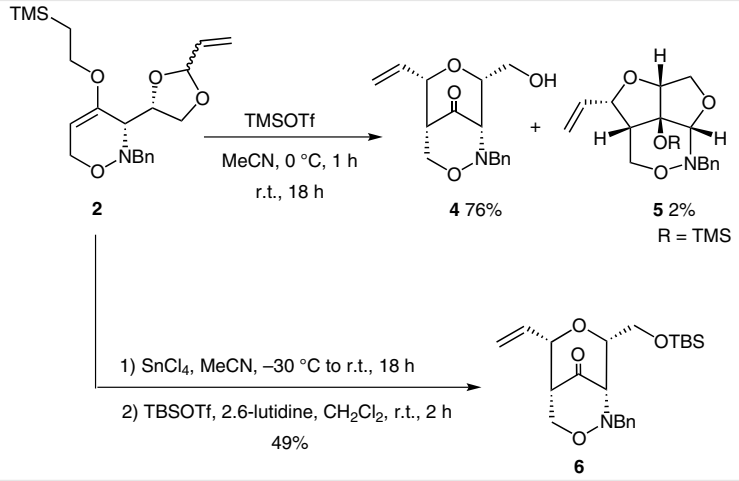



**Scheme 1** Examples of C-2-branched 4-amino sugar derivatives **G**, **H**, **I** and **J** obtained by a *de novo* strategy employing 1,3-dioxolanyl-substituted 1,2-oxazines **A**, **B** and **C**




**Scheme 2** Preparations of (2-vinyl-1,3-dioxolan-4-yl)-substituted 1,2-oxazine **2** and (2-but-3′-enyl-1,3-dioxolan-4-yl)-substituted 1,2-oxazine **3**

After some optimization, the Lewis acid induced rearrangement of 1,2-oxazine **2** with trimethylsilyl trifluoromethanesulfonate led to ketone **4** in 76% yield and with excellent stereoselectivity (Scheme 3). Product **4** is not very stable and should rapidly be transformed in subsequent products. In addition, an interesting side product **5** was isolated in 2% yield. A mechanism for the formation of a structurally comparable tricyclic product has earlier been proposed by our group.[12]

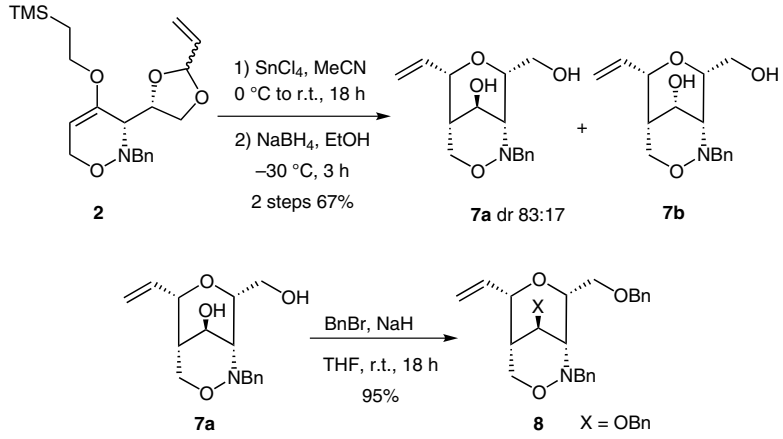



**Scheme 3** Preparation of enantiopure bicyclic compounds **4** and **6** by Lewis acid mediated rearrangements of 1,2-oxazine **2**

The tin tetrachloride mediated rearrangement and subsequent protection of the resulting primary hydroxyl group with *tert*-butyldimethylsilyl triflate under standard conditions provided the considerably more stable protected compound **6**, but only moderate overall yields of up to 49% could be achieved. The mechanism of these Lewis acid induced rearrangements can be understood as an intramolecular aldol or Prins reaction type cyclization. The sterically less hindered oxygen atom of the dioxolane moiety of 1,2-oxazine **2** is coordinated by the Lewis acid which opens the dioxolane ring by forming an oxocarbenium ion that is additionally stabilized by the vinyl moiety. This electrophilic intermediate then attacks intramolecularly the enol ether C-5 carbon atom of the 1,2-oxazine ring.[5a] The resulting configuration of the product may be explained plausibly by a six-membered chair-like transition state with the vinyl group in the sterically more favorable equatorial position.

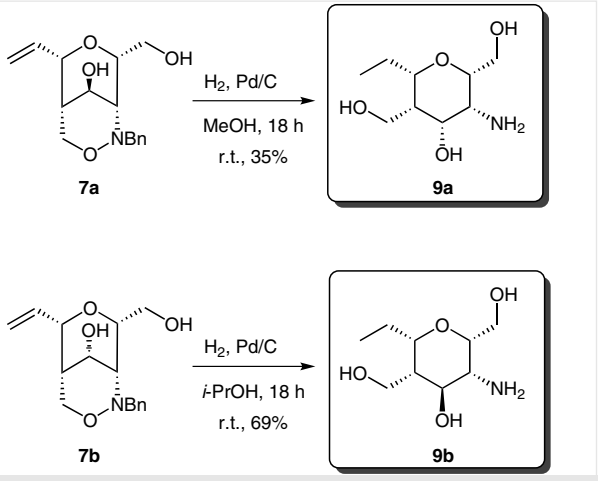
We also treated 1,2-oxazine derivative **3** with different Lewis acids in order to obtain a 3-butenyl-substituted bicyclic product. Unfortunately, the corresponding compound was obtained irreproducibly in low yields and selectivity under the formation of numerous unknown side-products. The reason for this disappointing result may be the lower stabilization of the intermediate oxocarbenium ion derived from 1,2-oxazine **3**.

By consecutive Lewis acid promoted rearrangement of 1,2-oxazine derivative **2** and direct reduction of the unpurified ketone **4** we could considerably improve the overall efficacy of the reaction sequence. Its treatment with sodium borohydride under standard conditions furnished the diastereomers **7a** and **7b** in a ratio of 83:17 and in a satisfactory overall yield of 67% (Scheme 4). Both isomers are fairly stable and after separation by column chromatography the major product **7a** was bis-O-benzylated under standard conditions to obtain the compound **8** in 95% yield.




**Scheme 4** Consecutive Lewis acid promoted rearrangement of 1,2-oxazine **2** and immediate reduction providing diols **7a** and **7b** and bis-O-benzylation of **7a** furnishing protected compound **8**

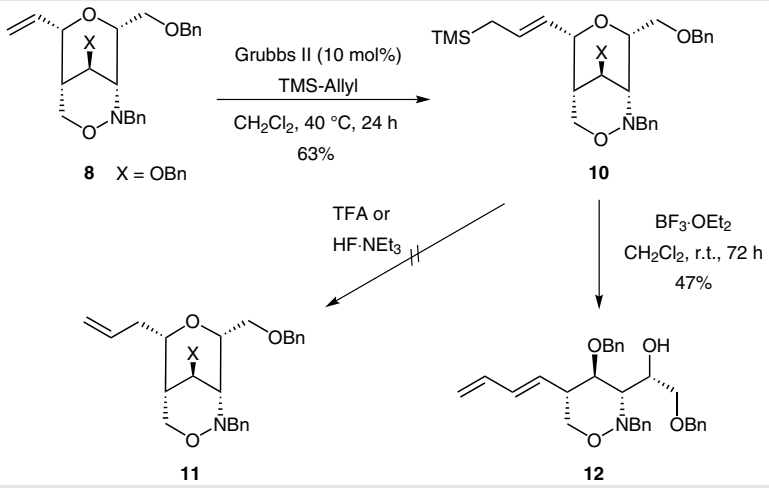
In order to prepare unnatural 6-ethyl-substituted *C*-glycosidic amino sugars, bicyclic compounds **7a** and **7b** were exhaustively reduced with hydrogen in the presence of palladium on charcoal. After conversion of the vinyl into an ethyl group, the N–O bond was reductively cleaved and the compounds were finally debenzylated to obtain 3-aminopyrans **9a** and **9b** (Scheme 5). Heterogenic hydrogenation is an important method in organic synthesis, but many catalysts are sensitive towards poisoning due to products such as amino alcohols.[13] We therefore applied a large amount of palladium on charcoal to achieve full conversion of **7a** and **7b** into **9a** and **9b**, compounds that are very polar and difficult to purify. Nevertheless, 1,2-oxazine **7a** was converted into 3-aminopyran **9a** by hydrogenolysis under standard conditions in methanol in a moderate yield of 35%. Methanol as solvent led to side products containing *N*,*O*-aminal subunits due to generation of formaldehyde and its subsequent reactions[14] (also see compounds **15** and **16** shown in Scheme 7). After some optimization, we discovered that 2-propanol is a more feasible solvent. Under these improved conditions 1,2-oxazine **7b** was converted into enantiopure 3-aminopyran **9b** in a good yield of 69%. Compound **9a** is a branched *C*-glycoside with β-D-talose configuration whereas isomer **9b** correlates to β-D-idose. These new *C*-glycosidic amino sugar derivatives may have antibiotic activity[2a] but have so far not been tested.



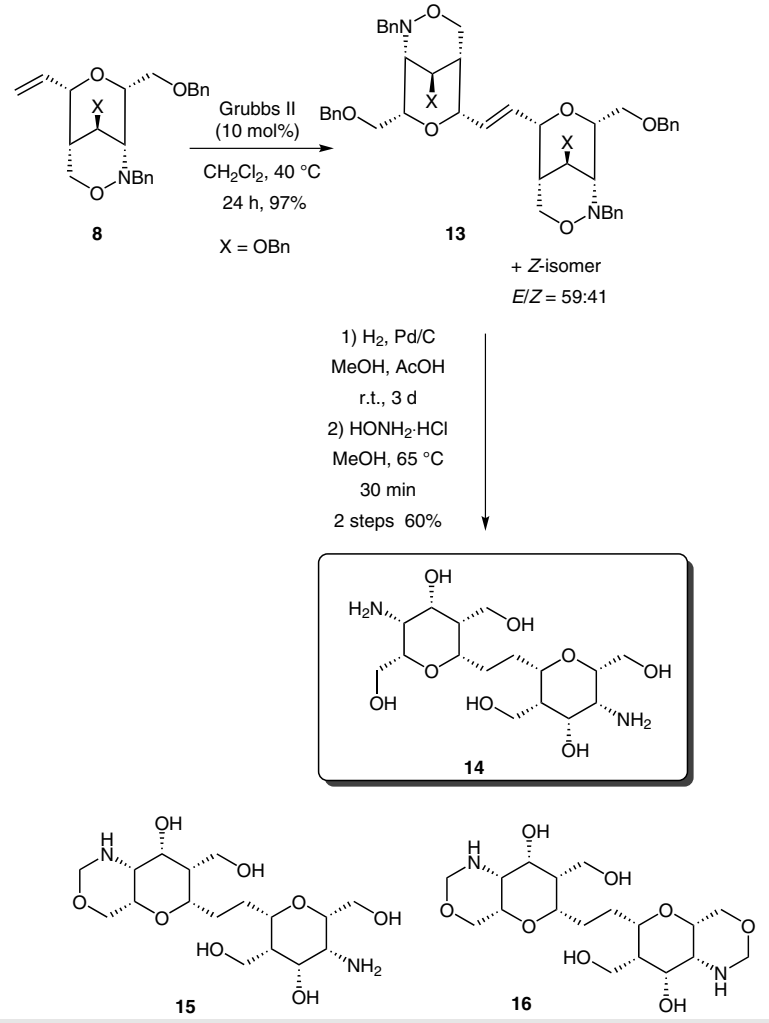

**Scheme 5** Syntheses of ethyl-substituted *C*-glycosidic amino sugars **9a** and **9b** by exhaustive hydrogenolysis of compounds **7a** and **7b**

The vinyl moiety of bicyclic compounds such as **7a**, **7b** or **8** should allow several useful transformations like dihydroxylation, epoxidation and ozonolysis leading to new interesting intermediates. We were more interested in carbon–carbon bond-forming reaction and therefore examined the olefin metathesis[15] with our substrates. Bicyclic compound **8** turned out to be a challenging substrate for this process due to the steric hindrance next to the vinyl group. We first examined compound **8** in a cross-metathesis reaction with allyltrimethylsilane (Scheme 6). After extensive optimization, for example using additives such as copper(I) chloride[16] or titanium(IV) isopropoxide,[17] we found that the desired product **10** could be isolated in 63% yield when 10 equivalents of allyltrimethylsilane were employed and when 10 mol% of the Grubbs II catalyst were added in three portions during a period of 24 hours; otherwise no full conversion of **8** was observed. The $^1$H NMR spectrum of the crude product showed signals of two diastereomers (ratio ca. 10:1), but only the major isomer was isolated after column chromatography. We then tried to prepare the 2-propenyl-substituted **11** by proto-desilylation of compound **10** by employing Brønsted or Lewis acids.[18] Whereas acids like trifluoroacetic acid or pyridine hydrofluoride did not induce any reaction boron trifluoride diethyl etherate led to the formation of 1,3-butadienyl-substituted pyran **12** in 47% yield (not optimized). The strong Lewis acid seems to coordinate predominantly at the pyran oxygen of **10** leading to a ring opening; the resulting allyl cation undergoes TMS displacement to deliver the 1,3-butadiene moiety of compound **12**. Only the *E*-isomer of product **12** was detected. This new enantiopure building block may serve as a suitable precursor for further functionalizations and lead to interesting amino polyol compounds.[19]

Encouraged by this successful cross-metathesis with allyltrimethylsilane we attempted the self-metathesis of compound **8**. Gratifyingly, this sterically very demanding reaction proceeded under similar conditions with excellent efficacy leading to 'dimeric' compound **13** in 97% yield with an *E*/*Z* ratio of 59:41 (Scheme 7). In the subsequent palladium-catalyzed hydrogenolysis of compound (*E*)-**13** we attempted to use 2-propanol as solvent (see reaction of **7b** in Scheme 5), but in this case the reaction was too slow and even after one week it did not go to completion. We therefore used methanol as solvent adding 10 equivalents of acetic acid[14] and then observed full conversion of **13** with the expected saturation of the alkene moiety, the cleavage of the N–O bonds and the required full O- and N-debenzylations. However, the resulting product mixture not only contained the desired product **14** but also side-products **15** and **16** (Scheme 7). These undesired compounds were obviously formed by in situ generated formaldehyde (due to dehydrogenation of methanol)[14,20] and subsequent *N*,*O*-aminal formation with aminopyran **14**. Surprisingly, the *N*,*O*-aminal moieties of **15** and **16** could not be hydrolyzed with trifluoroacetic acid even at 60 °C, however, when the mixture of **14**, **15** and **16** was treated with hydroxylamine hydrochloride[21] the *N*,*O*-aminals were smoothly cleaved and, after precipitation, the very polar product **14** was obtained in 60% overall yield as a pure solid.[22] This product may be regarded as divalent *C*-glycoside with β-D-talose configuration (pseudo disaccharide) that will be tested for its biological activities.




**Scheme 6** Cross-metathesis reaction of bicyclic 1,2-oxazine **8** with allyltrimethylsilane leading to product **10** followed by $BF_3$-mediated conversion into 1,3-butadiene derivative **12**




**Scheme 7** Synthesis of divalent *C*-aminoglycoside **14** by self-metathesis of compound **8** and subsequent hydrogenolysis of 'dimer' **13**

In summary, in this communication we have described the synthesis of the two new 1,3-dioxolanyl-substituted 1,2-oxazine derivatives **2** and **3**; however, only the vinyl-substituted derivative **2** could be transformed into the enantiopure bicyclic products **4** and **6** by the Lewis acid induced rearrangement. After the reduction of the carbonyl moiety and an N–O bond cleavage, two branched *C*-amino sugars with β-D-talose and β-D-idopyranose configuration could be prepared. Self-metathesis of the protected vinyl-substituted bicyclic compound **8** resulted in 'dimeric' compound **13**. By the subsequent hydrogenolysis a new divalent *C*-aminoglycoside **14** was obtained in a satisfactory yield. Our study demonstrates that 2-alkenyl-1,3-dioxolan-4-yl-substituted 1,2-oxazines such as **2** are versatile building blocks for the *de novo* synthesis of unique *C*-aminoglycosides.

## Acknowledgment

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## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379503.

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(22) Representative Experimental Procedures:
**(1*R*,5*S*,6*S*,8*S*,9*R*)-2-Benzyl-8-(hydroxymethyl)-6-vinyl-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (7a) and (1*R*,5*S*,6*S*,8*S*,9*S*)-2-Benzyl-8-(hydroxymethyl)-6-vinyl-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (7b):** 1,2-Oxazine **2** (50 mg, 128 μmol) was dissolved in MeCN (2 mL) and cooled to 0 °C. Tin(IV) chloride (45 μL, 100 mg, 384 μmol) was added and the solution was stirred for 3 h at 0 °C, then additional tin(IV) chloride (45 μL, 100 mg, 384 μmol) was added and the reaction mixture was stirred for 18 h at r.t. $H_2O$ (5 mL) was added and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was dissolved in EtOH (2 mL) and cooled to –30 °C. Sodium borohydride (10 mg, 256 μmol) was added and the suspension was stirred for 3 h at –30 °C. Then the solvent was removed in vacuo and the crude product was dissolved in $CH_2Cl_2$ (10 mL) and $H_2O$ (5 mL) was added. The aqueous layer was extracted with $CH_2Cl_2$ (5 × 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel; hexanes–EtOAc, 1:4) to yield **7a** (21 mg, 56%) and **7b** (4 mg, 11%) as colorless solids.

**Data of 7a:** mp 108–110 °C; $[\alpha]_D^{22}$ +47.9 (*c* = 1.04, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.96 ($m_c$, 1 H, 5-H), 2.75 (br s, 1 H, OH), 3.11 (br s, 1 H, 1-H), 3.69, 3.73 (AB part of ABX system, $J_{AX}$ = 4.6 Hz, $J_{BX}$ = 6.6 Hz, $J_{AB}$ = 11.0 Hz, 2 H, 8-$CH_2$), 3.70 (br s, 1 H, OH), 3.89 (br s, 1 H, 9-H), 3.99–4.03 (m, 1 H, 8-H), 4.09 (d, *J* = 14.1 Hz, 1 H, $NCH_2$), 4.16–4.18 (m, 1 H, 4-H), 4.17 (s, 1 H, 6-H), 4.19 (ddd, *J* = 0.6, 5.8, 12.1 Hz, 1 H, 4-H), 4.23 (d, *J* = 14.1 Hz, 1 H, $NCH_2$), 5.23 (br d, *J* = 10.8 Hz, 1 H, 2′-H), 5.36 (br d, *J* = 17.4 Hz, 1 H, 2′-H), 5.84 (ddd, *J* = 4.7, 10.8, 17.4 Hz, 1 H, 1′-H), 7.27–7.34 (m, 5 H, Ph). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 39.1 (d, C-5), 62.1 (d, C-1), 62.2 (t, $NCH_2$), 63.8 (t, 8-$CH_2$), 65.1 (t, C-4), 70.4 (d, C-9), 78.7 (d, C-6), 79.3 (d, C-8), 116.6 (t, C-2′), 127.7, 128.6, 128.8 (3 × d, Ph), 135.9 (d, C-1′), 137.2 (s, Ph). IR (ATR): 3580–3180 (O–H), 3025–3005 (=C–H), 2930–2855 (C–H), 1595 (C=C), 1455 (C–H), 1230 (C–O) $cm^{-1}$. HRMS (ESI–TOF): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{22}NO_4$: 292.1549; found: 292.1542; *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{21}NNaO_4$: 314.1368; found: 314.1366.

**Data of 7b:** mp 55–58 °C; $[\alpha]_D^{22}$ +12.8 (*c* = 0.40, $CHCl_3$). $^1H$ NMR (700 MHz, $CDCl_3$): δ = 1.79 ($m_c$, 1 H, 5-H), 2.81 ($m_c$, 1 H, 1-H), 3.79, 3.98 (AB part of ABX system, $J_{AX}$ = 4.0 Hz, $J_{BX}$ = 5.4 Hz, $J_{AB}$ = 11.6 Hz, 2 H, 8-$CH_2$), 4.11 (dd, *J* = 2.0, 12.1 Hz, 1 H, 4-H), 4.12 (d, *J* = 13.4 Hz, 1 H, $NCH_2$), 4.16–4.18 (m, 2 H, 4-H, 8-H), 4.27 (d, *J* = 13.4 Hz, 1 H, $NCH_2$), 4.62 (t, *J* = 4.0 Hz, 1 H, 9-H), 4.74 (dd, *J* = 1.5, 3.5 Hz, 1 H, 6-H), 5.24 (br d, *J* = 10.8 Hz, 1 H, 2′-H), 5.42 (br d, *J* = 17.3 Hz, 1 H, 2′-H), 5.92 (ddd, *J* = 5.2, 10.8, 17.3 Hz, 1 H, 1′-H), 7.25–7.28, 7.31–7.34 (2 × m, 1 H, 4 H, Ph); signals for OH could not be detected. $^{13}C$ NMR (175 MHz, $CDCl_3$): δ = 39.9 (d, C-5), 57.8 (t, $NCH_2$), 59.3 (d, C-1), 62.3 (d, C-9), 64.5 (t, C-4), 65.0 (t, 8-$CH_2$), 72.26 (d, C-6), 72.32 (d, C-8), 116.5 (t, C-2′), 124.9, 127.8, 128.7 (3 × d, Ph), 136.8 (d, C-1′), 136.9 (s, Ph). IR (ATR): 3425 (O–H), 3055–3030 (=C–H), 2950–2825 (C–H), 1645 (C=C), 1445 (C–H), 1250 (C–O) $cm^{-1}$. HRMS (ESI–TOF): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{22}NO_4$: 292.1549; found: 292.1537; *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{21}NNaO_4$: 314.1368; found: 314.1355. Anal. Calcd for $C_{16}H_{21}NO_4$ (291.3): C, 65.96; H, 7.27; N, 4.81. Found: C, 65.99; H, 7.22; N, 4.86.

**(1*R*,5*R*,6*S*,8*S*,9*R*)-2-Benzyl-9-(benzyloxy)-8-(benzyloxymethyl)-6-vinyl-3,7-dioxa-2-azabicyclo[3.3.1]nonane (8):** To a suspension of sodium hydride in mineral oil (15 mg, 60% NaH) in THF (1 mL) a solution of compound **7a** (20 mg, 67 µmol) in THF (1 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 1 h at r.t. and then cooled to 0 °C. Benzyl bromide (26 µL, 37 mg, 215 µmol) was added and the suspension was stirred for 18 h at r.t. The reaction was quenched with MeOH (1 mL) and the solvent was removed in vacuo. $H_2O$ (5 mL) and EtOAc (10 mL) were added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered through a pad of Celite® and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel; hexanes–EtOAc, 20:1) to yield **8** (30 mg, 95%) as a colorless solid; mp 45–47 °C; $[\alpha]_D^{22}$ +53.5 (*c* = 1.10, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.75 ($m_c$, 1 H, 5-H), 2.98 (br s, 1 H, 1-H), 3.53 (br t, *J* = 2.8 Hz, 1 H, 9-H), 3.58 (br d, *J* = 11.7 Hz, 1 H, 4-H), 3.64, 3.70, 3.79 (ABX system, $J_{BX}$ = 5.2 Hz, $J_{AX}$ = 8.8 Hz, $J_{AB}$ = 11.8 Hz, 3 H, 8-$CH_2$, 8-H), 4.15 ($m_c$, 1 H, 6-H), 4.21 (d, *J* = 13.7 Hz, 1 H, $NCH_2Ph$), 4.36, 4.42 (AB system, $J_{AB}$ = 11.8 Hz, 2 H, $OCH_2Ph$), 4.43 (td, *J* = 1.9, 11.7 Hz, 1 H, 4-H), 4.50 (d, s, *J* = 13.7 Hz, 3 H, $NCH_2Ph$, $OCH_2Ph$), 5.10 (br d, *J* = 10.8 Hz, 1 H, 2′-H), 5.26 (br d, *J* = 17.3 Hz, 1 H, 2′-H), 5.81 (ddd, *J* = 5.1, 10.8, 17.3 Hz, 1 H, 1′-H), 7.04–7.07, 7.09–7.20, 7.21–7.28 (3 × m, 1 H, 10 H, 4 H, Ph). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 37.4 (d, C-5), 55.2 (d, C-1), 57.6 (t, C-4), 58.4 (t, $NCH_2Ph$), 60.5 (t, $OCH_2Ph$), 70.5, 70.6 (2 × t, $OCH_2Ph$, 8-$CH_2$), 73.7 (d, C-9), 78.3 (d, C-8), 79.0 (d, C-6), 116.6 (t, C-2′), 127.0, 127.4, 127.7, 127.9, 128.0, 128.2, 128.4, 128.7, 128.8 (9 × d, Ph), 136.2 (d, C-1′), 138.1, 138.3, 138.9 (3 × s, Ph). IR (ATR): 3060–3025 (=C–H), 2930–2870 (C–H), 1645 (C=C), 1450 (C–H), 1240 (C–O) $cm^{-1}$. HRMS (ESI–TOF): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{34}NO_4$: 472.2488; found: 472.2524; (ESI–TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{33}NNaO_4$: 494.2307; found: 494.2345.

**(2*S*,3*R*,4*S*,5*S*,6*S*)-(3-Amino-6-ethyl-4-hydroxytetrahydro-2*H*-pyran-2,5-diyl)dimethanol (9b):** A suspension of Pd/C (10% Pd, 70 mg) and *i*-PrOH (3 mL) was saturated with hydrogen for 15 min. To this suspension bicyclic compound **7b** (70 mg, 240 µmol), dissolved in *i*-PrOH (1 mL), was added. The mixture was stirred for 18 h under hydrogen pressure (balloon). Then the mixture was filtrated through a pad of Celite®, the solvent was removed in vacuo and the crude material was purified by column chromatography (silica gel; $CH_2Cl_2$–MeOH, 10:1) to yield **9b** (34 mg, 69%) as a colorless solid; mp 143–145 °C; $[\alpha]_D^{22}$ +63.1 (*c* = 1.02, MeOH). $^1H$ NMR (700 MHz, $CD_3OD$): δ = 0.77 (t, *J* = 7.4 Hz, 3 H, 2′-H), 1.39–1.45 (m, 1 H, 1′-H), 1.56–1.62 (m, 2 H, 5-H, 1′-H), 2.91 (br s, 1 H, 3-H), 3.15 ($m_c$, 1 H, 6-H), 3.20 (br s, 1 H, 2-H), 3.37, 3.47 (AB part of ABX system, $J_{AX}$ = 5.6 Hz, $J_{BX}$ = 6.7 Hz, $J_{AB}$ = 11.5 Hz, 2 H, 2-$CH_2$), 3.44 (dd, *J* = 2.9, 11.4 Hz, 1 H, 5-$CH_2$), 3.60 (br d, *J* ≈ 11.4 Hz, 1 H, 5-$CH_2$), 3.80 (br t, *J* = 5.2 Hz, 1 H, 4-H). $^{13}C$ NMR (175 MHz, $CD_3OD$): δ = 11.3 (q, C-2′), 26.3 (t, C-1′), 44.6 (d, C-5), 51.0 (d, C-3), 55.6 (t, 5-$CH_2$), 62.9 (t, 2-$CH_2$), 72.2 (d, C-4), 79.7 (d, C-2), 82.1 (d, C-6). IR (ATR): 3365–3300 (O–H, N–H), 2960–2845 (C–H), 1460 (C–H) $cm^{-1}$. HRMS (ESI–TOF): *m*/*z* $[M + H]^+$ calcd for $C_9H_{20}NO_4$: 206.1392; found: 206.1402; *m*/*z* $[M + Na]^+$ calcd for $C_9H_{19}NNaO_4$: 228.1212; found: 228.1212.

**(*E*,1*R*,5*R*,6*S*,8*S*,9*R*)-1,2-Bis[2-benzyl-9-(benzyloxy)-8-(benzyloxymethyl)-3,7-dioxa-2-azabicyclo[3.3.1]nonan-6-yl]ethene (13a) and (*Z*,1*R*,5*R*,6*S*,8*S*,9*R*)-1,2-Bis-[2-benzyl-9-(benzyloxy)-8-(benzyloxymethyl)-3,7-dioxa-2-azabicyclo[3.3.1]-nonan-6-yl]ethane (13b):** Benzyl-protected bicyclic compound **8** (300 mg, 636 µmol) was dissolved in degassed $CH_2Cl_2$ (5 mL). Grubbs II catalyst (18 mg, 21 µmol) was added to this solution and the mixture was stirred for 3 h at 40 °C. Then a second portion of Grubbs II catalyst (18 mg, 21 µmol) was added and after another 3 h of stirring at 40 °C a third portion of the catalyst (18 mg, 21 µmol) was added. The reaction mixture was stirred for 18 h at 40 °C. The solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel; hexanes–EtOAc, 4:1) to yield **13a** and **13b** (165 mg, 57%, *E*-isomer; 117 mg, 40%, *Z*-isomer) as colorless oils.

**Data of *E*-isomer 13a:** $[\alpha]_D^{22}$ +66.1 (*c* = 1.04, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.95 (br s, 2 H, 5-H), 3.09 (br s, 2 H, 1-H), 3.66 (d, *J* = 1.9 Hz, 2 H, 9-H), 3.67 (d, *J* = 6.5 Hz, 2 H, 4-H), 3.77, 3.83, 3.90 (ABM part of ABMX system, $J_{MX}$ = 5.2 Hz, $J_{BM}$ = 6.4 Hz, $J_{AM}$ = 8.8 Hz, $J_{AB}$ = 11.6 Hz, 6 H, 8-H, 8-$CH_2$), 4.34 (br s, 2 H, 6-H), 4.39 (d, *J* = 13.5 Hz, 2 H, $NCH_2Ph$), 4.50, 4.56 (AB system, $J_{AB}$ = 11.8 Hz, 4 H, $OCH_2Ph$), 4.53 ($m_c$, 2 H, 4-H), 4.58 (d, *J* = 13.5 Hz, 2 H, $NCH_2Ph$), 4.62, 4.65 (AB system, $J_{AB}$ = 12.0 Hz, 4 H, $OCH_2Ph$), 5.96 (d, *J* = 1.5 Hz, 2 H, HC=CH), 7.20–7.36 (m, 20 H, Ph), 7.40–7.41 (m, 10 H, Ph). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 36.7 (d, C-5), 55.3 (d, C-1), 58.0 (t, C-4), 58.4 (t, $NCH_2Ph$), 70.5 (t, $OCH_2Ph$), 70.7 (t, 8-$CH_2$), 73.7 (t, $OCH_2Ph$), 76.1 (d, C-9), 77.9 (d, C-6), 78.3 (d, C-8), 127.1, 127.5, 127.7, 127.9, 128.2, 128.4, 128.7, 129.0 (8 × d, Ph), 129.3 (d, C=C), 138.1, 138.4, 138.8 (3 × s, Ph); one d for Ph could not be detected. IR (ATR): 3060–3030 (=C–H), 2920–2860 (C–H), 1735, 1660 (C=C), 1495 (C–H), 1240 (C–O) $cm^{-1}$. HRMS (ESI–TOF): *m*/*z* $[M + H]^+$ calcd for $C_{58}H_{63}N_2O_8$: 915.4584; found: 915.4577; *m*/*z* $[M + Na]^+$ calcd for $C_{58}H_{62}N_2NaO_8$:

937.4404; found: 937.4404. Anal. Calcd for $C_{58}H_{62}N_2O_8$ (915.1): C, 76.12; H, 6.83; N, 3.06. Found: C, 75.85; H, 7.20; N, 3.06.

**Data of *Z*-isomer 13b**: $[\alpha]_D^{22}$ +72.1 (*c* = 1.07, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): δ = 2.00 ($m_c$, 2 H, 5-H), 2.49 (s, 2 H, 1-H), 3.49 (t, *J* = 2.6 Hz, 2 H, 9-H), 3.58 (d, *J* = 11.8 Hz, 2 H, 4-H), 3.61, 3.70, 3.76 (ABM part of ABMX system, $J_{MX}$ = 5.2 Hz, $J_{AM}$ = 6.5 Hz, $J_{BM}$ = 8.8 Hz, $J_{AB}$ = 11.7 Hz, 6 H, 8-H, 8-$CH_2$), 4.23 (d, *J* = 13.7 Hz, 2 H, $NCH_2Ph$), 4.33, 4.38 (AB system, $J_{AB}$ = 11.8 Hz, 4 H, $OCH_2Ph$), 4.44, 4.52 (AB system, $J_{AB}$ = 11.8 Hz, 4 H, $OCH_2Ph$), 4.45–4.48 (m, 2 H, 4-H), 4.50 (d, *J* = 13.7 Hz, 2 H, $NCH_2Ph$), 4.54 (s, 2 H, 6-H), 5.65 (d, *J* = 3.6 Hz, 2 H, HC=CH), 7.05–7.27 (m, 30 H, Ph). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 36.9 (d, C-5), 55.4 (d, C-1), 57.7 (t, C-4), 58.4 (t, $NCH_2Ph$), 70.4 (t, $OCH_2Ph$), 70.8 (t, 8-$CH_2$), 73.7 (t, $OCH_2Ph$), 75.9 (d, C-9), 76.3 (d, C-6), 78.2 (d, C-8), 127.0, 127.4, 127.9, 128.0, 128.2, 128.5, 128.7, 128.8 (8 × d, Ph), 130.6 (d, C=C), 138.2, 138.3, 138.9 (3 × s, Ph); one d for Ph could not be detected. IR (ATR): 3085–3030 (=C–H), 2965–2855 (C–H), 1735, 1655 (C=C), 1495 (C–H), 1230 (C–O) $cm^{-1}$. HRMS (ESI–TOF): *m*/*z* $[M + H]^+$ calcd for $C_{58}H_{63}N_2O_8$: 915.4584; found: 915.4585; *m*/*z* $[M + Na]^+$ calcd for $C_{58}H_{62}N_2NaO_8$: 937.4404; found: 937.4407. Anal. Calcd for $C_{58}H_{62}N_2O_8$ (915.1): C, 76.12; H, 6.83; N, 3.06. Found: C, 75.33; H, 7.42; N, 3.06.

**Divalent *C*-Aminoglycoside 14:** A suspension of Pd/C (10% Pd, 330 mg), MeOH (35 mL) and acetic acid (108 mg, 103 µL, 1.80 mmol) was saturated with hydrogen for 15 min. The bicyclic compound **13a** (165 mg, 180 µmol) was dissolved in MeOH (2 mL), and added to the suspension. The mixture was stirred for 3 d under hydrogen pressure (balloon). The mixture was filtered through a pad of Celite® and the solvent was removed in vacuo. The crude product was dissolved in MeOH (1 mL), hydroxylamine hydrochloride (55 mg, 791 µmol) was added and the reaction mixture was stirred for 30 min at 65 °C. The solvent was removed in vacuo, the crude product was dissolved in MeOH (0.5 mL) and EtOAc (0.5 mL) was added. The precipitated solid was filtered off, washed with EtOAc (3 × 1 mL) and dried in vacuo to yield **14** (41 mg, 60%; for numbering see Figure 1) as a brownish solid. Since the product is highly hygroscopic no melting point was determined.

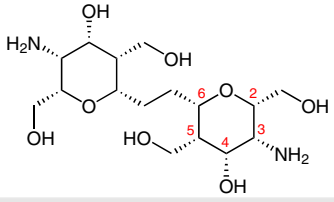


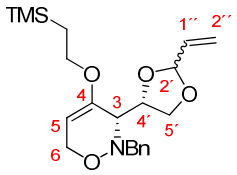

**Figure 1**

$[\alpha]_D^{22}$ –5.0 (*c* = 0.60, MeOH). $^1H$ NMR (700 MHz, $CD_3OD$): δ = 1.71–1.76 (m, 2 H, $CH_2$), 1.98 (ddd, *J* = 1.6, 3.1, 5.9 Hz, 2 H, 5-H), 2.10–2.15 (m, 2 H, $CH_2$), 3.52 (dd, *J* = 1.5, 4.4 Hz, 2 H, 3-H), 3.63, 3.80, 3.85 (ABX part of ABXY system, $J_{XY}$ = 1.5 Hz, $J_{AX}$ = $J_{BX}$ = 4.9 Hz, $J_{AB}$ = 11.8 Hz, 6 H, 2-H, 2-$CH_2$), 3.69–3.70 (m, 2 H, 6-H), 3.88, 3.97 (AB part of ABX system, $J_{AX}$ = 1.6 Hz, $J_{BX}$ = 3.1 Hz, $J_{AB}$ = 11.5 Hz, 4 H, 5-$CH_2$), 4.32 (dd, *J* = 4.4, 7.0 Hz, 2 H, 4-H). $^{13}C$ NMR (175 MHz, $CD_3OD$): δ = 29.8 (t, $CH_2$), 44.0 (d, C-5), 52.3 (d, C-3), 55.2 (t, 5-$CH_2$), 63.2 (t, 2-$CH_2$), 68.9 (d, C-4), 77.0 (d, C-2), 80.3 (d, C-6). IR (ATR): 3310 (O–H, N–H), 2935 (C–H), 1235 (C–O) $cm^{-1}$. HRMS (ESI–TOF): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{33}N_2O_8$: 381.2237; found: 381.2235; *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{32}N_2NaO_8$: 403.2056; found: 403.2041.

**General information**

Reactions were generally performed under inert atmosphere (argon) in flame-dried flasks. Solvents and reagents were added by syringe. Solvents were dried using standard procedures and were purified with a MB SPS-800-dry solvent system. Commercial available reagents were used as received without further purification unless otherwise stated. Products were purified by flash chromatography on silica gel (230–400 mesh, MACHERY-NAGEL). Unless otherwise stated, yields refer to analytical pure samples. Hydrogenolyses were performed with hydrogen from Air Liquide (Alphagaz 2). TLC-analyses were performed on silica gel coated aluminium plates purchased from Merck. Products were detected by UV-activity and by using staining reagents (Cer/molybdenum reagent, $KMnO_4$ and ninhydrine). NMR spectra were recorded on BRUKER (AV 400, AV 500, AV 700) and JEOL (ECP 500) instruments. Chemical shifts (δ) are listed in parts per million (ppm) and are reported relative to solvent residual signals: $CDCl_3$ ($^1H$: δ = 7.26 ppm, $^{13}C$: δ = 77.2 ppm), $CD_3OD$ ($^1H$: δ = 3.31 ppm, $^{13}C$: δ = 49.0 ppm) or $CD_2Cl_2$ ($^1H$: δ = 5.32 ppm,$^{13}C$: δ = 54.0 ppm). Integrals are in accordance with assignments; coupling constants (*J*) are given in Hz. All $^{13}C$ NMR spectra are proton-decoupled. Multiplicity is indicated as follows: s (singlet), $s_{br}$ (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), m (multiplet), $m_c$ (centered multiplet). For detailed peak assignments 2D spectra were measured (COSY and HMQC). IR spectra were measured with a Jasco spectrometer (FT/IR-4100 with DLATGS Detector). HRMS analyses were performed with Agilent 6210 (ESI–TOF, 10 µL/min, 1.0 bar, 4 kV) and Varian/Agilent Ionspec QFT-7 (ESI–FTICR, 4 µL/min, 1.0 bar, 4kV) instruments. Elemental analyses were carried out with instruments from Elementar (Vario EL, Vario EL III). Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected.

**(3*S*,4´*S*)-2-Benzyl-4-[2-(trimethylsilyl)ethoxy]-3-(2´-vinyl-1´,3´-dioxolan-4´-yl)-3,6-dihydro-2*H*-1,2-oxazine (2)**




Acrolein dimethyl acetal (6.75 mL, 56.9 mmol) and ceric ammonium nitrate (31 mg, 57 µmol) were dissolved in dichloromethane (10 mL) and stirred for 15 min. Then 1,2-oxazine **1** (2.00 g, 5.69 mmol) was added and the solution was stirred for 3 days at rt. The reaction mixture was quenched with water (10 mL) and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 20:1) to yield **2a** and **2b** (1.98 g, 89%, d.r. 63:37) as colorless oils.

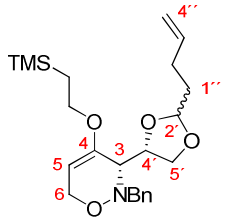
Major diasteromer **2a**:

$[\alpha]_D^{22}$ = -6.7 (*c* = 1.35, $CHCl_3$); $^1$H NMR (500 MHz, $CD_2Cl_2$): δ = 0.07 (s, 9 H, $Si(CH_3)_3$), 1.00-1.11 (m, 2 H, $CH_2Si(CH_3)_3$), 3.26 (d, *J* = 7.6 Hz, 1 H, 3-H), 3.76 (ddd, *J* = 5.5, 9.6, 10.3 Hz, 1 H, $CH_2CH_2Si(CH_3)_3$), 3.01-3.84 (m, 1 H, $CH_2CH_2Si(CH_3)_3$), 3.85, 4.00 (AB part of ABX system, $J_{AX}$ = 6.5 Hz, $J_{BX}$ = 7.6 Hz, $J_{AB}$ = 8.2 Hz, 2 H, 5´-H), 4.10-4.17 (m, 3 H, 6-H, $NCH_2$), 4.38 (dd, *J* = 1.9, 14.6 Hz, 1 H, 6-H), 4.53 (dt, *J* = 6.5, 7.6 Hz, 1 H, 4´-H), 4.75 (dd, *J* = 1.9, 3.5 Hz, 1 H, 5-H), 5.28 ($d_{br}$, *J* = 6.1 Hz, 1 H, 2´-H), 5.32 (ddd, *J* = 0.7, 1.4, 10.3 Hz, 1 H, 2´´-H), 5.46 (ddd, *J* = 0.7, 1.4, 17.2 Hz, 1 H, 2´´-H), 5.82 (ddd, *J* = 6.1, 10.3, 17.2 Hz, 1 H, 1´´-H), 7.24-7.28 (m, 1 H, Ph), 7.31-7.34 (m, 2 H, Ph), 7.41-7.42 (m, 2 H, Ph) ppm; $^{13}$C NMR (125 MHz, $CD_2Cl_2$): δ = -1.18 (q, $Si(CH_3)_3$), 17.9 (t, $CH_2Si(CH_3)_3$), 58.5 (t, $NCH_2$), 64.2 (d, C-3), 64.26 (t, C-6), 65.1 (t, $CH_2CH_2Si(CH_3)_3$), 67.5 (t, C-5´), 76.7 (d, C-4´), 93.7 (d, C-5), 104.3 (d, C-2´), 120.0 (t, C-2´´), 127.6, 128.7, 129.2 (3 d, Ph), 136.0 (d, C-1´´), 138.9 (s, Ph), 150.5 (s, C-4) ppm; IR (ATR): $\tilde{\nu}$ = 3070 (=C-H), 2940-2870 (C-H), 1595 (C=C), 1420 (C-H), 1200 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{32}NO_4Si$ $[M + H]^+$: 390.2101; found: 390.2103; calcd for $C_{21}H_{31}NNaO_4Si$ $[M + Na]^+$: 412.1920; found: 412.1922; elemental analysis calcd (%) for $C_{21}H_{31}NO_4Si$ (389.6): C, 64.75; H, 8.02; N, 3.60; found: C, 63.84; H, 8.05; N, 3.51.

Minor diastereomer **2b**:

$[\alpha]_D^{22}$ = +16.4 (*c* = 1.10, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ = 0.04 (s, 9 H, $Si(CH_3)_3$), 0.98-1.08 (m, 2 H, $CH_2Si(CH_3)_3$), 3.29 ($d_{br}$, *J* = 7.5 Hz, 1 H, 3-H), 3.66-3.74 (m, 1 H, $CH_2CH_2Si(CH_3)_3$), 3.77-3.87 (m, 1 H, $CH_2CH_2Si(CH_3)_3$), 3.86, 3.99 (AB of ABX system, $J_{AX}$ = 6.4, $J_{AB}$ = $J_{BX}$ = 8.1 Hz, 1 H, 5´-H), 4.13, 4.41 (AB part of ABX system, $J_{AX}$ = 1.9 Hz, $J_{BX}$ = 3.2 Hz, $J_{AB}$ = 14.5 Hz, 2 H, 6-H), 4.15 (s, 2 H, $NCH_2$), 4.56 (dd, *J* = 7.5, 14.0 Hz, 1 H, 4´-H), 4.71 (dd, *J* = 1.9, 3.2 Hz, 1 H, 5-H), 5.29 (d, *J* = 6.0 Hz, 1 H, 2´-H), 5.31 (d, *J* = 10.3 Hz, 1 H, 2´´-H), 5.45 (d, *J* = 17.2 Hz, 1 H, 2´´-H), 5.81 (ddd, *J* = 6.0, 10.3, 17.2 Hz, 1 H, 1´´-H), 7.23-7.25 (m, 1 H, Ph), 7.29-7.32 (m, 2 H, Ph), 7.41-7.42 (m, 2 H, Ph) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = -1.3 (q, $Si(CH_3)_3$), 17.5 (t, $CH_2Si(CH_3)_3$), 58.3 (t, $NCH_2$), 63.5 (d, C-3), 64.6 (2 t, C-6, $CH_2CH_2Si(CH_3)_3$), 67.0 (t, C-5´), 76.1 (d, C-4´), 93.2 (d, C-5), 103.9 (d, C-2´), 119.9 (t, C-2´´), 127.2, 128.3, 128.8 (3 d, Ph), 135.1 (d, C-1´´), 138.0 (s, Ph), 150.2 (s, C-4) ppm; IR (ATR): $\tilde{\nu}$ = 3070 (=C-H), 2840 (C-H), 1595 (C=C), 1420 (C-H), 1245 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{32}NO_4Si$ [*M* + H]$^+$: 390.2101; found: 390.2099; calcd for $C_{21}H_{31}NNaO_4Si$ [*M* + Na]$^+$: 412.1920; found: 412.1921; elemental analysis calcd (%) for $C_{21}H_{31}NO_4Si$ (389.6): C, 64.75; H, 8.02; N, 3.60; found: C, 62.89; H, 7.98; N, 3.30.

**(3*S*,4´*S*)-2-Benzyl-3-[2´-(but-3´´-enyl)-1´,3´-dioxolan-4´-yl]-4-[2-(trimethylsilyl)ethoxy]-3,6-dihydro-2*H*-1,2-oxazine (3)**




Pent-4-enal (1.00 mL, 10.1 mmol) was added to a mixture of ytterbium(III) triflate (79 mg, 127 µmol) in dichloromethane (1.2 mL). After 30 min, a solution of diol **1** (402 mg, 1.14 mmol) in dichloromethane (1 mL) was added and the reaction mixture was stirred for 25 h at rt. The reaction mixture was quenched with sat. sodium hydrogen carbonate solution (2 mL) and the aqueous phase was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 20:1) to yield **3a** and **3b** (311 mg, 65%, d.r. 80:20) as colorless oils.

Major diastereoisomer **3a**:

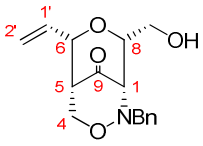
$[\alpha]_D^{22}$ = +16.5 (*c* = 1.10, $CHCl_3$); $^1$H NMR (500 MHz, $CD_2Cl_2$): δ = 0.09 (s, 9 H, $Si(CH_3)_3$), 1.02-1.13 (m, 2 H, $CH_2Si(CH_3)_3$), 1.73-1.77 (m, 2 H, 1´´-H), 2.18-2.22 (m, 2 H, 2´´-H), 3.25 (d, *J* = 7.5 Hz, 1 H, 3-H), 3.74-3.79 (m, 1 H, $CH_2CH_2Si(CH_3)_3$), 3.80-3.87 (m, 1 H, $CH_2CH_2Si(CH_3)_3$), 3.86, 4.00 (AB part of ABX system, $J_{AX}$ = 7.5 Hz, $J_{BX}$ = 8.2 Hz, $J_{AB}$ = 13.2 Hz, 2 H, 5´-H), 4.13, 4.40 (AB part of ABX system, $J_{AX}$ = 2.0 Hz, $J_{BX}$ = 3.4 Hz, $J_{AB}$ = 14.6 Hz, 2 H, 6-H), 4.16 (s, 2 H, $NCH_2$), 4.50 (dd, *J* = 7.5, 14.2 Hz, 1 H, 4´-H), 4.75 (dd, *J* = 2.0, 3.4 Hz, 1 H, 5-H), 4.99 (ddd, *J* = 1.2, 3.3, 5.0 Hz, 1 H, 4´´-H), 4.99 (d, *J* = 4.8 Hz, 1 H, 2´-H), 5.07 (ddd, *J* = 1.7, 3.3, 17.0 Hz, 1 H, 4´´-H), 5.89 (ddd, *J* = 6.6, 10.2, 17.0 Hz, 1 H, 3´´-H), 7.26-7.29 (m, 1 H, Ph), 7.33-7.35 (m, 2 H, Ph), 7.43-7.44 (m, 2 H, Ph) ppm; $^{13}$C NMR (125 MHz, $CD_2Cl_2$): δ = -1.14 (q, $Si(CH_3)_3$), 17.9 (t, $CH_2Si(CH_3)_3$), 28.8 (t, C-2´´), 34.1 (t, C-1´´), 58.6 (t, $NCH_2$), 64.3 (t, d, C-6, C-3), 65.1 (t, $CH_2CH_2Si(CH_3)_3$), 67.5 (t, C-5´), 76.5 (d, C-4´), 93.6 (d, C-5), 104.5 (d, C-2´), 114.9 (t, C-4´´), 127.6, 128.7, 129.2 (3 d, Ph), 139.0 (d, C-3´´), 150.7 (s, C-4) ppm; IR (ATR): $\tilde{\nu}$ = 3080–3030 (=C-H), 2955-2840 (C-H), 1670 (C=C), 1250 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{36}NO_4Si$ $[M + H]^+$: 418.2408, found: 418.2410, calcd for $C_{23}H_{35}NNaO_4Si$ $[M + Na]^+$: 440.2228, found: 440.2228; elemental analysis calcd (%) for $C_{23}H_{35}NO_4Si$ (417.6): C, 66.15; H, 8.45; N, 3.35; found: C, 66.14; H, 8.12; N, 3.40.

Minor diastereoisomer **3b**:

$[\alpha]_D^{22}$ = +32.3 (*c* = 0.99, $CHCl_3$); $^1$H NMR (500 MHz, $CD_2Cl_2$): δ = 0.09 (s, 9 H, $Si(CH_3)_3$), 1.01-1.12 (m, 2 H, $CH_2Si(CH_3)_3$), 1.73-1.78 (m, 2 H, 1´´-H), 2.22 ($m_c$, 2 H, 2´´-H), 3.24 (d, *J* = 7.0 Hz, 1 H, 3-H), 3.74-3.79 (m, 1 H, $CH_2CH_2Si(CH_3)_3$), 3.82-3.87 (m, 1 H, $CH_2CH_2Si(CH_3)_3$), 3.92, 4.01 (AB part of ABX system, $J_{AX}$ = 6.2 Hz, $J_{BX}$ = 8.0 Hz, $J_{AB}$ = 8.8 Hz, 2 H, 5´-H), 4.12, 4.39 (AB part of ABX system, $J_{AX}$ = 2.0 Hz, $J_{BX}$ = 3.5 Hz, $J_{AB}$ = 14.6 Hz, 2 H, 6-H), 4.14 (d, *J* = 3.5 Hz, 2 H, $NCH_2$), 4.50 (ddd, *J* = 6.2, 7.0, 8.0 Hz, 1 H, 4´-H), 4.76 (dd, *J* = 2.0, 3.5 Hz, 1 H, 5-H), 4.98 (d, *J* = 4.5 Hz, 1 H, 2´-H), 4.99 (ddd, *J* = 1.3, 1.9, 10.2 Hz, 1 H, 4´´-H), 5.08 (ddd, *J* = 1.9, 3.6, 17.0 Hz, 1 H, 4´´-H), 5.90 (ddd, *J* = 6.6, 10.2, 17.0 Hz, 1 H, 3´´-H), 7.25-7.28 (m, 1 H, Ph), 7.32-7.35 (m, 2 H, Ph), 7.42-7.43 (m, 2 H, Ph) ppm; $^{13}$C NMR (125 MHz, $CD_2Cl_2$): δ = -1.1 (q, $Si(CH_3)_3$), 18.0 (t, $CH_2Si(CH_3)_3$), 28.9 (t, C-2´´), 34.2 (t, C-1´´), 58.7 (t, $NCH_2$), 64.1 (d, C-3), 65.1 (2 t, C-6, $CH_2CH_2Si(CH_3)_3$), 68.6 (t, C-5´), 75.6 (d, C-4´), 93.7 (d, C-5), 104.3 (d, C-2´), 114.9 (t, C-4´´), 127.6, 128.7, 129.2 (3 d, Ph), 138.9, 139.0 (d, s, C-3´´, Ph), 150.8 (s, C-4) ppm; IR (ATR): $\tilde{\nu}$ = 3065–3035 (=C-H), 2955-2845 (C-H), 1670 (C=C), 1455 (C-H), 1250 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{35}NNaO_4Si$ $[M + Na]^+$: 440.2228, found: 440.2298; calcd for $C_{23}H_{35}KNO_4Si$ $[M + K]^+$: 456.1972, found: 456.1994,

elemental analysis calcd (%) for $C_{23}H_{35}NO_4Si$ (417.6): C, 66.15; H, 8.45; N, 3.35; found: C, 66.19; H, 8.16; N, 3.25.

**(1*S*,5*R*,6*S*,8*S*)-2-Benzyl-8-(hydroxymethyl)-6-vinyl-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-on (4)**

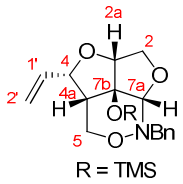



1,2-Oxazine **2** (552 mg, 1.42 mmol) was dissolved in acetonitrile (10 mL) and cooled to 0 °C. Then trimethylsilyl trifluoromethanesulfonate (1.23 mL, 1.00 g, 4.50 mmol) was added slowly and stirred for one hour at this temperature afterwards 18 h at rt. The reaction mixture was quenched with 5% ammonia solution (10 mL) and the aqueous phase was extracted with diethyl ether (5 x 10 mL). The combined organic layers were dried with $Na_2SO_4$ and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 10:1) to yield bicyclic ketone **4** (310 mg, 76%) as colorless oil and tricyclic compound **5** (9 mg, 2%) as yellow oil.

$^1$H NMR (400 MHz, $CD_3OD$): δ = 2.70 (ddd, *J* = 1.9, 3.3, 6.9 Hz, 1 H, 5-H), 3.45 ($m_c$, 1 H, 1-H), 3.69-3.75 (m, 2 H, 8-H, 8-$CH_2$), 3.87 (dd, *J* = 8.6, 13.2 Hz, 1 H, 8-$CH_2$), 3.94, 4.10 (AB system, $J_{AB}$ = 14.0 Hz, 2 H, $NCH_2$), 4.33-4.30 (m, 1 H, 6-H), 4.34, 4.52 (AB part of ABX system, $J_{AX}$ = 3.3 Hz, $J_{BX}$ = 6.9 Hz, $J_{AB}$ = 11.9 Hz, 2 H, 4-H), 5.27 ($d_{br}$, *J* = 10.8 Hz, 1 H, 2´-H), 5.47 ($d_{br}$, *J* = 17.4 Hz, 1 H, 2´-H), 5.87 (ddd, *J* = 4.4, 10.8, 17.4 Hz, 1 H, 1´-H), 7.19-7.35 (m, 5 H, Ph) ppm.

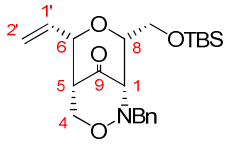
The compound is instable and was not fully characterized.

(2a*R*,4*S*,4a*R*,7a*S,7*b*S*)-7-Benzyl-7b-[2-(trimethylsil)oxy]-4-vinylhexahydro-2*H*,4*H*-1,3,6-trioxa-7-azacyclopenta[cd]indene (**5**)




$[\alpha]_D^{22}$ = +0.30 (*c* = 0.90, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 0.18 (s, 9 H, $Si(CH_3)_3$), 2.45 (ddd, *J* = 3.6, 6.5, 7.5 Hz,1 H, 4a-H), 3.89 (d, *J* = 14.1 Hz,1 H, $NCH_2$), 3.90, 4.00 (AB part of ABX system, $J_{AX}$ = 3.6 Hz, $J_{BX}$ = 7.5 Hz, $J_{AB}$ = 13.2 Hz, 2 H, 5-H), 3.98, 4.09 (AB part of ABX system, $J_{AX}$ = 2.3 Hz, $J_{BX}$ = 4.7 Hz, $J_{AB}$ = 11.5 Hz, 2 H, 2-H), 4.22 (d, *J* = 14.1 Hz, 1 H, $NCH_2$), 4.38 (dd, *J* = 2.3, 4.7 Hz, 1 H, 2a-H), 4.40 (s, 1 H, 7a-H), 4.75 (t, *J* = 7.5 Hz, 1 H, 4-H), 5.22 (d, *J* = 10.5 Hz, 1 H, 2´-H), 5.27 (d, *J* = 17.3 Hz, 1 H, 2´-H), 6.08 (ddd, *J* = 7.5, 10.5, 17.3 Hz, 1 H, 1´-H), 7.25-7.27 (m, 1 H, Ph), 7.31-7.34 (m, 2 H, Ph), 7.38-7.39 (m, 2 H, Ph) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 2.19 (q, $Si(CH_3)_3$), 48.3 (d, C-4a), 57.7 (t, $NCH_2$), 65.9 (t, C-5), 70.6 (t, C-2), 85.9 (d, C-4), 88.9 (s, C-7b), 90.0 (d, C-2a), 96.0 (d, C-7a), 118.4 (t, C-2´), 127.3, 128.4, 128.8 (d, Ph), 135.5 (d, C1´), 137.4 (s, Ph) ppm; IR (ATR): $\tilde{\nu}$ = 3020 (=C-H), 2955-2850 (C-H), 1735 (C=C), 1465 (C-H) 1215 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{28}NO_4Si$ [*M* + H]$^+$: 362.1782; found: 362.1819; calcd for $C_{19}H_{27}NNaO_4Si$ [*M* + Na]$^+$: 384.1602; found: 384.1646.

**(1*S*,5*R*,6*S*,8*S*)-2-Benzyl-8-[(*tert*-butyldimethylsiloxy)-methyl]-6-vinyl-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-on (6)**

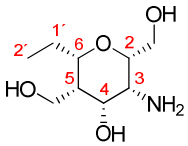



1,2-Oxazine **2** (885 mg, 2.27 mmol) was dissolved in acetonitrile (18 mL) and cooled to -30 °C. Tin(IV) chloride (1.77 g, 0.79 mL, 6.81 mmol) was added and the solution was stirred for 18 h and allowed to warm to rt. The mixture was quenched with water (20 mL) and extracted with dichloromethane (5 x 30 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was dissolved in dichloromethane (4.5 mL) and cooled to 0 °C, then 2,6-lutidine (449 mg, 4.09 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (779 mg, 2.95 mmol) were added and the mixture was stirred for 2 h at rt. The reaction mixture was quenched with ammonium chloride solution (5 mL) and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The

combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 30:1) to yield **6** (447 mg, 49%) as a colorless oil.

$[\alpha]_D^{22}$ = +75.3 (*c* = 0.83, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ = 0.02, 0.04 (2 s, 6 H, $Si(CH_3)_3$), 0.85 (s, 9 H, Si*t*-Bu), 2.68 ($m_c$, 1 H, 5-H), 3.57 ($m_c$, 1 H, 1-H), 3.74, 3.86, 3.99 (ABX part of ABXY system, $J_{AY}$ = 1.3 Hz, $J_{AX}$ = 5.2 Hz, $J_{AB}$ = 8.6 Hz, $J_{AB}$ = 9.6 Hz, 3 H, 8-H, 8-$CH_2$), 3.99, 4.14 (AB system, $J_{AB}$ = 14.1 Hz, 2 H, $NCH_2$), 4.30 (d, *J* = 5.0 Hz, 1 H, 6-H), 4.31, 4.45 (AB part of ABX system, $J_{AX}$ = 3.2 Hz, $J_{BX}$ = 5.3 Hz, $J_{AB}$ = 11.8 Hz, 2 H, 4-H), 5.29 ($d_{br}$, *J* = 10.8 Hz, 1 H, 2´-H), 5.43 ($d_{br}$, *J* = 17.3 Hz, 1 H, 2´-H), 5.81 (ddd, *J* = 5.0, 10.8, 17.3 Hz, 1 H, 1´-H), 7.25-7.28 (m, 1 H, Ph), 7.31-7.34 (m, 2 H, Ph), 7.35-7.37 (m, 2 H, Ph) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = -5.4, -5.3 (2 q, $Si(CH_3)_3$), 18.3, 25.9 (q, s, Si*t*-Bu), 53.8 (d, C-5), 61.2 (t, 8-$CH_2$), 61.5 (t, $NCH_2$), 67.4 (t, C-4), 72.0 (d, C-1), 80.8 (d, C-6), 81.6 (d, C-8), 117.7 (t, C-2´), 127.6, 128.5, 128.9 (3 d, Ph), 134.3 (d, C-1´), 136.7 (s, Ph), 207.4 (s, C-9) ppm; IR (ATR): $\tilde{\nu}$ = 3080 (=C-H), 2950-2830 (C-H), 1730 (C=O), 1595 (C=C), 1250 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{34}NO_4Si$ $[M + H]^+$: 404.2257; found: 404.2259; calcd for $C_{22}H_{33}NNaO_4Si$ $[M + Na]^+$: 426,2077; found: 426.2078; elemental analysis calcd (%) for $C_{22}H_{33}NO_4Si$ (403.6): C, 65.47; H, 8.24; N, 3.47; found: C, 64.77; H, 8.20; N, 3.49.

**(2*S*,3*R*,4*R*,5*S*,6*S*)-(3-Amino-6-ethyl-4-hydroxytetrahydro-2*H*-pyran-2,5-diyl)dimethanol (9a)**

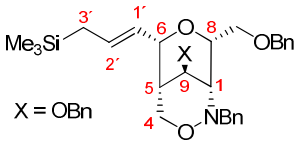



A suspension of Pd/C (10% Pd, 150 mg) and MeOH (3 mL) was saturated with hydrogen for 15 min. The bicycle compound **7a** (150 mg, 515 µmol) was dissolved in MeOH (1 mL), and added to the suspension. The mixture was stirred for 18 h under hydrogen pressure (balloon). Then the mixture was filtrated through a pad of Celite® and the solvent was removed in vacuo. The crude material was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 10:1) to yield **9a** (37 mg, 35%) as a colorless solid.

m.p. 156-158 °C; $[\alpha]_D^{22}$= +85.6 (*c* = 0.95, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD$): δ = 1.05 (t, *J* = 7.4 Hz, 3 H, 2´-H), 1.66-1.72 (m, 1 H, 1´-H), 1.87-1.93 (m, 1 H, 1´-H), 1.97 ($m_c$, 1 H, 5-H), 3.53 ($m_c$, 2 H, 3-H, 6-H), 3.60, 3.82, 3.86 (ABX system, $J_{AX}$ = 5.0 Hz, $J_{BX}$ = 8.2 Hz, $J_{AB}$ = 11.9

Hz, 3 H, 2-H, 2-$CH_2$), 3.86, 3.95 (AB system, $J_{AB}$ = 11.5 Hz, 2 H, 5-$CH_2$), 4.30 (dd, $J$ = 4.5, 6.8 Hz, 1 H, 4-H), ppm; $^{13}$C NMR (175 MHz, $CD_3OD$): δ = 11.2 (q, C-2´), 26.0 (t, C-1´), 43.6 (d, C-5), 52.4 (d, C-6), 55.0 (t, 5-$CH_2$), 63.2 (t, 2-$CH_2$), 69.0 (d, C-4), 76.7 (d, C-3), 82.3 (d, C-2) ppm; IR (ATR): $\tilde{\nu}$ = 3235 (O-H, N-H), 2950-2845 (C-H), 1465 (C-H) 1255 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_9H_{20}NO_4$ [*M* + H]$^+$: 206.1392; found: 206.1387.

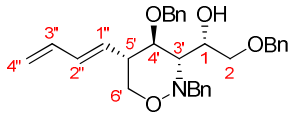
**(*E*,1*R*,5*R*,6*S*,8*S*,9*R*)-2-Benzyl-9-(benzyloxy)-8-(benzyloxymethyl)-6-[-3´-(trimethylsilyl)-prop-1´-enyl]-3,7-dioxa-2-azabicyclo[3.3.1]nonane (10)**




The bicyclic compound **8** (110 mg, 233 µmol) was dissolved in degassed dichloromethane (1.5 mL) and allyltrimethylsilane (266 mg, 2.33 mmol) was added. Over a period of 6 h Grubbs catalyst 2nd generation (21 mg, 23 µmol) was added in 3 portions and stirred for another 18 h at 40 °C. Then the solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel, hexanes/EtOAc 10:1) to yield **10** (82 mg, 63%) as brown oil.

$[\alpha]_D^{22}$= +45.1 (*c* = 0.91, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 0.01 (s, 9 H, $Si(CH_3)_3$), 1.50 ($d_{br}$, $J$ = 8.2 Hz, 2 H, 3´-H), 1.81 ($m_c$, 1 H, 5-H), 3.12 ($s_{br}$, 1 H, 1-H), 3.67 (t, $J$ = 2.8 Hz, 1 H, 9-H), 3.76, 3.82, 3.94 (ABX system, $J_{AB}$ = 5.2 Hz, $J_{AX}$ = 6.9 Hz, $J_{BX}$ = 9.0 Hz, 3 H, 8-H, 8-$CH_2$), 3.78 ($d_{br}$, $J$ = 11.7 Hz, 1 H, 4-H), 4.23 (d, $J$ = 7.0 Hz, 1 H, 6-H), 4.36 (d, $J$ = 13.8 Hz, 1 H, $NCH_2Ph$), 4.51, 4.56 (AB system, $J_{AB}$ = 11.8 Hz, 2 H, $OCH_2Ph$), 4.59 (td, $J$ = 1.8, 11.7 Hz, 1 H, 4-H), 4.64, 4.67 (AB system, $J_{AB}$ = 11.8 Hz, 2 H, $OCH_2Ph$), 4.65 (d, $J$ = 13.8 Hz, 1 H, $NCH_2Ph$), 5.53 (dd, $J$ = 7.0, 15.4 Hz, 1 H, 1´-H), 5.75 (ddd, $J$ = 0.8, 8.2, 15.4 Hz, 1 H, 2´-H), 720-7.22 (m, 1 H, Ph), 7.25-7.28 (m, 5 H, Ph), 7.30-7.35 (m, 5 H, Ph), 7.39-7.43 (m, 4 H, Ph) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = -1.8 (q, $Si(CH_3)_3$), 23.1 (t, C-3´), 38.7 (d, C-5), 55.2 (d, C-1), 57.9 (t, C-4), 58.4 (t, $NCH_2Ph$), 70.6 (2 t, $OCH_2Ph$, 8-$CH_2$), 73.7 (t, $OCH_2Ph$), 76.4 (d, C-9), 78.2 (d, C-8), 79.7 (d, C-6), 126.6 (d, C-1´), 127.0, 127.5, 127.7, 127.9, 128.1, 128.2, 128.5, 128.7, 128.9 (9 d, Ph), 130.2 (d, C-2´), 138.3, 138.4, 139.0 (3 s, Ph) ppm; IR (ATR): $\tilde{\nu}$ = 3060-3030 (=C-H), 2920-2860 (C-H), 1720 (C=C), 1455 (C-H), 1245 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{34}H_{44}NO_4Si$ [*M* + H]$^+$: 558.3040; found: 558.3053; calcd for $C_{34}H_{43}NNaO_4Si$ [*M* + Na]$^+$: 580.2859; found: 580.2888.

**(*Z*,1*S*,3'*S*,4'*R*,5'*S*)-1-[2'-Benzyl-4'-(benzyloxy)-5'-(buta-1'',3''-dien-1''-yl)-1',2'-oxazinan-3'-yl]-2-(benzyloxy)ethan-1-ol (12)**




Under argonatmosphere bicyclic compound **10** (30 mg, 54 µmol) was dissolved in dichloromethane (1 mL) and boron trifluoride diethyl etherate (8 mg, 7 µL, 54 µmol) was added. The solution was stirred for 72 h at rt and then quenched with sat. sodium bicarbonate solution (3 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 20:1) to yield **12** (14 mg, 47%) as a colorless oil.

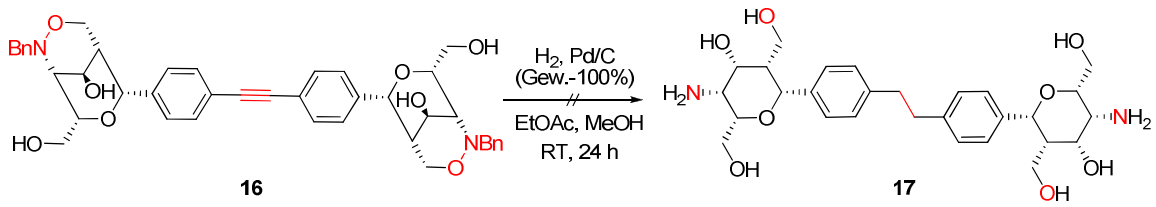
$[\alpha]_D^{22}$ = + 25.6 (*c* = 12.0, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 2.64 ($m_c$, 1 H, 5´-H), 3.10 (dd, *J* = 5.2, 7.0 Hz, 1 H, 3´-H), 3.56-3.58 (m, 2 H, 2-H, 6´-H), 3.63 (dd, *J* = 3.3, 10.3 Hz, 1 H, 2-H), 3.65 ($s_{br}$, 1 H, OH), 3.74 (t, *J* = 7.0 Hz, 1 H, 4´-H), 3.99 (dd, *J* = 4.8, 12.0 Hz, 1 H, 6´-H), 4.07 (d, *J* = 13.9 Hz, 1 H, $NCH_2Ph$), 4.21 ($s_{br}$, 1 H, 1-H), 4.25 (d, *J* = 13.9 Hz, 1 H, $NCH_2Ph$), 4.52, 4.66 (AB system, $J_{AB}$ = 10.9 Hz, 2 H, $OCH_2Ph$), 4.53 (s, 2 H, $OCH_2Ph$), 5.07 (dd, *J* = 1.0, 10.0 Hz, 1 H, 4´´-H), 5.16 (dd, *J* = 1.0, 16.8 Hz, 1 H, 4´´-H), 5.65 (dd, *J* = 8.4, 15.3 Hz, 1 H, 1´´-H), 6.20 (dd, *J* = 10.3, 15.3 Hz, 1 H, 2´´-H), 6.30 (dd, *J* = 10.3, 16.8 Hz, 1 H, 3´´-H), 7.24-7.34 (m, 15 H, Ph) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 45.5 (d, C-5´), 58.1 (t, $NCH_2Ph$), 66.4 (t, C-6´), 69.3 (d, C-3´), 71.8 (d, C-1), 72.8 (t, C-2), 73.5, 73.6 (2 t, $OCH_2Ph$), 117.3 (t, C-4´´), 127.3, 127.9, 128.0, 128.1, 128.4, 128.6, 128.7, 128.8 (8 d, Ph), 131.9 (d, C-1´´), 134.1 (d, C-2´´), 136.6 (d, C-3´´), 137.7, 137.8, 138.2 (3 s, Ph) ppm; one doublet for Ph could not be detected; IR (ATR): $\tilde{\nu}$ = 3600-3190 (O-H), 3090-3030 (=C-H), 2925-2865 (C-H), 1720 (C=C), 1455 (C-H)  1270 (C-O) $cm^{-1}$; HRMS (ESI-TOF): m/z calcd for $C_{31}H_{36}NO_4$ [*M* + H]$^+$: 486.2639; found: 486.2638; calcd for $C_{31}H_{35}NNaO_4$ [*M* + Na]$^+$: 508.2458; found: 508.2470; elemental analysis calcd (%) for $C_{31}H_{35}NO_4$ (485.6): C, 76.41; H, 7.05; N, 2.97; found: C, 74.09; H, 7.63; N, 3.00.

## 3.4 Weitere bisher unveröffentlichte Ergebnisse

Die in diesem Kapitel beschriebenen Experimente wurden im Rahmen dieser Arbeit durchgeführt, aber bisher noch nicht publiziert. Die Verbindungen **20** und **21** wurde von Frau Claudia Gutsche im Rahmen ihrer Bachelorarbeit dargestellt und die Verbindungen **40** und **41** wurden von Herrn Jann Sonnenfeld im Rahmen seiner Bachelorarbeit synthetisiert.

### 3.4.1 Studien zur Debenzylierung und N-O-Spaltung des *para*-bromphenyl-substituierten Bicyclus

Wie im Kapitel 3.1 und 3.2 beschrieben, konnten oligovalente bicyclische Produkte nicht durch die in der Arbeitsgruppe etablierte Methode durch Hydrogenolyse in ihre *N*-debenzylierten und N-O gespaltenen Produkte übergeführt werden (siehe Schema 9). Stattdessen erhält man komplexe Gemische, in denen auch durch massenspektrometrische Messungen kein Produkt nachgewiesen werden konnte. Dieses Problem wurde durch eine Kombination von *N*-Debenzylierung durch Hydrogenolyse und Samariumdiiodid-induzierter N-O-Spaltung gelöst. In Rahmen dieser Arbeit wurden noch weitere Studien zur *N*-Debenzylierung und N-O-Spaltung durchgeführt, die in diesem Kapitel beschrieben werden sollen.




Schema 9: Erwarteter Reaktionsablauf der Hydrogenolyse des divalenten Aminopyranvorläufers **16**.

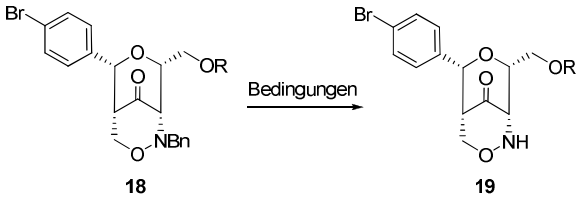
In der Tabelle 1 sind einige Ergebnisse zur *N*-Debenzylierung des bicyclischen Produktes **18** dargestellt. Im Eintrag 1 wurde mit Cer(IV)ammoniumnitrat (CAN) als Ein-Elektronen-Oxidationsmittel versucht, das TBS-geschützte Produkt **18** zu *N*-debenzylieren. Die Reaktionsbedingungen wurden der Literatur[39] entnommen. Nach zwei Stunden Reaktionszeit konnte jedoch nur ein komplexes Reaktionsgemisch isoliert werden. Im $^1$H-NMR-Spektrum waren Signale im Bereich von Aldehyden zu beobachten, was den Schluss nahe legt, dass unter diesen Bedingungen lediglich die TBS-Gruppe entschützt und die primäre Hydroxylgruppe zum Aldehyd oxidiert wird. Die Reaktion wurde daher mit einem acetylgeschützten Bicyclus unter den gleichen Bedingungen wiederholt (Tabelle 1, Eintrag

2). Hierbei konnte ebenfalls nur ein komplexes Reaktionsgemisch detektiert werden. Geringere Mengen an Oxidationsmittel (1 Äq. bzw. 1.5 Äq.) oder eine Erniedrigung der Temperatur führten zu keinem Umsatz des Edukts.

Eine weitere zur Debenzylierung von Aminen beschriebene Methode stellt die Reaktion mit Chlorameisensäure-(1-chlor)-ethylester dar (Eintrag 3), die als sehr mild, selektiv und effizient beschrieben wird.[40] Unter diesen Bedingungen konnte der acetylgeschütze Bicyclus durch Umsetzung mit Chlorameisensäure-(1-chlor)-ethylester und anschließender Methanolyse in den entschützten Bicyclus **20** und das Vollacetal **21** umgesetzt werden. Dieses Ergebnis zeigt, dass der erste Schritt der Reaktion, die *N*-Acetylierung, nicht erfolgt ist. Folglich wurde die Reaktionszeit verlängert und die Reaktionstemperatur erhöht. Auch nach diesen Veränderungen konnte nur das Edukt isoliert werden. Wahrscheinlich ist der Stickstoff des 1,2-Oxazins nicht ausreichend nucleophil, um von dem Chlorameisensäure-(1-chlor)-ethylester acyliert zu werden.

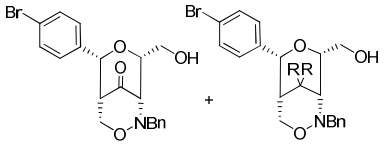
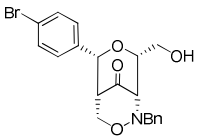
Eine weitere beschriebene Methode zur *N*-Debenzylierung nutzt einen photokatalytischen Ansatz (Eintrag 4) mit Riboflavin (Vitamin $B_2$) als Promoter.[41] Hierbei wurde das Edukt **18** unter sauren Bedingungen mit Riboflavin sieben Stunden mit Sonnenlicht bestrahlt; es konnte jedoch kein Umsatz festgestellt werden.

Harschere Bedingungen nach Haddach et al. erzwingen *N*-Debenzylierungen mit Kalium-*tert*-butanolat und DMSO in Gegenwart von Sauerstoff.[42] Hierbei wird die benzylische Position deprotoniert, so dass das entstehende Carbanion mit Sauerstoff zum Peroxidanion reagieren kann. Anschließend wird das Peroxidanion mit DMSO reduziert. Aus dem entstandenen instabilen Halb-Aminal wird dann das Amin und Benzaldehyd gebildet. Unter diesen Bedingungen entstand beim Einsatz von **18** nach zehn Minuten Reaktionszeit ein komplexes Gemisch mit Nebenprodukt **20**, jedoch konnte das erwartete Produkt nicht erhalten werden. Es ist daher anzunehmen, dass diese Methode, bedingt durch die große Anzahl acider Protonen im Molekül, nicht zur *N*-Debenzylierung von **18** geeignet ist.

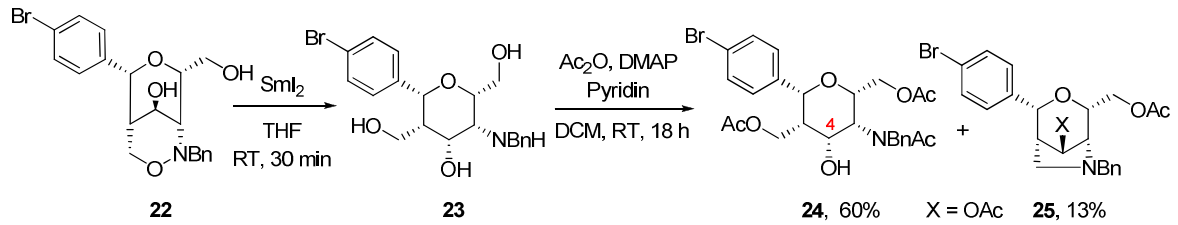



**18** **19**

Tabelle 1: Angewendete *N*-Debenzylierungsmethoden für die bicyclische Verbindung **18**.

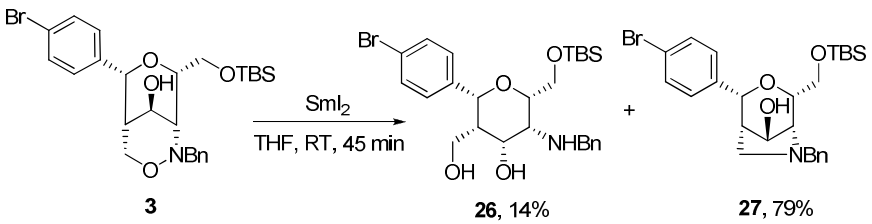
| Eintrag | R | Bedingungen | Ergebnis |
|---|---|---|---|
| 1 | TBS | CAN (2.1 Äq.), $CH_3CN$, $H_2O$, RT, 2 h | komplexes Reaktionsgemisch<br>TBS-entschützter Produkte |
| 2 | Ac | CAN (2.1 Äq.), $CH_3CN$, $H_2O$, RT, 1.5 h | komplexes Reaktionsgemisch |
| 3 | Ac | a) Chlorameisensäure-(1-chlor)-ethylester<br>$CH_2Cl_2$, -10 °C -> 0°C 3 h; b) MeOH<br>Rückfluss,1.5 h |  <br>**20**, 33% R = OMe **21**, 50% |
| 4 | Ac | Vitamin $B_2$, hv, $CH_3CN$ / $H_2O$, pH 3, RT, 7 h | Edukt |
| 5 | Ac | DMSO, KO*t*-Bu, $O_2$, RT, 10 min |  <br>**20**, 28% |

Nachdem es mit den in Tabelle 1 zusammengestellten Methoden nicht gelungen ist, die bicyclische Verbindung **18** zu *N*-debenzylieren, wurde versucht, die Abfolge der Reaktionsschritte zu ändern, wobei zunächst die N-O-Bindung mit Samariumdiiodid gespalten und anschließend *N*-debenzyliert werden sollte. Die N-O-Bindung des Bicyclus **22** konnte in einer Reaktionszeit von 30 min mit Samariumdiiodid vollständig und sauber gespalten werden (Schema 10). Um das stark polare Produkt **23** besser reinigen zu können, wurde dieses im Anschluss mit einer guten Ausbeute von 60% (2 Schritte) acetylgeschützt. Interessanterweise wurde unter diesen Bedingungen die Hydroxylgruppe an C-4 nicht acetylgeschützt, da wahrscheinlich die benachbarten Gruppen sterisch zu anspruchsvoll sind. Zudem konnte noch ein zweites bicyclisches Produkt **25** mit einer Ausbeute von 13% isoliert werden.



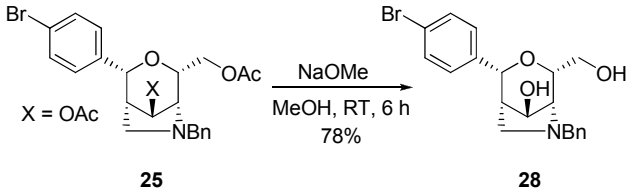

Schema 10: Darstellung des Aminopyrans **24** und des bicyclischen Produktes **25** durch Samarium-induzierte N-O-Spaltung und anschließender Aceytlschützung.

Eine ähnliche Struktur wie **25** wurde bereits im Kapitel 3.1 beschrieben. Dort wurde bei der Reaktion mit Samariumdiiodid ein sehr ähnlicher bicyclisches 1,2-Oxazin **27** allerdings mit einer erheblich höheren Ausbeute von 79% erhalten (Schema 11). Es ist anzunehmen, dass der Stickstoff und die 5-$CH_2$-Position räumlich sehr nahe sind und bereits eine schwache Lewis-Säure ausreicht, um die intramolekulare nucleophile Substitution zu katalysieren, indem sie die Hydroxylgruppe zu einer besseren Abgangsgruppe macht. Die große TBS-Gruppe scheint die Substitution zu begünstigen, weil der sterische Anspruch dieser Gruppe offensichtlich den Abstand der Substituenten noch zusätzlich verringert.




Schema 11: Beispiel aus Kapitel 3.1 einer Samariumdiiodid-induzierten N-O-Spaltung und deren Nebenprodukt **27**.

Die Struktur des bicyclischen Produkts **25** aus Schema 10 konnte zunächst anhand der NMR-Daten nicht eindeutig geklärt werden. Da es sich bei dem Produkt **25** um ein Öl handelt, wurde dieses unter Standardbedingungen entschützt, wobei das Diol **28** in 78% Ausbeute als farbloser Feststoff erhalten wurde. Dieser konnte erfolgreich kristallisiert werden, so dass Einkristalle für eine Röntgenstrukturanalyse zur Verfügung standen. Damit konnte die Konstitution und Konfiguration von **28** eindeutig bewiesen werden.




Schema 12: Entschützung des bicyclischen Produktes **25** mit Natriummethanolat zum Diol **28**.

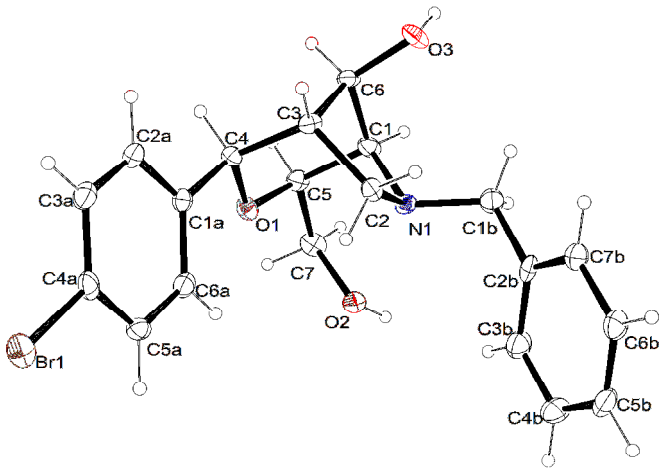
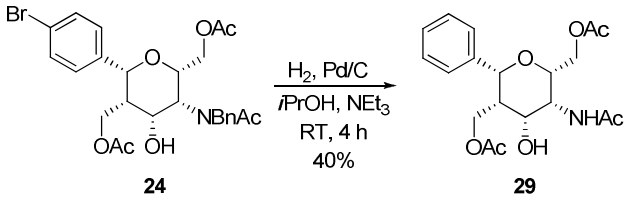


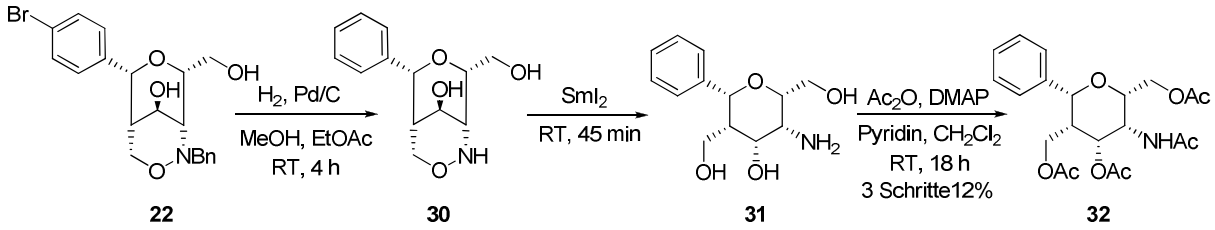

Abbildung 7: Kristallstrukturanalyse der bicyclischen Verbindung **28** (ORTEP, Schwingungsellipsoide mit 50% Aufenthaltswahrscheinlichkeit).

Das in Schema 10 gezeigte Aminopyran **24** konnte durch Hydrogenolyse in einer Ausbeute von 40% *N*-debenzyliert werden. Diese mäßige Ausbeute ist durch das Auftreten zahlreicher Nebenprodukte, die aus verschieden acetylierten Produkten bestanden, zu erklären.



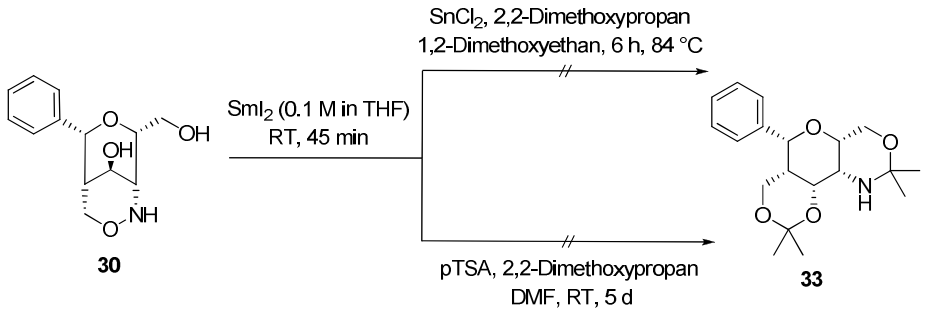

Schema 13: Hydrogenolyse des Aminopyrans **24** zum debenzylierten Aminopyran **29**.

In einem weiteren Versuch mit Verbindung **22** wurde zunächst eine kurze Hydrogenolyse durchgeführt und anschließend das Rohprodukt unmittelbar einer Reaktion mit Samariumdiiodid unterzogen (Schema 14). Beide Schritte wurden mit $^{1}$H-NMR-Spektroskopie und ESI-ToF verfolgt, wobei ein vollständiger Umsatz detektiert wurde. Da das sehr polare Produkt schwer von den Samariumsalzen zu trennen war, wurde anschließend versucht, die Amino- und Hydroxylgruppen mit Acetyleinheiten zu schützen. Nach 18 Stunden Reaktionszeit konnten hierbei 12% des Produktes **32** isoliert werden. Da sich die Reinigung dieses Reaktionsproduktes als schwierig gestaltete (instabil auf Kieselgel, nicht umkristallisierbar), ist der tatsächliche Umsatz der Reaktion vermutlich wesentlich höher als 12%. Außerdem wurde eine komplexe Mischung aus verschieden acetylierten Verbindungen erhalten. Interessant ist, dass in diesem Beispiel, im Gegensatz zu Verbindung **24** (Schema 10), die 4-Position acetylgeschützt werden konnte.



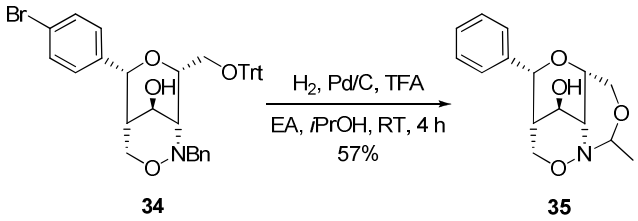

Schema 14: Mehrstufensynthese des Aminopyrans **32** aus Verbindung **31** durch Hydrogenolyse, Samariumdiiodid-Reaktion und Acetylschützung.

Da die Verbindung **32** nicht stabil war, wurde versucht, eine andere Schutzgruppe einzuführen. Das aus der Hydrogenolyse erhaltene *N*-debenzylierte Produkt **30** wurde mit Samariumdiiodid N-O gespalten und anschließend nach Entfernen des Lösungsmittels mit 2,2-Dimethoxypropan in Gegenwart von verschiedenen Säuren zur Reaktion gebracht (Schema 15). Unter allen gewählten Bedingungen wurde kein Umsatz beobachtet; es konnte lediglich das Edukt isoliert werden.




Schema 15: Erwarteter Reaktionsablauf zum Schutz des Aminopyrans mit 2,2-Dimethoxypropan unter Säure-Katalyse.

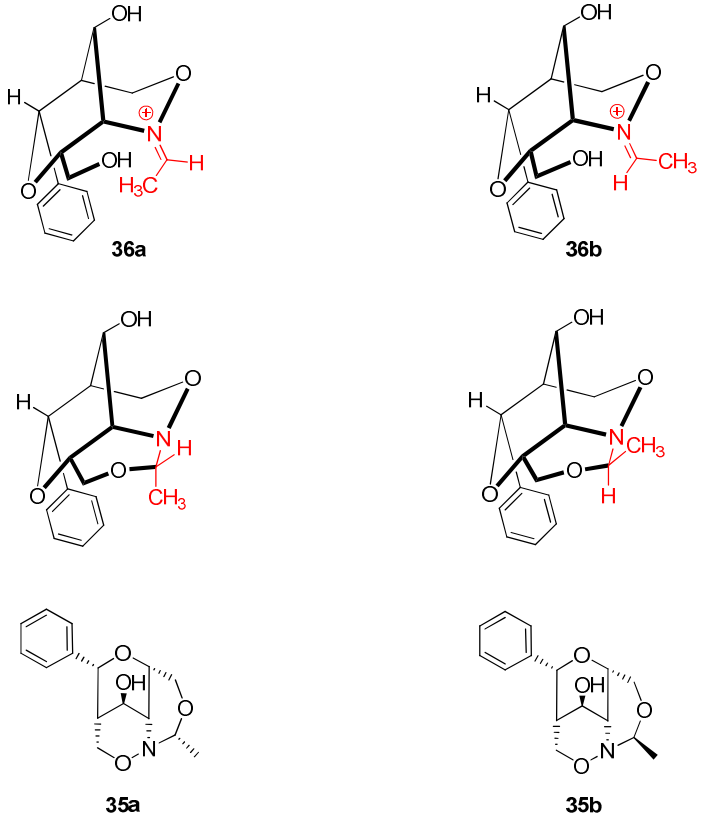
Wie von Bouché und Salta bereits berichtet, können Methanol und Ethanol als Lösungsmittel bei der Hydrogenolyse von bicyclischen 1,2-Oxazinen zu Nebenprodukten führen.[34, 43] Diese Besonderheit der bicyclischen 1,2-Oxazine konnte erneut an zwei Beispielen verdeutlicht werden. Im Beispiel 1 sollte das bicyclische 1,2-Oxazin **34** durch Hydrogenolyse unter sauren Bedingungen *N*-debenzyliert, debromiert und die Tritylgruppe entschützt werden (Schema 16). Nach vier Stunden Reaktionszeit konnte mittels Dünnschichtchromatographie ein Produkt nachgewiesen werden. Es handelte sich aber nicht um das erwartete Produkt, sondern um das *N*,*O*-Acetal **35**, das in einer Ausbeute von 57% als einheitliches Diastereomer isoliert wurde. Die Bildung dieses Produktes lässt sich dadurch erklären, dass im Reaktionsablauf die Trifluoressigsäure zunächst den Essigsäureethylester hydrolysiert, das entstandene Ethanol dann durch Palladium zum Aldehyd oxidiert wird und mit dem Amin ein Imin bildet **36a** und **36b**, das vom Alkohol angegriffen wird und zum *N*,*O*-Acetal **35** reagiert.




**34** **35**

Schema 16: Bildung des *N,O*-Acetals **35** durch saure Hydrolyse von Essigsäureethylester.

Wie bereits erwähnt, entsteht bei dieser Reaktion nur ein Diastereomer. Zunächst wurden mit dem entstanden Aldehyd Iminiumionen **36a** und **36b** gebildet, welche nach Ringschluß vermutlich das thermodynamisch stabilere Produkt bilden. In Abbildung 8 sind die beiden möglichen Konfigurationen des *N-O*-Acetals **35a** und **35b** dargestellt. Bei Verbindung **35a** befindet sich die Methylgruppe in der äquatorialen Position und damit sehr nahe am Phenylsubstituenten des 1,2-Oxazins. Bei **36b** ist die Methylgruppe in axialer Position, damit von bicyclischen 1,2-Oxazin abgewandt, so dass dieses wahrscheinlich das stabilere Diastereomer ist.



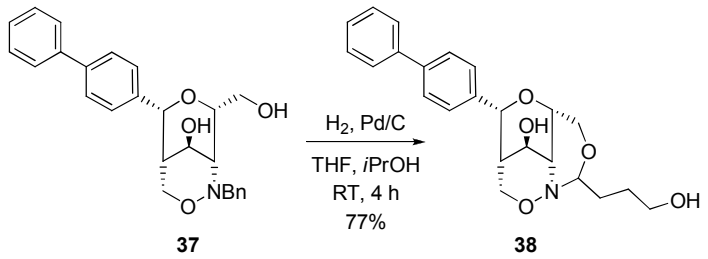

**36a** **36b**

**35a** **35b**

Abbildung 8: Mögliche Konfigurationen des bicyclischen 1,2-Oxazins **35a** und **35b**.

Ein zweites Beispiel ist in Schema 17 dargestellt. Hier wurde die Hydrogenolyse des diphenylsubstituierten bicyclischen 1,2-Oxazin **37** in an Licht gelagertem Tetrahydrofuran vorgenommen. Nach vier Stunden Reaktionszeit konnte das tricyclische Produkt **38** in 77% Ausbeute isoliert werden. Dieses Produkt wird höchstwahrscheinlich durch das in Schema

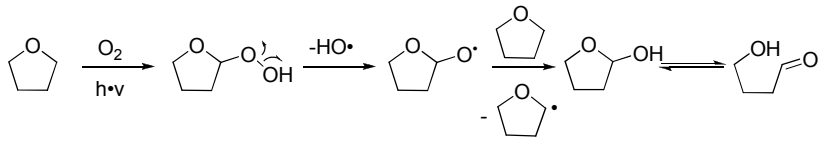
18 abgebildete Autooxidationsprodukt des THF verursacht und vergleichbar zu dem Ethanal in Schema 16 eingeführt.




**37** **38**

Schema 17: Bildung des unerwarteten tricyclischen Produkt **38** mit an Licht gelagertem Tetrahydrofuran.

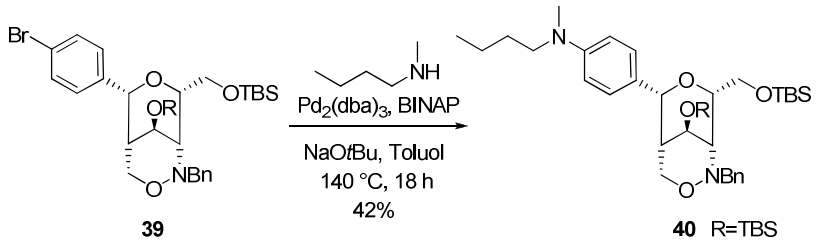
Eine Wiederholung der Reaktion in einwandfreien THF führte zum erwarteten Produkt (siehe Kapitel 3.1, Schema 8).




Schema 18: Bildung eines der zahlreichen Produkte der Autooxidation von Tetrahydrofuran.

Wie im Kapitel 3.1 und 3.2 beschrieben, konnte eine erfolgreiche und für viele Derivate anwendbare Methode für die *N*-Debenzylierung und N-O-Spaltung gefunden werden. Dabei wird zunächst durch Kurzzeithydrogenolyse (4-8 h) debenzyliert und anschließend in einer Samariumdiiodid vermittelten Reaktion die N-O-Bindung gespalten. Die erhaltenen Samariumsalze können durch Größenausschlusschromatographie (Sephadex®, LH-20) vom sehr polaren Produkt getrennt und die salzfreien Produkte anschließend durch Umkehrphasen-Hochleistungsflüssigkeitschromatographie (Gemini-NX, C18 Phenomenex) gereinigt werden.

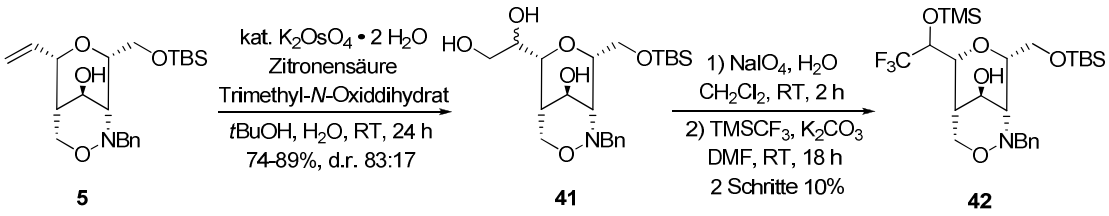
Eine Folgereaktion des *para*-bromsubstituierten Bicyclus **39**, der im Kapitel 3.1 beschrieben wurde, ist die Buchwald-Hartwig-Aminierung (Schema 19). Als Versuch wurde *N*-Methyl-1-butylamin nach einer Vorschrift von Yamada[44] mit dem Bicyclus **39** in einer mäßigen Ausbeute von 42% gekuppelt. Aufgrund der nur mäßigen Ausbeute wurde diese Reaktion nicht weiter verfolgt, prinzipiell ist es aber möglich, diese Reaktion zu nutzen, um nach Optimierung der Reaktionsbedingungen weitere oligovalente Produkte zu erhalten.




Schema 19: Buchwald-Hartwig-Aminierung des bicyclischen Produktes **39** mit *N*-Methyl-1-butylamin.

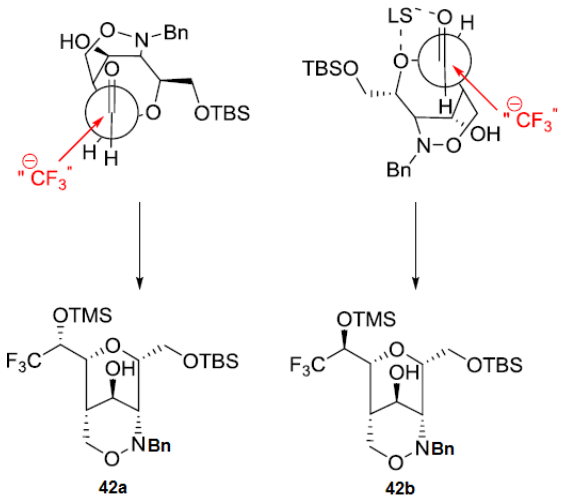
### 3.4.2 Folgereaktionen des vinylsubstituierten bicyclischen 1,2-Oxazins

In der medizinischen Chemie werden häufig labile funktionelle Gruppen durch stabile fluorierte Einheiten ausgetauscht, um einerseits die Wirkstoffe metabolisch zu stabilisieren und andererseits durch zusätzliche hydrophobe Gruppen erhöhte Bindungsaffinitäten zu erreichen.[45] Das vinylsubstituierte bicyclische 1,2-Oxazin **5** konnte durch Dihydroxylierung in das Diol **41** in einer guten Ausbeute von 74-89% übergeführt werden. Hierbei wurden zwei Diastereomere in einen Verhältnis von 83 : 17 isoliert. Anschließend wurde das Diol **41** durch eine Glykolspaltung und eine Trifluormethylierung mit Ruppert-Prakash-Reagenz zum Produkt **42** umgesetzt. Es konnte nur ein Diastereomer des Produktes mit einer Ausbeute von 10% isoliert werden. Die schlechte Ausbeute dieser Reaktion kann möglicherweise auf nicht vollständig wasserfreie Bedingungen zurückgeführt werden, denn als Nebenprodukt wurde der aus der Glykolspaltung erhaltene Aldehyd detektiert.




Schema 20: Dihydroxylierung, Glykolspaltung und Umsatz mit Ruppert-Prakash-Reagenz des vinylsubstituierten bicyclischen 1,2-Oxazins **5**.

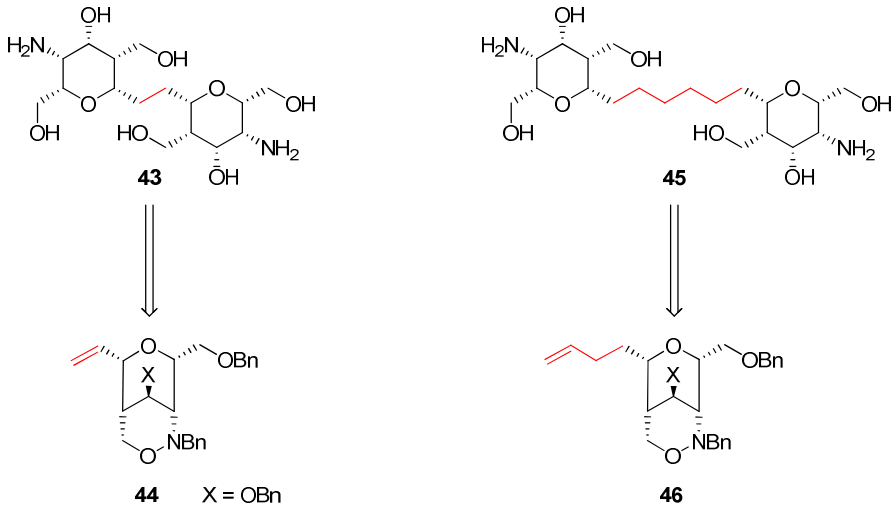
Unter diesen Bedingungen erfolgt der Angriff an dem Aldehyd hierbei wahrscheinlich entsprechend dem Felkin-Anh-Modell (Schema 21). Hierbei wird aufgrund des sterisch weniger gehinderten Angriffs des Nucleophils im Überganszustand bevorzugt das Diastereomer **42** gebildet; die relative Konfiguration des Produkt **42** wurde allerdings nicht bestimmt. Das Produkt **42** könnte ein interessanter Baustein für neue fluorierte Kohlenhydratmimetika sein.




Schema 21: Darstellung zweier möglicher Angriffe des Nucleophils nach dem FELKIN-ANH-Modell.

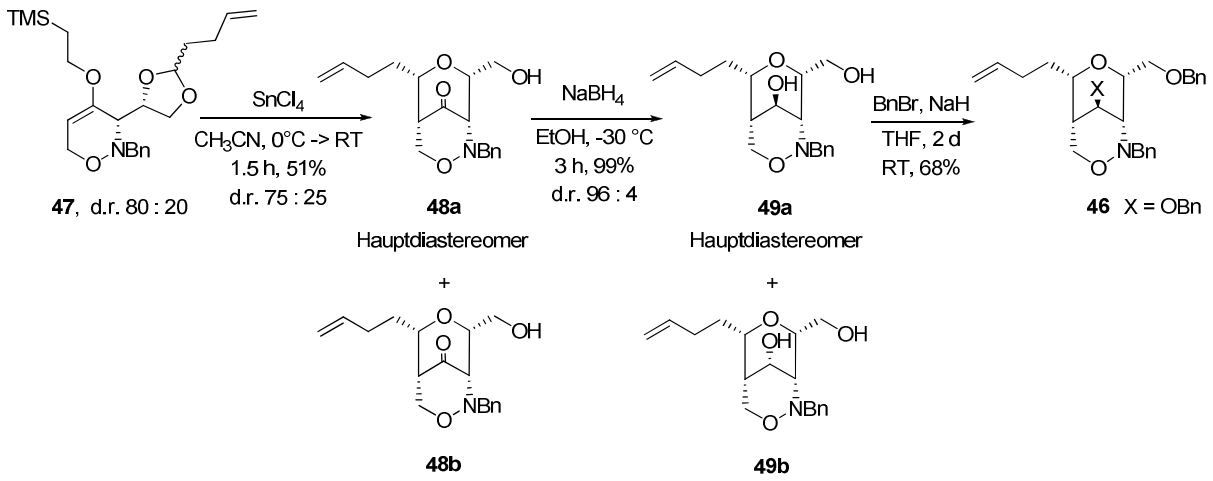
### 3.4.3 Synthese des homoallylsubstituierten bicyclischen 1,2-Oxazins und dessen Olefinmetathese

Im Kapitel 3.3 konnte das Pseudodisaccharid **43** durch Olefinmetathese des vinylsubstituierten Bicyclus **44** erhalten werden, in dem die Aminopyrane durch zwei $CH_2$-Einheiten miteinander verbunden sind (Schema 22). Um die Struktur-Wirkungs-Beziehung zwischen den oligovalenten Kohlenhydratmimetika und den Selektinen zu studieren, wurde versucht, dass Pseudodisaccharid **45** mit einer längeren Alkylkette als Verbindungsstück als weiteres Produkt zu erhalten. Hierfür sollte der homoallylsubstituierte Bicyclus **46** synthetisiert werden.



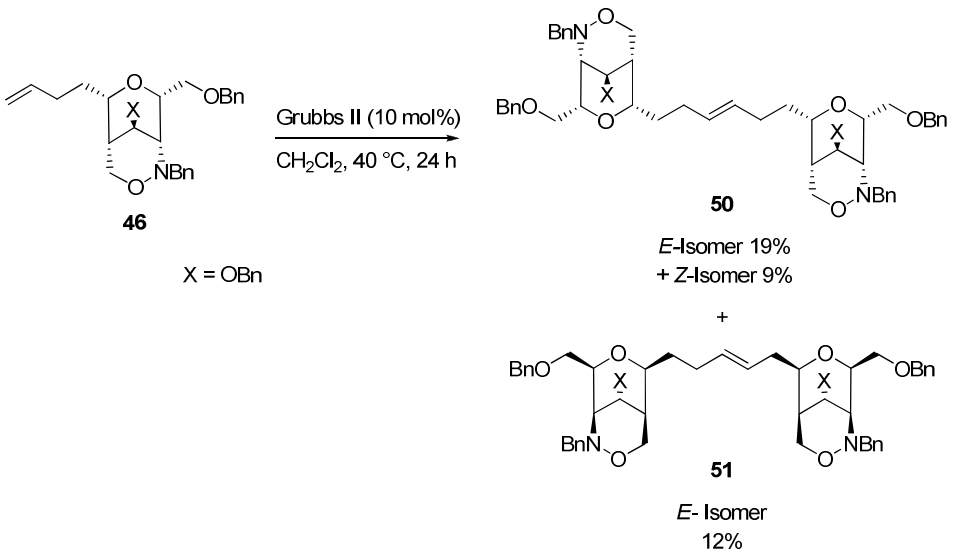

Schema 22: Retrosynthese der Pseudodisaccharide **43** und **45** aus ihren entsprechenden bicyclischen 1,2-Oxazinen **44** und **46**.

Das im Kapitel 3.3 erhaltene homoallylsubstituierte 1,2-Oxazin **47** wurde dazu durch Lewis-Säure-induzierte Umlagerung in den entsprechenden bicyclischen 1,2-Oxazins **48a** und **48b** übergeführt (Schema 23). Für diese Reaktion wurde Zinntetrachlorid als Lewis-Säure verwendet und das Produkt **48a** in einer Ausbeute von 51% isoliert. Unter Verwendung von Trimethylsilyltriflat als Lewis-Säure wurde Verbindung **48a** nur mit einer geringen Ausbeuten von 18% erhalten. Längere Reaktionszeiten konnten die Ausbeute ebenfalls nicht verbessern, zudem waren diese Ergebnis nicht gut reproduzierbar. Im $^1$H-NMR-Spektrum des Rohproduktes konnten zwei Diastereomere beobachtet, jedoch wurde nur das Hauptdiastereomer isoliert. Zudem ist das bicyclische 1,2-Oxazin **48a** nicht stabil, so dass es unter Standardbedingungen umgehend reduziert wurde. Die erhaltenen Diole **49a** und **49b** wurden in einer exzellenten Ausbeute von 99% und in einen Verhältnis von 96 : 4 gebildet. Das Hauptdiastereomer **49a** wurde anschließend mit 68% Ausbeute benzylgeschützt.




Schema 23: Lewis-Säure-induzierte Umlagerung des 1,2-Oxazins **47** zu Produkt **48a** dessen Reduktion zu den Diolen **49a** und **49b** und anschließender Schutz des Diols **49a** unter Standardbedingungen.

In Analogie zu dem vinylsubstituierten bicyclischen 1,2-Oxazin **44** wurde das homoallylsubstituierte bicyclischen 1,2-Oxazin **46** einer Olefinmetathese bei Anwendung gleicher Bedingungen unterzogen (Schema 24). Nach 24 h konnte eine Produktmischung isoliert werden, wovon ein Produkt die erwartete Verbindung **50** und ein weiteres dem um ein Kohlenstoffatom kürzerem Produkt **51** entspricht. Das Produkt **51** entsteht vermutlich durch Isomerisierung der Doppelbindung des Edukts **46** zu einem 2-Butenylsubstituenten, der anschließend eine Kreuzmetathese mit dem Edukt **46** eingeht. Diese Isomerisierungen sind aus der Literatur bekannt und werden vor allem bei langsam reagierenden Substraten beobachtet.[46] Das Ergebnis ist dennoch sehr überraschend, da bei dem vinylsubstituierten bicyclischen 1,2-Oxazin **44** unter gleichen Bedingungen kein entsprechendes Isomerisierungsprodukt isoliert werden konnte. In der Literatur sind Lösungsvorschläge zur Vermeidung von Isomerisierungsprodukten beschrieben, z.B. die Verwendung von Additiven, wie Benzochinon, Phenolen oder Zinnhalogeniden bzw. die Verwendung des Grubbs-Katalysators der ersten Generation, der unreaktiver ist, aber weniger Isomerisierungen auslöst.[47]




Schema 24: Olefinmetathese von bicyclischen 1,2-Oxazin **46** zu Produkt **50** und dem unerwarteten Produkt **51**.

### 3.4.4 Polysulfatierung der erhaltenen Kohlenhydratmimetika

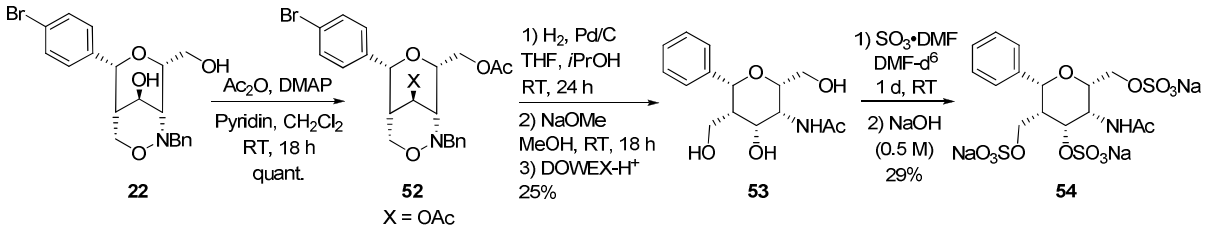
In der Natur werden Kohlenhydrate oder Proteine, wie z.B. Heparin, durch Sulfotransferasen sulfatiert. Das Enzym ist auch beteiligt an der Hormonregulierung, bei Entgiftungen, bei molekularen Erkennungsprozessen und am Eindringprozess von Viren in Zellen, indem es bestimmte Verbindungen sulfatiert. Diese Enzyme finden immer mehr Anwendung in der chemoenzymatischen Synthese vieler Naturstoffe und sie eignen sich vor allem für die regioselektive Sulfatierung von Kohlenhydraten, da für diese Verbindungen sehr spezifische Sulfotransferasen erhältlich sind. Für die Sulfatierung sind nur kleine Mengen des Enzyms notwendig und es lässt sich prinzipiell wiedergewinnen; dennoch braucht man zusätzlich das Kosubstrat 3´-Phosphoadenosin-5´-phosphosulfat, welches das Enzym ständig mit neuen Substrat belädt, was die Methode noch sehr teuer macht.[48] Nach meinem Wissen gibt es noch keine publizierten Versuche, in denen nicht natürliche Substrate mit Sulfotransferasen sulfatiert wurden.

Eine Alterative zu Sulfotransferasen ist die chemische Sulfatierung von Donoren wie Hydroxyl- oder Aminogruppen. Dafür sind eine überschaubare Menge an Reagenzien und Methoden bekannt, wie das Sulfatieren mit Schwefelsäure, Schwefeltrioxid-Aminkomplexen (wie z.B. $SO_3 \cdot DMF$, $SO_3 \cdot NEt_3$)[49] oder $N(SO_3Na)_3$.[50] Diese Methoden sind nicht regioselektiv, eignen sich aber für das Polysulfatieren von Substanzen. Das Polysulfatieren von Verbindungen mit niedriger Molmasse ist nicht trivial, da bei der Reinigung polysulfatierter Verbindungen die entstandenen Salze von den sehr polaren, wasserlöslichen Substanzen getrennt werden müssen. Größenausschlußchromatographie unter Verwendung von stationären Phasen, wie z.B. Sephadex® LH-20 oder G-10, und Dialysen eignen sich vor allem für Substanzen mit einer Molekularmasse größer 1000 g/mol, wobei gilt: je größer die Moleküle, umso einfacher die Trennung von den Salzen.[51] Um weitere Herausforderungen, wie die Trennung von Nebenprodukten oder von nicht vollständig sulfatierten Produkten zu vermeiden, ist eine Reaktionskontrolle entscheidend. Dafür hat sich in unserer Arbeitsgruppe die Kontrolle mit $^1$H-NMR-Spektroskopie (700 MHz) bewährt, indem die Reaktionen in deuteriertem Lösungsmittel durchgeführt werden. Die Massenspektrometrie bietet eine weitere Methode zur Reaktionskontrolle; leider sind jedoch bei hohen Salzkonzentrationen die Produkte im ESI-ToF nicht detektierbar.

Die erhaltenen, oligovalenten Kohlenhydratmimetika aus Kapitel 3.2 sind selbst in geringen Konzentrationen nicht wasserlöslich und eignen sich somit nicht für biologische Tests. Um die Verbindungen wasserlöslich zu machen, und die Bindungsaffinität der Produkte zu steigern, sie mit vorher erhaltenen Verbindungen vergleichbar zu machen, wurden diese polysulfatiert.

Um den Effekt der Multivalenz untersuchen zu können, wurde zunächst ein *N*-acetyliertes monovalentes sulfatiertes Produkt **54** (Schema 26). Dafür wurde das bicyclische 1,2-Oxazin **22** acetylgeschützt, was in quantitativer Ausbeute gelang, um anschließend durch eine Hydrogenolyse den Bromsubstituenten abzuspalten, zu debenzylieren und die N-O-Bindung zu öffnen. Zusätzlich kommt es bei dieser Reaktion zu einer intramolekularen Acetylwanderung, da durch die entstandene Bromwasserstoffsäure schnell umgeestert werden kann, bis ein Amid entsteht, welches nicht weiter reagiert. Nach der Reaktion erhält man eine Mischung aus verschieden *O*-acetylierten Produkten, die durch Natriummethanolat entschützt werden können. Durch das Ionenaustauschharz (DOWEX®-$H^+$) wird die basische Lösung neutralisiert und es werden die Natriumionen der Lösung entzogen. Nach den drei Schritten wurde das Produkt **53** in einer Ausbeute von 25% isoliert. Zusätzlich konnte das nicht N-O gespaltene Produkt identifiziert werden, was die geringe Ausbeute erklärt und mit einer unvollständigen Hydrogenolyse zu erklären ist.

Daraufhin konnte das Aminopyran **53** unter Standardbedingungen erfolgreich sulfatiert werden. Die Reaktion wurde in deuteriertem DMF vorgenommen und die Reaktion mit $^1$H-NMR-Spektroskopie (700 MHz) verfolgt. Bereits nach 18 Stunden Reaktionszeit konnte die Sulfatierung abgebrochen werden, indem der pH-Wert mit 0.5 M Natronlauge basisch gestellt wurde. Die entstandenen Salze wurden durch Dialyse entfernt, wodurch das Produkt **54** in einer mäßigen Ausbeute von 29% erhalten wurde. Die verfügbaren Dialyseschläuche mit einem Cut off von 100-500 g/mol sind für die Größe des sulfatierten Moleküls nicht gut geeignet, da die Poren für einen vollständigen Rückhalt zu groß sind. Dies erklärt die mäßige Ausbeute. Bedauerlicherweise gibt es offenbar keine Dialyseschläuche mit einer kleineren Porengröße.




Schema 25: Mehrstufensynthese des bicyclischen 1,2-Oxazins **53** und dessen Sulfatierung zum monovalenten Aminopyran **54**.

Nach der erfolgreichen Sulfatierung des monovalenten Produkts **54** wurde versucht, vier divalente Produkte zu sulfatieren (Tabelle 2). Die Vorgehensweise war für alle Derivate gleich, wobei die Edukte in deuteriertem DMF gelöst und mit zwölf Äquivalenten des Schwefeltrioxid-DMF-Komplexes umgesetzt wurden. Nach 24 h wurde die Vollständigkeit der Reaktion durch $^1$H-NMR-Spektroskopie kontrolliert; alle Reaktionen waren in diesem Zeitraum abgeschlossen. Anschließend wurde der pH-Wert mit einer 0.5 M Natriumhydroxid-

Lösung auf 8 bis 9 eingestellt, was die Reaktion beendete und das Natriumsalz der sulfatierten Kohlenhydratmimetika bildete. Die Reinigung der Produkte erfolgte durch Dialyse und dauerte drei Tage, um die Produkte komplett salzfrei zu erhalten. Die Produkte konnten in mäßigen bis guten Ausbeuten isoliert werden. Zwischen den Strukturen der Kohlenhydratmimetika und deren Ausbeuten bei der Sulfatierung besteht kein direkter Zusammenhang. Die Reaktionen wurden in kleinem Maßstab durchgeführt (ca. 10 mg), wobei bereits kleine Verluste zu stark unterschiedlichen Ausbeuten führen können.

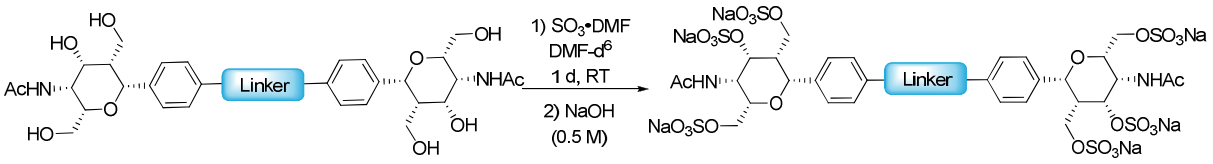
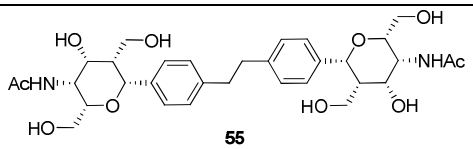
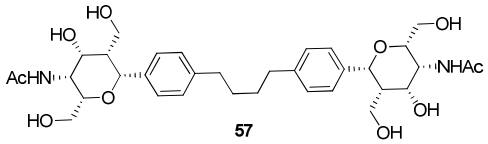
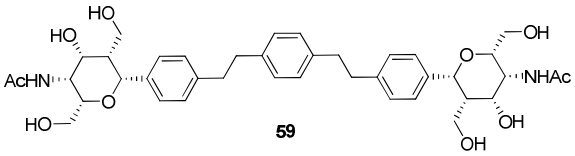
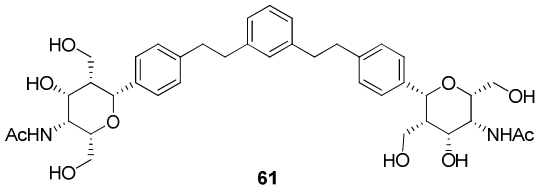
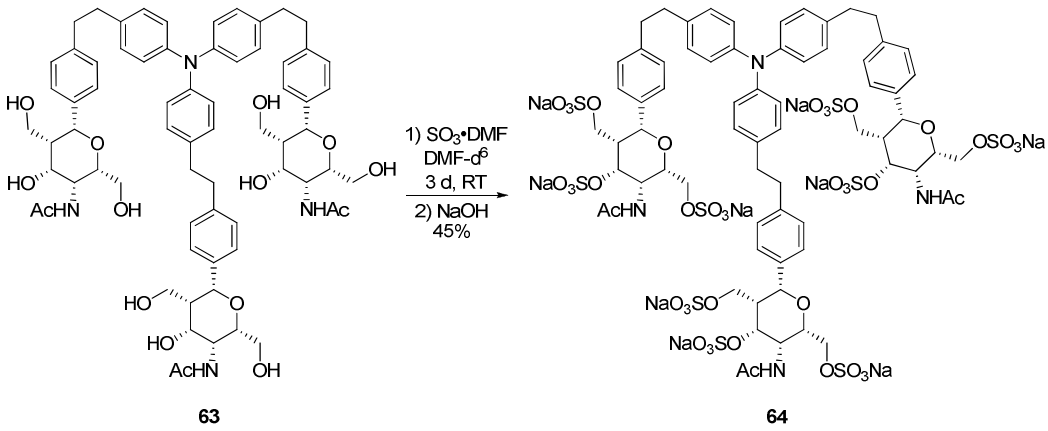



Tabelle 2: Sulfatierung der divalenten Kohlenhydratmimetika **55**, **57**, **59** und **61**.

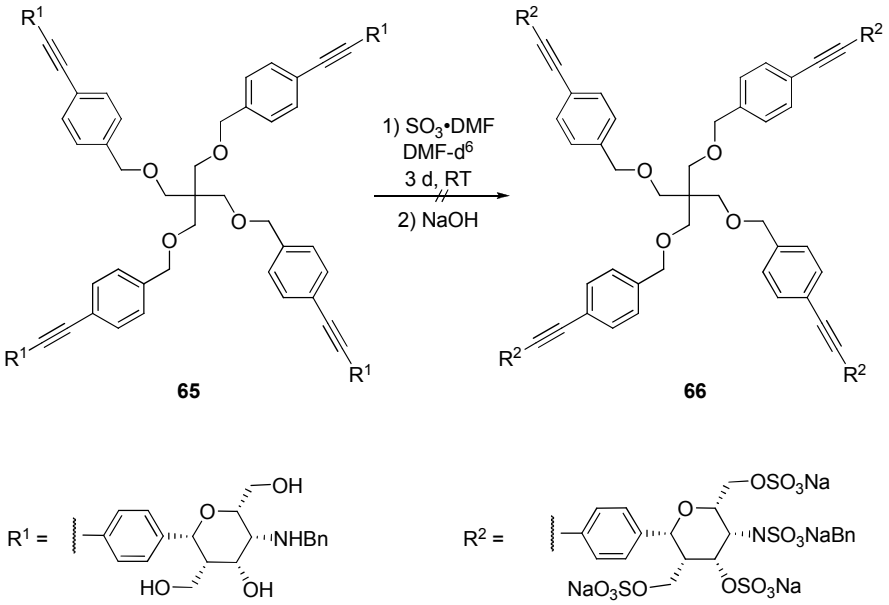
| Eintrag | Edukt | Ausbeute in % | Produkt-nummer |
|---|---|---|---|
| 1 |  **55** | 54 | **56** |
| 2 |  **57** | 82 | **58** |
| 3 |  **59** | 54 | **60** |
| 4 |  **61** | 81 | **62** |

Ein trivalentes polysulfatiertes Produkt **64** konnte ebenfalls durch $SO_3$·DMF in einer Ausbeute von 45% sulfatiert werden (Schema 26). Das Rohprodukt musste insgesamt sechs Tage dialysiert werden, um die Salze vollständig zu entfernen, was die mäßige Ausbeute erklärt.



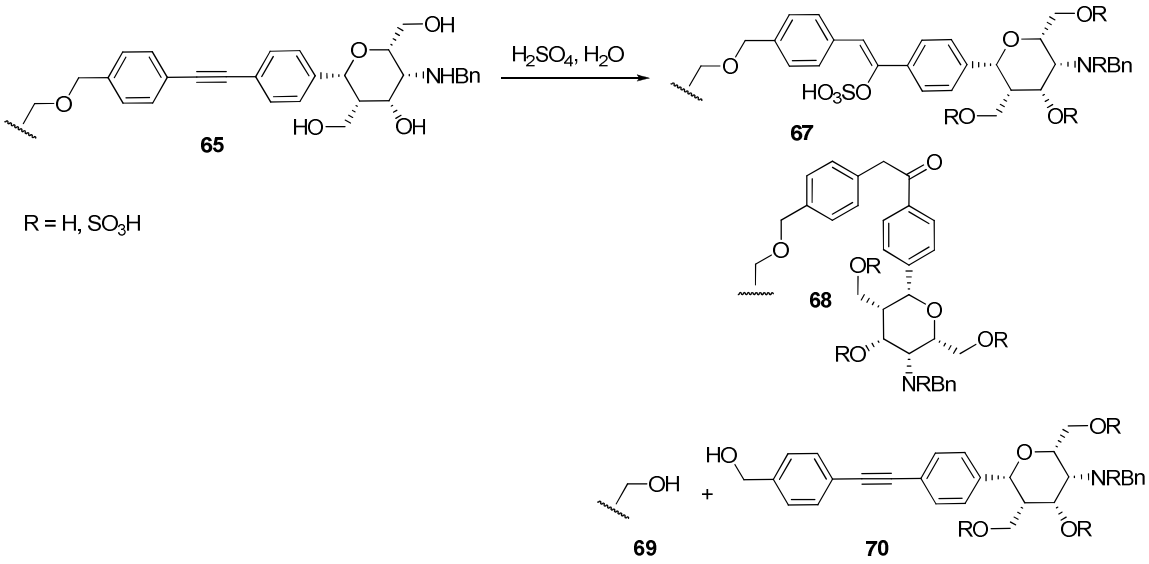

Schema 26: Sulfatierung des trivalenten, triarylverknüpften Kohlenhydratmimetikums **63**.

Das sulfatierte tetravalente Produkt **66** konnte unter den beschriebenen Bedingungen nicht erhalten werden. Nach der Zugabe des Schwefeltrioxid-Reagenz verfärbte sich die Lösung augenblicklich schwarz und nach vier Tagen, in denen weitere 6 Äquivalente pro Tag des Reagenzenz $SO_3$·DMF hinzugefügt wurden, konnte kein einheitliches Produkt im $^1$H-NMR nachgewiesen werden.




Schema 27: Darstellung eines sulfatierten tetravalenten Kohlenhydratmimetikas **66**.

Die Struktur der tetravalenten Verbindung **65** unterscheidet sich von den bereits erwähnten divalenten und trivalenten Verbindungen durch zusätzliche Ether- und Alkineinheiten, wodurch diese Struktur im sauren Medium weniger stabil ist. In Schema 28 sind einige der möglichen Nebenreaktionen gezeigt. Zum einen könnte das Alkin eine elektrophile Addition ($Ad_E3$) mit Schwefelsäure zu Verbindung **67** eingehen, die mit Wasser nach Hydrolyse und Tautomerie das Keton **68** ergeben könnte. Alternativ kann auch die Etherbindung unter sauren Bedingungen zu den Produkten **69** und **70** hydrolysiert werden. Der Benzylalkohol **70** könnte sich weiter zersetzen.




Schema 28: Mögliche Nebenreaktionen des tetravalenten Kohlenhydratmimetikums **65** unter sauren Bedingungen.

Bei den durchgeführten Reaktionen war die Qualität des $SO_3$-Komplexes entscheidend für den Erfolg der Reaktion. Es wurden bereits vorher versucht, Kohlenhydratmimetika mit einer länger im Kühlschrank gelagerten Probe ohne Erfolg zu synthetisieren. Der $SO_3$-Komplex ist sehr hygroskopisch und sollte idealerweise in einer Glovebox gelagert und abgewogen werden. Alternativ sollte im Argongegenstrom abgewogen und die Flasche unter Argon gelagert werden. Nach Hydrolyse des $SO_3$-Komplexes entsteht Schwefelsäure, die theoretisch auch die Hydroxylgruppen sulfatierten kann, aber wesentlich unreaktiver ist.

Eine Ionenaustauschchromatographie der sulfatierten Produkte, wie von Salta vorgeschlagen, wurde nicht vorgenommen, da bei einen pH-Wert von 8-9 die stark sauren Sulfateinheiten vollständig deprotoniert sein müssten. So wurde auf diesen zusätzlichen Aufarbeitungsschritt verzichtet. Eine Reinigung durch Dialyse ist nur bedingt geeignet, da damit außer Salzen zum einen keine anderen Verunreinigen abgetrennt werden können und andererseits diese Reinigungstechnik sehr zeitaufwendig und nur für Produkte mit großem Molekulargewicht geeignet ist. Als alternative Reinigungsmethode sollte die Nanofiltration geeignet sein, die als druckgetriebener Filtrationsprozess zur Entfernung niedrigmolekularer Verunreinigungen einsetzbar ist und den Reinigungsprozess beschleunigen sollte.[52] Die Verwendung von speziellem HPLC-Säulenmaterial, wie Carbograph™, das für die Reinigung besonders polarer Substanzen geeignet ist und nicht nur Salze, sondern auch Nebenprodukte entfernt, stellt eine weitere Alternative zur Reinigung dar.

### 3.4.5 Diskussion der Struktur der polysulfatierten Kohlenhydratmimetika

Es ist sehr schwer vorherzusagen, welches der synthetisierten Produkte eine besonders hohe Bindungsaffinität zu den Selektinen aufweisen wird, da nicht bekannt ist, ob die Kohlenhydratmimetika spezifisch binden. Wahrscheinlich binden sie durch ionische Wechselwirkungen an das Calciumion der Selektine. In Abbildung 9 sind die erhaltenen sulfatierten divalenten Kohlenhydratmimetika nach ihrem Aminopyranabstand in gestreckter Konformation aufgelistet. Dieser Abstand zwischen den beiden Stickstoffatomen beträgt 1 bis 2 nm (bestimmt mit GaussView 3.0). Abbildung 10 zeigt die Lektindomäne des P-Selektin mit dem monovalenten Kohlenhydratmimetika **54** und der kürzesten und längsten divalenten Verbindungen **56** und **60**. Bei der Abbildung handelt es sich nicht um errechnete Positionierung und Orientierung durch eine molekulare Dockingmethode, sondern um die frei gewählte Anordnung der Kohlenhydratmimetika in der Lektindomäne. Die Abbildung lässt vermuten, dass ein divalentes Kohlenhydratmimetikum nur ein Selektin binden kann, da es von der Größe gerade in die Lektindomäne des Selektins passt und der Abstand zwischen den Aminopyraneinheiten wahrscheinlich zu klein für die Bindung eines weiteren Selektins ist. Da sich die Selektine auf einer Oberfläche (dem Gewebe) befinden und sich somit nicht frei bewegen, erschwert dies zusätzlich eine Bindung eines weiteren Selektins an das Kohlenhydratmimetikum.

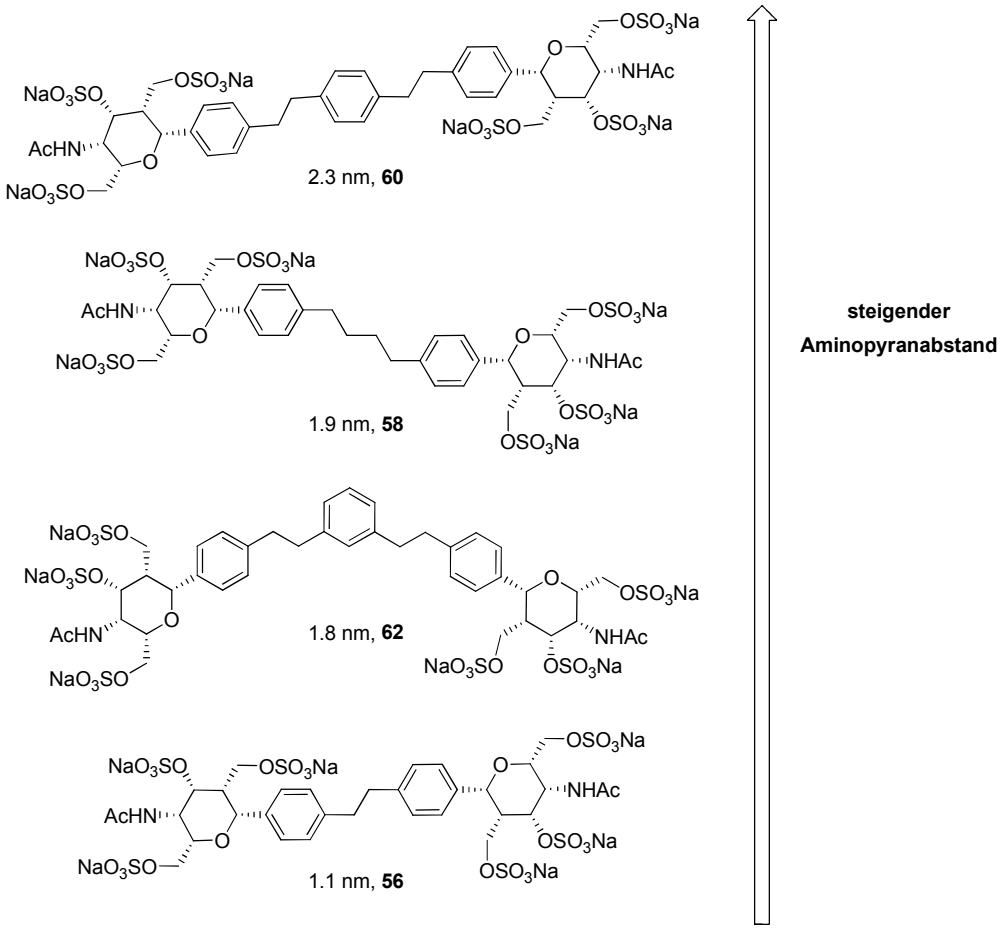



Abbildung 9: Sulfatierte divalente Kohlenhydratmimetika geordnet nach ihrem mit GaussView 3 berechnetem Aminopyranabstand.

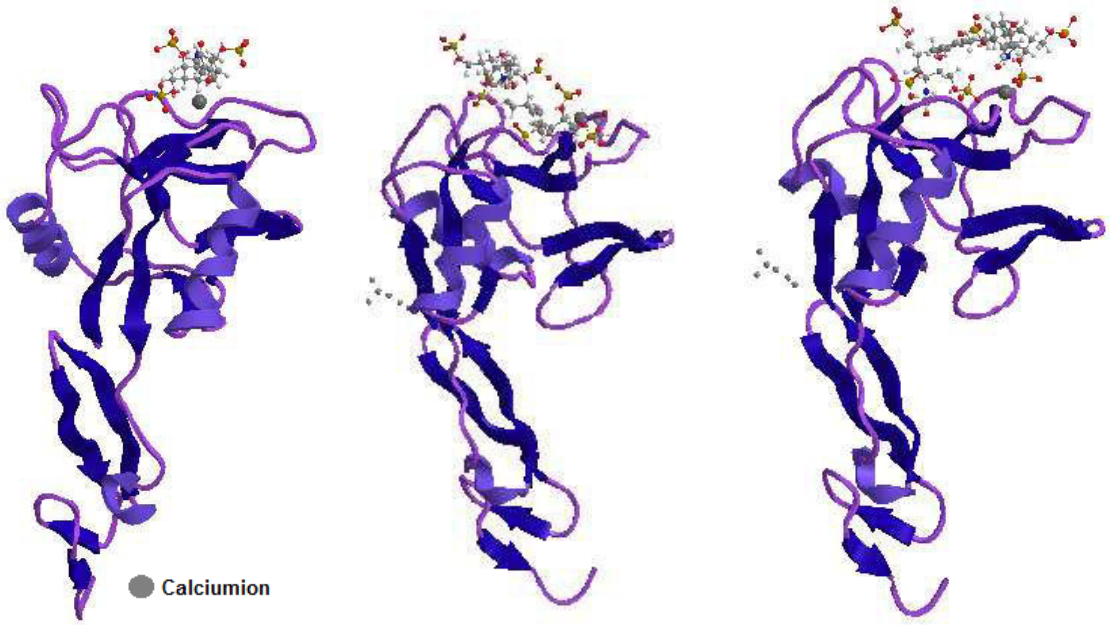
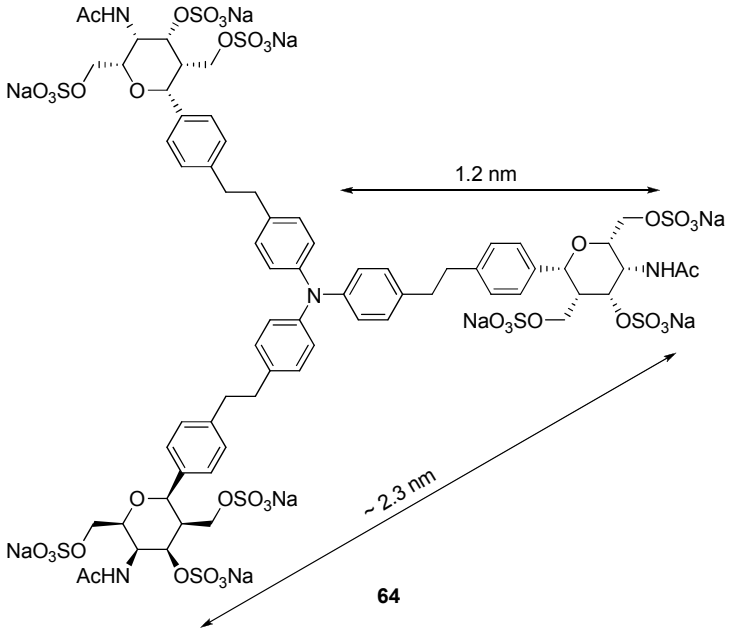



Abbildung 10: Schematische Darstellung von P-Selektin und den synthetisierten Kohlenhydratmimetika **54**, **56** und **60**.

Bei der trivalenten Struktur **64** wurde einerseits der Abstand zwischen dem Amin der Triaryleinheit und dem Amin des Acetylamins mit 1.24 nm und andererseits der direkte Abstand zwischen den Acetylamineinheiten bei maximalem Abstand der drei Aminopyrane zueinander mit 2.3 nm bestimmt (Abbildung 11).




**64**

Abbildung 11: Aminopyranabstände des trivalenten Kohlenhydratmimetikums **64**.

Trotz der Tatsache, dass die Abstände zwischen den Aminopyranen noch vergleichsweise klein sind, besteht dennoch vielleicht die Möglichkeit, dass durch „Clustering“ mit diesem Kohlenhydratmimetikum trotzdem zwei Selektine gebunden werden können (Abbildung 12).[53]

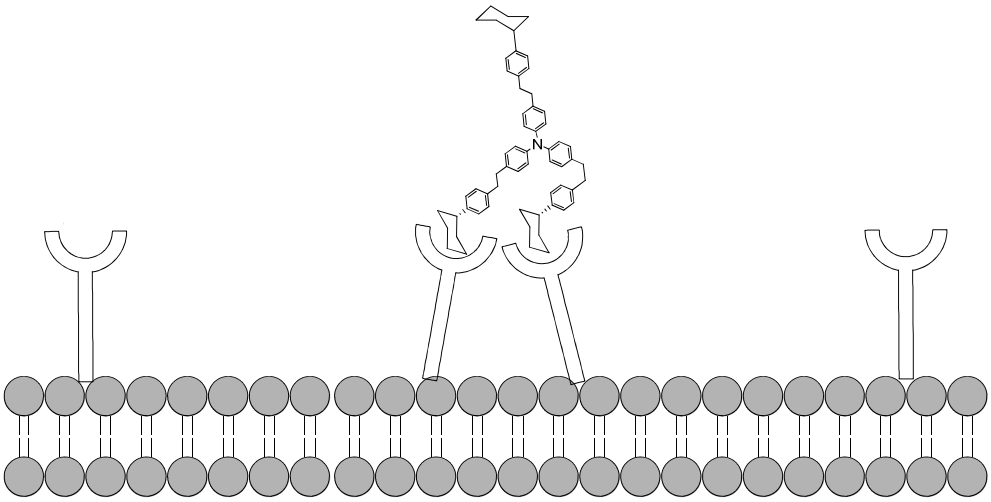



Abbildung 12: Mögliches “Clustering” von Selektinen durch ein trivalentes Kohlenhydratmimetikums.

Um genauere Aussagen zur Struktur-Wirkungs-Beziehung zwischen Selektinen und den synthetisierten Kohlenhydratmimetika treffen zu können und ihre Bindungsaffinität exakt zu bestimmen, sind SPR-Messungen notwendig. Zusätzlich wären auch Saturation transfer difference spectroscopy (STD-NMR)-Messungen hilfreich um zu erfahren, ob diese Bindung spezifisch ist.[54] Ideal wäre eine Röntgenkristallstrukturanalyse eines Einkristalls aus Selektin und einem Kohlenhydratmimetika, wodurch die Anordnung vom Selektin und Kohlenhydratmimetikum eindeutig bestimmt werden könnte. Zusätzlich wären Zytotoxizitätstest zweckmäßig, um eine mögliche Toxizität der Substanzen zu bestimmen.

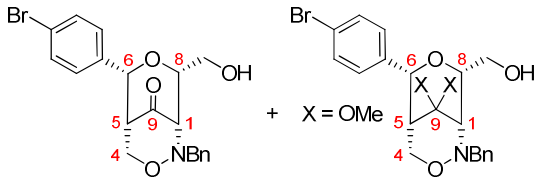
## 3.5 Experimenteller Teil der unveröffentlichten Ergebnisse

### 3.5.1 General Aspects

Reactions were generally performed under inert atmosphere (argon) in flame-dried flasks. Solvents and reagents were added by syringe. Solvents were dried using standard procedures and were purified with a MB SPS-800-dry solvent system. Commercial available reagents were used as received without further purification unless otherwise stated. Products were purified by flash chromatography on silica gel (230–400 mesh, MACHEREY-NAGEL) or dialyses (Roth, MWCO: 100-500). Unless otherwise stated, yields refer to analytical pure samples. Hydrogenolyses were performed with hydrogen from Air Liquide (Alphagaz 2). TLC-analyses were performed on silica gel coated aluminium plates purchased from VWR. Products were detected by UV-activity and by using staining reagents (cer/molybdenum reagent, $KMnO_4$ and ninhydrine). NMR spectra were recorded on BRUKER (AV 500, AV 700) and JEOL (ECP 500) instruments. Chemical shifts (δ) are listed in parts per million (ppm) and are reported relative to solvent residual signals: $CDCl_3$ ($^1H$: δ = 7.26 ppm, $^{13}C$: δ = 77.2 ppm), $CD_3OD$ ($^1H$: δ = 3.31 ppm, $^{13}C$: δ = 49.0 ppm) or $D_2O$ ($^1H$: δ = 4.79 ppm). Integrals are in accordance with assignments; coupling constants (*J*) are given in Hz. All $^{13}C$ NMR spectra are proton-decoupled. Multiplicity is indicated as follows: s (singlet), $s_{br}$ (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), m (multiplet), $m_c$ (centered multiplet). For detailed peak assignments 2D spectra were measured (COSY and HMQC). IR spectra were measured with a Jasco spectrometer (FT/IR-4100 with a DLATGS detector). HRMS analyses were performed with Agilent 6210 (ESI–TOF, 10 µL/min, 1.0 bar, 4 kV) and Varian/Agilent Ionspec QFT-7 (ESI–FTICR, 4 µL/min, 1.0 bar, 4kV) instruments. Elemental analyses were carried out with instruments from Elementar (Vario EL, Vario EL III). Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected. Optical rotations ($[\alpha]_D$) were determined with Perkin–Elmer 241 polarimeters at the temperatures given.

### 3.5.2 Investigation of the debenzylation and N-O-bond cleavage of the *para*-bromophenyl-substituted bicyclic 1,2-oxazines

**(1*S*,5*R*,6*R*,8*S*)-2-Benzyl-6-(4-bromophenyl)-8-(hydroxymethyl)-3,7-dioxa-2-azabicyclo-[3.3.1]nonan-9-one (20) and {(1*S*,5*R*,6*R*,8*S*)-2-Benzyl-6-(4-bromophenyl)-9,9-dimethoxy-3,7-dioxa-2-azabicyclo[3.3.1]-nonan-8-yl}methanol (21):**



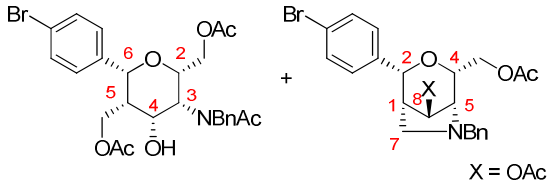

Under argon atmosphere bicyclic compound **18** (100 mg, 217 µmol) was dissolved in dichloromethane (1 mL). The solution was cooled to -10 °C and 1-chloroethyl chloroformate (31 µL, 283 µmol) was added. The solution was warmed up to 0 °C in a period of 3 h and the solvent was removed in vacuo. The crude product was dissolved in methanol (4 mL) and stirred under reflux for 1.5 h, then the solvent was removed in vacuo. The crude material was purified by column chromatography (silica gel, hexanes/EtOAc 2:1) to yield **20** (30 mg, 33%) and **21** (50 mg, 50%) as yellowish oils.

Bicyclic ketone **20**:
$[\alpha]_D^{22}$ = +13.3 (*c* = 0.98, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ = 2.66-2.69 (m, 1 H, 5-H), 3.35-3.36 (m, 1 H, 1-H), 3.88, 3.91, 4.07 (ABM part of ABMX system, $J_{MX}$ = 1.5 Hz, $J_{AM}$ = $J_{BM}$ = 5.0 Hz, $J_{AB}$ = 11.1 Hz, 3 H, 8-H, 8-$CH_2$), 3.99, 4.22 (AB system, $J_{AB}$ = 13.1 Hz, 2 H, $NCH_2$), 4.19, 4.35 (AB part of ABX system, $J_{AX}$ = 2.1 Hz, $J_{BX}$ = 4.8 Hz, $J_{AB}$ = 12.2 Hz, 2 H, 4-H), 4.93 (s, 1 H, 6-H), 7.27-7.35 (m, 7 H, Ar), 7.49-7.52 (m, 2 H, Ar) ppm; signals for OH could not be detected; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 55.1 (d, C-5), 60.0 (t, $NCH_2$), 63.3 (t, 8-$CH_2$), 67.4 (t, C-4), 70.8 (d, C-1), 80.7 (d, C-8), 81.2 (d, C-6), 122.2 (s, Ar), 127.6, 128.2, 128.9, 129.2, 131.8 (5 d, Ph, Ar), 135.3, 136.9 (2 s, Ar, Ph), 207.0 (s, C-9) ppm; IR (ATR): v= 3360 (O-H), 3030 (=C-H), 2930-2845 (C-H), 1715 (C=O), 1485 (C-H), 1220 (C-O) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{21}BrNO_4$ [*M* + H]$^+$: 418.0648, found: 418.0668; calcd for $C_{20}H_{20}BrNNaO_4$ [*M* + Na]$^+$: 440.0468, found: 440.0489.

Bicyclic ketal **21**:

$[\alpha]_D^{22}$ = +15.5 (*c* = 0.98, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.90-1.92 (m, 1 H, 5-H), 2.99 ($m_c$, 1 H, 1-H), 3.26, 3.33 (2 s, 6 H, OMe), 3.49 (dd, *J* = 2.8, 12.0 Hz, 1 H, 4-H), 3.92 (dd, *J* = 5.8, 13.0 Hz, 1 H, 8-$CH_2$), 4.02-4.07 (m, 2 H, 8-$CH_2$, 8-H), 4.23 ($d_{br}$, *J* = 12.0 Hz, 1 H, 4-H), 4.32, 4.43 (AB system, $J_{AB}$ = 13.2 Hz, 2 H, $NCH_2$), 5.15 (s, 1 H, 6-H), 7.23-7.28 (m, 1 H, Ar), 7.30-7.38 (m, 6 H, Ar), 7.43-7.47 (m, 2 H, Ar) ppm; signals for OH could not be detected; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 21.2 (t, C-5), 46.8, 47.4 (2 q, OMe), 58.0 (d, C-1), 58.4 (t, $NCH_2$), 60.5 (t, 8-$CH_2$), 61.0 (t, C-4), 75.7 (d, C-8), 76.5 (d, C-6), 96.3 (s, C-9), 121.2 (s, Ar), 127.6, 128.2, 128.6, 129.1, 131.4 (5 d, Ar, Ph), 137.9, 139.5 (2 s, Ar, Ph) ppm; IR (ATR): v = 3395 (O-H), 3030 (=C-H), 2940-2880 (C-H), 1500 (C-H), 1220 (C-O) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{27}BrNO_5$ [*M* + H]$^+$: 464.1067, found: 464.1036; calcd for $C_{22}H_{26}BrNNaO_5$ [*M* + Na]$^+$: 486.0887, found: 486.0862.

**[(2*S*,3*R*,4*R*,5*S*,6*R*)-3-(*N*-Benzylacetamido)-6-(4-bromophenyl)-4-hydroxytetrahydro-2*H*-pyran-2,5-diyl]bis(methylene) diacetate (24) and [(1*R*,2*R*,4*S*,5*R*,8*S*)-8-Acetoxy-6-benzyl-2-(4-bromophenyl)-3-oxa-6-azabicyclo[3.2.1]octan-4-yl]methyl acetate (25):**




Bicyclic compound **22** (261 mg, 621 µmol) was dissolved in degased THF (2 mL) and a samarium(II) iodide solution (41.4 mL, 0.09 M solution in THF, 3.73 mmol) was added. The solution was stirred for 30 min at rt and then a sat. potassium sodium tartrate solution (5 mL) was added and the solution was stirred for 2 h at rt. The aqueous layer was extracted with ethyl acetate (5 x 10 mL) and the combined organic layers were dried with $NaSO_4$, filtered and the solvent was removed in vacuo. The crude material was purified by HPLC (5% *i*PrOH/hexanes, flow 6.4 mL/min) to yield **24** (204 mg, 60%) and **25** (39 mg, 13%) as colorless oils.

Aminopyran **24** is instable and slowly cycles into bicyclic compound **25**.

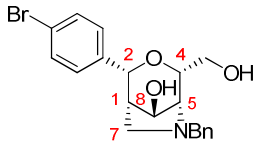
Aminopyran **24**:

$[\alpha]_D^{22}$= +10.9 (*c* = 1.01, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 1.46, 1.98, 2.00 (3 s, 9 H, Ac), 2.52 ($m_c$, 1 H, 5-H), 3.02 (dd, *J* = 2.0, 3.1 Hz, 1 H, 3-H), 3.78 (ddd, *J* = 2.0, 5.2, 6.9 Hz, 1 H, 2-H), 3.81 (s, 2 H, $NCH_2$), 4.13 (dd, *J* = 5.2, 11.6 Hz, 1 H, 2-$CH_2$), 4.18, 4.26 (AB part of ABX system, $J_{AX}$ = 8.4 Hz, $J_{BX}$ = 0.0 Hz, $J_{AB}$ =11.8 Hz, 2 H, 5-$CH_2$), 4.34 (dd, *J* = 6.9, 11.6 Hz, 1 H, 2-$CH_2$), 4.62 (d, *J* = 2.0 Hz, 1 H, 4-H), 5.13 (dd, *J* = 3.7, 5.5 Hz, 1 H, 6-H), 7.13, 7.28 (2 d, *J* = 8.5 Hz, 4 H, Ar), 7.17-7.22 (m, 1 H, Ph), 7.26-7.27 (m, 4 H, Ph) ppm; signals for OH could not be detected; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 20.3, 21.0, 21.2 (3 q, Ac), 43.2 (d, C-5), 54.3 (t, $NCH_2$), 54.6 (d, C-3), 59.8 (t, 5-$CH_2$), 63.7 (t, 2-$CH_2$), 74.6 (d, C-6), 78.2 (d, C-2), 78.8 (d, C-4), 121.0 (s, Ar), 127.3, 128.4, 128.5, 128.6, 131.1 (5 d, Ar, Ph), 138.1, 140.4 (2 s, Ar, Ph), 170.2, 170.5, 170.7 (3 s, Ac) ppm; IR (ATR): v = 3570-3250 (O-H), 3025 (=C-H), 2965 (C-H), 1740 (C=O), 1460 (C-H) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{26}H_{31}BrNO_7$ [*M* + H]$^+$: 548.1278, found: 548.1330, calcd for $C_{26}H_{30}BrNNaO_7$ [*M* + Na]$^+$: 570.1103; found: 570.1136.

Bicyclic compound **25**:

$[\alpha]_D^{22}$= +35.8 (*c* = 1.02, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 1.91, 2.16 (2 s, 6 H, Ac), 2.44, 2.59, 2.95 (ABX system, $J_{AX}$ = 5.7 Hz, $J_{BX}$ = 0.0 Hz, $J_{AB}$ = 10.3 Hz, 3 H, 7-H, 1-H), 3.23 (d, *J* = 1.5 Hz, 1 H, 5-H), 3.70 ($t_{br}$, *J* ≈ 6.3 Hz, 1 H, 4-H), 3.83, 3.90 (AB system, $J_{AB}$ = 12.8 Hz, 2 H, $NCH_2$), 4.05, 4.19 (AB part of ABX system, $J_{AX}$ = 5.8 Hz, $J_{BX}$ = 6.9 Hz, $J_{AB}$ = 10.7 Hz, 2 H, 4-$CH_2$), 4.72 (s, 1 H, 8-H), 5.11 (s, 1 H, 2-H), 7.21, 7.45 (2 d, *J* = 8.2 Hz, 4 H, Ar), 7.23-7.24 (m, 1 H, Ph), 7.29-7.34 (m, 4 H, Ph) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 21.0, 21.5 (2 q, Ac), 47.8 (d, C-1), 51.6 (t, C-7), 62.6 (d, C-5), 63.0 (t, $NCH_2$), 63.9 (t, 4-$CH_2$), 76.5 (d, C-4), 78.3 (d, C-8), 80.4 (d, C-2), 121.3 (s, Ar), 127.2, 127.7, 128.5, 129.0, 131.4 (5 d, Ar, Ph), 139.2, 140.1 (2 s, Ar, Ph), 170.4, 170.7 (2 s, Ac) ppm; IR (ATR): v = 3455 (N-H), 3060-3025 (=C-H), 2960-2865 (C-H), 1740 (C=O) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{24}H_{27}BrNO_5$ [*M* + H]$^+$: 488.1073, found: 488.1089, calcd for $C_{24}H_{26}BrNNaO_5$ [*M* + Na]$^+$: 510.0892; found: 510.0897.

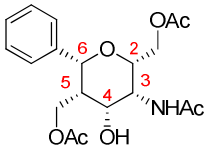
**(1*S*,2*R*,4*S*,5*R*,8*S*)-6-Benzyl-2-(4-bromophenyl)-4-(hydroxymethyl)-3-oxa-6-azabicyclo[3.2.1]-octan-8-ol (28):**




Bicyclic compound **25** (102 mg, 209 µmol) was dissolved in methanol (2 mL) and sodium methoxide (12 mg, 230 µmol) was added. The solution was stirred for 6 h at rt, then a brine solution (5 mL) and dichloromethane (5 mL) were added. The aqueous layer was extracted with dichloromethane (5 x 5 mL). The combined organic layers were dried with $NaSO_4$, filtered and the solvent was removed in vacuo. The crude material was purified by column chromatography (silica gel, $CH_2Cl_2$/$CH_3OH$ 10:1) to yield **28** (66 mg, 78%) as a colorless solid.

m.p. 70-72 °C; $[\alpha]_D^{22}$= +82.7 (*c* = 1.05, $CH_3OH$); $^1$H NMR (500 MHz; $CD_3OD$): δ = 2.45, 2.51, 2.74 (ABX system, $J_{AX}$ = 5.6 Hz, $J_{BX}$ = 0.0 Hz, $J_{AB}$ = 10.2 Hz, 3 H, 1-H, 7-H), 3.30 ($s_{br}$, 1 H, 5-H), 3.48, 3.68, 3.75 (ABX system, $J_{AX}$ = $J_{BX}$ = 4.5 Hz, $J_{AB}$ = 11.0 Hz, 3 H, 4-H, 4-$CH_2$), 3.94, 4.10 (AB system, $J_{AB}$ = 12.9 Hz, 2 H, $NCH_2$), 4.20 (s, 1 H, 8-H), 4.63 (s, 1 H, 2-H), 7.17-7.20 (m, 1 H, Ph), 7.25-7.28 (m, 4 H, Ph, Ar), 7.31-7.33 (m, 2 H, Ph), 7.40-7.41 (m, 2 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CD_3OD$): δ = 51.1 (d, C-1), 52.1 (t, C-7), 64.3 (t, $NCH_2$), 65.2 (t, 4-$CH_2$), 68.6 (d, C-5), 78.6 (d, C-4), 78.9 (d, C-8), 79.3 (d, C-2), 121.7 (s, Ar), 128.1, 128.8, 129.4, 129.9, 132.1 (5 d, Ar), 141.0, 141.5 (2 s, Ar) ppm; IR (ATR): v = 3450-3140 (O-H, N-H), 3065-3025 (=C-H), 2920-2850 (C-H) cm$^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{23}BrNO_3$ [*M* + H]$^+$: 404.0856, found: 404.0869; elemental analysis calcd (%) for $C_{20}H_{22}BrNO_3$ (404.3): C, 59.42; H, 5.48; N, 3.46; C, 59.57; H, 5.49; N, 3.49.

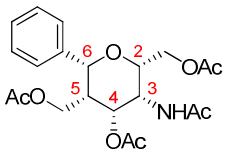
**[(2*S*,3*R*,4*R*,5*S*,6*R*)-3-Acetamido-4-hydroxy-6-phenyltetrahydro-2*H*-pyran-2,5-diyl]bis-(methylene) diacetate (29):**




A suspension of Pd/C (116 mg, 10% Pd) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. The bicyclic compound **24** (116 mg, 212 µmol) was dissolved in *i*PrOH (1 mL) and added to the suspension. The mixture was stirred for 4 h under hydrogen pressure (balloon). The mixture was filtrated through a pad of Celite® and the solvent was removed in vacuo. The crude material was purified by column chromatography (silica gel, $CH_2Cl_2$/$CH_3OH$ 40:1) to yield **29** (32 mg, 40%) as a colorless solid.

m.p. 59-61 °C; $[\alpha]_D^{22}$ = -3.0 (*c* = 1.00, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD$): δ =1.48, 2.06, 2.09 (3 s, 9 H, Ac), 2.55 ($m_c$, 1 H, 5-H), 4.04 (ddd, *J* = 2.2, 5.4, 7.5 Hz, 1 H, 2-H), 4.08 ($d_{br}$, *J* = 11.0 Hz, 1 H, 5-$CH_2$), 4.23, 4.33 (AB part of ABX system, $J_{AX}$ = 5.4 Hz, $J_{BX}$ = 7.5 Hz, $J_{AB}$ = 11.5 Hz, 2 H, 2-$CH_2$), 4.33-4.34 (m, 1 H, 4-H), 4.34 (dd, *J* = 3.5, 11.0 Hz, 1 H, 5-$CH_2$), 4.38 (dd, *J* = 2.2, 4.0 Hz, 1 H, 3-H), 4.79 (d, *J* = 2.4 Hz, 1 H, 6-H), 7.24-7.26 (m, 1 H, Ph), 7.33-7.35 (m, 2 H, Ph), 7.40-7.42 (m, 2 H, Ph) ppm; $^{13}$C NMR (175 MHz, $CD_3OD$): δ = 20.3, 20.7, 22.6 (3 q, Ac), 46.3 (d, C-5), 50.6 (d, C-3), 60.1 (t, 5-$CH_2$), 64.4 (t, 2-$CH_2$), 71.8 (d, C-4), 77.2 (d, C-2), 80.7 (d, C-6), 126.6, 128.0, 129.0 (3 d, Ph), 141.0 (s, Ph), 172.52, 172.53, 175.2 (3 s, Ac) ppm; IR (ATR): ν = 3630-3140 (O-H, N-H), 3030 (=C-H), 2925-2855 (C-H), 1735 (C=O) cm$^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{25}NNaO_7$ [*M* + Na]$^+$: 402.1529, found: 402.1551; calcd for $C_{38}H_{50}N_2NaO_{14}$ [2*M* + Na]$^+$: 781.3160, found: 781.3185.

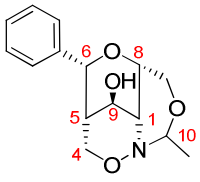
**[(2*S*,3*R*,4*R*,5*R*,6*R*)-3-Acetamido-4-acetoxy-6-phenyltetrahydro-2*H*-pyran-2,5-diyl]bis-(methylene) diacetate (32):**




A suspension of Pd/C (25 mg, 10% Pd) and methanol (3 mL) was saturated with hydrogen for 15 min. The bicyclic compound **22** (50 mg, 119 µmol) was dissolved in EtOAc/$CH_3OH$ (2 mL/0.5 mL) and added to the suspension. The mixture was stirred for 4 h under hydrogen pressure (balloon). The mixture was filtrated through a pad of Celite® and the solvent was removed in vacuo. Under an argon atmosphere the crude material was dissolved in degassed THF (0.5 mL), a samarium(II) iodide solution (3.57 mL, 0.1 M in THF, 357 µmol) was added dropwise and the mixture was stirred for 30 min at rt. After completion of the reaction (control by TLC) the mixture was stirred under air for 10 min, sat. potassium sodium tartrate solution (5 mL) was added and the aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent removed in vacuo. The obtained solid was dissolved in a $CH_2Cl_2$/pyridine mixture (1 mL/0.5 mL) and DMAP (6 mg, 50 µmol) and acetic anhydride (18 mg, 20 µL, 178 µmol) were added. The mixture was stirred at rt for 18 h. Water (5 mL) was added to the mixture and the aqueous layer was extracted with dichloromethane (5 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:2) to yield **32** (6 mg, 12%) as a colorless solid.

m.p. 57-59 °C; $[\alpha]_D^{22}$= -19.5 (*c* = 0.60, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 1.61 (s, 3 H, Ac), 2.05 (s, 6 H, 2 Ac), 2.06 (s, 3 H, Ac), 2.65 ($m_c$, 1 H, 5-H), 4.00 (ddd, *J* = 2.0, 5.6, 7.2 Hz, 1 H, 2-H), 4.07, 4.11 (AB part of ABX system, $J_{AX}$ = 3.3 Hz, $J_{BX}$ = 6.9 Hz, $J_{AB}$ = 11.5 Hz, 2 H, 5-$CH_2$), 4.15, 4.31 (AB part of ABX system, $J_{AX}$ = 5.6 Hz, $J_{BX}$ = 7.2 Hz, $J_{AB}$ = 11.7 Hz, 2 H, 2-$CH_2$), 4.59 (ddd, *J* = 2.0, 4.1, 9.7 Hz, 1 H, 3-H), 4.80 (d, *J* = 2.3 Hz, 1 H, 6-H), 5.35 (dd, *J* = 4.1, 5.8 Hz, 1 H, 4-H), 5.80 (d, *J* = 9.7 Hz, 1 H, NH), 7.24-7.27 (m, 1 H, Ph), 7.28-7.29 (m, 2 H, Ph), 7.32-7.35 (m, 2 H, Ph) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 20.4, 20.9, 21.1, 23.5 (4 q, Ac), 42.3 (d, C-5), 46.4 (d, C-3), 58.9 (t, 5-$CH_2$), 62.8 (t, 2-$CH_2$), 71.0 (d, C-4), 76.6 (d, C-2), 79.4 (d, C-6), 125.2, 127.6, 128.4 (3 d, Ph), 138.2 (s, Ph), 170.2, 170.3, 170.5, 170.8 (4 s, Ac) ppm; IR (ATR): v = 3605-3120 (N-H), 3015 (=C-H), 2955-2850 (C-H), 1740 (C=O), 1670 (NC=O) cm$^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{28}NNaO_8$ [*M* + Na]$^+$: 444.1628, found: 444.1607; calcd for $C_{42}H_{54}N_2NaO_{16}$ [2*M* + Na]$^+$: 865.3366, found 865.3326.

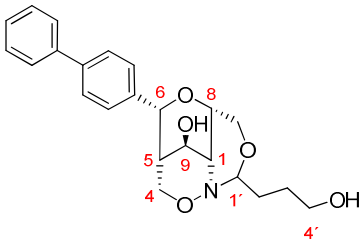
**Tricyclic compound 35:**




A suspension of Pd/C (25 mg, 10% Pd) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. The bicyclic compound **34** (25 mg, 38 µmol) was dissolved in EtOAc (1 mL) and added to the suspension. Then a drop of trifluoroacetic acid was added and the mixture was stirred for 4 h under hydrogen pressure (balloon). The mixture was filtered through a pad of Celite® and the solvent was removed in vacuo. The crude material was purified by column chromatography (silica gel, hexanes/EtOAc 1:2) to yield **35** (6 mg, 57%) as a colorless solid.

m.p. 48-52 °C; $[\alpha]_D^{22}$= +13.5 (*c* = 0.6, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 5.9 Hz, 3 H, $CH_3$), 1.78 ($m_c$, 1 H, 5-H), 3.12 (s, 1 H, 1-H), 3.72 (s, 1 H, 8-H), 3.82 (d, *J* = 12.3 Hz, 1 H, 4-H), 3.89 (dd, *J* = 2.0, 12.7 Hz, 1 H, 8-$CH_2$), 4.13 (t, *J* = 3.1 Hz, 1 H, 9-H), 4.18 ($d_{br}$, *J* = 12.3 Hz, 1 H, 4-H), 4.26 (q, *J* = 5.9 Hz, 1 H, 10-H), 4.32 ($d_{br}$, *J* = 12.7 Hz, 1 H, 8-$CH_2$), 4.89 (s, 1 H, 6-H), 7.27-7.29 (m, 1 H, Ph), 7.35-7.37 (m, 2 H, Ph), 7.47-7.48 (m, 2 H, Ph) ppm; signals for OH could not be detected; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 18.7 (q, $CH_3$), 40.4 (d, C-5), 59.4 (d, C-1), 63.3 (t, C-4), 68.2 (d, C-9), 69.6 (d, C-8), 70.1 (t, 8-$CH_2$), 80.0 (d, C-6), 89.6 (d, C-10), 126.3, 127.6, 128.4 (3 d, Ph), 139.9 (s, Ph) ppm; IR (ATR): ν = 3580-3150 (O-H), 3115-3060 (=C-H), 2955-2850 (C-H), 1495 (C-H) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{20}NO_4$ $[M + H]^+$: 278.1393, found: 278.1400; calcd for $C_{15}H_{19}NNaO_4$ $[M + Na]^+$: 300.1212, found: 300.1218.

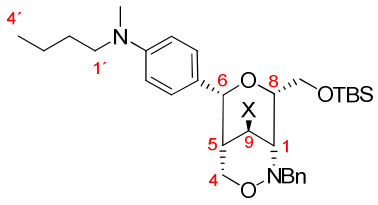
**Tricyclic compound 38:**




A suspension of Pd/C (70 mg, 10% Pd) and *i*PrOH (3 mL) was saturated with hydrogen for 15 min. The bicyclic compound **37** (70 mg, 168 µmol) was dissolved in THF (2 mL) and added to the suspension. The mixture was stirred for 4 h under hydrogen pressure (balloon), filtered through a pad of Celite® and the solvent was removed in vacuo. The crude material was purified by column chromatography (silica gel, $CH_2Cl_2/CH_3OH$ 60:1) to yield **38** (51 mg, 77%) as a colorless solid.

m.p. 86-88 °C; $[\alpha]_D^{22}$= + 57.0 (*c* = 1.16, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD$): δ = 1.66-1.73 (m, 2 H, 3´-H), 1.74 ($m_c$, 1 H, 5-H), 1.89 ($m_c$, 2 H, 2´-H), 3.22 ($m_c$, 1 H, 1-H), 3.61 (t, *J* = 6.5 Hz, 2 H, 4´-H), 3.70 ($d_{br}$, *J* = 11.8 Hz, 1 H, 4-H), 3.74 ($m_c$, 1 H, 8-H), 3.96 (dd, *J* = 1.9, 12.6 Hz, 1 H, 8-$CH_2$), 4.20-4.23 (m, 3 H, 9-H, 1´-H, 8-$CH_2$), 4.31 ($d_{br}$, *J* = 11.8 Hz, 1 H, 4-H), 5.01 (s, 1 H, 6-H), 7.32-7.35 (m, 1 H, Ph), 7.42-7.45 (m, 2 H, Ph), 7.61-7.64 (m, 6 H, Ph) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 29.4 (t, C-3´), 29.8 (t, C-2´), 41.7 (d, C-5), 60.1 (d, C-1), 63.0 (t, C-4´), 64.1 (t, C-4), 68.9 (d, C-9), 71.2 (t, 8-$CH_2$), 71.3 (d, C-8), 81.0 (d, C-6), 93.9 (d, C-1´), 127.6, 127.7, 127.9, 128.3, 129.8 (5 d, Ph), 141.0, 141.3, 142.1 (3 s, Ph) ppm; IR (ATR): v = 3390 (O-H), 3030-3005 (=C-H), 2950-2855 (C-H), 1450 (C-H), 1250 (C-O) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{27}NNaO_5$ $[M + Na]^+$: 420.1787, found 420.1809.

**4-(1*S*,5*R*,6*R*,8*S*,9*R*)-2-Benzyl-9-(*tert*-butyldimethylsilyloxy)-8-[(*tert*-butyldimethylsiloxy)-methyl)-3,7-dioxa-2-azabicyclo[3.3.1]nonan-6-yl]-*N*-butyl-*N*-methylaniline (40):**



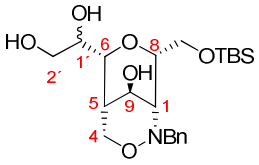

R = OTBS

Compound **39** (50 mg, 77 µmol), $Pd_2(dba)_3$ (7 mg, 8 µmol), (-)-BINAP (10 mg, 116 µmol) and sodium *tert*-butoxide (11 mg, 116 µmol) were filled in a sealed tube and flushed with argon. Degassed toluene (1 mL) and *N*-methyl-1-butylamine (18 µL, 13 mg, 154 µmol) were added and the mixture was stirred for 18 h at 140 °C. The solution was cooled to rt, sat. ammonium chloride solution (5 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 20:1) to yield **40** (21 mg, 42%) as a brown solid.

m.p. 58-60 °C; $[\alpha]_D^{22}$= + 7.8 (*c* = 0.60, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 0.07, 0.09, 0.18, 0.20 (4 s, 12 H, $SiCH_3$), 0.89, 1.01 (2 s, 18 H, Si*t*-Bu), 0.94 (t, *J* = 7.4 Hz, 3 H, 4-H´), 1.30-1.35 (m, 2 H, 3´-H), 1.51-1.56 (m, 2 H, 2´-H), 1.64 ($m_c$, 1 H, 5-H), 2.91 (s, 3 H, $NCH_3$), 3.01 (s, 1 H, 1-H), 3.29 (t, *J* = 6.9 Hz, 1 H, 1´-H), 3.43 (d, *J* = 11.7 Hz, 1 H, 4-H), 3.83, 3.91, 4.22 (ABM part of ABMX system, $J_{MX}$ = 2.8 Hz, $J_{AM}$ = 4.9 Hz, $J_{BM}$ = 7.7 Hz, $J_{AB}$ = 9.4 Hz, 3 H, 8-H, 8-$CH_2$), 4.10 (t, *J* = 2.8 Hz, 1 H, 9-H), 4.13 (d, *J* = 14.7 Hz, 1 H, $NCH_2$), 4.48 ($d_{br}$, *J* = 11.7 Hz, 1 H, 4-H), 4.82 (s, 1 H, 6-H), 4.90 (d, *J* = 14.7 Hz, 1 H, $NCH_2$), 6.65, 7.28 (2 d, *J* = 8.5 Hz, 4 H, Ar), 7.22-7.24 (m, 1 H, Ph), 7.30-7.33 (m, 2 H, Ph), 7.41-7.42 (m, 2 H, Ph) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = -5.2, -5.1, -4.7, -4.6 (4 q, $SiCH_3$), 14.3 (q, C-4´), 14.4 (t, C-3´), 18.2, 18.4, 26.0, 26.1 (2 s, 2 q, Si*t*-Bu), 28.9 (t, C-2´), 38.5 (q, $NCH_3$), 42.9 (d, C-5), 52.7 (t, C-1´), 56.2 (t, C-4), 58.7 (t, $NCH_2$), 58.8 (d, C-1), 63.1 (t, 8-$CH_2$), 70.7 (d, C-9), 80.1 (d, C-8), 80.6 (d, C-6), 112.0, 126.9, 127.4, 128.2, 128.6 (5 d, Ar, Ph), 129.9, 140.0, 148.9 (3 s, Ar, Ph) ppm; IR (ATR): v = 3010 (=C-H), 2965-2855 (C-H), 1450 (C-H), 1255 (C-O) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{37}H_{63}N_2O_4Si_2$ [*M* + H]$^+$: 655.4326, found: 655.4363; calcd for $C_{37}H_{62}N_2NaO_4Si_2$ [*M* + Na]$^+$: 677.4146, found: 677.4185.

### 3.5.3 Further reactions of the vinyl-substituted bicyclic 1,2-oxazine (5)

**1´-{(1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-8-[(*tert*-butyldimethylsiloxy)methyl]-9-hydroxy-3,7-dioxa-2-azabicyclo[3.3.1]nonan-6-yl}ethane-1´,2´-diol (41):**

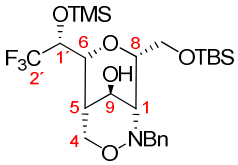



Bicyclic compound **5** (258 mg, 636 µmol) was dissolved in *tert*-butanol (2 ml) and water (1 mL), citric acid (62 mg, 323 µmol), trimethylamine *N*-oxide dihydrate (71 mg, 639 µmol) and potassium osmate dihydrate (2 mg, 6 µmol) were added. The emulsion was stirred for 24 h at rt, then the solvent was removed in vacuo. Dichloromethane (5 mL) and brine solution (5 mL) were added to the crude product. The aqueous layer was extracted with dichloromethane (5 x 5 mL) and the combined organic layers were dried with $NaSO_4$, filtered and the solvent was removed in vacuo. The crude material was purified by column chromatography (silica gel, $CH_2Cl_2/CH_3OH$ 10:1) to yield a diastereomeric mixture of **41** (249 mg, 89%, d.r. 5 : 1) as a colorless solid.

The diastereomeric mixture was not separated. The signals of the major product are labeled with *.

m.p. 55 °C; $[\alpha]_D^{22}$ = +17.1 (*c* = 1.14, $CHCl_3$); $^1$H NMR (500 MHz, $CD_3OD$): δ = 0.06 (s, 6 H, $SiCH_3$, $SiCH_3$*), 0.07 (s, 6 H, $SiCH_3$, $SiCH_3$*), 0.89 (s, 9 H, Si*t*-Bu*), 0.90 (s, 9 H, Si*t*-Bu), 1.93 ($s_{br}$, 1 H, 5-H), 2.15 ($s_{br}$, 1 H, 5-H*), 3.15 ($s_{br}$, 2 H, 1-H, 1-H*), 3.47 (d, *J* = 8.9 Hz, 1 H, 6-H*), 3.49-3.53 (m, 1 H, 6-H), 3.56-3.65 (m, 4 H, 9-H, 9-H*, 4-H, 4-H*), 3.76-3.92 (m, 2 H, 1´-H, 1´-H*), 4.02 (d, *J* = 12.5 Hz, 2 H, 4-H, 4-H´), 4.15 (d, *J* = 14.8 Hz, 2 H, $NCH_2$, $NCH_2$*), 4.22 (d, *J* = 14.8 Hz, 2 H, $NCH_2$, $NCH_2$*), 4.25 (d, *J* = 6.4 Hz, 2 H, 8-$CH_2$, 8-$CH_2$*), 3.76-3.83 (m, 4 H, 8-H, 8-$CH_2$, 8-H´, 8-$CH_2$´), 3.84-3.92 (m, 4 H, 2´-H, 2´-H*), 7.21-7.27 (m, 2 H, Ph, Ph*), 7.28-7.34 (m, 8 H, Ph, Ph*) ppm; $^{13}$C NMR (125 MHz, $CD_3OD$): δ = -5.3, -5.2 (2 q, $SiCH_3$, $SiCH_3$*), 18.2, 26.0 (s, q, Si*t*-Bu*), 18.3, 26.0 (s, q, Si*t*-Bu), 35.4, 37.0 (2 d, C-1, C-1*), 60.59, 60.61 (2 d, C-5, C-5*), 61.6, 61.7 (2 t, $NCH_2$, $NCH_2$*), 62.6, 62.7 (2 t, 8-$CH_2$, 8-$CH_2$*), 63.1 (2 d, C-8, C-8*), 64.5, 64.7 (2 t, C-4, C-4*), 70.2, 70.3 (2 t, C-2‘, C-2‘*), 70.5, 72.4 (2 d, C-1‘, C-1‘*), 78.4, 79.2 (2 d, C-6, C-6*), 79.9, 80.0 (2 d, C-9, C-9*), 127.3, 127.4, 128.4, 128.4, 138.2 (5 d, Ph, Ph*), 138.5 (s, Ph, Ph*) ppm; IR (ATR): ν = 3600-3130 (O-H), 3090-3020 (=C-H), 2950-2850 (C-H), 1455 (C-H), 1250 (C-O) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{38}NO_6Si$ [*M* + H]$^+$: 440.2468, found: 440.2557, calcd for $C_{22}H_{37}NNaO_6Si$ [*M* + Na]$^+$: 462.2288, found: 462.2384.

**(1´*R*,1*R*,5*S*,6*R*,8*S*,9*R*)-2-Benzyl-8-[(*tert*-butyldimethylsiloxy)methyl]-6-[2´,2´,2´-trifluoro-1´-(trimethylsiloxy)ethyl]-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (42):**

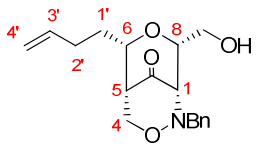



The diol **41** (58 mg, 132 µmol) was dissolved in dichloromethane (1 mL) and water (0.5 mL), sodium bicarbonate (3 mg, 36 µmol) and sodium periodate (61 mg, 285 µmol) were added. The solution was stirred for 3 h at rt, then $NaSO_4$ (100 mg) was added, the solution was filtered and the solvent was removed in vacuo. The crude material was dissolved in dry DMF (1 mL), then trifluoromethyltrimethylsilane (0.06 ml, 406 µmol) and potassium carbonate (4 mg, 29 µmol) were added and the solution was stirred for 18 at rt. Dichloromethane (5 mL), water (2.5 mL) and brine (2.5 mL) were added and the aqueous layer was extracted with dichloromethane (5 x 10 mL). The combined organic layers were dried with $NaSO_4$, filtered and the solvent was removed in vacuo. The crude material was purified by HPLC (5% EtOAc/hexanes, flow 2 ml/min) to yield **42** (7 mg, 10%) as a colorless oil.

$^1$H NMR (700 MHz, $CDCl_3$): δ = 0.08, 0.10 (2 s, 6 H, $SiCH_3$), 0.17 [s, 9 H, $Si(CH_3)_3$], 0.91 (s, 9 H, *t*-BuSi), 2.27 ($s_{br}$, 1 H, 5-H), 3.30 ($s_{br}$, 1 H, 1-H), 3.63 (dd, *J* = 6.4, 8.1 Hz, 1 H, 9-H), 3.66-3.70 (m, 1 H, OH), 3.75 (d, *J* = 6.9 Hz, 1 H, 6-H), 3.81 (dd, *J* = 5.9, 9.9 Hz, 1 H, 8-H), 3.83-3.87 (m, 2 H, 8-$CH_2$), 4.05-4.09 (m, 1 H, 1´-H), 4.09, 4.25 (AB system, $J_{AB}$ = 15.0 Hz, 2 H, $NCH_2$), 4.11, 4.18 (AB part of ABX system, $J_{AX}$ = 2.9 Hz, $J_{BX}$ = 6.5 Hz, $J_{AB}$ = 12.0 Hz, 2 H, 4-H), 7.28-7.31 (m, 1 H, Ph), 7.37-7.40 (m, 4 H, Ph) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = -5.5, -5.4 (2 q, $SiCH_3$), -0.1 [q, $Si(CH_3)_3$], 18.1, 25.8 (s, q, Si*t*-Bu), 35.5 (d, C-5), 61.1 (d, C-1), 61.8 (d, C-8), 62.5 (t, $NCH_2$), 65.9 (t, C-4), 70.8 (t, 8-$CH_2$), 71.5 (dq, $^2J_{(C,F)}$ = 30.0 Hz, C-1´), 76.6 (d, C-6), 79.7 (d, C-9), 124.6 (q, $^1J_{(C,F)}$ = 283.7 Hz, $CF_3$), 127.2, 128.2, 128.3 (3 d, Ph), 138.2 (s, Ph) ppm; $^{19}$F NMR (400 MHz, $CDCl_3$): δ = -77.0 (d, *J* = 6.9 Hz, $CF_3$) ppm; HRMS (ESI-TOF): *m/z* calcd for $C_{25}H_{43}F_3NO_5Si_2$ [*M* + H]$^+$: 550.2632; found: 550.2636; calcd for $C_{25}H_{42}F_3NNaO_5Si_2$ [*M* + Na]$^+$: 572.2451; found: 572.2458.

### 3.5.4 Synthesis of homoallylsubstituted bicyclic 1,2-oxazine and olefinmetathesis

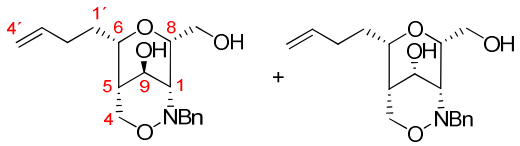
**(1*S*,5*R*,6*S*,8*S*)-2-Benzyl-6-(but-3´-enyl)-8-(hydroxymethyl)-3,7-dioxa-2-azabicyclo[3.3.1]-nonan-9-one (48a):**




Acetal **47** (83 mg, 199 µmol) was dissolved in acetonitrile (2 ml) and the solution was cooled to 0℃. At this temperature tin( IV) chloride (0.06 ml, 514 µmol) was added and the reaction mixture was stirred for 1 h. The reaction mixture was allowed to warm-up within 30 min and then quenched with brine solution (5 mL) and dichloromethane (5 mL) was added. The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 20:1, 15:1) to yield **48a** (32 mg, 51%) as yellow oil.

The compound is instable and was not characterized.

**(1*R*,5*S*,6*S*,8*S*,9*R*)-2-Benzyl-6-(but-3´-enyl)-8-(hydroxymethyl)-3,7-dioxa-2-azabicyclo-[3.3.1]-nonan-9-ol (49a) and (1*R*,5*S*,6*S*,8*S*,9*S*)-2-Benzyl-6-(but-3´-enyl)-8-(hydroxyl-methyl)-3,7-dioxa-2-azabicyclo[3.3.1]-nonan-9-ol (49b):**




Crude compound **48a** (96 mg, 303 µmol) was dissolved in ethanol (4.5 mL) and cooled to -30 ℃. Sodium borohydride (23 mg, 605 µmol) was added and the suspension was stirred for 3 h at -30 ℃. Then the solvent was removed in vacuo and the crude product was dissolved in dichloromethane (5 mL) and water (4 mL). The aqueous layer was extracted with dichloromethane (5 x 5 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1.5:1) to yield **49a** (92 mg, 95%) and **49b** (4 mg, 4%) as colorless solids.

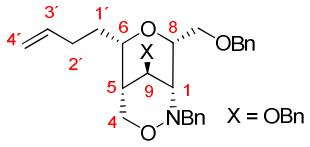
Major diastereomer **49a**:

m.p. 87-90 °C; $[\alpha]_D^{22}$= +37.4 (*c* = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.44-1.53 (m, 1 H, 1´-H), 1.80-1.89 (m, 2 H, 5-H, 1´-H), 2.05-2.14 (m, 1 H, 2´-H), 2.17-2.26 (m, 1 H, 2´-H), 2.79 ($s_{br}$, 1 H, OH), 3.03 (s, 1 H, 1-H), 3.56 (dd, *J* = 5.0, 8.4 Hz, 1 H, 6-H), 3.58, 3.67, 3.94 (ABM part of ABMX system, $J_{MX}$ = 1.2 Hz, $J_{AM}$ = 4.4 Hz, $J_{BM}$ = 6.2 Hz, $J_{AB}$ = 11.1 Hz, 3 H, 8-$CH_2$, 8-H), 3.80 ($s_{br}$, 1 H, 9-H), 4.02, 4.24 (AB part of ABX system, $J_{AX}$ = 2.6 Hz, $J_{BX}$ = 6.0 Hz, $J_{AB}$ = 12.0 Hz, 2 H, 4-H), 4.08, 4.20 (AB system, $J_{AB}$ = 14.0 Hz, 2 H, $NCH_2$), 4.97 (dd, *J* = 3.3, 10.2 Hz, 1 H, 4´-H), 5.02 (dd, *J* = 3.3, 17.0 Hz, 1 H, 4´-H), 5.79 (dd, *J* = 10.2, 17.0 Hz, 1 H, 3´-H), 7.24-7.28 (m, 1 H, Ph), 7.30-7.34 (m, 4 H, Ph) ppm; one OH could not be detected;$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 30.1 (t, C-2´), 32.0 (t, C-1´), 38.7 (d, C-5), 62.1 (t, d, $NCH_2$, C-1), 63.7 (t, 8-$CH_2$), 64.6 (t, C-4), 70.8 (d, C-9), 78.0 (d, C-6), 79.5 (d, C-8), 115.2 (t, C-4´), 127.5, 128.5, 128.7 (3 d, Ph), 137.4 (d, C-3´), 137.9 (s, Ph) ppm; IR (ATR): v = 3440 (O-H), 3055 (=C-H), 2960-2855 (C-H), 1640 (C=C), 1495 (C-H), 1265 (C-O) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{26}NO_4$ $[M + H]^+$: 320.1862; found: 320.1882; calcd for $C_{18}H_{25}NNaO_4$ $[M + Na]^+$: 342.1681; found: 342.1702.

Minor diastereomer **49b**:

m.p. 31-34 °C; $[\alpha]_D^{22}$= +39.5 (*c* = 0.40, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 1.80-1.86 (m, 2 H, 1´-H), 1.92 ($s_{br}$, 1 H, 5-H), 2.06-2.09 (m, 1 H, 2´-H), 2.13-2.18 (m, 1 H, 2´-H), 2.99 ($s_{br}$, 1 H, 1-H), 3.26 (dd, *J* = 2.4, 8.8 Hz, 1 H, 6-H), 3.55 (t, *J* = 2.7 Hz, 1 H, 9-H), 3.59, 3.66, 3.75 (ABX system, $J_{AX}$ = 2.3 Hz, $J_{BX}$ = 9.4 Hz, $J_{AB}$ = 12.4 Hz, 3 H, 8-H, 8-$CH_2$), 3.77-3.86 (m, 2 H, 4-H, OH), 4.01, 4.09 (AB system, $J_{AB}$ = 13.4 Hz, 2 H, $NCH_2$), 4.05-4.14 (m, 2 H, 4-H, OH), 4.17-4.22 (m, 1 H, 8-$CH_2$), 4.97 ($d_{br}$, *J* = 10.2 Hz, 1 H, 4´-H), 5.03 (dd, *J* = 1.4, 17.0 Hz, 1 H, 4´-H), 5.77 (dd, *J* = 10.2, 17.0 Hz, 1 H, 3´-H), 7.32-7.35 (m, 5 H, Ph) ppm; $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 31.4 (t, C-2´), 31.9 (t, C-1´), 38.3 (d, C-5), 56.0 (d, C-1), 61.2 (d, C-4), 62.3 (t, 8-$CH_2$), 62.8 (t, $NCH_2$), 71.1 (d, C-9), 78.1 (d, C-6), 78.5 (d, C-8), 115.4 (t, C-4´), 127.7, 128.4, 128.9 (3 d, Ph), 137.7 (d, C-3´), 137.8 (s, Ph) ppm; IR (ATR): v = 3445 (O-H), 3060-3030 (=C-H), 2955-2850 (C-H), 1455 (C-H), 1250 (C-O) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{26}NO_4$ $[M + H]^+$: 320.1862; found: 320.1849; calcd for $C_{18}H_{25}NNaO_4$ $[M + Na]^+$: 342.1681; found: 342.1675.

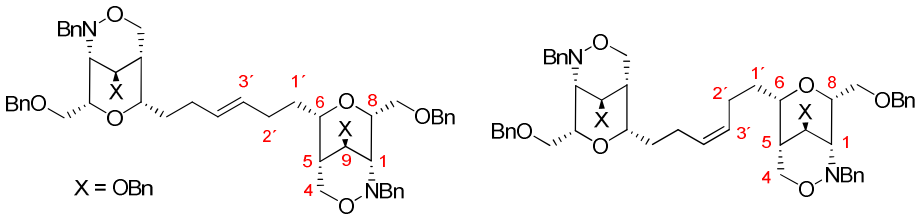
**(1*R*,5*R*,6*S*,8*S*,9*R*)-2-Benzyl-9-(benzyloxy)-8-(benzyloxymethyl)-6-(but-3´-enyl)-3,7-dioxa-2-azabicyclo[3.3.1]nonane (46):**




To a suspension of sodium hydride in mineral oil (33 mg, 60% NaH) in THF (3 mL) a solution of compound **49a** (89 mg, 279 µmol) in THF (2 mL) was added drop-wise at 0 °C. The reaction mixture was stirred for 1 h at rt and then cooled to 0 °C. Benzyl bromide (83 µL, 119 mg, 697 µmol) was added and the suspension was stirred for 18 h at rt. The reaction was quenched with methanol (1 mL) and the solvent was removed in vacuo. Water (5 mL) and ethyl acetate (10 mL) were added and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered through a pad of Celite® and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 20:1) to yield **46** (94 mg, 68%) as a colorless oil.

$[\alpha]_D^{22}$= +50.2 (*c* = 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.59-1.66 (m, 1 H, 1´-H), 1.83 ($m_c$, 1 H, 5-H), 2.00-2.06 (m, 1 H, 1´-H), 2.11-2.18 (m, 1 H, 2´-H), 2.26-2.33 (m, 1 H, 2´-H), 3.14 ($s_{br}$, 1 H, 1-H), 3.64 (t, *J* = 2.6 Hz, 1 H, 9-H), 3.71-3.83 (m, 4 H, 6-H, 4-H, 8-H, 8-$CH_2$), 3.96 (dd, *J* = 5.5, 7.7 Hz, 1 H, 8-$CH_2$), 4.37 (d, *J* = 13.9 Hz, 1 H, $NCH_2Ph$), 4.53, 4.60 (AB system, $J_{AB}$ = 11.7 Hz, 2 H, $OCH_2Ph$), 4.46-4.71 (m, 2 H, $OCH_2Ph$), 4.70 (d, *J* = 13.9 Hz, $NCH_2Ph$), 4.66 (d, *J* = 11.9 Hz, 1 H, 4-H), 5.00 (dd, *J* = 1.9, 10.2 Hz, 1 H, 4´-H), 5.06 (dd, *J* = 1.9, 17.1 Hz, 1 H, 4´-H), 5.85 (dd, *J* = 10.2, 17.1 Hz, 1 H, 3´-H), 7.22-7.25 (m, 1 H, Ph), 7.28-7.38 (m, 11 H, Ph), 7.41-7.46 (m, 3 H, Ph) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 30.2 (t, C-2´), 32.1 (t, C-1´), 36.4 (d, C-5), 55.5 (d, C-1), 57.6 (t, C-4), 58.4 (t, $NCH_2Ph$), 70.5 (t, $OCH_2Ph$), 70.7 (t, 8-$CH_2$), 73.7 (t, $OCH_2Ph$), 76.6 (d, C-9), 77.8, 78.4 (2 d, C-8, C-6), 115.0 (t, C-4´), 126.9, 127.4, 127.7, 127.8, 128.0, 128.2, 128.4, 128.6, 128.7 (9 d, Ph), 138.2 (d, C-3´), 138.21, 138.4, 139.0 (3 s, Ph) ppm; IR (ATR): v = 3020 (=C-H), 2980-2855 (C-H), 1465 (C-H), 1240 (C-O) cm$^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{32}H_{38}NO_4$ [*M* + H]$^+$: 500.2801; found: 500.2786; calcd for $C_{32}H_{37}NNaO_4$ [*M* + Na]$^+$: 522.2620; found: 522.2607.

**(*E*)-1´,6´-Bis[(1*R*,5*R*,6*S*,8*S*,9*R*)-2-benzyl-9-(benzyloxy)-8-(benzyloxymethyl)-3,7-dioxa-2-azabicyclo[3.3.1]nonan-6-yl]hex-3´-ene (50a) and (*Z*)-1´,6´-Bis[(1*R*,5*R*,6*S*,8*S*,9*R*)-2-benzyl-9-(benzyloxy)-8-(benzyloxymethyl)-3,7-dioxa-2-azabicyclo[3.3.1]nonan-6-yl]hex-3´-ene (50b):**




The benzyl-protected bicyclic compound **46** (94 mg, 188 µmol) was dissolved in degassed dichloromethane (1 mL). Grubbs II catalyst (5.3 mg, 6 µmol) was added to the reaction mixture and stirred for 3 h at 40 °C. Then another portion Grubbs II catalyst (5.3 mg, 6 µmol) was added to the solution and after 3 h at 40 °C a third portion Grubbs II catalyst (5.3 mg, 6 µmol) was added. The reaction mixture was stirred for further 18 h at 40 °C. Then the solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel, hexanes/EtOAc 4:1) to yield **50a** (17 mg, 19%), **50b** (8 mg, 9%) and **51** (11 mg, 12%) as yellowish oils.

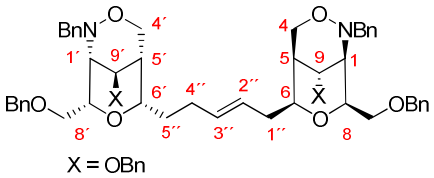
*E*-Isomer **50a**:

$[\alpha]_D^{22}$= +46.6 (*c* = 1.07, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.49-1.55 (m, 2 H, 1´-H), 1.78 ($m_c$, 2 H, 5-H), 1.90-1.97 (m, 2 H, 1´-H), 1.99-2.05 (m, 2 H, 2´-H), 2.14-2.18 (m, 2 H, 2´-H), 3.09 ($s_{br}$, 2 H, 1-H), 3.60 (t, *J* = 2.8 Hz, 2 H, 9-H), 3.65-3.69 (m, 2 H, 6-H), 3.71-3.76 (m, 4 H, 4-H, 8-$CH_2$), 3.90 (dd, *J* = 5.2, 7.5 Hz, 2 H, 8-$CH_2$), 4.32 (d, *J* = 13.9 Hz, 2 H, $NCH_2Ph$), 4.48, 4.56 (AB system, $J_{AB}$ = 11.7 Hz, 4 H, $OCH_2Ph$), 4.60-4.67 (m, 4 H, 4-H, 8-H), 4.62, 4.65 (AB system, $J_{AB}$ = 11.8 Hz, 2 H, $OCH_2Ph$), 4.65 (d, *J* = 13.9 Hz, 2 H, $NCH_2Ph$), 5.41 (t, *J* = 3.6 Hz, 2 H, 3´-H), 7.18-7.21 (m, 2 H, Ph), 7.24-7.34 (m, 20 H, Ph), 7.37-7.42 (m, 8 H, Ph) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 29.0 (t, C-1´), 32.8 (t, C-2´), 36.4 (d, C-5), 55.6 (d, C-1), 57.7 (t, C-4), 58.4 (t, $NCH_2Ph$), 70.6, 70.8 (2 t, $OCH_2Ph$, 8-$CH_2$), 73.7 (t, $OCH_2Ph$), 76.7 (d, C-9), 77.8 (d, C-6), 78.4 (d, C-8), 127.0, 127.4, 127.7, 127.9, 128.1, 128.2, 128.5, 128.7, 128.8 (9 d, Ph), 130.1 (d, C-3´), 138.3, 138.4, 139.0 (3 s, Ph) ppm; IR (ATR): v = 3090-3030 (=C-H), 2920-2850 (C-H), 1610 (C=C), 1495 (C-H), 1240 (C-O) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{62}H_{71}N_2O_8$ [*M* + H]$^+$: 971.5210; found: 971.5222; calcd for $C_{62}H_{70}N_2NaO_8$ [*M* + Na]$^+$: 993.5030; found: 993.5052.

*Z*-Isomer **50b**:

$[\alpha]_D^{22}$= +17.9 (*c* = 0.80, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.45-1.52 (m, 2 H, 1´-H), 1.17 ($m_c$, 2 H, 5-H), 1.90-1.97 (m, 2 H, 1´-H), 2.10-2.17 (m, 4 H, 2´-H), 3.08 ($s_{br}$, 2 H, 1-H), 3.57 (t, *J* = 2.6 Hz, 2 H, 9-H), 3.62-3.68 (m, 4 H, 4-H, 6-H), 3.70-3.75 (m, 4 H, 8-H, 8-$CH_2$), 3.90 (dd, *J* = 5.2, 7.3 Hz, 2 H, 8-$CH_2$), 4.30 (d, *J* = 13.9 Hz, 2 H, $NCH_2Ph$), 4.46, 4.53 (AB system, $J_{AB}$ = 11.7 Hz, 4 H, $OCH_2Ph$), 4.58-4.62 (m, 2 H, 4-H), 4.59, 4.62 (AB system, $J_{AB}$ = 11.7 Hz, 2 H, $OCH_2PH$), 4.65 (d, *J* = 13.9 Hz, 2 H, $NCH_2Ph$), 5.36 (t, *J* = 4.7 Hz, 2 H, 3´-H), 7.17-7.23 (m, 2 H, Ph), 7.23-7.33 (m, 20 H, Ph), 7.36-7.40 (m, 8 H, Ph) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 23.9 (t, C-1´), 33.0 (t, C-2´), 36.6 (d, C-5), 55.6 (d, C-1), 57.7 (t, C-4), 58.4 (t, $NCH_2Ph$), 70.5, 70.7 (2 t, $OCH_2Ph$, 8-$CH_2$), 73.7 (t, $OCH_2Ph$), 76.6 (d, C-9), 77.9 (d, C-6), 78.4 (d, C-8), 127.0, 127.4, 127.7, 127.9, 128.0, 128.2, 128.5, 128.7, 128.8 (9 d, Ph), 129.8 (d, C-3´), 138.3, 138.4, 139.0 (3 s, Ph) ppm; IR (ATR): v = 3085-3025 (=C-H), 2950-2850 (C-H), 1495 (C-H), 1240 (C-O) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{62}H_{71}N_2O_8$ [*M* + H]$^+$: 971.5210; found: 971.5257; calcd for $C_{62}H_{70}N_2NaO_8$ [*M* + Na]$^+$: 993.5030; found: 993.5085.

**(*E*,1*R*,1'*R*,5*R*,5'*R*,6*S*,6'*S*,8*S*,8'*S*,9*R*,9'*R*)-6,6'-(Pent-2´´-ene-1´´,5´´-diyl)bis[2-benzyl-9-(benzyloxy)-8-(benzyloxymethyl)-3,7-dioxa-2-azabicyclo[3.3.1]nonane] (51):**

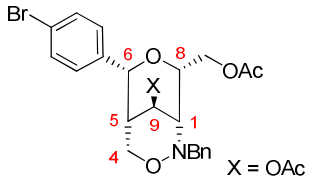



$[\alpha]_D^{22}$= +53.5 (*c* = 1.10, $CHCl_3$); $^1$H NMR (700 MHz, $CDCl_3$): δ = 1.52-1.57 (m, 1 H, 5´´-H), 1.79 ($m_c$, 1 H, 5-H), 1.85 ($m_c$, 1 H, 5-H´), 1.93-1.98 (m, 1 H, 4´´-H), 2.19-2.24 (m, 1 H, 4´´-H), 2.32-2.36 (m, 1 H, 1´´-H), 2.56-2.60 (m, 1 H, 1´´-H), 3.11 (s, 2 H, 1-H, 1-H´), 3.61 (t, *J* = 2.9, 2 H, 9-H, 9-H´), 3.66-3.69 (m, 1 H, 6-H), 3.69-3.81 (m, 5 H, 6-H´, 8-$CH_2$, 8-$CH_2$´, 4-H, 4-H´), 3.90-3.93 (m, 2 H, 8-$CH_2$, 8-$CH_2$´), 4.33 (d, *J* = 13.9 Hz, 1 H, $NCH_2Ph$), 4.34 (d, *J* = 13.8 Hz, 1 H, $NCH_2Ph$´) 4.506, 4.578 (AB system, $J_{AB}$ = 11.9 Hz, 2 H, $OCH_2Ph$), 4.508, 4.581 (AB system, $J_{AB}$ = 11. 7 Hz, 2 H, $OCH_2Ph$´), 4.61-4.68 (m, 4 H, 8-H, 8-H´, 4-H, 4-H´), 4.66 ($d_{br}$, *J* = 13.8 Hz, 2 H, $NCH_2Ph$, $NCH_2Ph$´), 5.39-5.43 (m, 1 H, 2´´-H), 5.49-5.53 (m, 1 H, 3´´-H), 7.21-7.23 (m, 2 H, Ph, Ph´), 7.27- 7.29 (m, 10, Ph, Ph´), 7.31-7.35 (m, 10, Ph, Ph´), 7.39-7.43 (m, 8 H, Ph, Ph´) ppm;. $^{13}$C NMR (175 MHz, $CDCl_3$): δ = 29.2 (t, C-4´´), 29.8 (t, C-5´´), 35.4 (d, C-5), 36.1 (t, C-1´´), 36.5 (d, C-5´), 55.55, 55.58, (2 d, C-1, C-1´), 57.4, 57.7 (2 t, C-4, C-4´), 58.38, 58.44 (2 t, $NCH_2Ph$, $NCH_2Ph$´), 70.55, 70.62, 70.77, 70.78 (4 t, $OCH_2Ph$, $OCH_2Ph$´, 8-$CH_2$, 8-$CH_2$´), 76.67, 76.68 (2 d, C-9, C-9´), 77.9, 78.47, 78.48, 78.52 (4 d, C-6, C-6´, C-8, C-8´), 126.3 (d, C-2´´), 126.99, 127.0, 127.43, 127.45, 127.7, 127.88, 127.90, 128.06, 128.09,

128.23, 128.23, 128.5, 128.68, 128.69, 128.7 (d 15, Ph, Ph´), 132.7 (d, C-3´´), 138.26, 138.27, 138.41, 138.43, 139.0, 139.4 (6 s, Ph, Ph´) ppm; signals for 3 d for Ph/Ph´ could not be detected; both bicyclic moietys could not be distinguished; IR (ATR): v = 3085-3030 (=C-H), 2960-2850 (C-H), 1645 (C=C), 1495 (C-H), 1240 (C-O) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{61}H_{69}N_2O_8$ $[M + H]^+$: 957.5054; found: 957.5092; calcd for $C_{61}H_{68}N_2NaO_8$ $[M + Na]^+$: 979.4873; found: 979.4925.

### 3.5.5 Sulfation of mono- and oligovalent carbohydrate mimetics

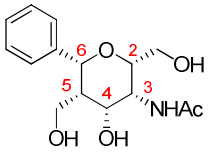
**[(1*R*,5*R*,6*R*,8*S*,9*R*)-9-Acetoxy-2-benzyl-6-(4-bromophenyl)-3,7-dioxa-2-azabicyclo[3.3.1]-nonan-8-yl]methyl acetate (52):**




Compound **22** (200 mg, 476 µmol) was dissolved in dichloromethane (4 mL). Acetic anhydride (146 mg, 135 µL, 1.43 mmol), DMAP (93 mg, 761 µmol) and pyridine (226 mg, 230 µL, 2.86 mmol) were added and the solution was stirred for 18 h at rt. Water (5 mL) was added to the mixture and the aqueous layer was extracted with dichloromethane (5 x 10 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 1:1) to yield **52** (240 mg, quant.) as a colorless solid.

m.p. 38-40°C; $[\alpha]_D^{22}$ = +43.9 (*c* = 0.80, $CHCl_3$); $^1$H NMR (500 MHz, $CD_3OD$): δ = 1.97 ($s_{br}$, 4 H, 5-H, Ac), 2.25 (s, 3 H, Ac), 3.09 ($m_c$, 1 H, 1-H), 3.37 (d, *J* = 12.2 Hz, 1 H, 4-H), 4.04-4.13 (m, 1 H, 8-H), 4.31, 4.46 (AB system, $J_{AB}$ = 13.5 Hz, 2 H, $NCH_2$), 4.32 (d, *J* = 12.2 Hz, 1 H, 4-H), 4.47 ($m_c$, 2 H, 8-$CH_2$), 4.98 ($s_{br}$, 1 H, 6-H), 5.14 (t, *J* = 2.6 Hz, 1 H, 9-H), 7.24-7.27 (m, 1 H, Ph), 7.30-7.33 (m, 6 H, Ar, Ph), 7.45-7.47 (m, 2 H, Ar) ppm; $^{13}$C NMR (125 MHz, $CD_3OD$): δ = 21.0 (q, Ac), 21.5 (q, Ac), 38.4 (d, C-5), 55.0 (d, C-1), 57.4 (t, C-4), 58.4 (t, $NCH_2$), 64.8 (t, 8-$CH_2$), 70.8 (d, C-9), 76.9 (d, C-8), 79.3 (d, C-6), 121.6 (s, Ar), 127.6, 128.0, 128.5, 128.8, 131.5 (5 d, Ar, Ph), 137.6, 138.4 (2 s, Ar, Ph), 170.1, 170.8 (2 s, Ac) ppm; IR (ATR): v = 3085-3030 (=C-H), 2930-2870 (C-H), 1740 (C=O), 1640 (NC=O), 1460 (C-H), 1230 (C-O) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{24}H_{26}BrNNaO_6$ $[M + Na]^+$: 526.0841; found: 526.0788; calcd for $C_{24}H_{26}BrKNO_6$ $[M + K]^+$: 542.0581; found: 542.0523; elemental analysis calcd (%) for $C_{24}H_{26}BrNO_6$ (504.4): C, 57.15; H, 5.20; N, 2.78; found: C, 57.14; H, 5.26; N, 2.77.

**_N_-[(2_S_,3_R_,4_R_,5_S_,6_R_)-4-Hydroxy-2,5-bis(hydroxymethyl)-6-phenyltetrahydro-2_H_-pyran-3-yl]acetamide (53):**



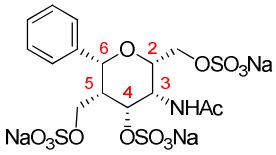

A suspension of Pd/C (10% Pd, 195 mg) and *i*PrOH (5 mL) was saturated with hydrogen for 15 min. Compound **52** (195 mg, 387 µmol) was dissolved in THF (2 mL) and added to the suspension. The mixture was stirred for 24 h under hydrogen atmosphere (balloon), filtered through a pad of Celite® and the solvent was removed in vacuo. The crude product was dissolved in $CH_3OH$ (2 mL) and sodium methoxide (23 mg, 425 µmol) was added. The reaction mixture was stirred for 18 h at rt and then DOWEX® 50WX8 (hydrogen form) was added until the solution had a pH of 1. The reaction was stirred for 5 min, the resin was filtered off, washed with $CH_3OH$ (15 mL) and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/$CH_3OH$ 15:1) to yield **53** (28 mg, 25%) as a colorless solid.

m.p. 74-76 °C; $[\alpha]_D^{22}$ = +98.0 (*c* = 0.74, $CH_3OH$); $^1$H NMR (700 MHz, $CD_3OD$): δ = 2.04 (s, 3 H, Ac), 2.23 ($m_c$, 1 H, 5-H), 3.34 ($m_c$, 1 H, 5-$CH_2$), 3.60, 3.69, 3.75 (ABX system, $J_{AX}$ = 5.6 Hz, $J_{BX}$ = 6.8 Hz, $J_{AB}$ = 11.6 Hz, 3 H, 2-H, 2-$CH_2$), 3.68-3.70 (m, 1 H, 5-$CH_2$), 4.29 (dd, *J* = 1.8, 4.8 Hz, 1 H, 3-H), 4.40 (dd, *J* = 4.8, 6.6 Hz, 1 H, 4-H), 4.79 (d, *J* = 3.7 Hz, 1 H, 6-H), 7.26-7.28 (m, 1 H, Ph), 7.35-7.37 (m, 2 H, Ph), 7.46-7.47 (m, 2 H, Ph) ppm; $^{13}$C NMR (175 MHz, $CD_3OD$): δ = 22.9 (q, Ac), 46.8 (d, C-5), 49.9 (d, C-3), 56.4 (t, 5-$CH_2$), 62.9 (t, 2-$CH_2$), 71.5 (d, C-4), 81.2 (d, C-2), 81.8 (d, C-6), 126.9, 128.0, 129.0 (3 d, Ph), 141.2 (s, Ph), 174.4 (s, Ac) ppm; IR (ATR): v = 3325-3260 (O-H, N-H), 3065 (=C-H), 2960-2850 (C-H), 1650 (NC=O), 1445 (C-H), 1265 (C-O) cm$^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{22}NO_5$ [*M* + H]$^+$: 296.1498; found: 296.1483; calcd for $C_{15}H_{21}NNaO_5$ [*M* + Na]$^+$: 318.1317; found: 318.1321; elemental analysis calcd (%) for $C_{15}H_{21}NO_5$ (295.3): C, 61.00; H, 7.17; N, 4.74; found: C, 59.76; H, 7.18; N, 4.65.

**General procedure for polysulfation of carbohydrate mimetics (GP):**

The carbohydrate mimetic (1 equiv.) was dissolved in deuterated DMF (0.7 mL) and sulfur trioxide-*N*,*N*-dimethylformamide complex (6 equiv. per aminopyrane unit) was added. The reaction mixture was stirred for 24 h at rt (completion of the reaction was determined by $^{1}$H NMR, 700 MHz) and then the reaction was quenched with 0.5 M sodium hydroxide solution until the solution reached a pH value of 8-9. The mixture was purified by dialyses (Roth, MWCO: 100-500).

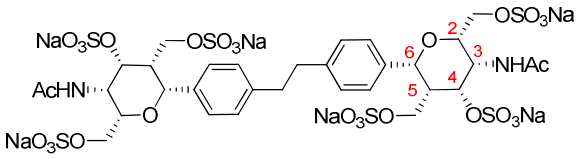
**Sulfated monovalent compound 54:**




According to the **GP**, compound **53** (20 mg, 68 µmol) was dissolved in deuterated DMF (0.7 mL) and sulfur trioxide-*N*,*N*-dimethylformamide complex (62 mg, 406 µmol) was added to yield **54** (12 mg, 29%) as colorless solid.

Decomposition > 210 °C; $[\alpha]_D^{22}$ = -21.8 (*c* = 0.40, $H_2O$); $^{1}$H NMR (700 MHz, $D_2O$): δ = 2.15 (s, 3 H, Ac), 2.85 ($m_c$, 1 H, 5-H), 3.80 (dd, *J* = 2.2, 10.1 Hz, 1 H, 5-$CH_2$), 4.16 (dd, *J* = 8.2, 12.5 Hz, 1 H, 2-$CH_2$), 4.20-4.25 (m, 3 H, 5-$CH_2$, 2-$CH_2$, 2-H), 4.64 ($m_c$, 1 H, 3-H), 5.03 (d, *J* = 3.3 Hz, 1 H, 6-H), 5.12 (dd, *J* = 5.0, 6.3 Hz, 1 H, 4-H), 7.38-7.40 (m, 1 H, Ph), 7.45-7.48 (m, 2 H, Ph), 7.50-7.51 (m, 2 H, Ph) ppm; $^{13}$C NMR (175 MHz, $D_2O$): δ = 22.3 (q, Ac), 42.3 (d, C-5), 46.7 (d, C-3), 61.9 (t, 5-$CH_2$), 67.5 (t, 2-$CH_2$), 74.8 (d, C-4), 76.3 (d, C-2), 79.3 (d, C-6), 126.0, 127.7, 128.4 (3 d, Ph), 137.7 (s, Ph) ppm; IR (ATR): v = 3435 (N-H), 3020 (=C-H), 2965-2855 (C-H), 1640 (C=O), 1455 (C-H) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{18}NNa_4O_{14}S_3$ [*M* + Na]$^+$: 623.9480; found: 623.9511; calcd for $C_{30}H_{36}N_2Na_7O_{28}S_6$ [2 *M* + Na]$^+$: 1224.9063; found: 1224.9125.

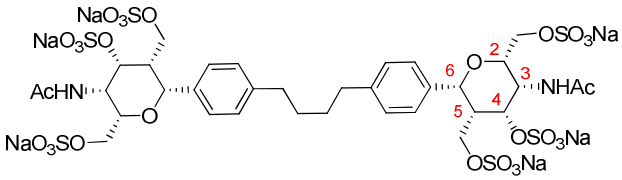
**Sulfated divalent carbohydrate mimetic 56:**




According to the **GP**, compound **55** (12 mg, 19 µmol) was dissolved in deuterated DMF (0.7 mL) and sulfur trioxide-*N*,*N*-dimethylformamide complex (36 mg, 234 µmol) was added to yield **56** (13 mg, 54%) as colorless solid.

Decomposition > 210 °C; $[\alpha]_D^{22}$ = -10.0 (*c* = 0. 40, $H_2O$); $^1$H NMR (700 MHz, $D_2O$): δ = 2.15 (s, 6 H, Ac), 2.81 ($m_c$, 2 H, 5-H), 2.96 ($m_c$, 4 H, $CH_2$), 3.81 (dd, *J* = 1.5, 10.2 Hz, 2 H, 5-$CH_2$), 4.15 (dd, *J* = 8.4, 14.5 Hz, 2 H, 2-$CH_2$), 4.19-4.23 (m, 6 H, 2-H, 2-$CH_2$, 5-$CH_2$), 4.63 ($m_c$, 2 H, 3-H), 4.99 (d, *J* = 2.7 Hz, 2 H, 6-H), 5.11 (dd, *J* = 4.8, 5.7 Hz, 2 H, 4-H), 7.33, 7.41 (2 d, *J* = 7.7 Hz, 8 H, Ar) ppm; $^{13}$C NMR (175 MHz, $D_2O$): δ = 22.3 (q, Ac), 37.1 (t, $CH_2$), 42.4 (d, C-5), 46.7 (d, C-3), 62.0 (t, 5-$CH_2$), 67.4 (t, 2-$CH_2$), 74.8 (d, C-4), 76.3 (d, C-2), 79.5 (d, C-6), 126.1, 128.5 (2 d, Ar), 135.2, 141.9 (2 s, Ar) ppm; IR (ATR): v = 3380 (N-H), 2915-2845 (C-H), 1640 (NC=O), 1455 (C-H), 1220 (C-O) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{32}H_{38}N_2Na_7O_{28}S_6$ [*M* + Na]$^+$: 1250.9219; found: 1250.9205.

**Sulfated divalent carbohydrate mimetic 58:**

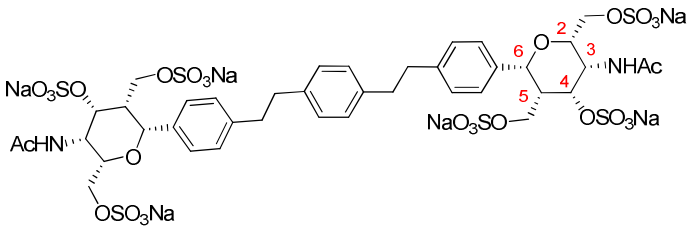



According to the **GP**, compound **57** (10 mg, 16 µmol) was dissolved in deuterated DMF (0.7 mL) and sulfur trioxide-*N*,*N*-dimethylformamide complex (28 mg, 186 µmol) was added to yield **58** (16 mg, 82%) as colorless solid.

Decomposition: > 215°C; $[\alpha]_D^{22}$ = +6.8 (*c* = 0.80, $H_2O$); $^1$H NMR (700 MHz, $D_2O$): δ = 1.69 ($m_c$, 4 H, $CH_2$), 2.15 (s, 6 H, Ac), 2.70 ($m_c$, 4 H, $CH_2$), 2.81 ($m_c$, 2 H, 5-H), 3.81 (dd, *J* = 2.4, 10.1 Hz, 2 H, 5-$CH_2$), 4.15 ($m_c$, 2 H, 2-$CH_2$), 4.20-4.24 (m, 6 H, 2-H, 2-$CH_2$, 5-$CH_2$), 4.63 ($m_c$, 2 H, 3-H), 4.99 (d, *J* = 3.3 Hz, 2 H, 6-H), 5.12 (dd, *J* = 5.0, 6.3 Hz, 2 H, 4-H), 7.32, 7.41 (2 d, *J* = 8.0 Hz, 8 H, Ar) ppm; $^{13}$C NMR (175 MHz, $D_2O$): δ = 22.3 (q, Ac), 30.4, 34.5 (2 t, $CH_2$),

42.4 (d, C-5), 46.7 (d, C-3), 61.9 (t, 5-$CH_2$), 67.4 (t, 2-$CH_2$), 74.8 (d, C-4), 76.3 (d, C-2), 79.5 (d, C-6), 126.0, 128.4 (2 d, Ar), 134.9, 142.8 (2 s, Ar), 174.6 (s, Ac) ppm; IR (ATR): v = 3420 (N-H), 2930-2850 (C-H), 1645 (NC=O), 1460 (C-H) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{34}H_{42}N_2Na_7O_{28}S_6$ [*M* + Na]$^+$: 1278.9532; found: 1278.9518.

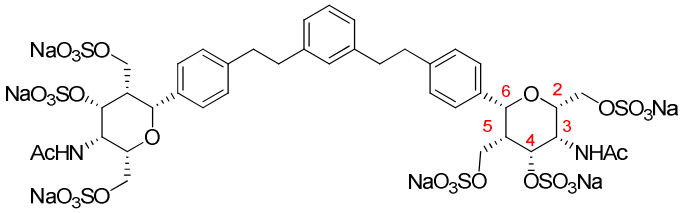
**Sulfated divalent carbohydrate mimetic 60:**




According to the **GP**, compound **59** (8 mg, 11 µmol) was dissolved in deuterated DMF (0.7 mL) and sulfur trioxide-*N*,*N*-dimethylformamide complex (20 mg, 133 µmol) was added to yield **60** (8 mg, 54%) as colorless solid.

Decomposition > 230 °C; $[\alpha]_D^{22}$ = +20.8 (*c* = 0.50, $H_2O$); $^1$H NMR (700 MHz, $D_2O$): δ = 2.16 (s, 6 H, Ac), 2.80 ($m_c$, 2 H, 5-H), 2.88-2.93 (m, 4 H, $CH_2$), 2.94-2.99 (m, 4 H, $CH_2$), 3.79 (dd, *J* = 2.6, 10.1 Hz, 2 H, 5-$CH_2$), 4.14-4.17 (m, 2 H, 2-$CH_2$), 4.20-4.24 (m, 6 H, 2-H, 5-$CH_2$, 2-$CH_2$), 4.64 ($m_c$, 2 H, 3-H), 4.99 (d, *J* = 3.5 Hz, 2 H, 6-H), 5.12 (dd, *J* = 5.1, 6.4 Hz, 2 H, 4-H), 7.17 (s, 4 H, Ar), 7.27, 7.39 (2 d, *J* = 8.0 Hz, 8 H, Ar) ppm; $^{13}$C NMR (175 MHz, $D_2O$): δ = 22.3 (q, Ac), 36.7, 37.9 (2 t, $CH_2$), 42.4 (d, C-5), 46.7 (d, C-3), 61.9 (t, 5-$CH_2$), 67.4 (t, 2-$CH_2$), 74.8 (d, C-4), 76.3 (d, C-2), 79.5 (d, C-6), 125.9, 128.6, 128.7 (3 d, Ar), 135.2, 139.7, 141.7 (3 s, Ar), 174.6 (s, Ac) ppm; IR (ATR): v = 3450 (N-H), 3070 (=C-H), 2960-2855 (C-H), 1645 (NC=O), 1460 (C-H) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{40}H_{46}N_2Na_7O_{28}S_6$ [*M* + Na]$^+$: 1354.9845; found: 1354.9853.

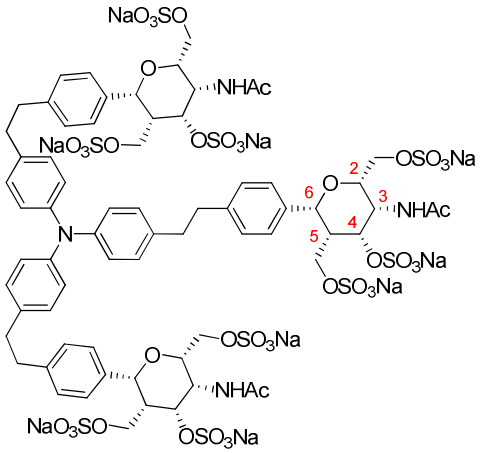
**Sulfated divalent carbohydrate mimetic 62:**




According to the **GP**, compound **61** (10 mg, 14 µmol) was dissolved in deuterated DMF (0.7 mL) and sulfur trioxide-*N*,*N*-dimethylformamide complex (25 mg, 166 µmol) was added to yield **62** (15 mg, 81%) as colorless solid.

Decomposition > 200 °C; $[\alpha]_D^{22}$ = -7.3 (*c* = 0.40, $H_2O$); $^1$H NMR (700 MHz, $D_2O$): δ = 2.15 (s, 6 H, Ac), 2.79 ($m_c$, 2 H, 5-H), 2.88-2.97 (m, 8 H, $CH_2$), 3.79 (dd, *J* = 2.5, 10.2 Hz, 2 H, 5-$CH_2$), 4.14 ($m_c$, 2 H, 2-$CH_2$), 4.19-4.21 (m, 6 H, 2-H, 5-$CH_2$, 2-$CH_2$), 4.63 ($m_c$, 2 H, 3-H), 4.98 (d, *J* = 3.3 Hz, 2 H, 6-H), 5.11 (dd, *J* = 5.3, 6.2 Hz, 2 H, 4-H), 7.03-7.04 (m, 1 H, Ar), 7.14 (s, 2 H, Ar), 7.20-7.22 (m, 1 H, Ar), 7.26, 7.39 (2 d, *J* = 7.9 Hz, 8 H, Ar) ppm; $^{13}$C NMR (175 MHz, $D_2O$): δ = 22.3 (q, Ac), 36.96, 37.03 (2 t, $CH_2$), 42.3 (d, C-5), 46.7 (d, C-3), 61.9 (t, 5-$CH_2$), 67.4 (t, 2-$CH_2$), 74.8 (d, C-4), 76.3 (d, C-2), 79.5 (d, C-6), 126.0, 126.3, 126.5, 128.6, 129.0 (5 d, Ar), 129.9, 135.2, 142.3 (3 s, Ar), 170.6 (s, Ac) ppm; IR (ATR): v = 3280 (N-H), 3070 (=C-H), 2960-2850 (C-H), 1640 (NC=O), 1455 (C-H) cm$^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{40}H_{46}N_2Na_7O_{28}S_6$ [*M* + Na]$^+$: 1354.9845; found: 1354.9887.

**Sulfated trivalent carbohydrate mimetic 64:**




According to the **GP**, compound **63** (10 mg, 8 µmol) was dissolved in deuterated DMF (0.7 mL) and sulfur trioxide-*N*,*N*-dimethylformamide complex (23 mg, 149 µmol) was added to yield **64** (8 mg, 45%) as yellowish solid.

Decomposition > 205 °C; $[\alpha]_D^{22}$ = -25.5 (*c* = 0.20, $H_2O$); $^1$H NMR (700 MHz, $D_2O$): δ = 2.15 (s, 9 H, Ac), 2.79 ($m_c$, 3 H, 5-H), 2.90-2.99 (m, 6 H, $CH_2$), 3.04-3.19 (m, 6 H, $CH_2$), 3.77 (d, *J* = 9.9 Hz, 3 H, 5-$CH_2$), 4.15-4.23 (m, 12 H, 5-$CH_2$, 2-H, 2-$CH_2$), 4.64 ($m_c$, 3 H, 3-H), 3.77 (dd, *J* = 1.7, 9.9 Hz, 3 H, 6-H), 5.12 (dd, *J* = 4.8, 6.3 Hz, 3 H, 4-H), 7.02, 7.22 (2 d, *J* = 7.9 Hz, 12 H, Ar), 7.32, 7.41 (2 d, *J* = 7.8 Hz, 12 H, Ar) ppm; $^{13}$C NMR (175 MHz, $D_2O$): δ = 22.3 (q, Ac), 36.5, 37.1 (2 t, $CH_2$), 42.4 (d, C-5), 46.7 (d, C-3), 61.9 (t, 5-$CH_2$), 67.4 (t, 2-$CH_2$), 74.8 (d, C-4), 76.3 (d, C-2), 79.5 (d, C-6), 123.8, 126.0, 128.5, 129.6 (4 d, Ar), 135.2, 136.9, 141.8, 145.9 (s, Ar), 174.6 (s, Ac) ppm; IR (ATR): v = 3350 (O-H), 3035 (=C-H), 2920-2850 (C-H), 1640 (C=O), 1460 (C-H) $cm^{-1}$; HRMS (ESI-TOF): *m/z* calcd for $C_{69}H_{75}N_4Na_{11}O_{42}S_9$ [*M* + 2Na]$^+$: 1086.0109; found: 1086.0066.

# 4 Ergebnisse aus Kooperationen mit Gruppen aus dem SFB 765

### 4.1.1 Kooperation mit der AG Schlecht:

Die Aminopyrane **71**, **72**, **73** und **74** wurden der Arbeitsgruppe Schlecht (Justus-Liebig-Universität Gießen) zur Anbindung an Goldnanopartikel und deren Testung als Selektininhibitoren bereitgestellt (Abbildung 13). Die Aminopyrane konnten durch Amidbindung erfolgreich an 7 nm große Goldnanopartikel gebunden und anschließend sulfatiert werden (Schema 29). Es wurden zwei mit Aminopyranen funktionalisierte Nanopartikel bezüglich L-Selektin getestet.

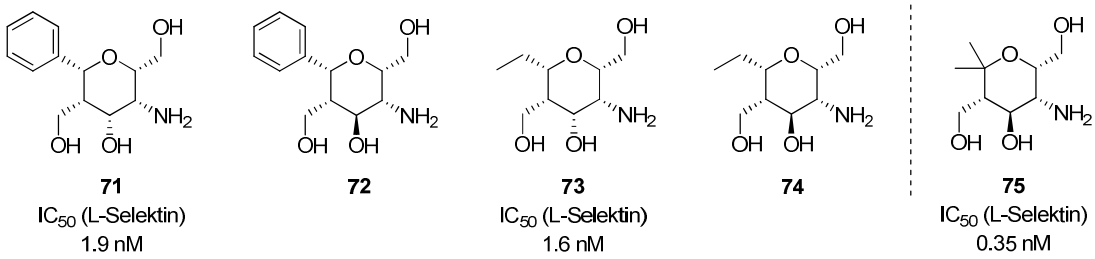
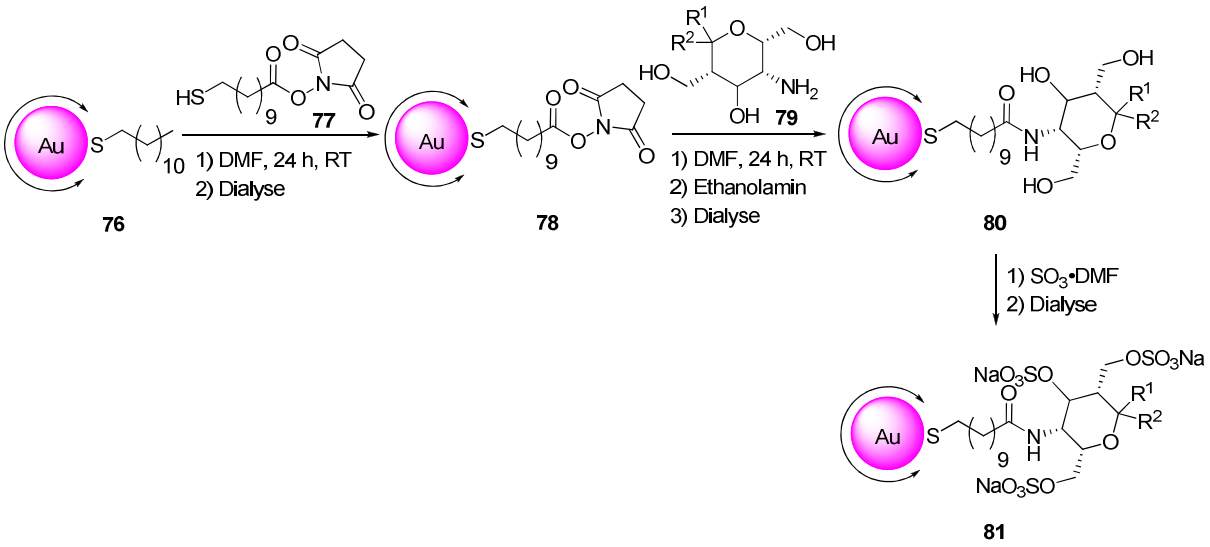



Abbildung 13: Aminopyrane, die zur Anbindung auf Goldnanopartikel zur Verfügung gestellt wurden.

Die mit Aminopyran **71** funktionalisierten Goldnanopartikel ergaben bezüglich L-Selektin einen $IC_{50}$-Wert von 1.90 nM und mit Aminopyran **73** funktionalisiert einen $IC_{50}$-Wert von 1.60 nM. Dies entspricht einer hohen Affinität, ist aber im Vergleich zu dem mit dimethylsubstituiertem Aminopyran funktionalisierten Goldnanopartikeln **75** mit einen $IC_{50}$-Wert von 0.35 nM eher als gering zu bewerten. Da die Aminopyran funktionalisierten Goldnanopartikel **72** und **74** (D-Idose Konfiguration wie in Aminopyran **75**) bisher noch nicht getestet wurden, ist es schwierig, Aussagen bezüglich der Struktur-Wirkungs-Beziehung zu treffen. Die mit den neu getesteten Aminopyranen ermittelte, schwächere Bindungsaffinität kann sowohl durch die neuen Substituenten verursacht werden, aber auch durch die veränderte Konfiguration der Aminopyrane **71** und **73** bedingt sein.[55] Eine fundierte Bewertung ist beim gegenwärtigen Bearbeitungsstand daher nicht möglich.




Schema 29: Anbindung und Sulfatierung der Aminopyrane **79** an Goldnanopartikel.

### 4.1.2 Kooperation mit der AG Rademacher

Das Aminopyran **71** wurde der Arbeitsgruppe Rademacher zu Verfügung gestellt, um dessen Bindungsvermögen hinsichtlich dem C-Typ-Lektin Langerin zu testen. Langerin bindet spezifisch Mannose und spielt eine entscheidende Rolle in der Bildung von Birbeck-Granules im menschlichen Körper.[56] Als Messmethode wurde hierbei die STD-NMR-Technik verwendet, um mögliche Ligand-Protein Wechselwirkungen zu studieren. In den Untersuchungen konnte keine spezifische Affinität des Aminopyrans **71** bezüglich des Langerins nachgewiesen werden.

# 5 Diskussion und Ausblick

Hochfunktionalisierte 1,2-Oxazine sind flexibel einsetzbare Bausteine, die sich hervorragend zur Synthese von enantiomerenreinen Kohlenhydratmimetika eignen. Erste Untersuchungen zu Herstellung dieser Startmaterialien wurden bereits in meiner Masterarbeit beschrieben.[38] Für eine effektive Bereitstellung dieser Synthesebausteine in für präparative Arbeiten ausreichenden Mengen war es jedoch erforderlich, die Synthese hinsichtlich ihrer Ausbeuten und der Schutzgruppenstrategie zu optimieren. Die Ergebnisse der vorliegenden Arbeit belegen, dass es gelungen ist, *para*-bromphenyl- und vinylsubstituierte 1,2-Oxazine mit reduzierter Anzahl an Syntheseschritten bei minimaler Zahl von Schutzgruppen darzustellen. So konnte zum Beispiel das *para*-bromphenylsubstituierte 1,2-Oxazin in sechs Schritten in einer guten Gesamtausbeute von 46% erhalten werden. Erstmals wurde ein homoallylsubstituiertes 1,2-Oxazin dargestellt, Lewis-Säure-induziert umgelagert und erfolgreich durch Selbst-Kreuzmetathese zum „Homodimer“ umgesetzt.

Des Weiteren konnten erfolgreich sechs monovalente Produkte mit verschiedenen, für biologische Untersuchungen interessanten Substituenten erhalten werden, die zum Teil der AG Schlecht zur Anbindung an Goldnanopartikel, Sulfatierung und Testung als Selektininhibitoren zur Verfügung gestellt wurden. Die AG Rademacher testete eines der Aminopyrane auf spezifische Affinität bezüglich des Lektins Langerin. Durch die im Kapitel 3.1 beschriebene, erfolgreiche Synthese des *para*-bromphenylsubstituierten bicyclischen 1,2-Oxazins könnten in Zukunft weitere Aminopyrane dargestellt werden. Durch die umfangreiche Verfügbarkeit von kommerziell erhältlichen Boronsäuren (für Suzuki-Reaktionen), Alkinen (für Sonogashira-Reaktionen) und von Aminen (für Buchwald-Hartwig-Reaktionen) eröffnen sich daher vielfältige Möglichkeiten für Kreuz-Kupplungsreaktionen an diesem Substrat. Darüber hinaus kann zusätzlich die Aminofunktion des Aminopyrans modifiziert werden (z. B. durch reduktive Aminierung oder Diazo-Transfer).

Einen ebenso bemerkenswerten, neuen Baustein stellt das im Kapitel 3.3 beschriebene, vinylsubstituierte bicyclische 1,2-Oxazin dar, aus dem bisher zwei verschiedene Monosaccharidmimetika erhalten wurden. Dieses bicyclische 1,2-Oxazin ermöglicht eine Vielzahl von weiteren Modifikationen, wie zum Beispiel durch Olefinmetathese mit verschiedenen alkensubstituierten Substraten, durch Dihydroxylierung, Epoxidierung oder Ozonoylse. Es ist auch denkbar, dass sich das Produkt zu einer multivalenten Kette polymerisieren lässt.

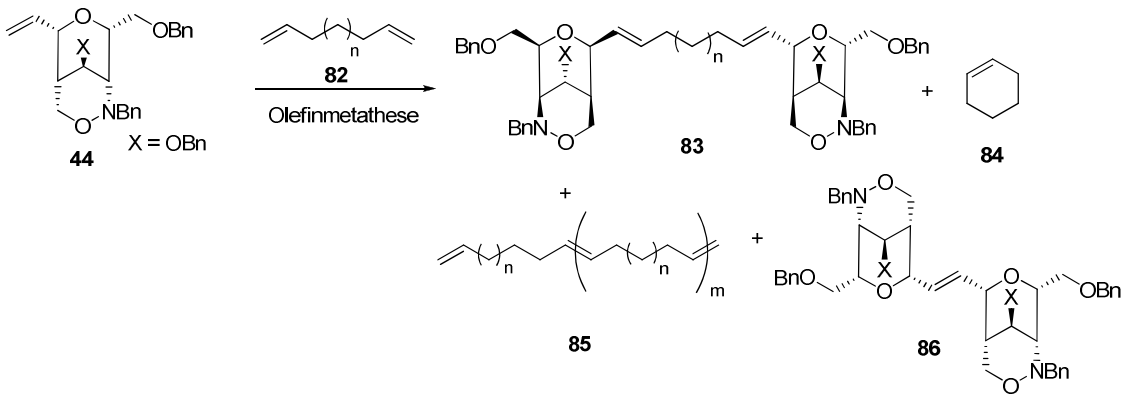
Neben diesen Synthesen konnten drei unterschiedliche Methoden zur Synthese von oligovalenten Kohlenhydratmimetika entwickelt werden:

Die im Kapitel 3.1 diskutierte Darstellung von *C*-Aryldimeren durch Suzuki-Kreuz-Kupplung als Schlüsselschritt ist eine interessante Methode für die Synthese besonders rigider Verbindungen. Diese Verbindungen könnten attraktive Wirkstoffe darstellen, da sie durch ihre Rigidität keine großen Entropieverluste beim Binden an Rezeptoren erzeugen. Jedoch führt diese Steifheit zu zusätzlichen Problemen, wie zum Beispiel einer schlechteren Löslichkeit, wodurch weiterführende Synthesen nur eingeschränkt möglich sind. Die begrenzte Löslichkeit, insbesondere in wässrigen Medien, limitiert auch deren Einsatz in biologischen Systemen. Ein weiterer, interessanter Ansatz für neue Synthesen bietet die Verwendung von aliphatischen Oligoboronsäurederivaten. Beim gegenwärtigen Entwicklungsstand müssten hierfür jedoch noch geeignete Bedingungen gefunden werden, um diese flexibleren Derivate reproduzierbar darzustellen.

Das Kapitel 3.2 behandelt die Synthese von interessanten, funktionalisierten Aminopyranen und oligovalenten Kohlenhydratmimetika, die durch Sonogashira-Kupplung mit geeigneten Linkern verknüpft wurden. Diese Methode ist sehr flexibel, reproduzierbar und liefert hohe Ausbeuten. Durch die große Anzahl an kommerziell erhältlichen Oligohalogenphenyl-derivaten bzw. die Möglichkeit Halogene leicht in Aromaten einzuführen die als Linkereinheit fungieren können, ist diese Methode exzellent geeignet, um verschiedene, weitere Derivate variabler Struktur darzustellen.

Zudem könnte das *para*-bromphenylsubstituierte bicyclische 1,2-Oxazin auch für andere Kreuz-Kupplungen, wie zum Beispiel Buchwald-Hartwig-Kupplungen mit geeigneten Aminlinkern, Stille-Kupplungen mit Stannan-Alkylverbindungen oder Heck-Kupplungen mit aktivierten Olefinen, eingesetzt werden.

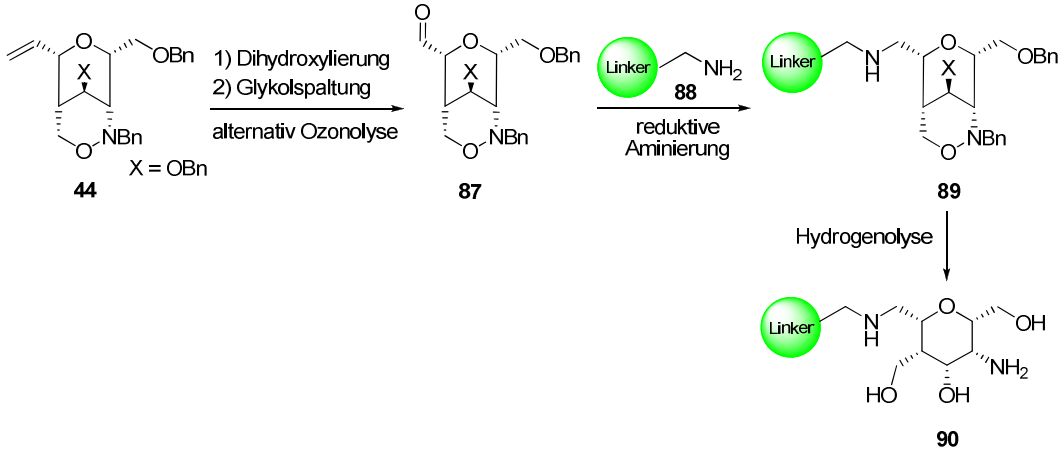
Durch Olefinmetathese des vinylsubstituierten bicyclischen 1,2-Oxazins, die im Kapitel 3.3 diskutiert wird, konnte erfolgreich ein interessantes *C*-Aminodissacharid dargestellt werden. Die angewandte Methode weist allerdings bisher nur eine geringe Variabilität auf. Es wäre ebenfalls denkbar, ein 1,n-Dien wie Verbindung **82** einzusetzen (Schema 30), wobei jedoch ein großer Überschuss an vinylsubstituierten bicyclischen 1,2-Oxazin **44** notwendig wäre, um einen vollständigen Umsatz der Olefineinheiten von **82** zu Produkt **71** zu gewährleisten und mögliche Nebenprodukte, wie **83**, **84**, **85** und **86**, durch Homokupplungen zu vermeiden.




Schema 30: Olefinmetathese des vinylsubstituierten bicyclischen 1,2-Oxazin **44** mit dem 1,n-Dien **82** und mögliche Nebenprodukte.

Zudem konnte, wie im Kapitel 3.4 beschrieben, die Synthese eines homoallylsubstituierten bicyclischen 1,2-Oxazins und dessen Homodimerisierung zu Pseudodisacchariden mit einer C-6-Kette als Linker durch Olefinmetathese bis zur „Dimerisierung“ erfolgreich durchgeführt werden. Hier sind allerdings weiterführende Arbeiten notwendig, um die Synthese zu optimieren und abzuschließen.

Eine Alternative zur Olefinmetathese bietet sich mit einer Überführung des vinylsubstituierten bicyclische 1,2-Oxazin **44** durch Dihydroxylierung mit anschließender Glykolspaltung in den entsprechenden Aldehyd **87** (Schema 31). Der entsprechende Aldehyd **87** könnte dann mit einem Linker mit oligovalenten Aminen **88** durch reduktive Aminierung und anschließende Hydrogenolyse zu oligovalent funktionalisierten Kohlenhydratmimetika **90** übergeführt werden.




Schema 31: Darstellung von oligovalenten Kohlenhydratmimetika **90** durch reduktive Aminierung als Schlüsselschritt.

Die in der Arbeit neu synthetisierten, sulfatierten oligovalenten Kohlenhydratmimetika (siehe ausgewählte Beispiele in Abbildung 14) sollen nachfolgend auf ihre Bindungsaffinität bezüglich L-, E- und P-Selektin getestet werden und wurden für diese Untersuchungen der Arbeitsgruppe Dernedde/Tauber zu Verfügung gestellt. Anschließend könnten Rückschlüsse

über die Struktur-Wirkungs-Beziehungen gezogen werden, was die gezielte Synthese von verbesserten Derivaten ermöglichen sollte.

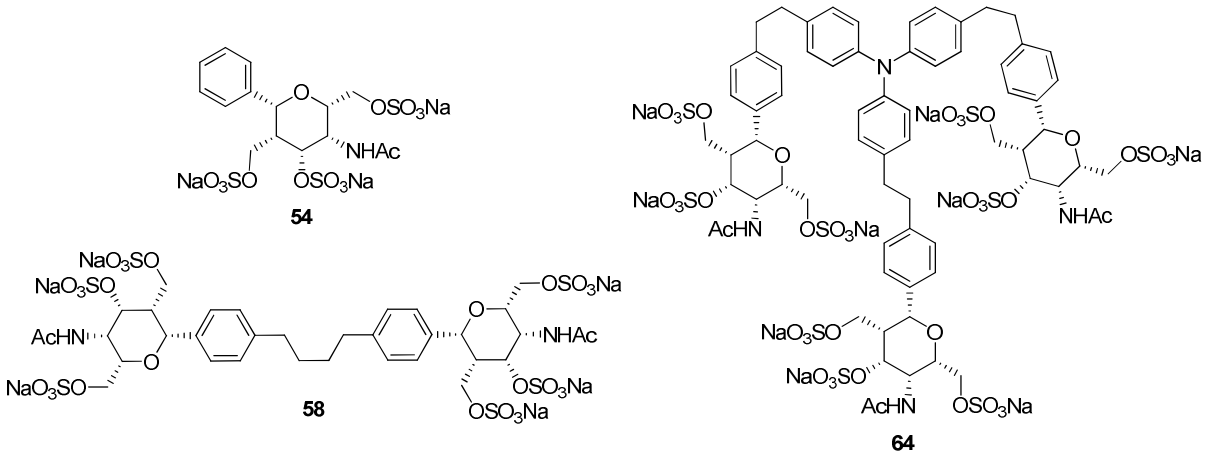



Abbildung 14: Ausgewählte Beispiele für sulfatierte Kohlenhydratmimetika, die auf ihre Bindungsaffinität bezüglich L-, P- und E-Selektin getestet werden.

Basis der Bewertung dieser neu synthetisierten Kohlenhydratmimetika bilden Vergleichsdaten von Bindungsaffinitäten bereits untersuchter Kohlenhydratmimetika.[36, 43] Als wesentliche Unterschiede zu z. B. von Salta bereits untersuchten Verbindungen wurden die folgenden strukturellen Änderungen vorgenommen (Abbildung 15):

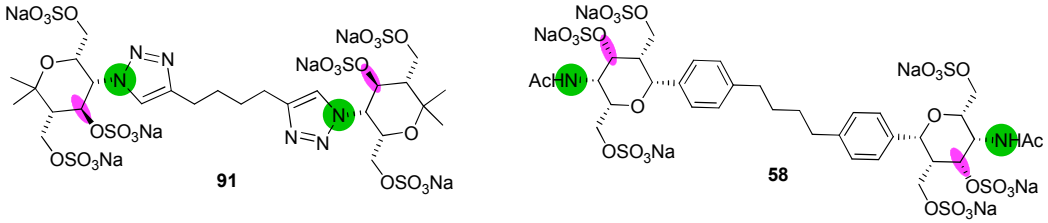


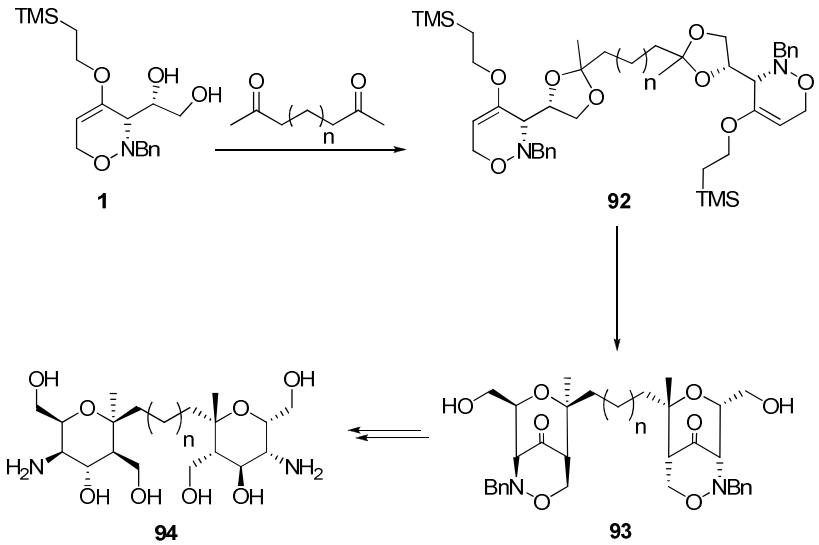

Abbildung 15: Beispiele für Kohlenhydratmimetika, die in der Arbeitsgruppe Reißig synthetisiert wurden. Links: Verbindung **91**, synthetisiert von Joana Salta. Rechts: Verbindung **58**, dargestellt in dieser Arbeit.

- Einerseits weisen die hier synthetisierten Aminopyrane (wie z.B. in Verbindung **58**) im Gegensatz zu den bereits untersuchten D-Idose-Analoga (wie z.B. in Verbindung **91**) eine D-Talose Konfiguration auf.
- Zum anderen besitzt das Pseudodisaccharid **58** durch das Acetylamin eine weitere bifunktionelle Gruppe, die zusätzlich Wasserstoffbrückenbindungen ausbilden kann.
- Ein weiterer Unterschied besteht in der chemischen Struktur des Linkers. Die in dieser Arbeit hergestellten Kohlenhydratmimetika besitzen entweder einen aliphatischen oder einen aromatischen Linker, die hydrophobe Wechselwirkungen eingehen können, während die von Salta verwendeten Triazol-Linker als Amidmimetika[57] betrachtet werden können, da sie ähnliche physikalische Eigenschaften haben wie Amide und somit zusätzliche Wasserstoffbrückenbindungen ausbilden können. Durch die

zusätzliche geminale Dimethylgruppierung dieser Aminopyrane sind auch hier hydrophobe Wechselwirkungen möglich.

- Die Anzahl der funktionellen Gruppen (wie z.B. je sechs Sulfatgruppen pro Molekül), die Wechselwirkungen mit dem Selektin eingehen können, ist gleich, aber die Anordnung der Gruppen ist unterschiedlich. Es wäre somit besonders interessant, diesen Effekt der unterschiedlichen Anordnung mit Oberflächen-plasmonenresonanzspektroskopie zu untersuchen.

Weitere erfolgversprechende Möglichkeiten zur Darstellung von oligovalenten Kohlenhydrat-mimetika könnten sich über eine Ketalbildung des literaturbekannten Diols **1**[58] mit Linkern ergeben, die mit oligovalenten Ketonen funktionalisiert sind (Schema 30). In der Arbeitsgruppe konnte schon anhand mehrerer Beispiele gezeigt werden (siehe Kapitel 3.3), dass unterschiedliche 1,3-dioxolanyl-substituierte 1,2-Oxazine mit dieser Methode erfolgreich dargestellt werden können. Auf diesem Syntheseweg sollte es möglich sein, durch die Wahl von Linkern mit unterschiedlicher Anzahl an Keto-Gruppen und der Linkerlänge eine Vielzahl an oligovalenten Kohlenhydratmimetika nach einem einheitlichen Syntheseprinzip darzustellen und deren Struktur gezielt zu variieren. In der AG Reißig wurde bereits die Lewis-Säure-induzierte Umlagerung von dialkyl-1,3-dioxolanyl-substituierten 1,2-Oxazinen mit hohem Umsatz beschrieben. Auch die stereoselektive Reduktion der Carbonylgruppe und die Hydrogenolyse zur N-O-Spaltung und Debenzylierung des dimethyl-1,3-dioxolanyl-substituierten Bicyclus verlaufen in hohen Ausbeuten[33, 35] und sollten ähnlich erfolgreich auf das Pseudodimer **94** übertragbar sein.




Schema 32: Vorgeschlagene Syntheseroute zur Darstellung divalenter Kohlenhydratmimetika **94** unter Verwendung von 1,3-dioxolanyl-substituierten 1,2-Oxazinen.

Bei dieser Reaktion können bei der Lewis-Säure-induzierten Umlagerung bis zu drei Stereoisomeren entstehen (Abbildung 16). Sollte es keine Selektivität bezüglich eines der

Stereoisomeren geben, werden die Produkte in einen statistischen Verhältnis von 2:1:1 gebildet.

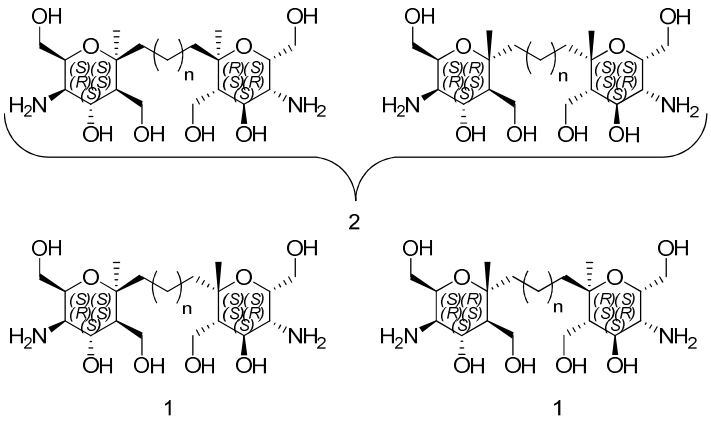
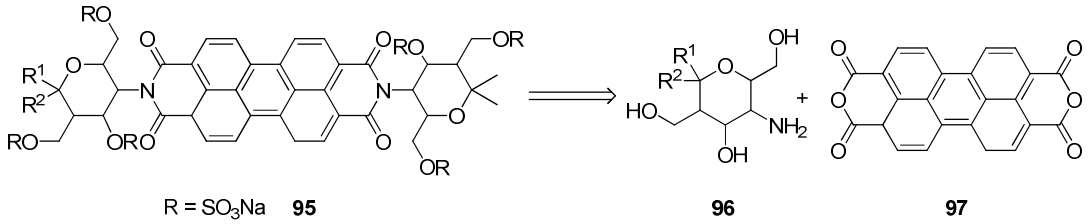


Abbildung 16: Mögliche Stereoisomere der in Schema 31 beschriebenen Reaktion.

Um zukünftig mit möglichst geringem synthetischen Aufwand höher multivalente Systeme zu erhalten, könnte man die bereits synthetisierten Aminopyrane und Aminooxepane der Arbeitsgruppe Reißig auch mit 3,4,9,10-Perylentetracarbonsäuredianhydrid **97** über Amidbindungen verknüpfen (Schema 33). Aus der Literatur ist bekannt, dass durch den besonders rigiden, hydrophoben Kern Perylene dreidimensionale supramolekulare Strukturen ausbilden.[59] Diese werden durch π-π-Wechselwirkungen zwischen den Peryleneinheiten gebildet und führen zu zylinderartigen Systemen. Der zu erwartende Vorteil dieser Form gegenüber globulären Systemen, wie Nanopartikeln oder Dendrimeren besteht darin, dass Bindungsstellen (wie z.B. bei Selektinen), die sich auf einer Fläche befinden, effektiver abgedeckt und gebunden werden können. In einem Vorversuch wurde ein Aminooxepan erfolgreich an 3,4,9,10-Perylentetracarbonsäuredianhydrid **97** gebunden. Das Produkt war trotz des rigiden Kernstücks sowohl in Wasser als auch in DMSO löslich.



Schema 33: Vorgeschlagener Syntheseweg zur Darstellung von multivalenten Kohlenhydratmimetika **95** aus Aminopyranen **96** bzw. Aminooxepanen mit 3,4,9,10-Perylentetracarbonsäuredianhydrid **97**.

Die Realisierung der vorgeschlagenen Synthesen könnte eine Vielzahl unterschiedlich strukturierter Kohlenhydratmimetika generieren, die nach Testung ihrer Bindungsaffinitäten an Selektine ein verbessertes Verständnis der Struktur-Wirkungs-Beziehung erwarten lässt.

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# 7 Anhang zu den Publikationen

## 7.1 Spektrenanhang zur Publikation:

## Synthesis of rigid *p*-terphenyl-linked carbohydrate mimetics

Die Publikation wurde im Kapitel 3.1 vorgestellt und in der folgenden Zeitschrift publiziert:

M. Kandziora, H.-U. Reissig, *Beilstein J. Org. Chem.* **2014**, *10,* 1749–1758.

# Supporting Information File 2

# for

# Synthesis of rigid *p*-terphenyl-linked carbohydrate mimetics

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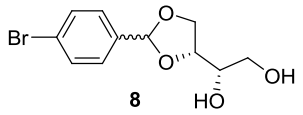
## Characterization data $^{1}$H NMR and $^{13}$C NMR spectra of synthesized compounds

**Table of contents:**

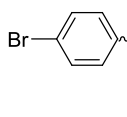
**$^{1}$H NMR (500 MHz, $CDCl_3$)**




8




**$^{13}$C NMR (125 MHz, $CDCl_3$)**

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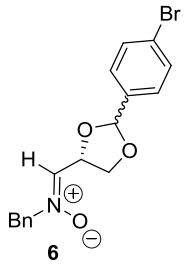
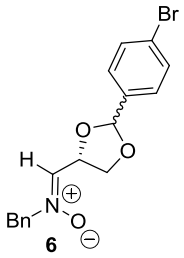
**$^1$H NMR (500 MHz, $CDCl_3$)**



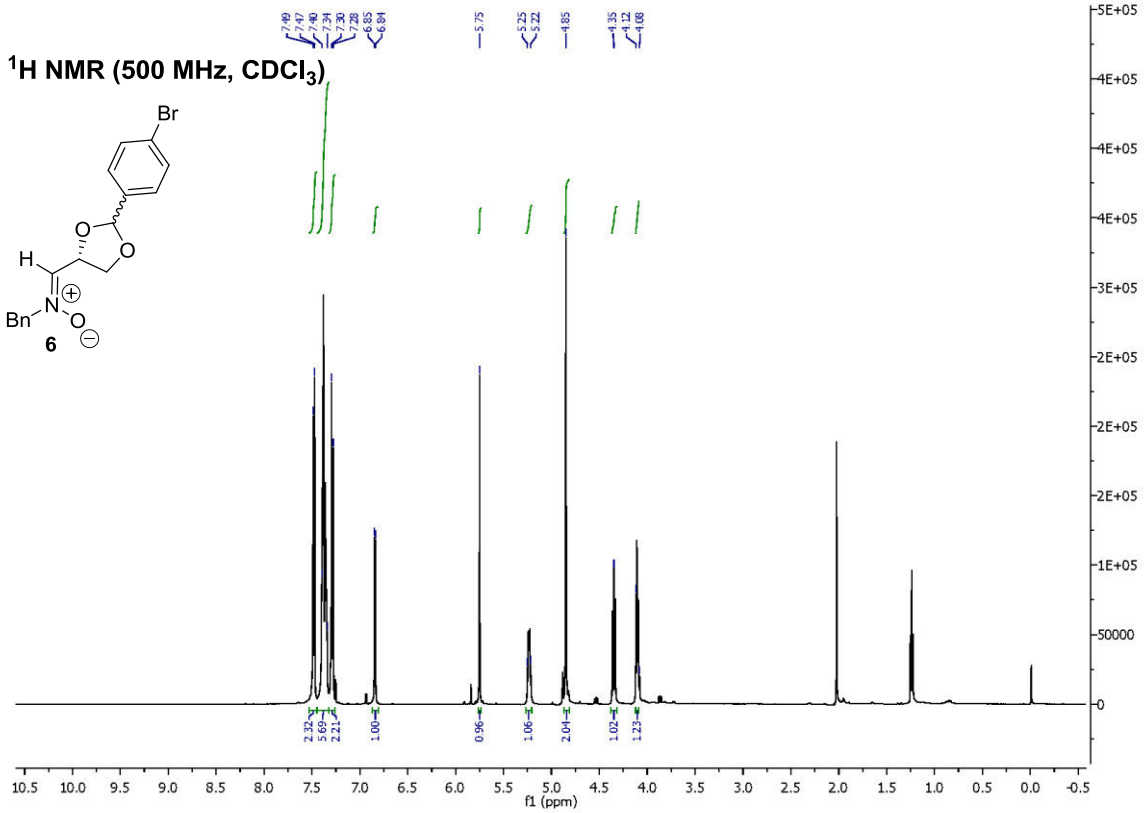

**6**

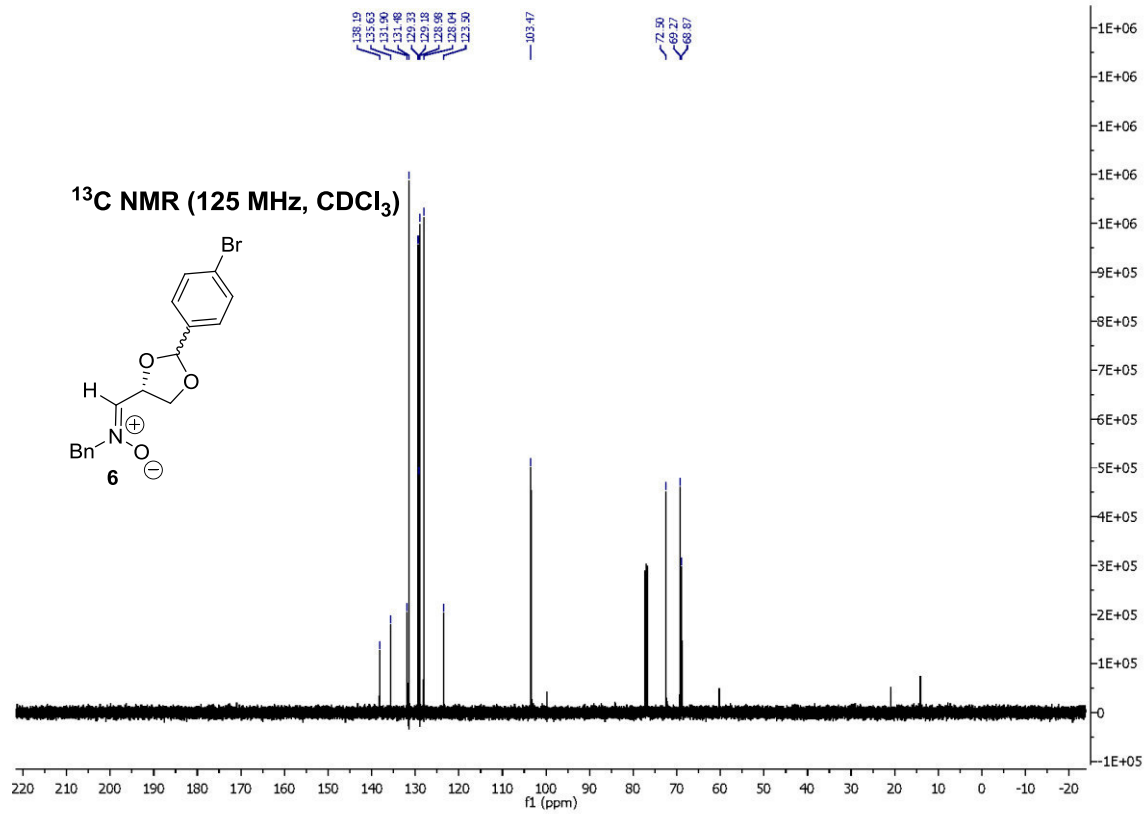



**$^{13}$C NMR (125 MHz, $CDCl_3$)**

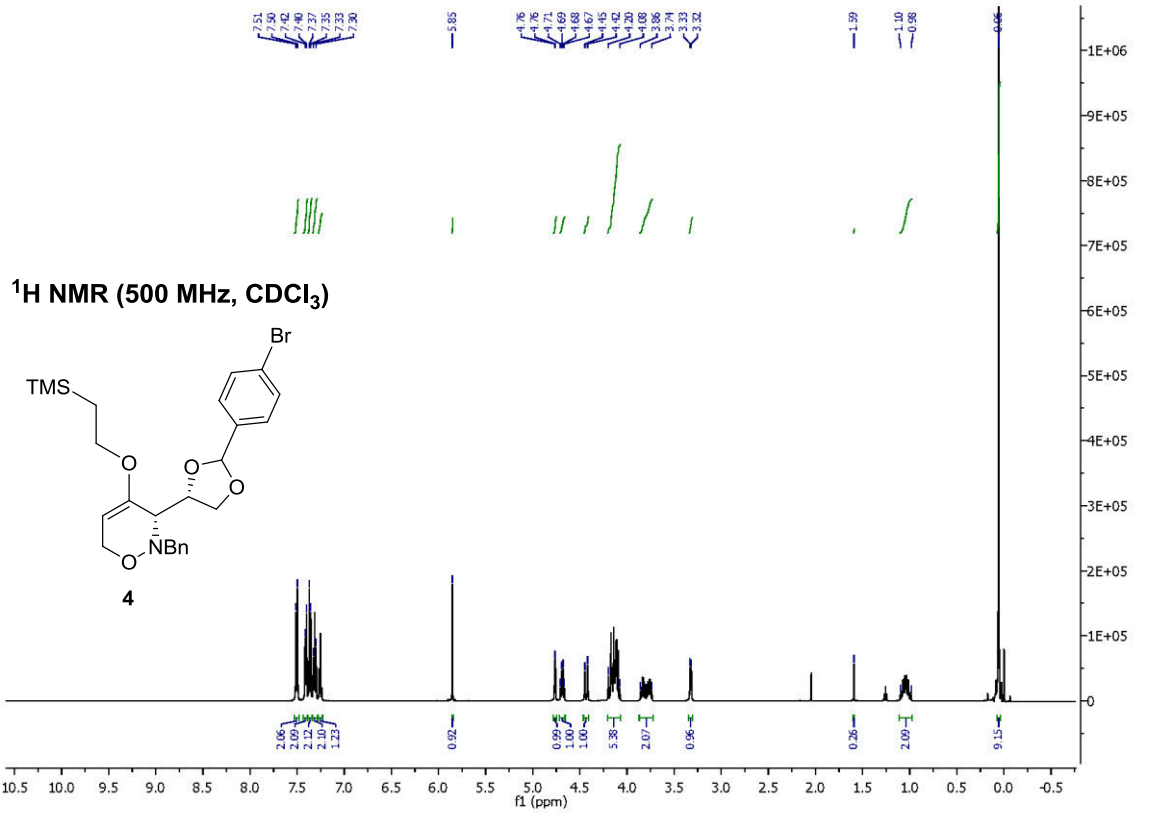



**6**

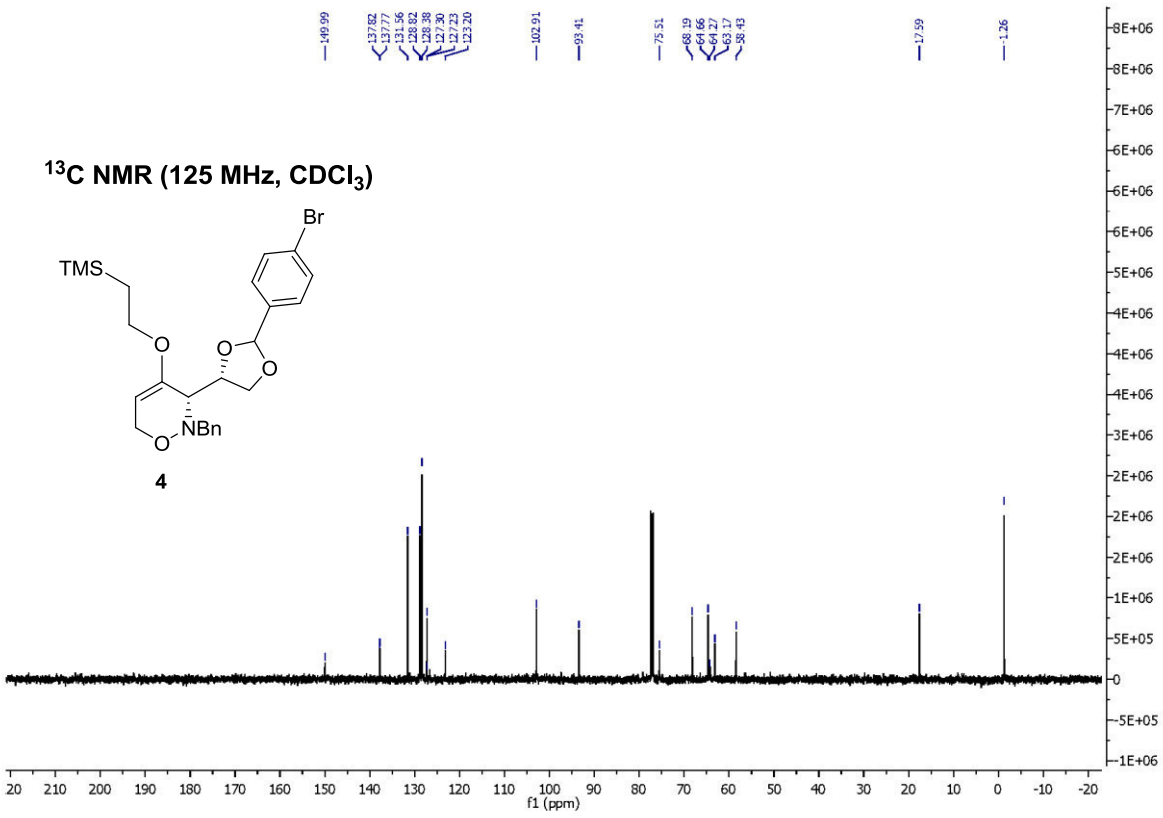

$^1$H NMR (500 MHz, CDCl$_3$)
Br
O
O
H
N
Bn
O
6
7.49
7.47
7.40
7.34
7.30
7.28
6.85
6.84
5.75
5.25
5.22
4.85
4.35
4.12
4.08
2.32
5.69
2.21
1.00
0.96
1.06
2.04
1.02
1.23
f1 (ppm)


$^{13}$C NMR (125 MHz, CDCl$_3$)
Br
O
O
H
N
Bn
O
6
138.19
135.63
131.90
131.48
129.33
129.18
128.98
128.04
123.50
103.47
72.50
69.27
68.87
f1 (ppm)

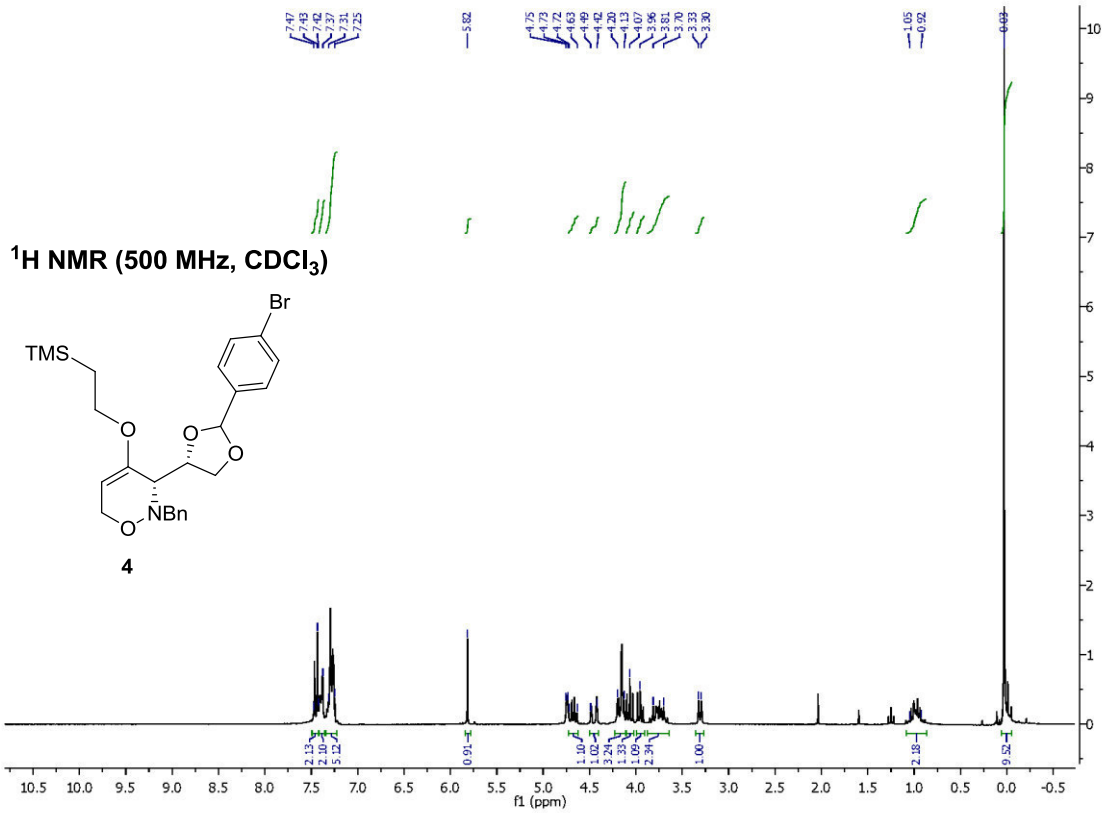
**$^{1}$H NMR (500 MHz, $CDCl_3$)**




**$^{13}$C NMR (125 MHz, $CDCl_3$)**



**$^{1}$H NMR (500 MHz, $CDCl_3$)**




**4**

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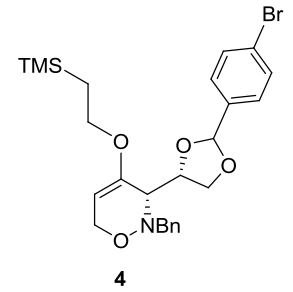
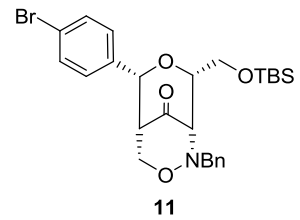



**4**

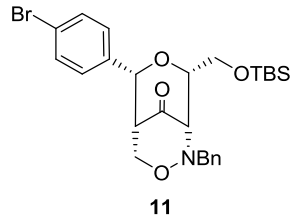
**$^1$H NMR (500 MHz, $CDCl_3$)**




**11**

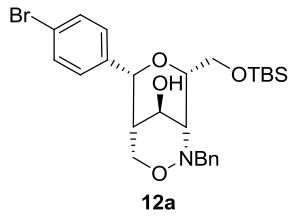



**$^{13}$C NMR (125 MHz, $CDCl_3$)**




**11**

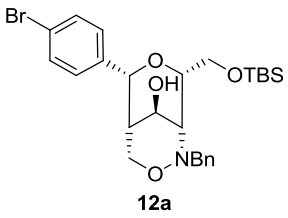
**$^1$H NMR (500 MHz, $CDCl_3$)**




**12a**

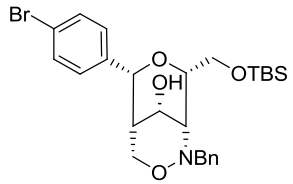



**$^{13}$C NMR (125 MHz, $CDCl_3$)**




**12a**

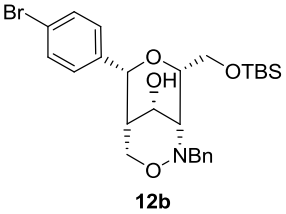
**$^{1}$H NMR (500 MHz, $CDCl_3$)**




**12b**

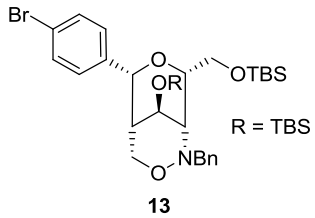



**$^{13}$C NMR (125 MHz, $CDCl_3$)**




**12b**

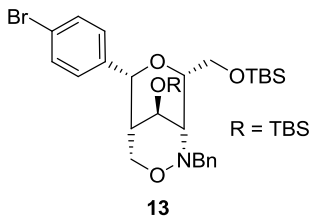
**$^{1}$H NMR (500 MHz, $CDCl_3$)**




**13**

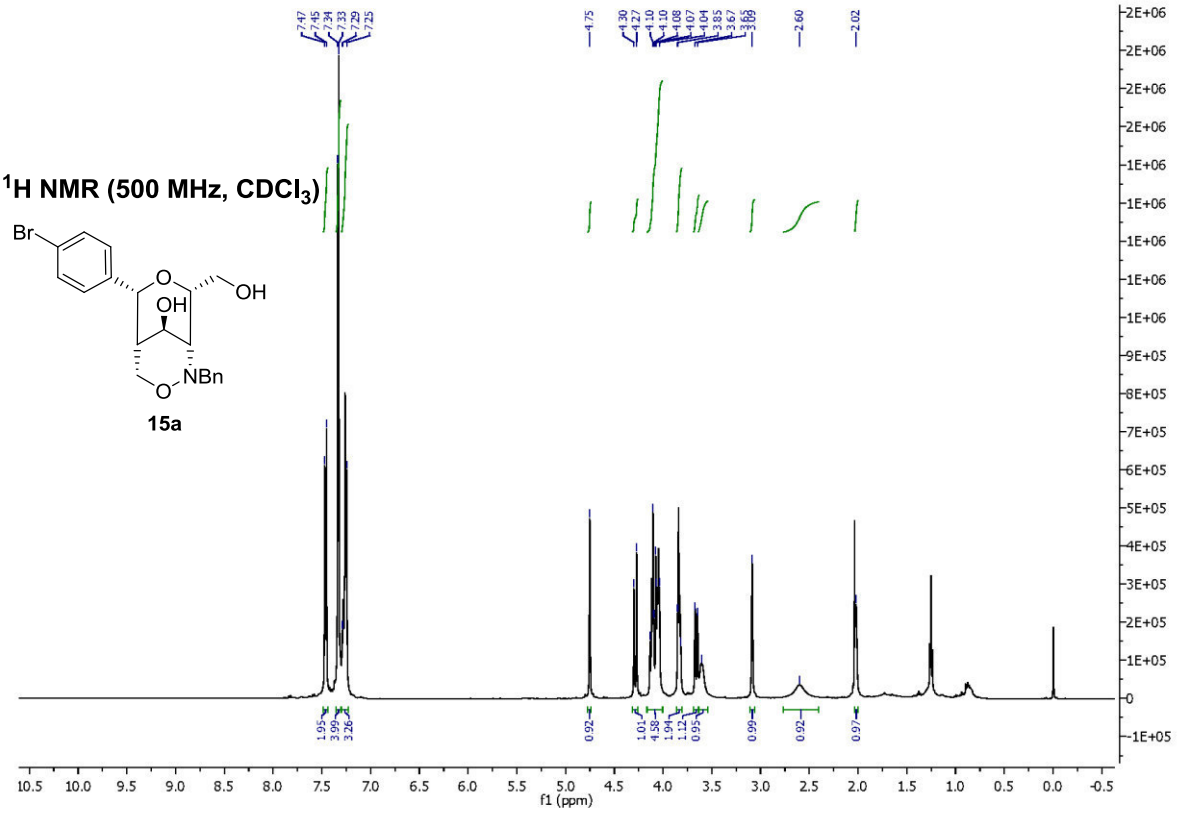



**$^{13}$C NMR (125 MHz, $CDCl_3$)**

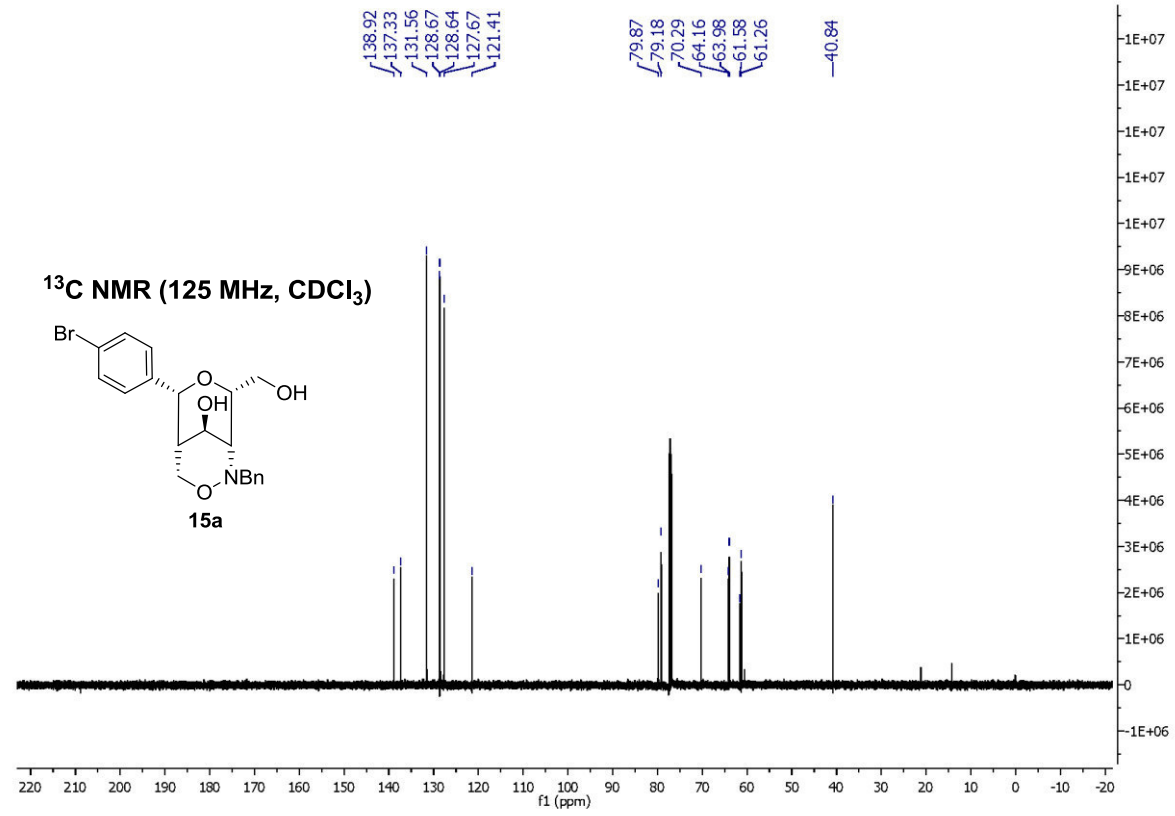



**13**

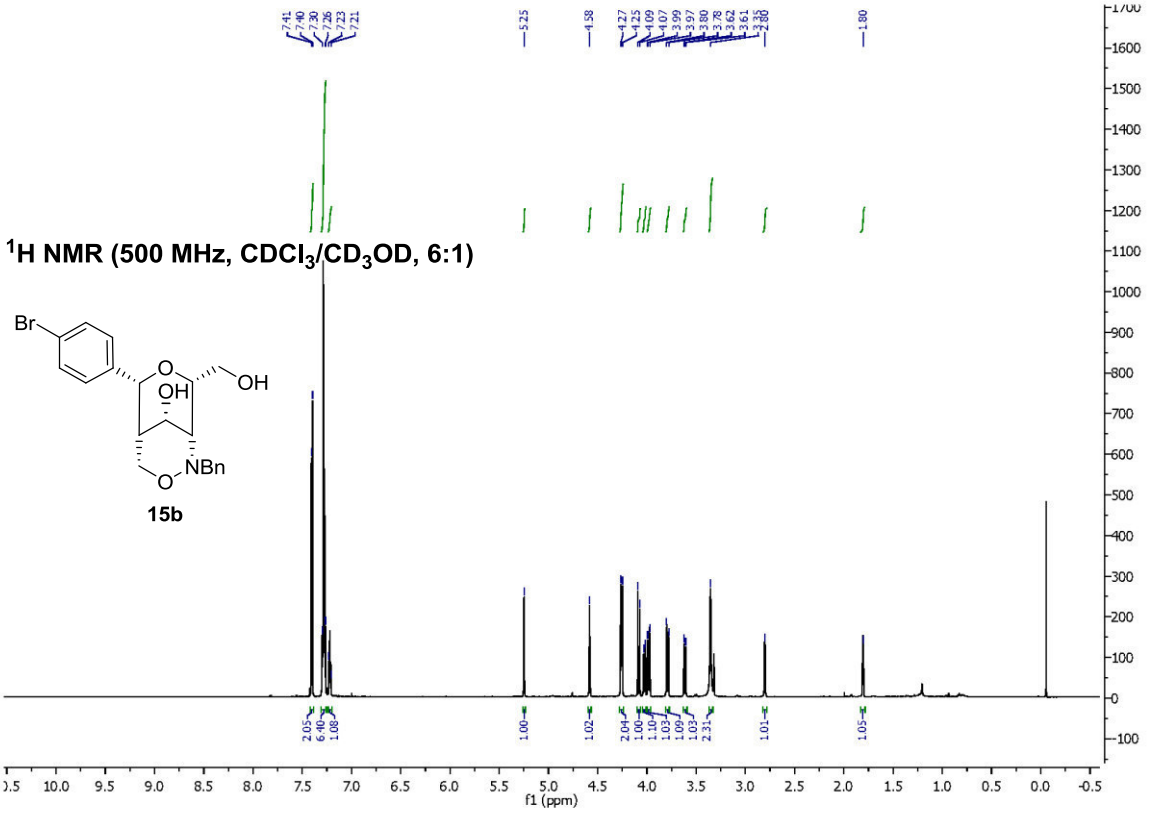
**$^1$H NMR (500 MHz, $CDCl_3$)**

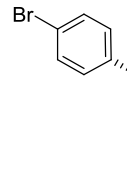



**$^{13}$C NMR (125 MHz, $CDCl_3$)**



**$^1$H NMR (500 MHz, $CDCl_3/CD_3OD$, 6:1)**




**15b**

**$^{13}$C NMR (125 MHz, $CDCl_3/CD_3OD$, 6:1)**

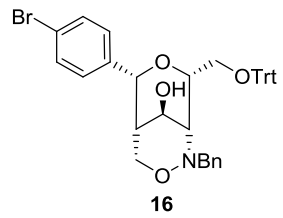






**15b**

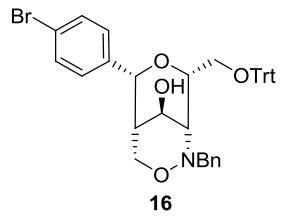
**$^{1}$H NMR (500 MHz, $CDCl_3$)**




**16**

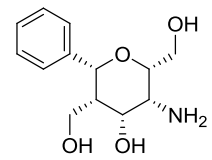



**$^{13}$C NMR (125 MHz, $CDCl_3$)**




**16**

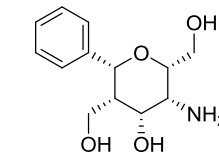
**$^1$H NMR (500 MHz, $CD_3OD$)**




**17a**

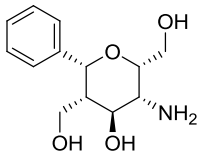



**$^{13}$C NMR (175 MHz, $CD_3OD$)**




**17a**

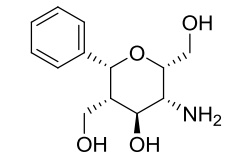
**$^1$H NMR (500 MHz, $CD_3OD$)**




**17b**

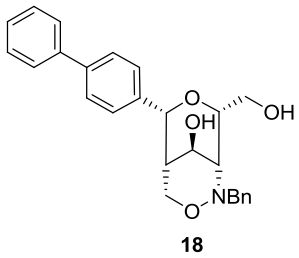



**$^{13}$C NMR (125 MHz, $CD_3OD$)**




**17b**

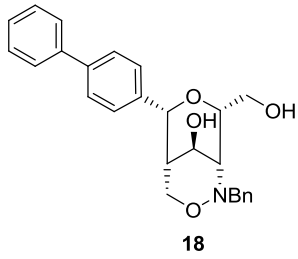
**$^{1}$H NMR (500 MHz, $CDCl_3$)**




**18**

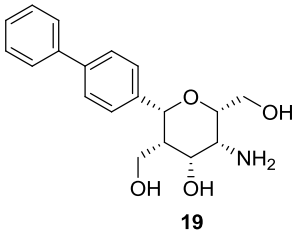



**$^{13}$H NMR (125 MHz, $CDCl_3$)**




**18**

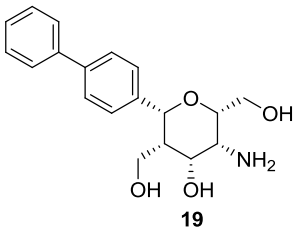
**$^1$H NMR (700 MHz, $CD_3OD/CDCl_3$, 2:1)**



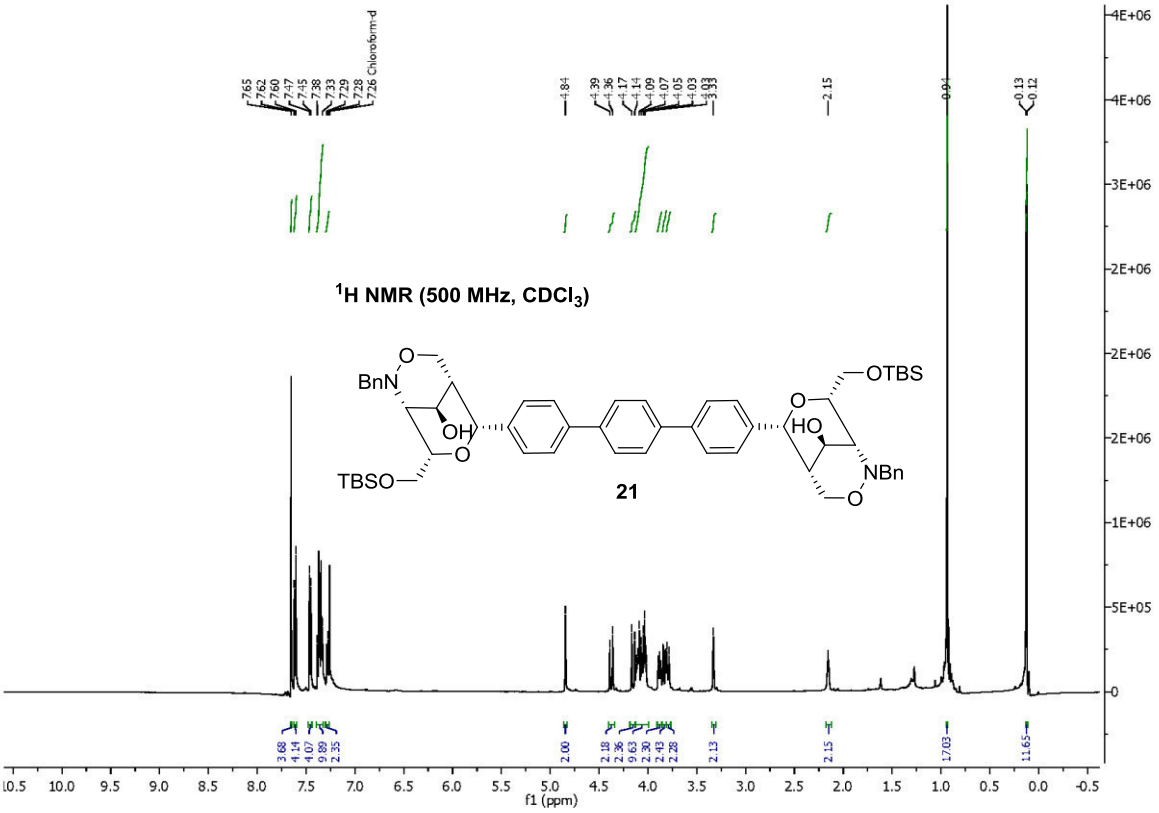

**19**

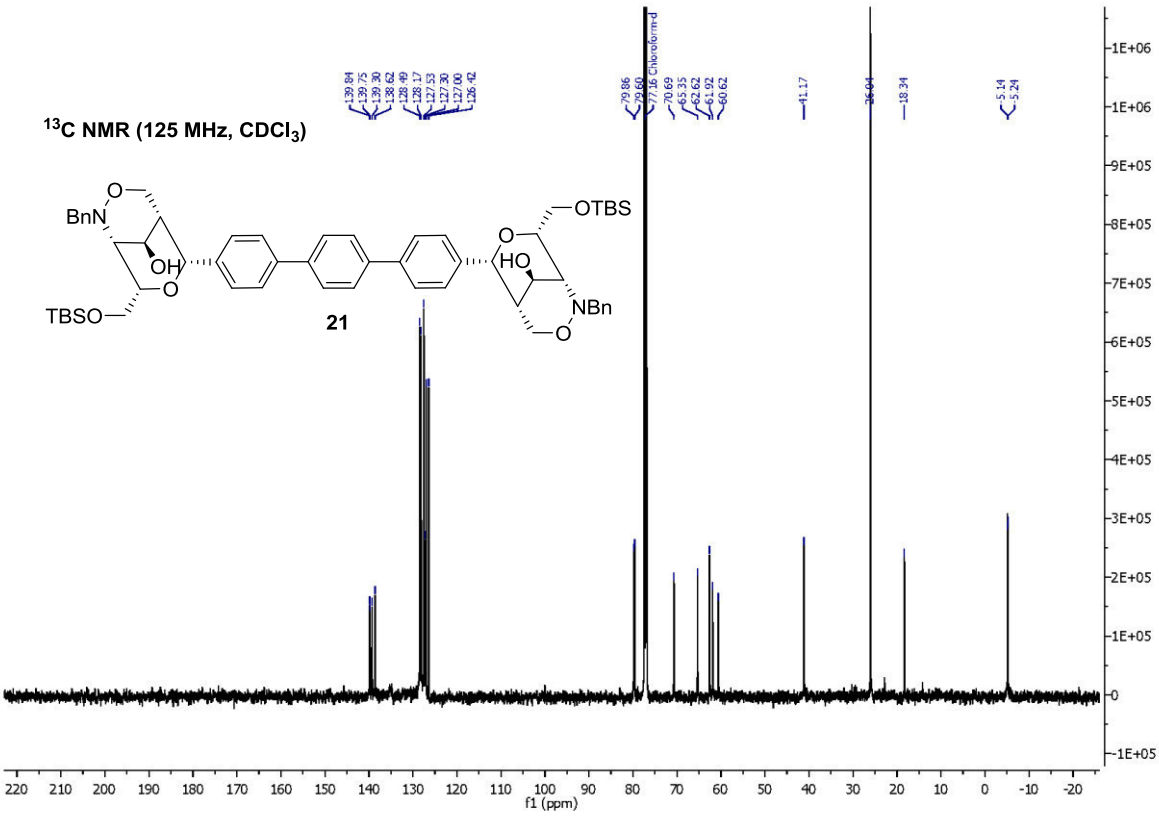



**$^{13}$C NMR (175 MHz, $CD_3OD/CDCl_3$, 2:1)**

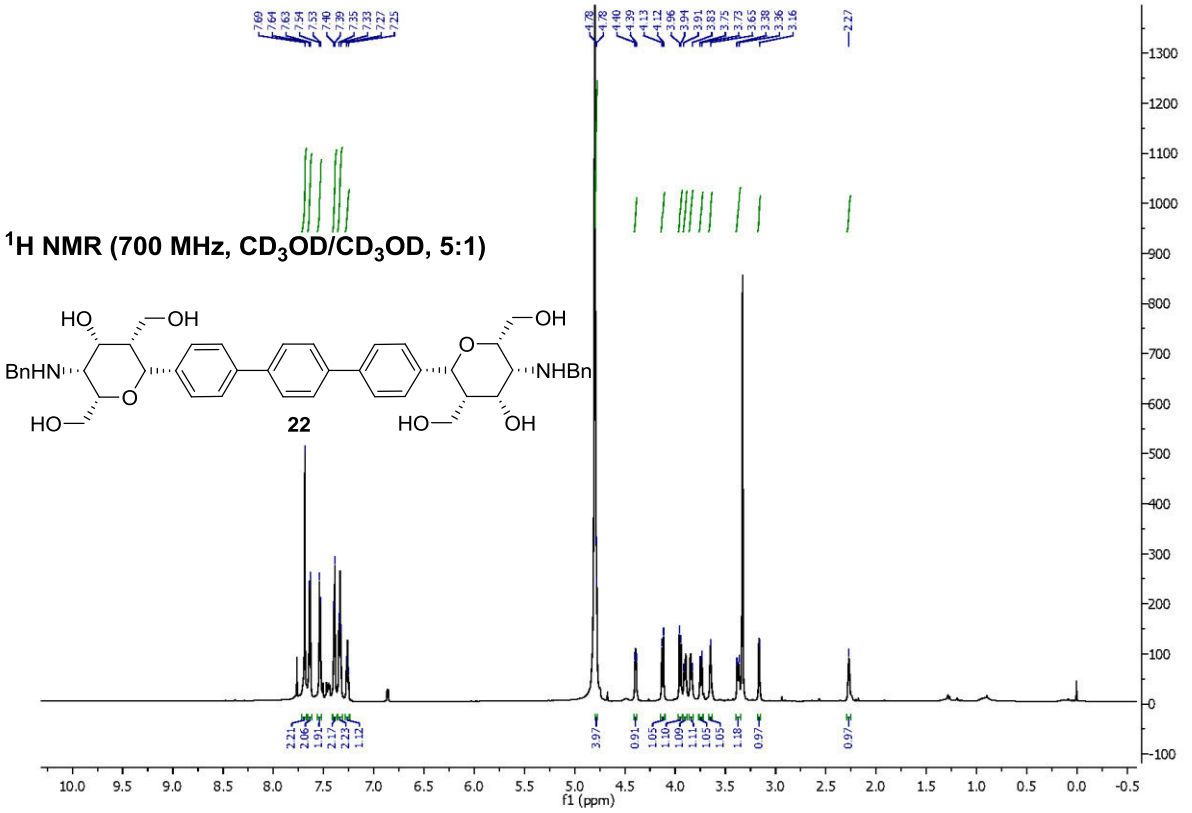



**19**

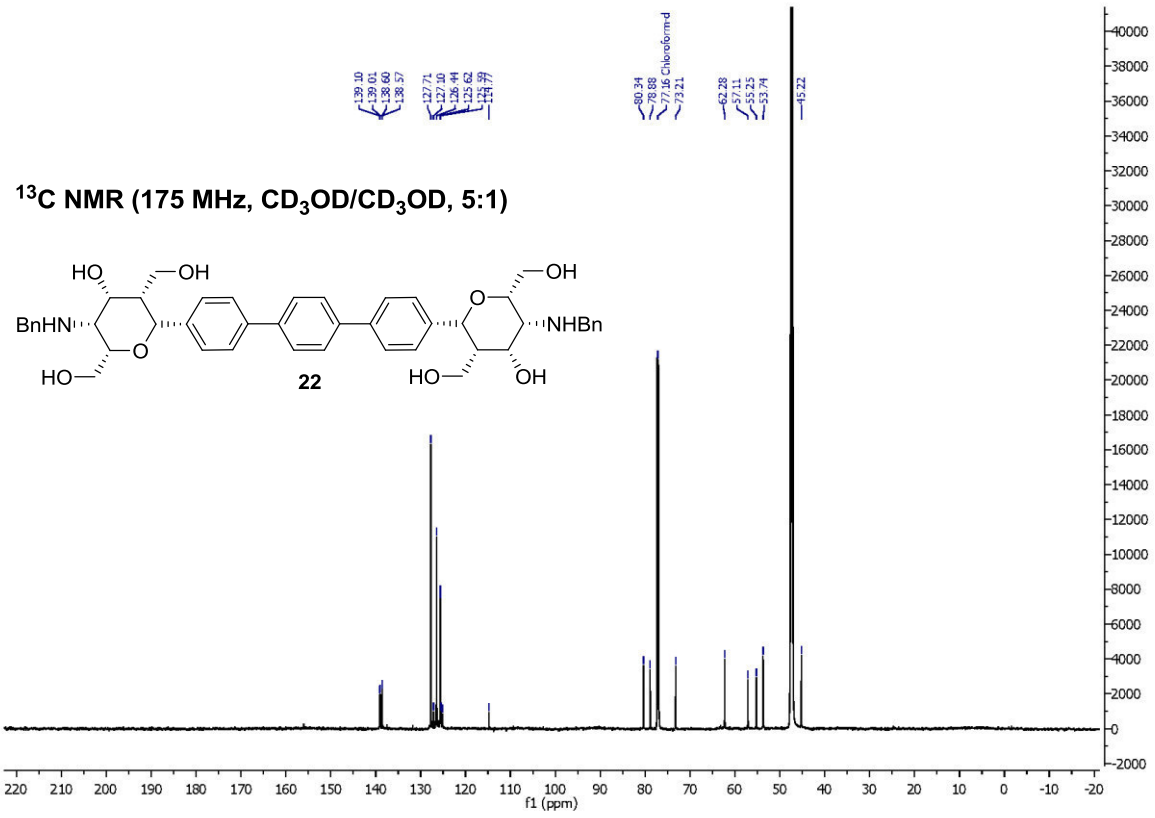

$^1$H NMR (500 MHz, $CDCl_3$)
BnN
OH
TBSO
OTBS
HO
NBn
21


$^{13}$C NMR (125 MHz, $CDCl_3$)
BnN
OH
TBSO
OTBS
HO
NBn
21

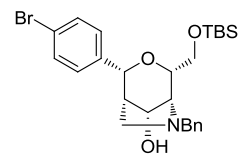
**$^{1}$H NMR (700 MHz, $CD_3OD/CD_3OD$, 5:1)**




**$^{13}$C NMR (175 MHz, $CD_3OD/CD_3OD$, 5:1)**



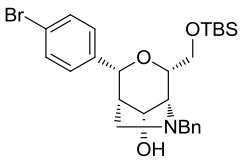
**$^{1}$H NMR (500 MHz, $CDCl_3$)**




**24**

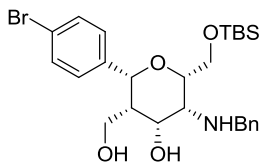



**$^{13}$C NMR (125 MHz, $CDCl_3$)**




**24**

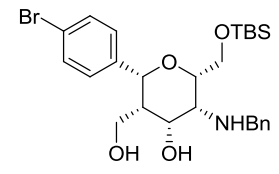
**$^{1}$H NMR (700 MHz, $CD_3OD$)**



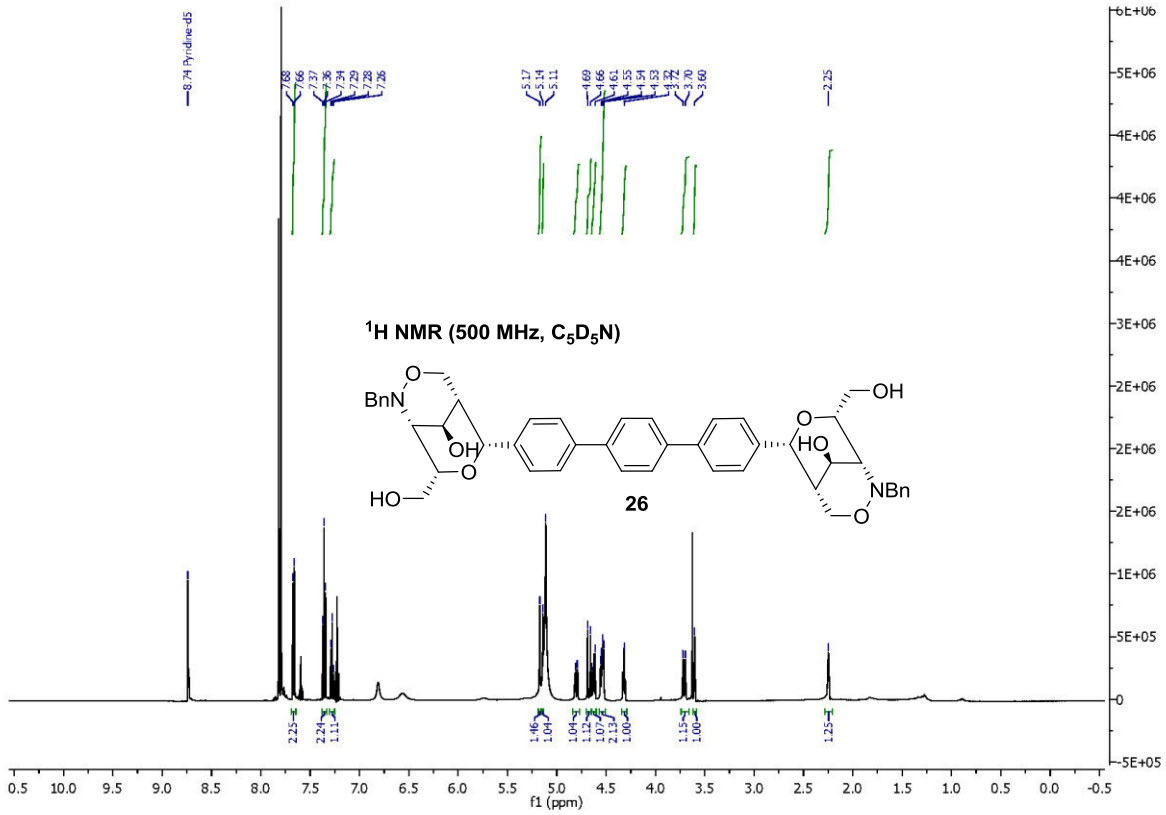

**25**

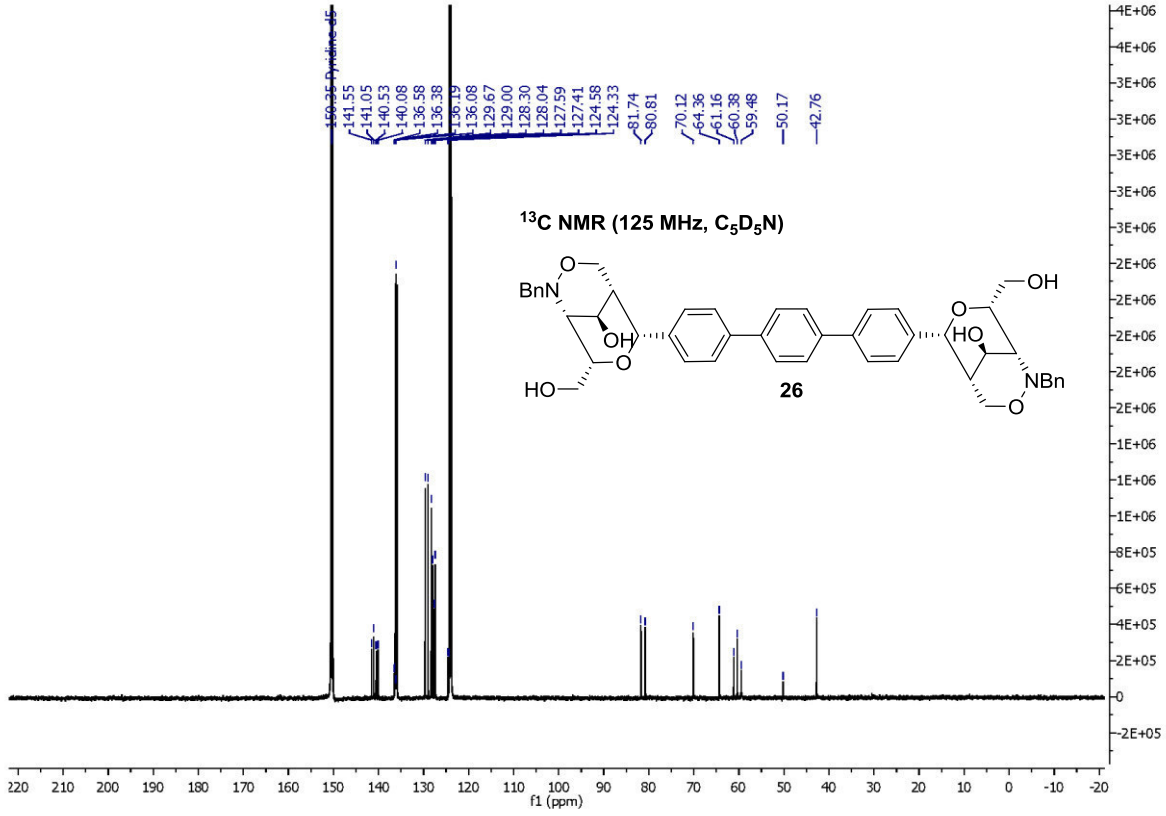


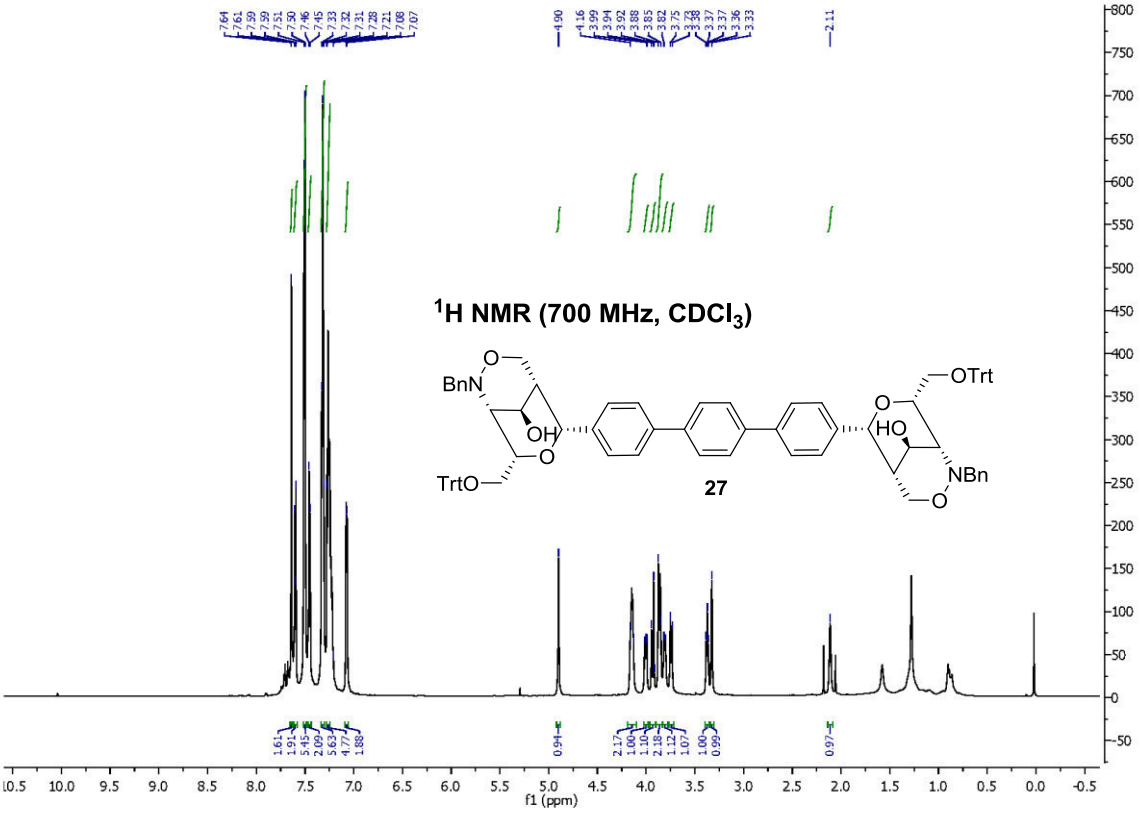

**$^{13}$C NMR (175 MHz, $CD_3OD$)**

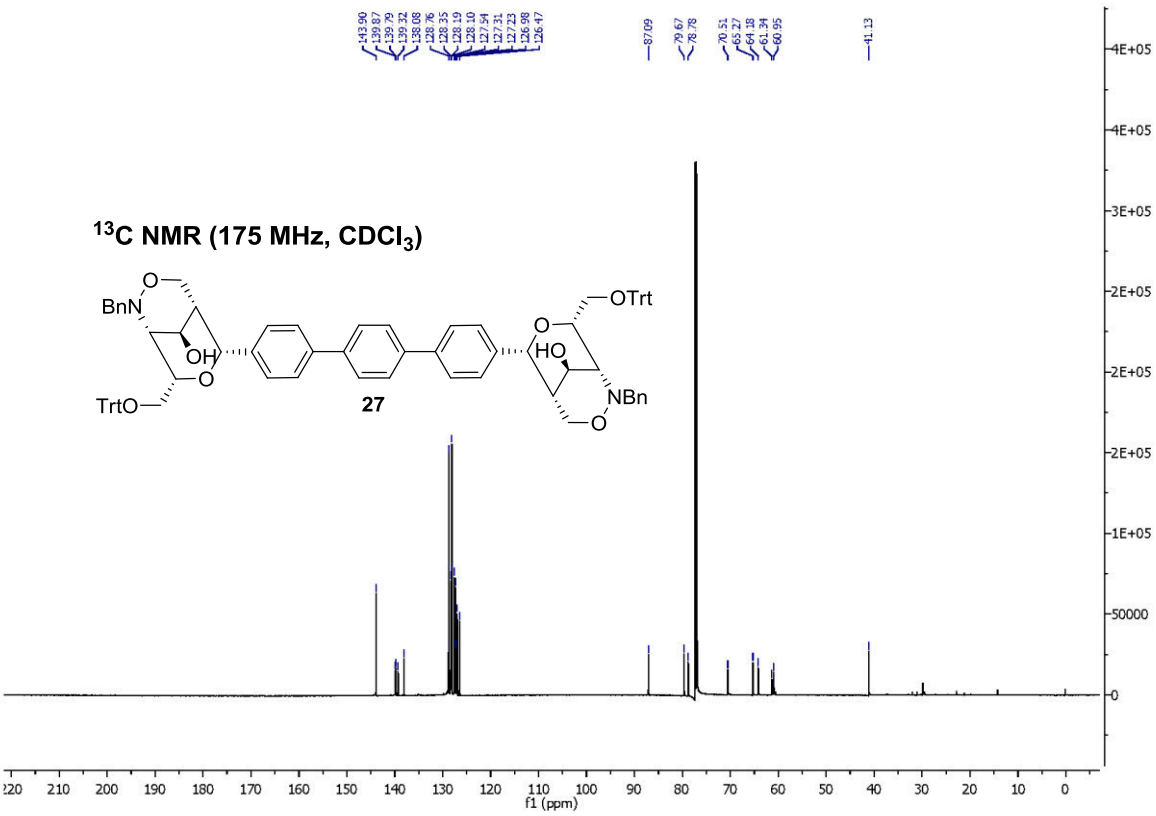



**25**

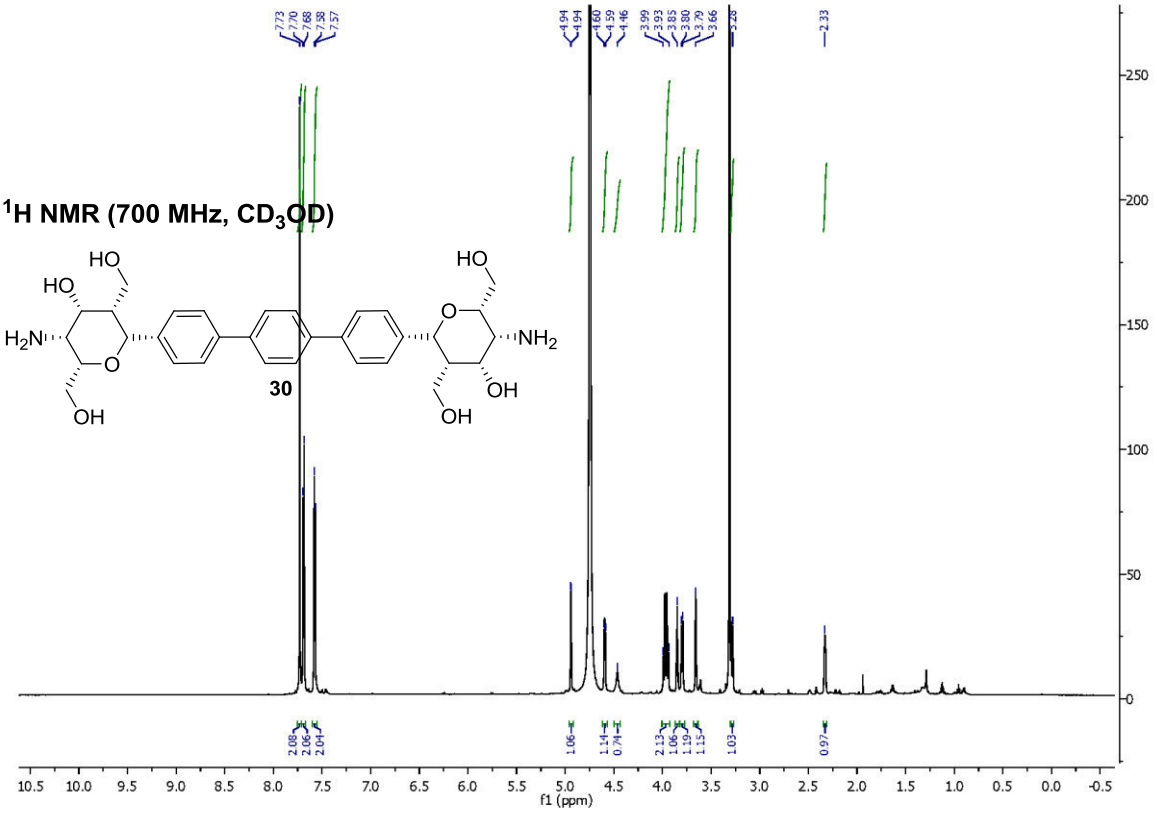

$^1$H NMR (500 MHz, $C_5D_5N$)
26


$^{13}$C NMR (125 MHz, $C_5D_5N$)
26


$^1$H NMR (700 MHz, CDCl$_3$)
BnN
OH
TrtO
OTrt
HO
NBn
27


$^{13}$C NMR (175 MHz, CDCl$_3$)
BnN
OH
TrtO
OTrt
HO
NBn
27

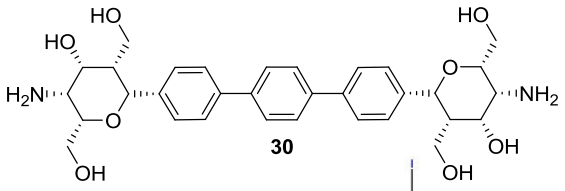
**$^1$H NMR (700 MHz, $CD_3OD$)**



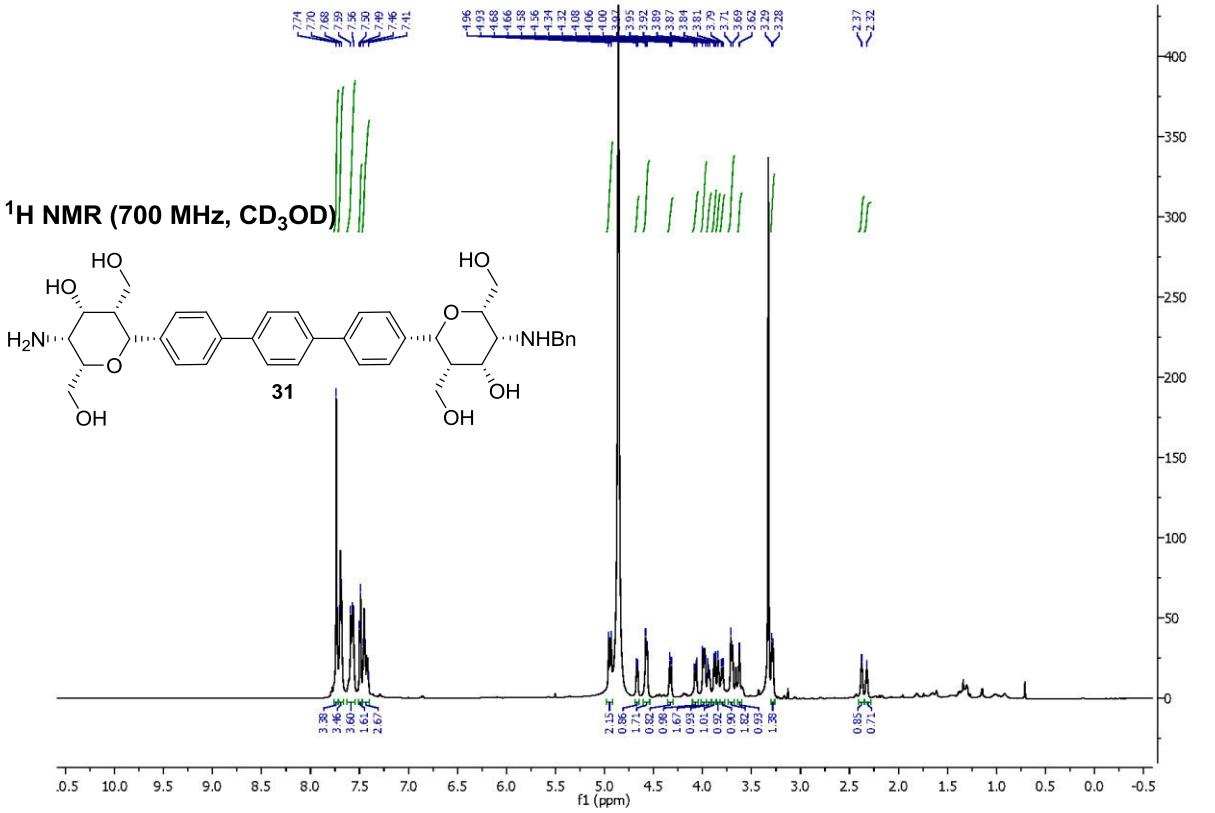




**$^{13}$C NMR (175 MHz, $CD_3OD$)**



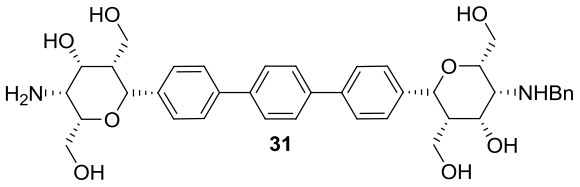
**$^{1}$H NMR (700 MHz, $CD_3OD$)**







**$^{13}$C NMR (175 MHz, $CD_3OD$)**

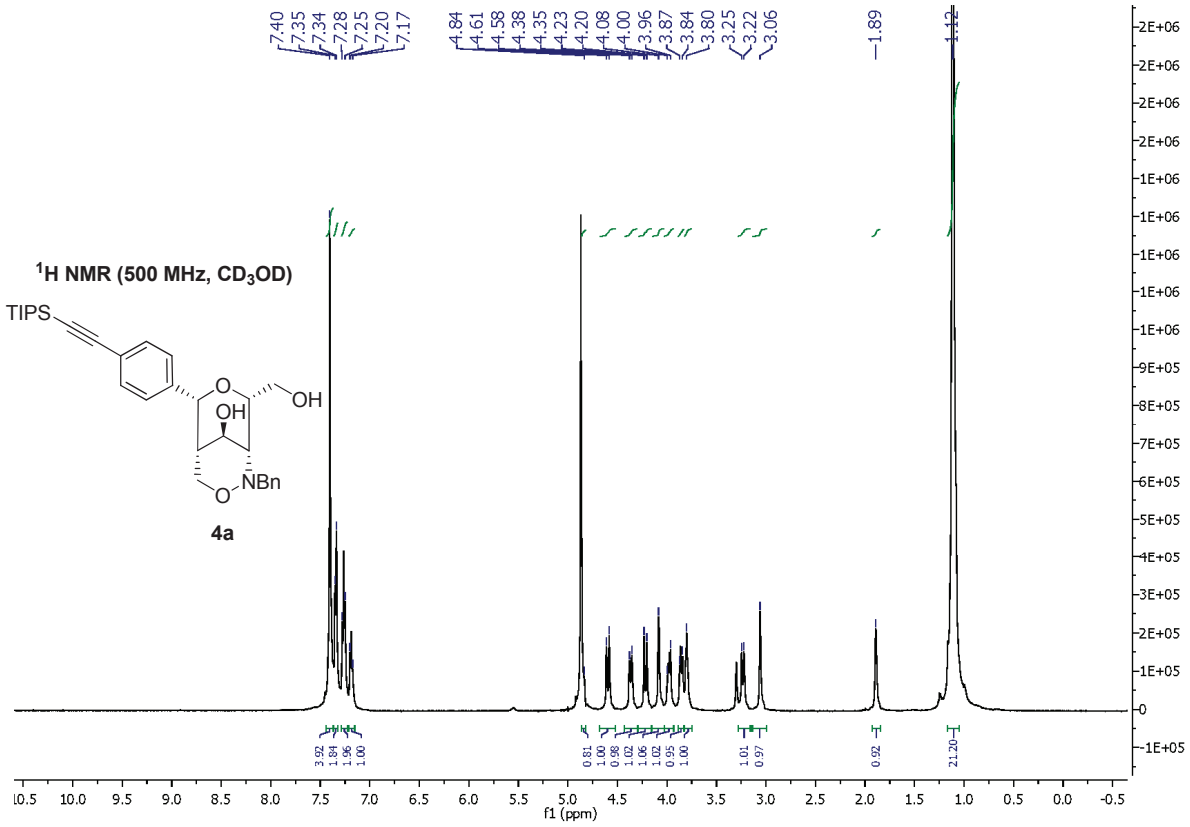


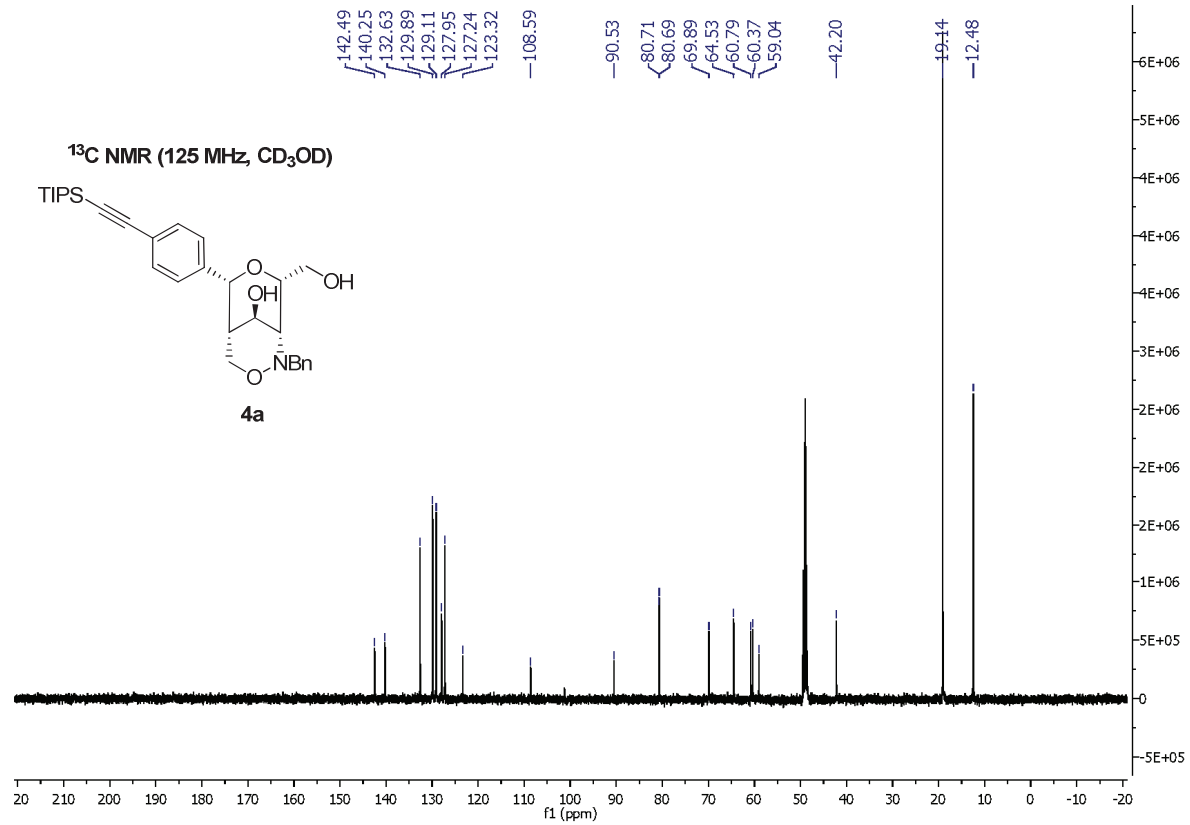
## 7.2 Spektrenanhang zur Publikation:

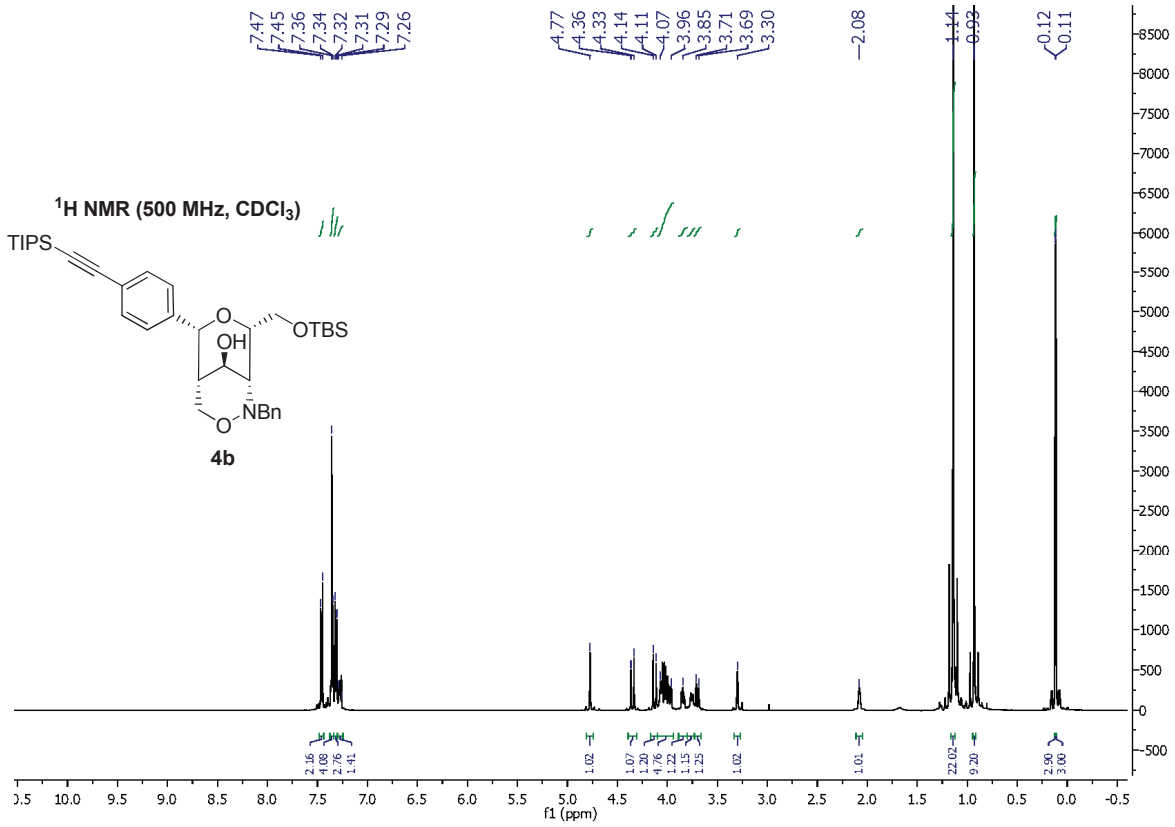
### Preparation of Multivalent Carbohydrate Mimetics Based on Enantiopure 1,2-Oxazines by Sonogashira Couplings and Subsequent Reductive Ring Openings

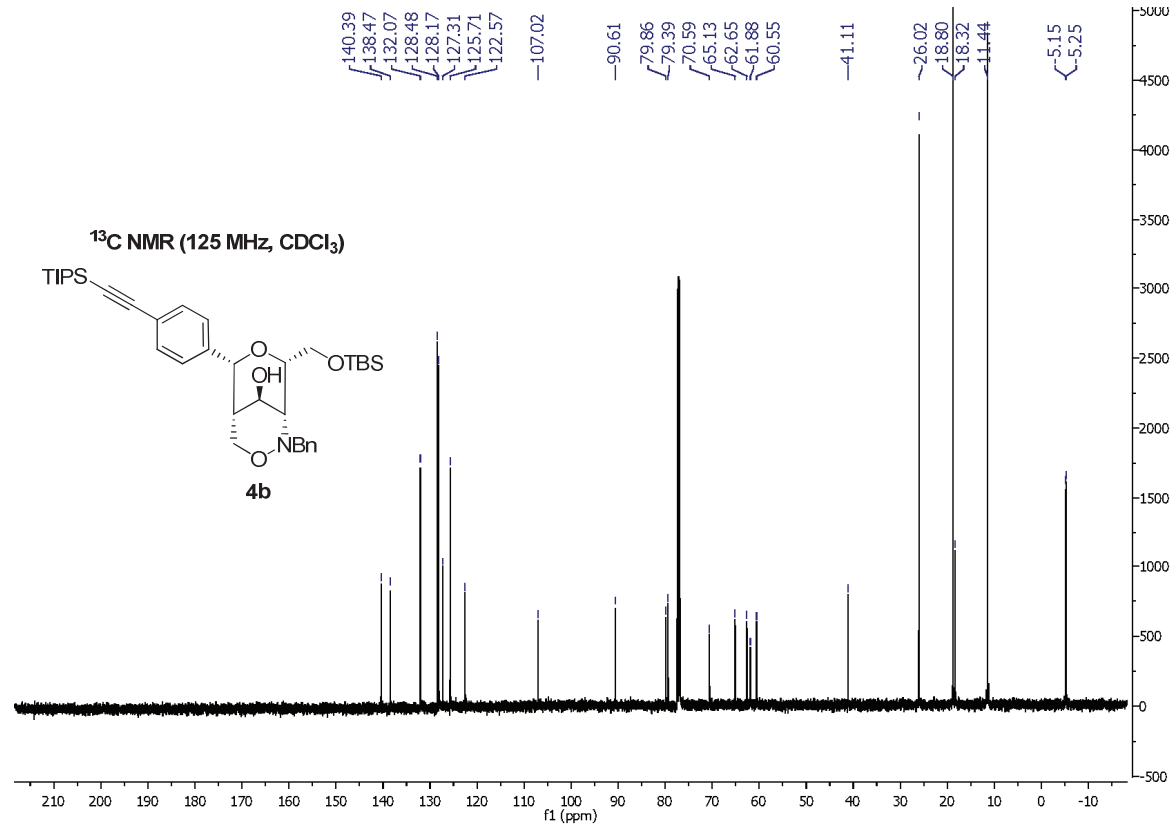
Die Publikation wurde im Kapitel 3.2 vorgestellt und in der folgenden Zeitschrift publiziert:

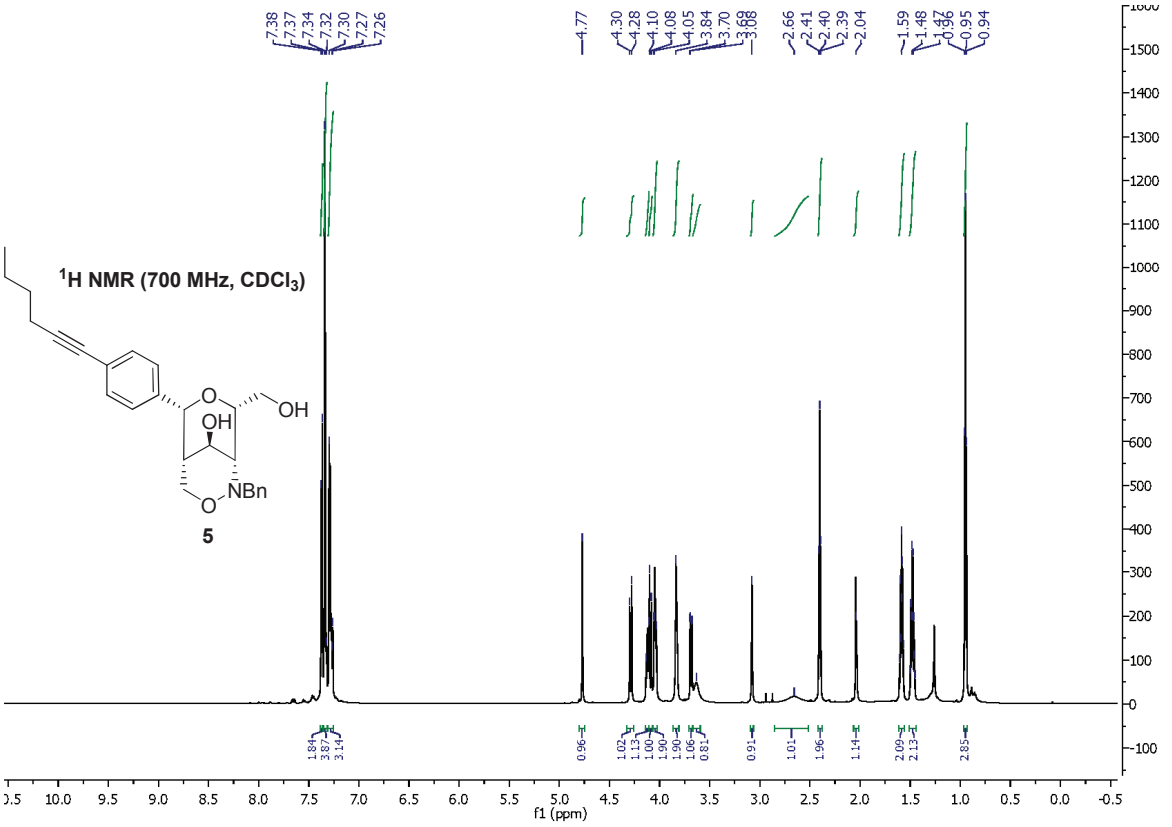
M. Kandziora, H.-U. Reissig, *Eur. J. Org. Chem.* **2015**, 370-377.


7.40
7.35
7.34
7.28
7.25
7.20
7.17
4.84
4.61
4.58
4.38
4.35
4.23
4.20
4.08
4.00
3.96
3.87
3.84
3.80
3.25
3.22
3.06
1.89
1.12
$^1$H NMR (500 MHz, CD$_3$OD)
TIPS
O
OH
OH
NBn
O
4a
3.92
1.89
1.96
1.00
0.81
1.00
0.98
1.02
1.06
1.02
0.95
1.00
1.01
0.97
0.92
21.20
f1 (ppm)


142.49
140.25
132.63
129.89
129.11
127.95
127.24
123.32
108.59
90.53
80.71
80.69
69.89
64.53
60.79
60.37
59.04
42.20
19.14
12.48
$^{13}$C NMR (125 MHz, CD$_3$OD)
TIPS
O
OH
OH
NBn
O
4a
f1 (ppm)


7.47
7.45
7.36
7.34
7.32
7.31
7.29
7.26
4.77
4.36
4.33
4.14
4.11
4.07
3.96
3.85
3.71
3.69
3.30
2.08
1.14
0.93
0.12
0.11
1H NMR (500 MHz, CDCl3)
TIPS
OTBS
OH
NBn
4b
f1 (ppm)

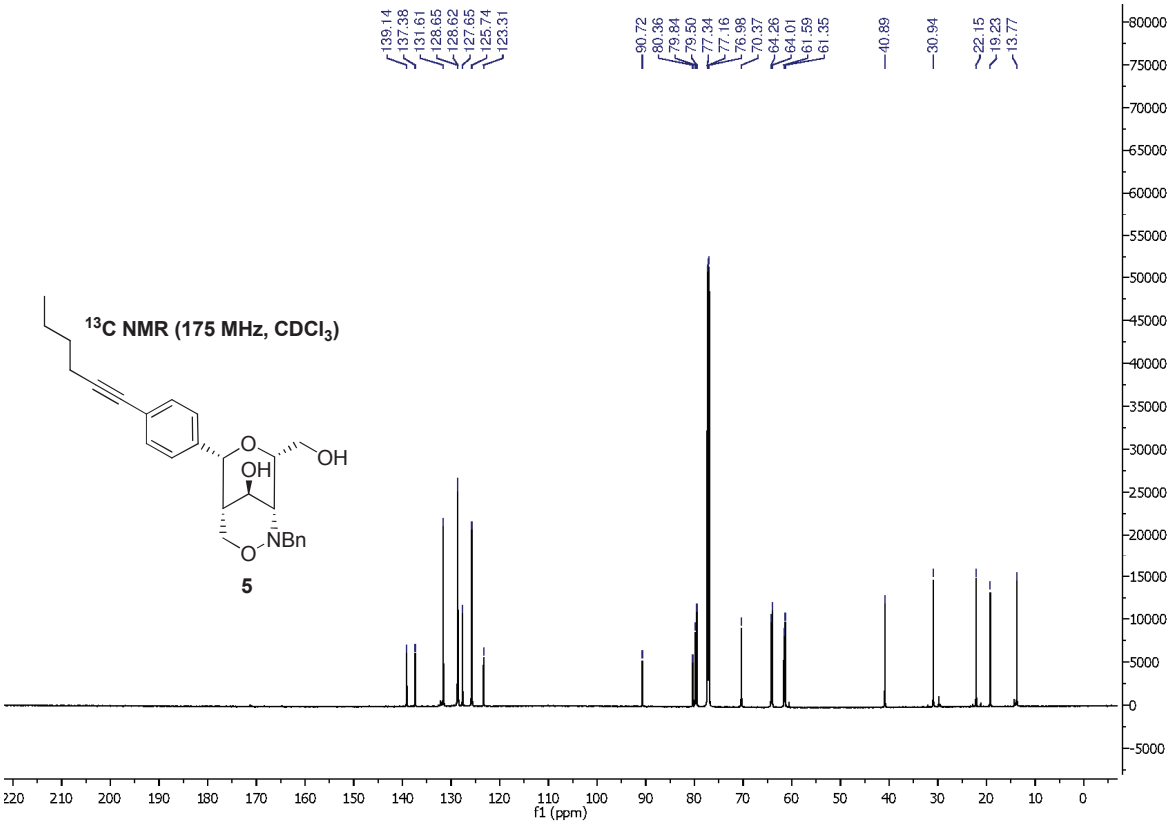

140.39
138.47
132.07
128.48
128.17
127.31
125.71
122.57
107.02
90.61
79.86
79.39
70.59
65.13
62.65
61.88
60.55
41.11
26.02
18.80
18.32
11.44
5.15
5.25
13C NMR (125 MHz, CDCl3)
TIPS
OTBS
OH
NBn
4b
f1 (ppm)




$^{1}$H NMR (700 MHz, $CDCl_3$)



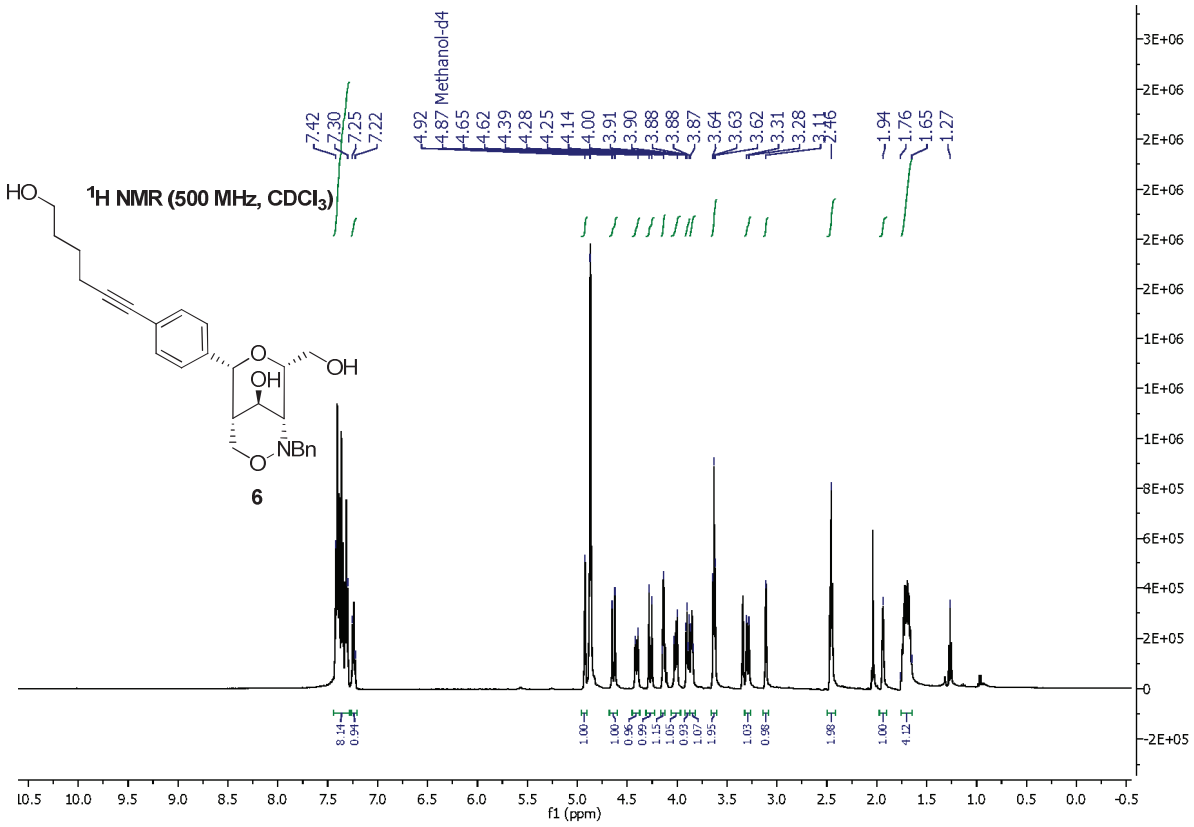

**5**

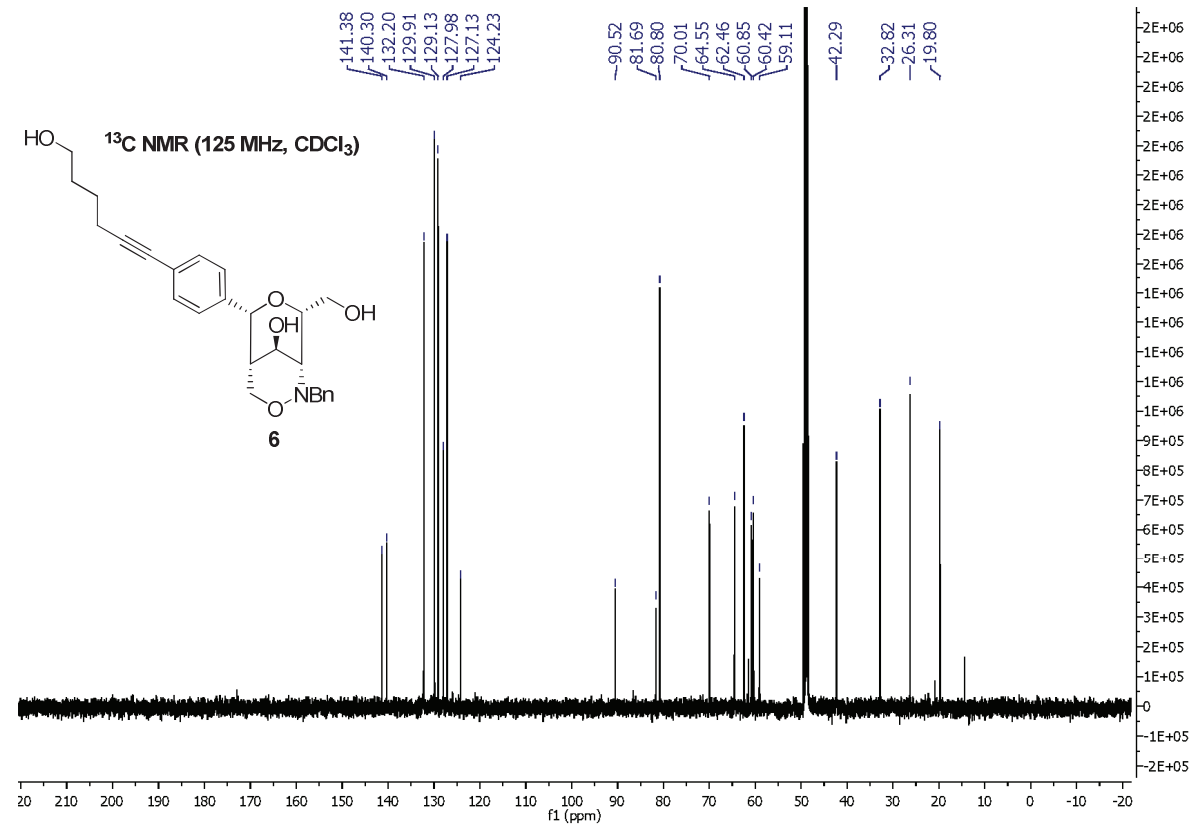


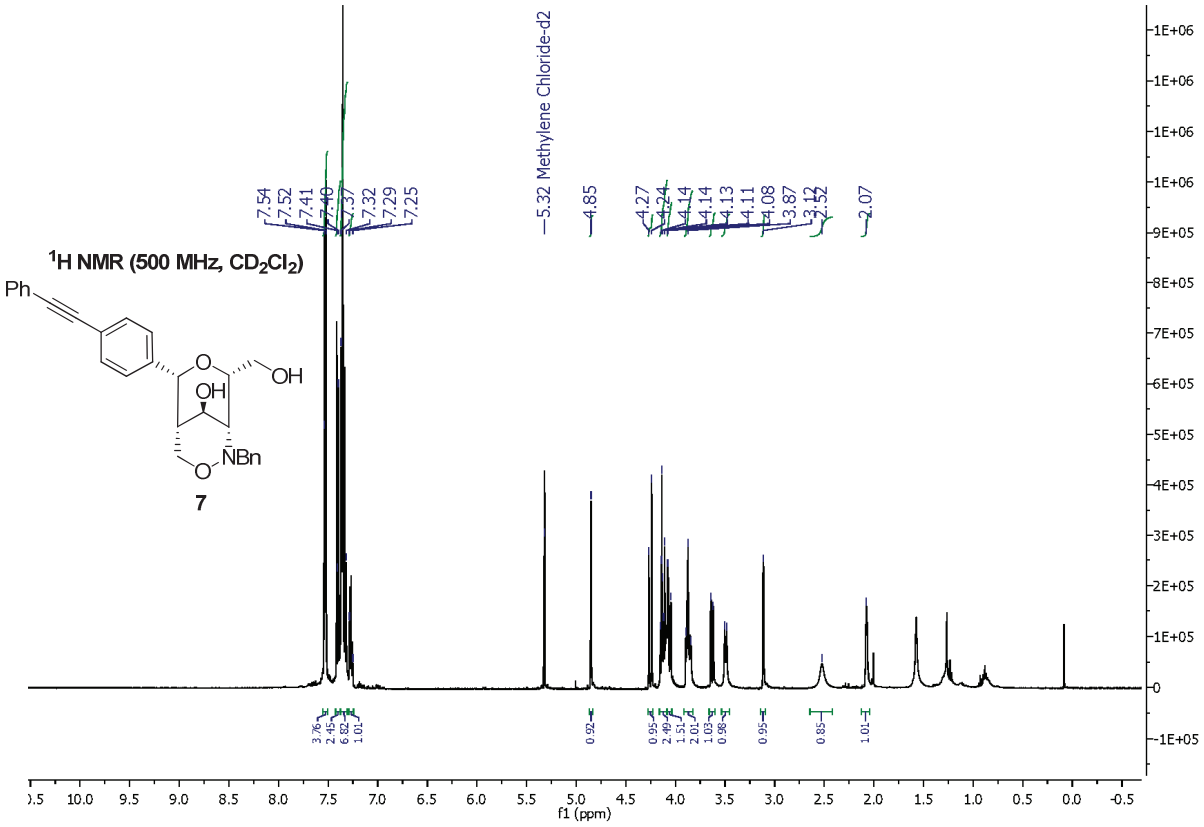

$^{13}$C NMR (175 MHz, $CDCl_3$)

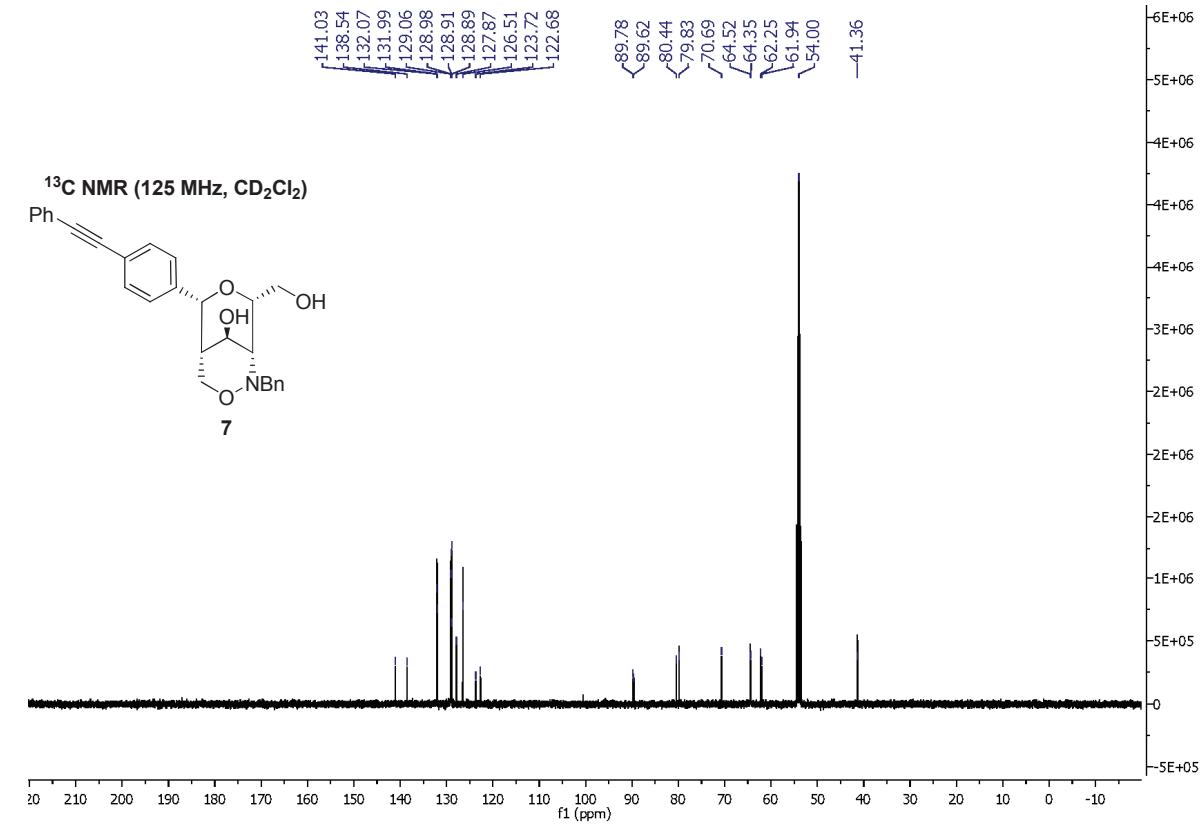


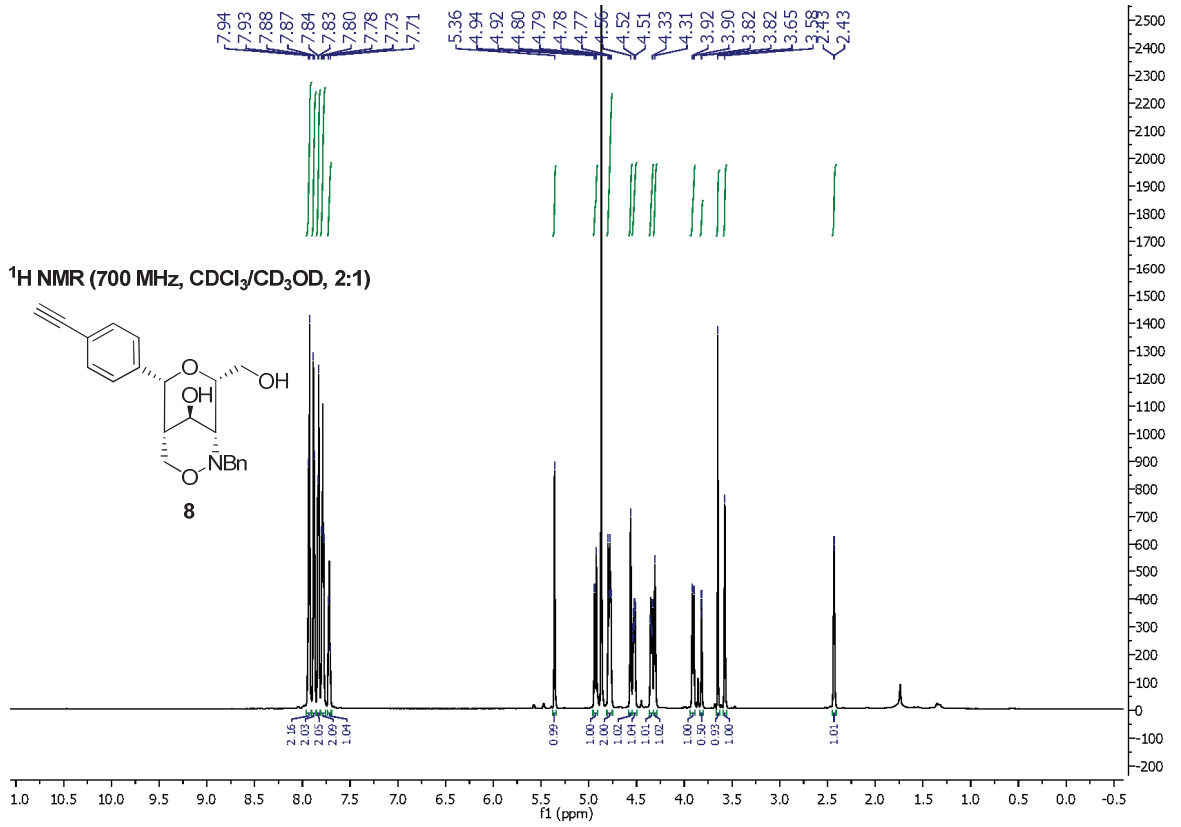

**5**

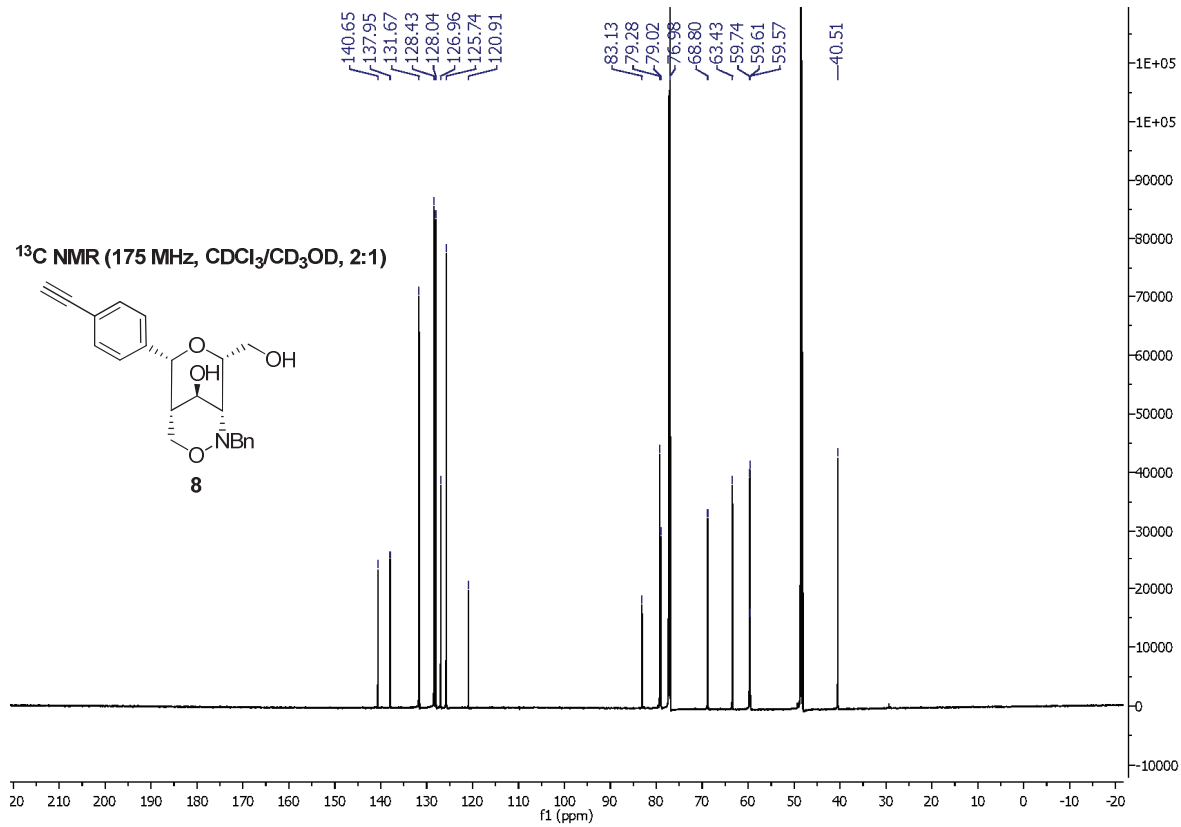

$^1$H NMR (500 MHz, CDCl$_3$)
HO
OH
OH
NBn
6
Methanol-d4
7.42
7.30
7.25
7.22
4.92
4.87
4.65
4.62
4.39
4.28
4.25
4.14
4.00
3.91
3.90
3.88
3.88
3.87
3.64
3.63
3.62
3.31
3.28
3.11
2.46
1.94
1.76
1.65
1.27
f1 (ppm)

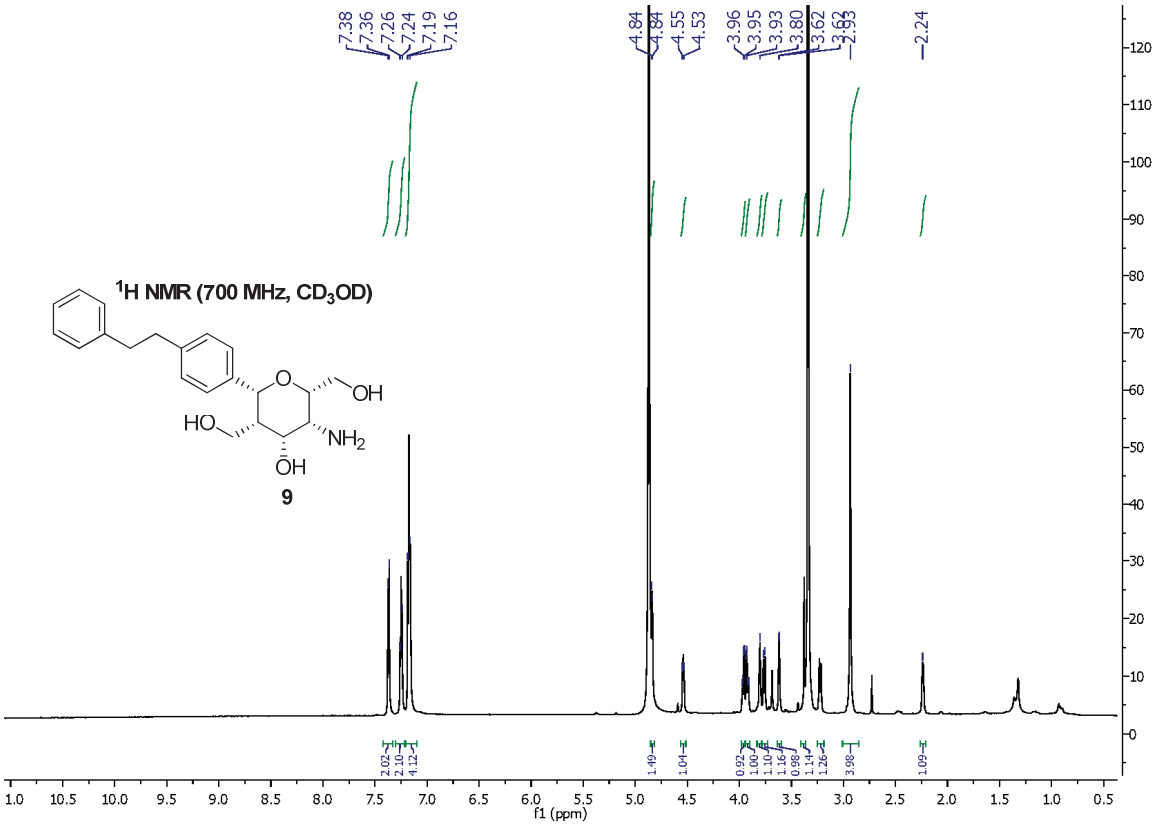

$^{13}$C NMR (125 MHz, CDCl$_3$)
HO
OH
OH
NBn
6
141.38
140.30
132.20
129.91
129.13
127.98
127.13
124.23
90.52
81.69
80.80
70.01
64.55
62.46
60.85
60.42
59.11
42.29
32.82
26.31
19.80
f1 (ppm)

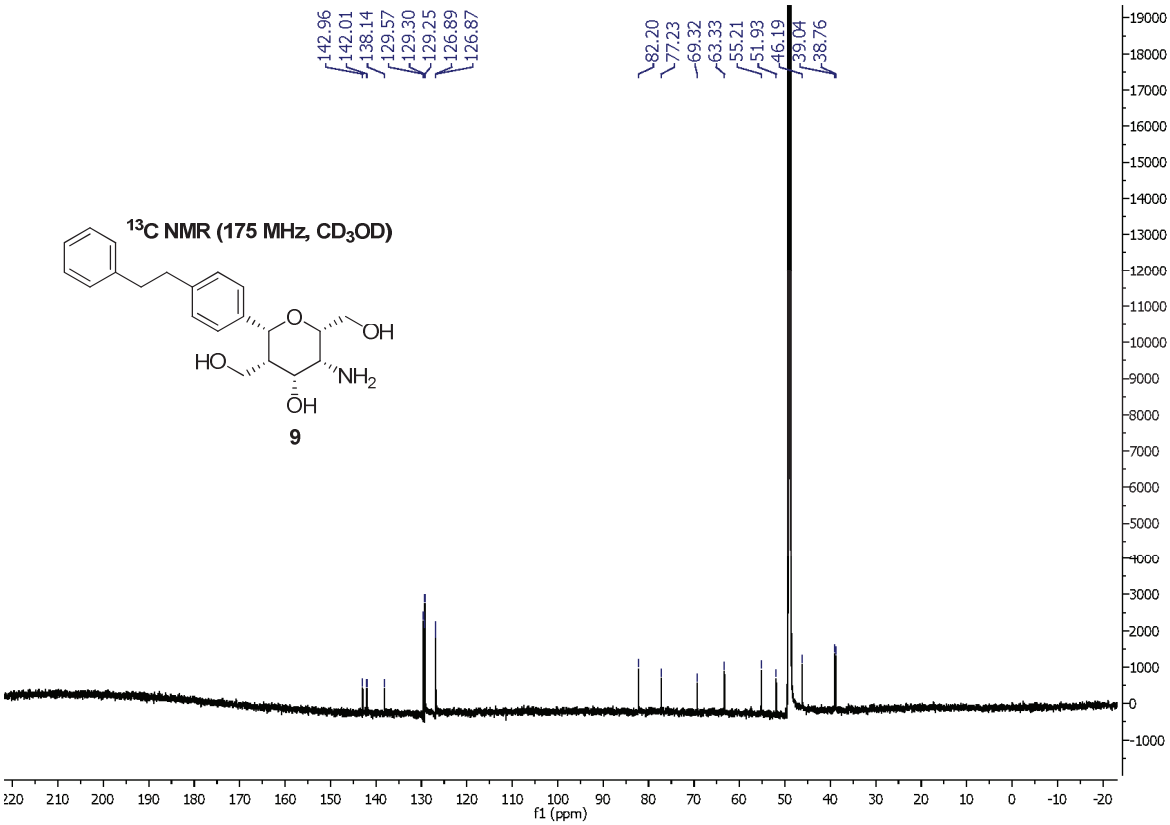

$^1$H NMR (500 MHz, $CD_2Cl_2$)
Ph
O
OH
OH
O
NBn
7
7.54
7.52
7.41
7.40
7.37
7.32
7.29
7.25
5.32 Methylene Chloride-d2
4.85
4.27
4.24
4.14
4.14
4.13
4.11
4.08
3.87
3.12
3.12
2.32
2.07
f1 (ppm)

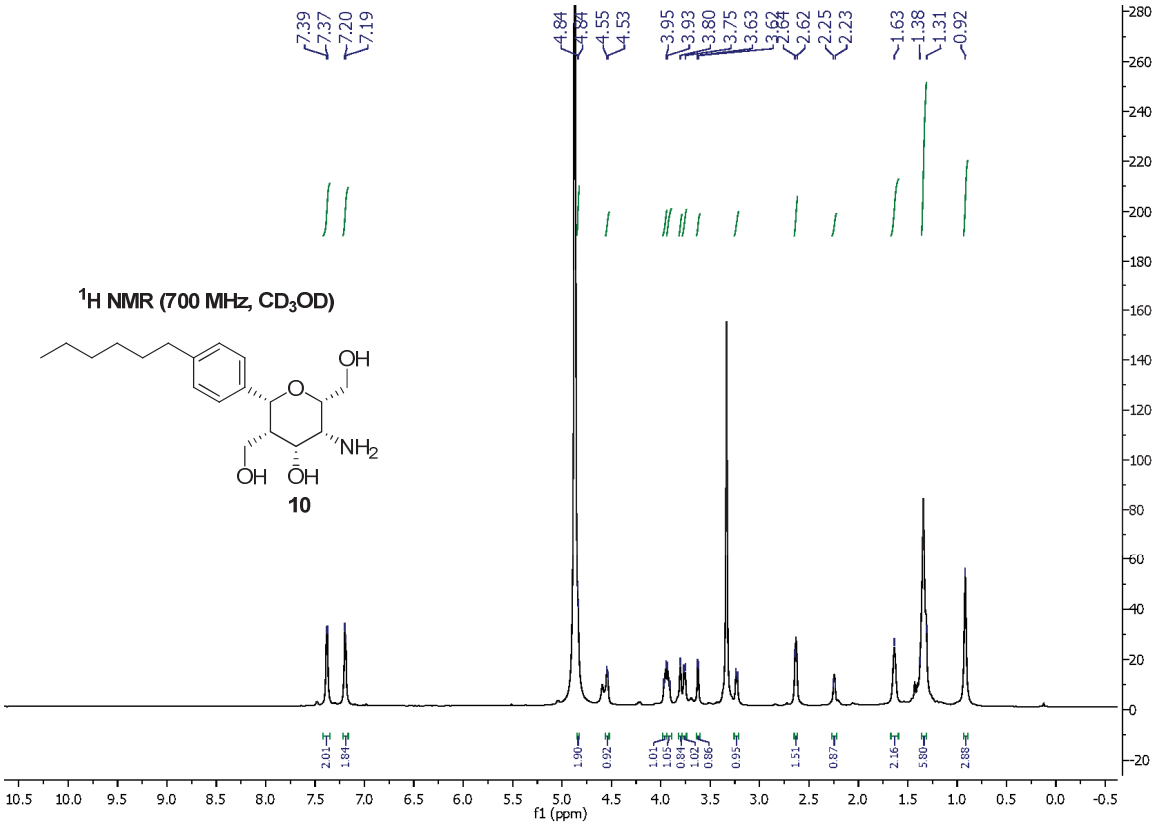

$^{13}$C NMR (125 MHz, $CD_2Cl_2$)
Ph
O
OH
OH
O
NBn
7
141.03
138.54
132.07
131.99
129.06
128.98
128.91
128.89
127.87
126.51
123.72
122.68
89.78
89.62
80.44
79.83
70.69
64.52
64.35
62.25
61.94
54.00
41.36
f1 (ppm)


7.94
7.93
7.88
7.87
7.84
7.83
7.80
7.78
7.73
7.71
5.36
4.94
4.92
4.80
4.79
4.78
4.77
4.56
4.52
4.51
4.33
4.31
3.92
3.90
3.82
3.82
3.65
3.58
2.43
2.43
1H NMR (700 MHz, CDCl3/CD3OD, 2:1)
OH
OH
NBn
8
f1 (ppm)


140.65
137.95
131.67
128.43
128.04
126.96
125.74
120.91
83.13
79.28
79.02
76.98
68.80
63.43
59.74
59.61
59.57
40.51
13C NMR (175 MHz, CDCl3/CD3OD, 2:1)
OH
OH
NBn
8
f1 (ppm)


7.38
7.36
7.26
7.24
7.19
7.16
4.84
4.84
4.55
4.53
3.96
3.95
3.93
3.80
3.62
3.62
2.93
2.24
$^1$H NMR (700 MHz, CD$_3$OD)
O
OH
HO
NH$_2$
OH
9
f1 (ppm)

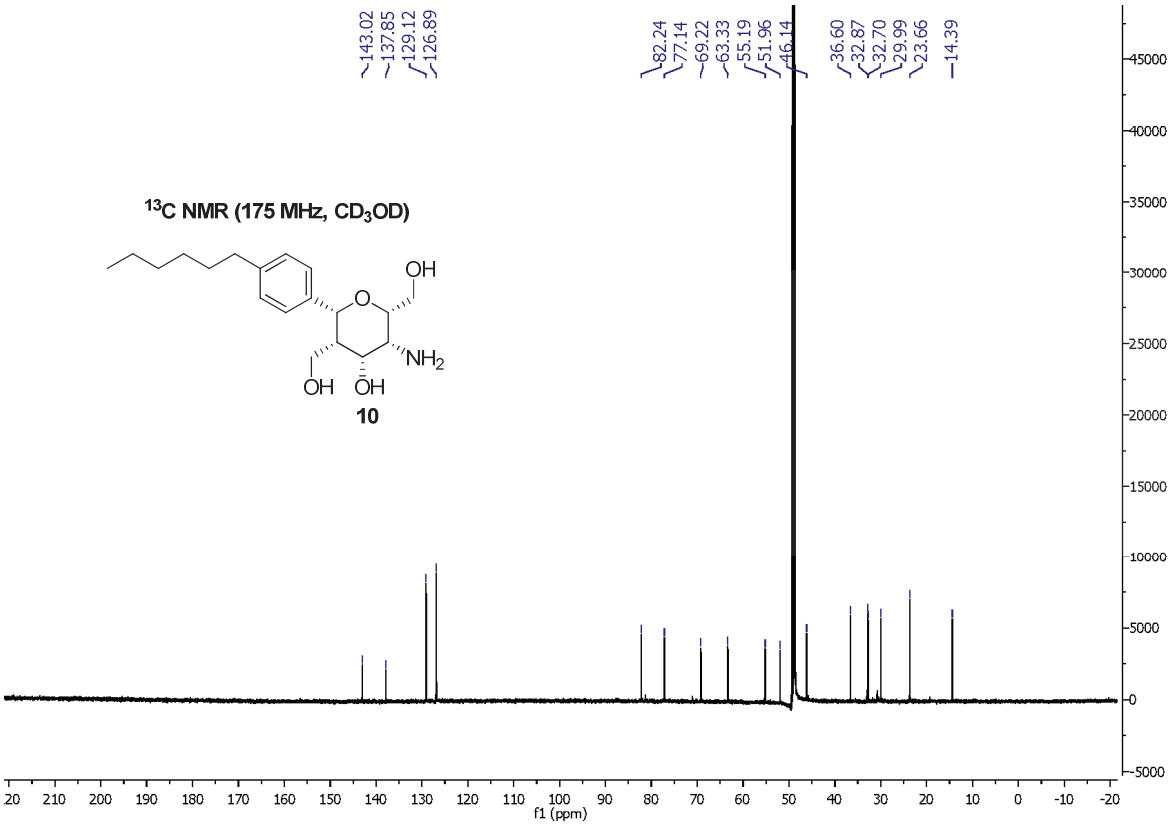

142.96
142.01
138.14
129.57
129.30
129.25
126.89
126.87
82.20
77.23
69.32
63.33
55.21
51.93
46.19
39.04
38.76
$^{13}$C NMR (175 MHz, CD$_3$OD)
O
OH
HO
NH$_2$
OH
9
f1 (ppm)




$^{1}$H NMR (700 MHz, $CD_3OD$)



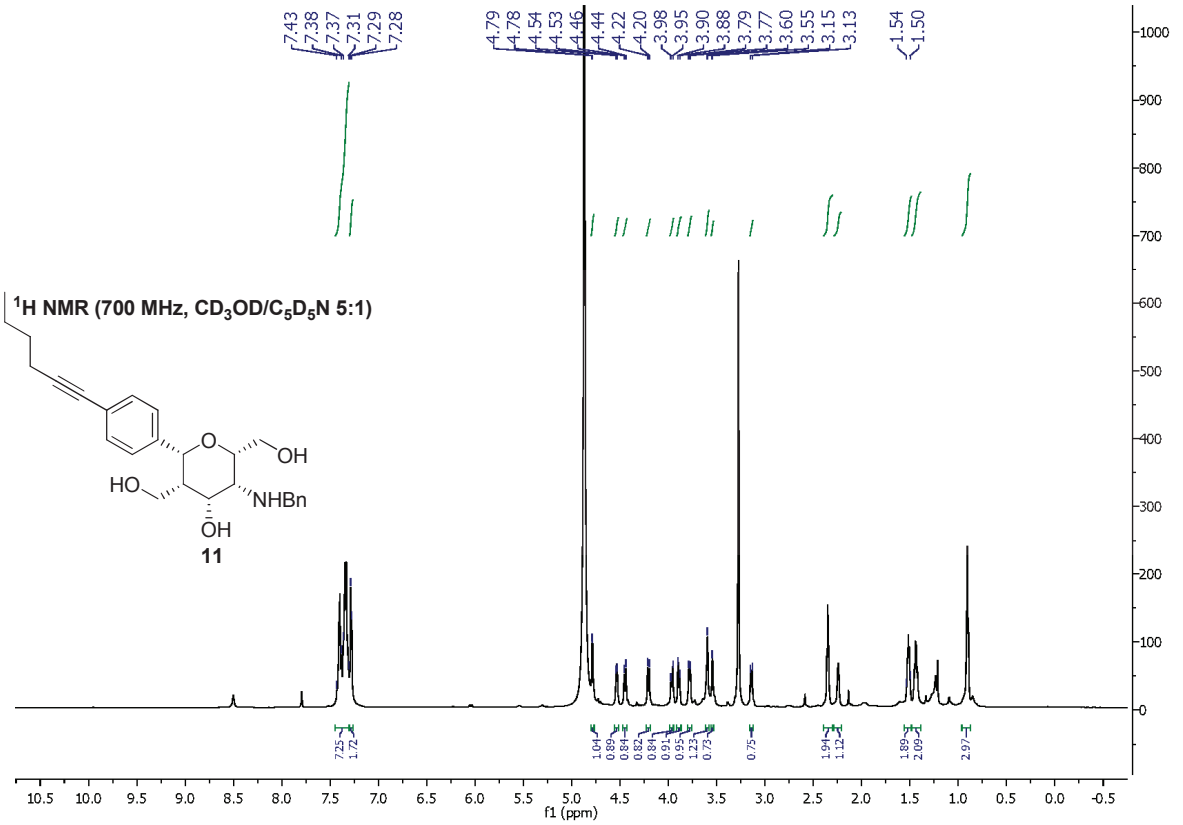

**10**

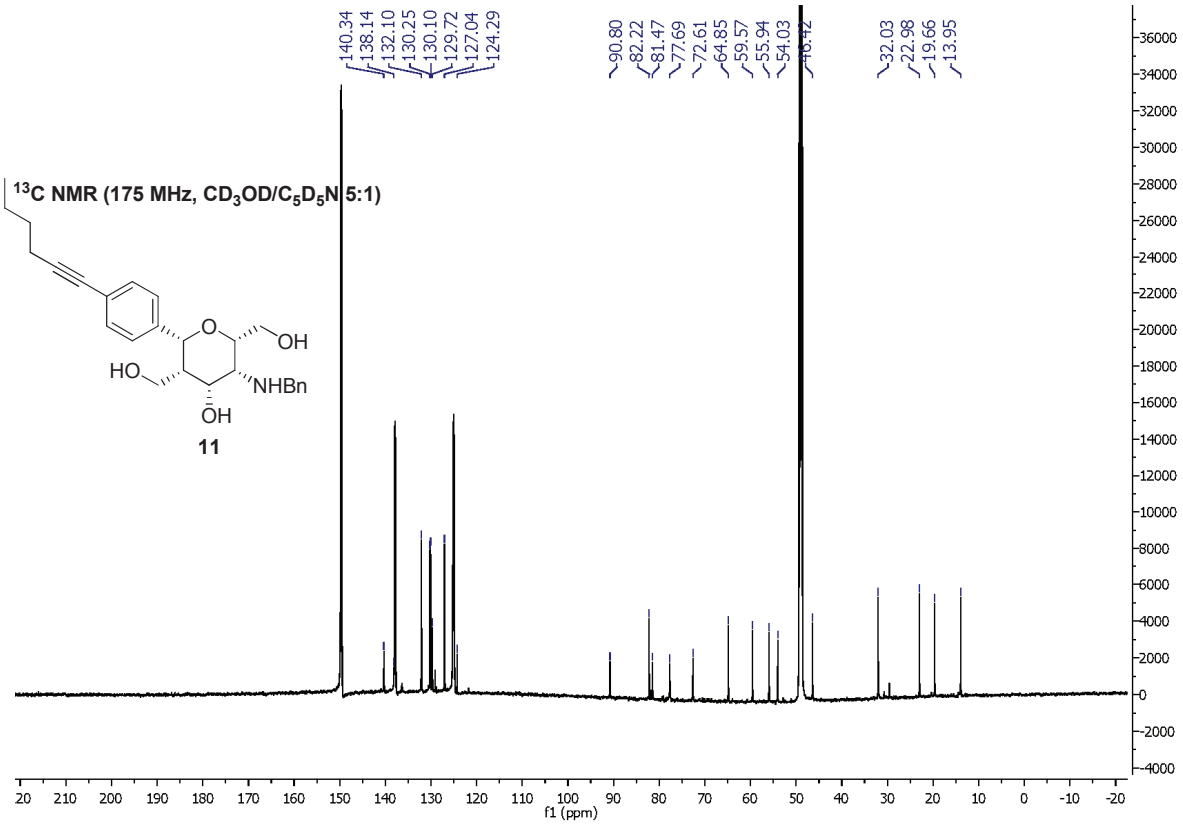


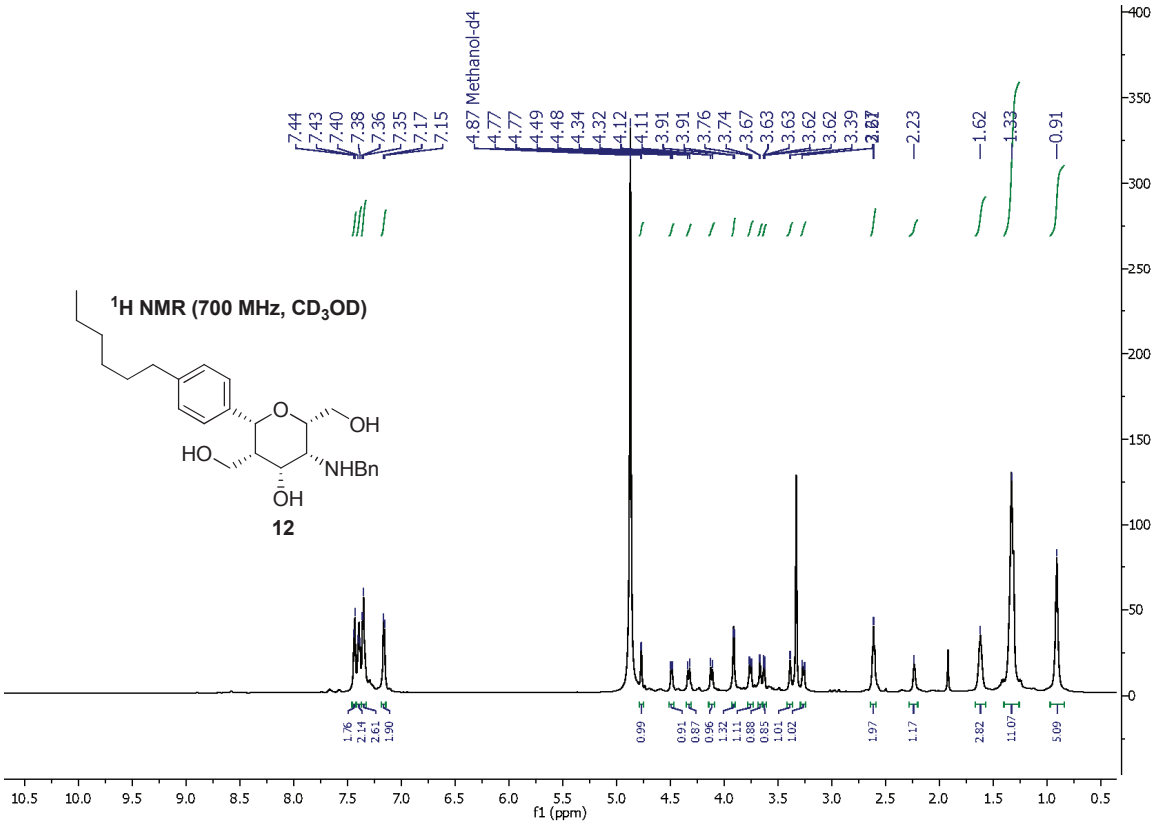

$^{13}$C NMR (175 MHz, $CD_3OD$)

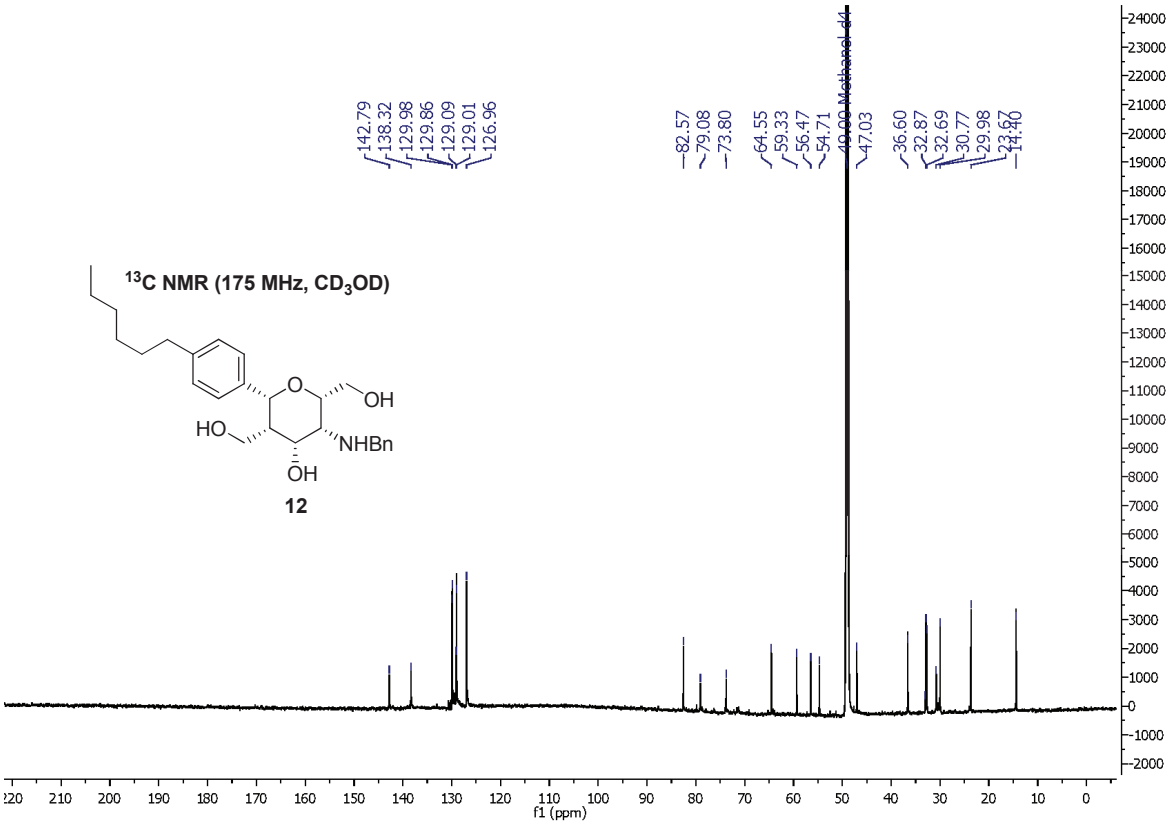


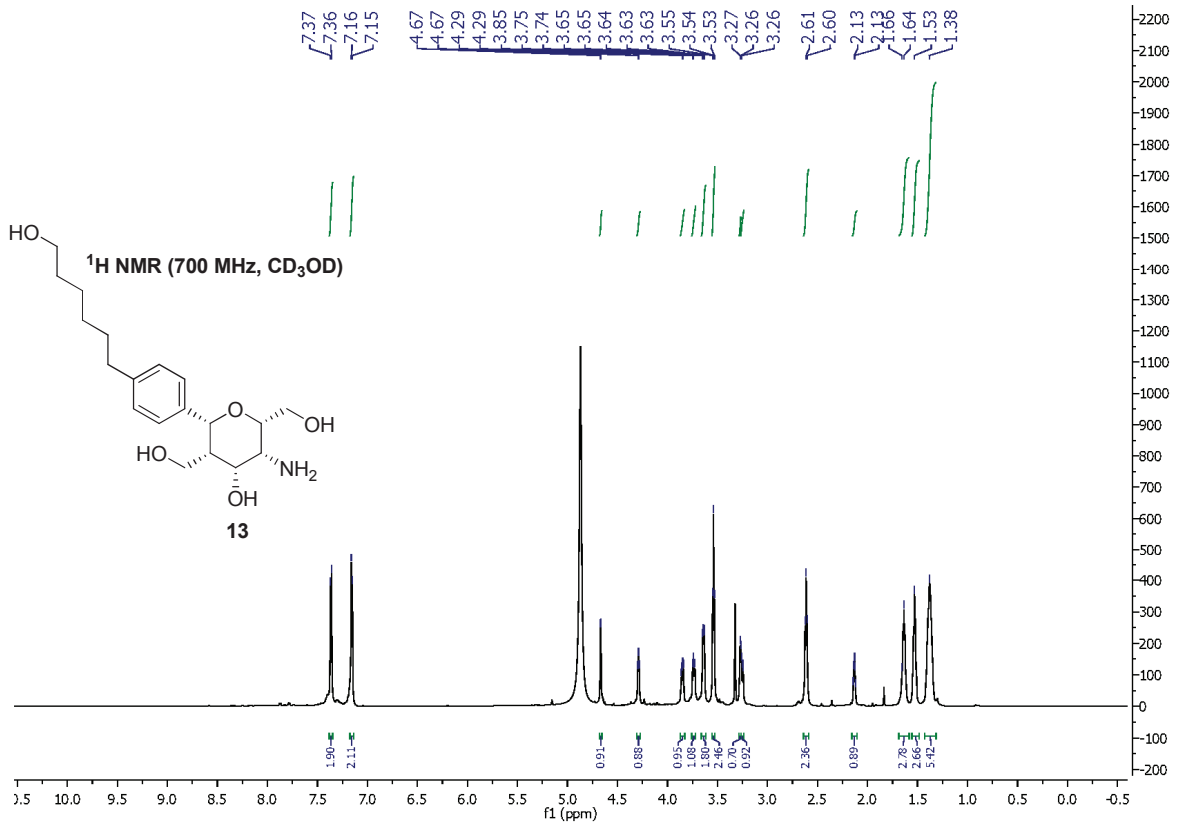

**10**

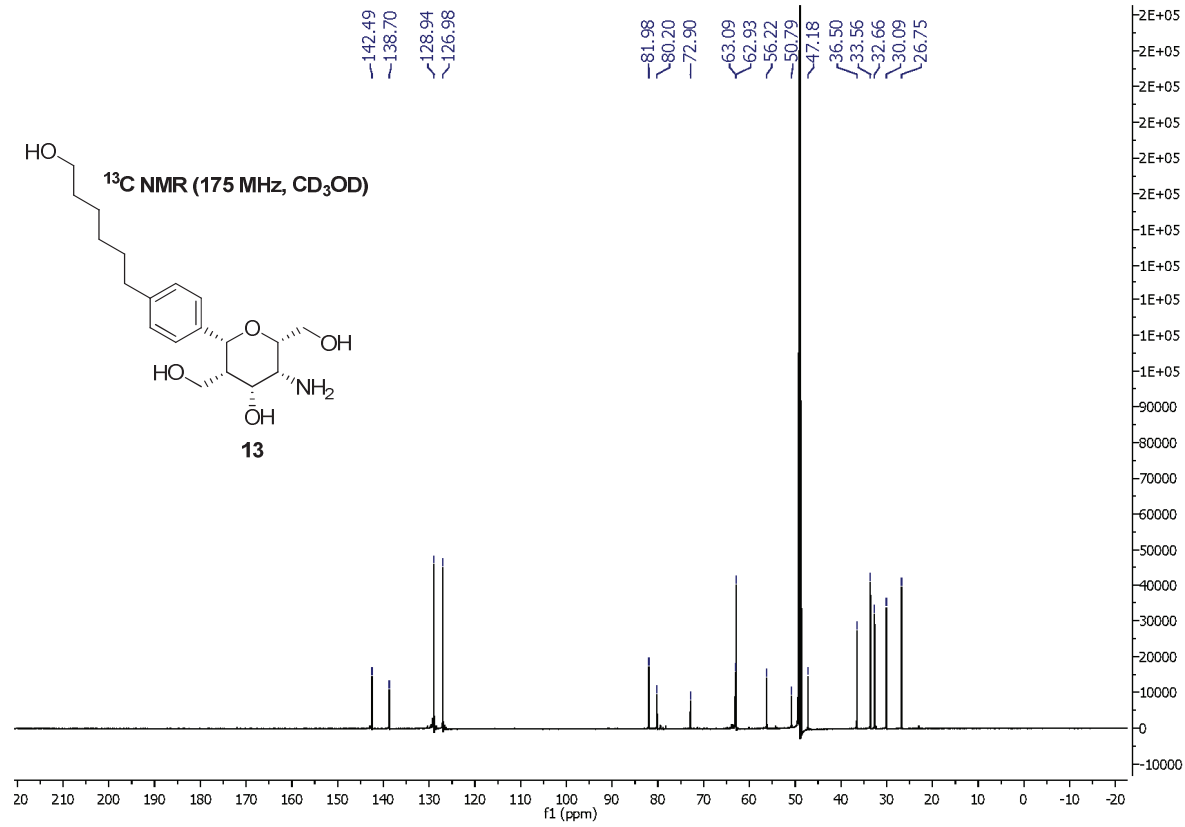

7.43
7.38
7.37
7.31
7.29
7.28
4.79
4.78
4.54
4.53
4.46
4.44
4.22
4.20
3.98
3.95
3.90
3.88
3.79
3.77
3.60
3.55
3.15
3.13
1.54
1.50
1H NMR (700 MHz, CD3OD/C5D5N 5:1)
O
OH
HO
NHBn
OH
11
f1 (ppm)

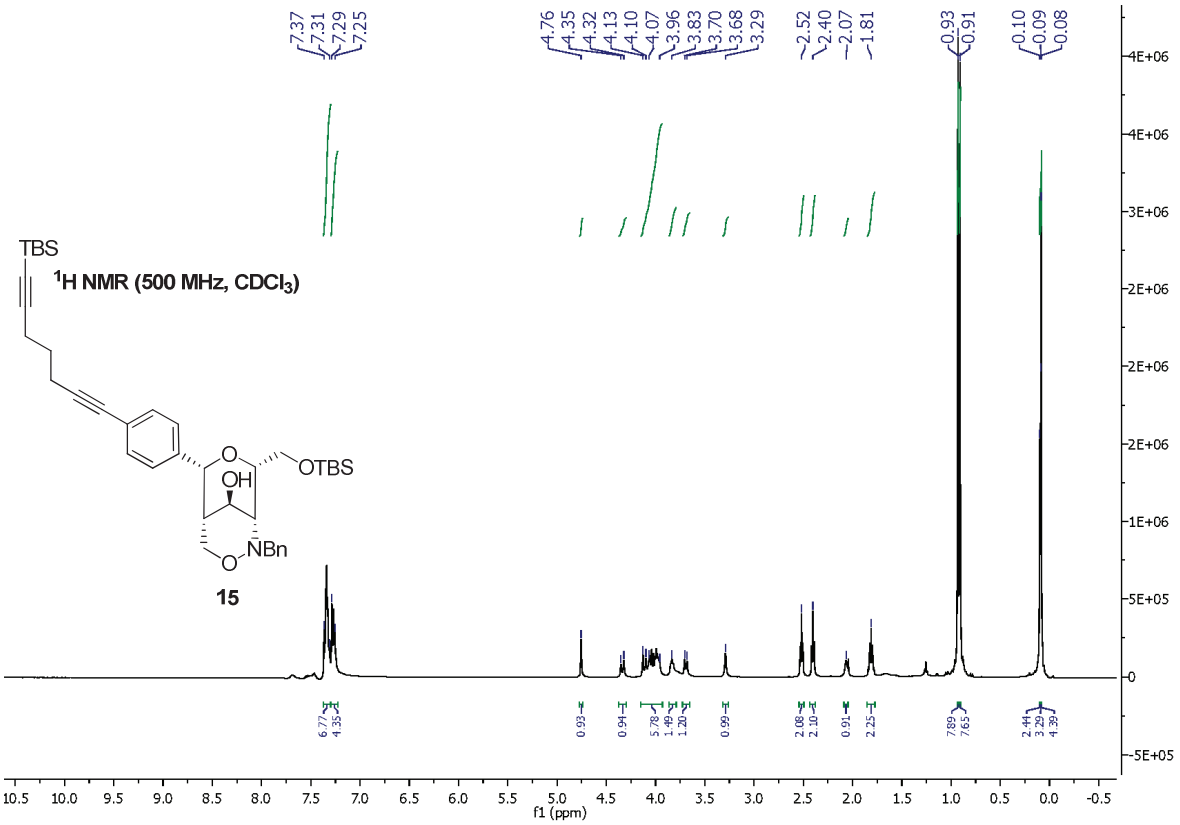

140.34
138.14
132.10
130.25
130.10
129.72
127.04
124.29
90.80
82.22
81.47
77.69
72.61
64.85
59.57
55.94
54.03
48.42
32.03
22.98
19.66
13.95
13C NMR (175 MHz, CD3OD/C5D5N 5:1)
O
OH
HO
NHBn
OH
11
f1 (ppm)

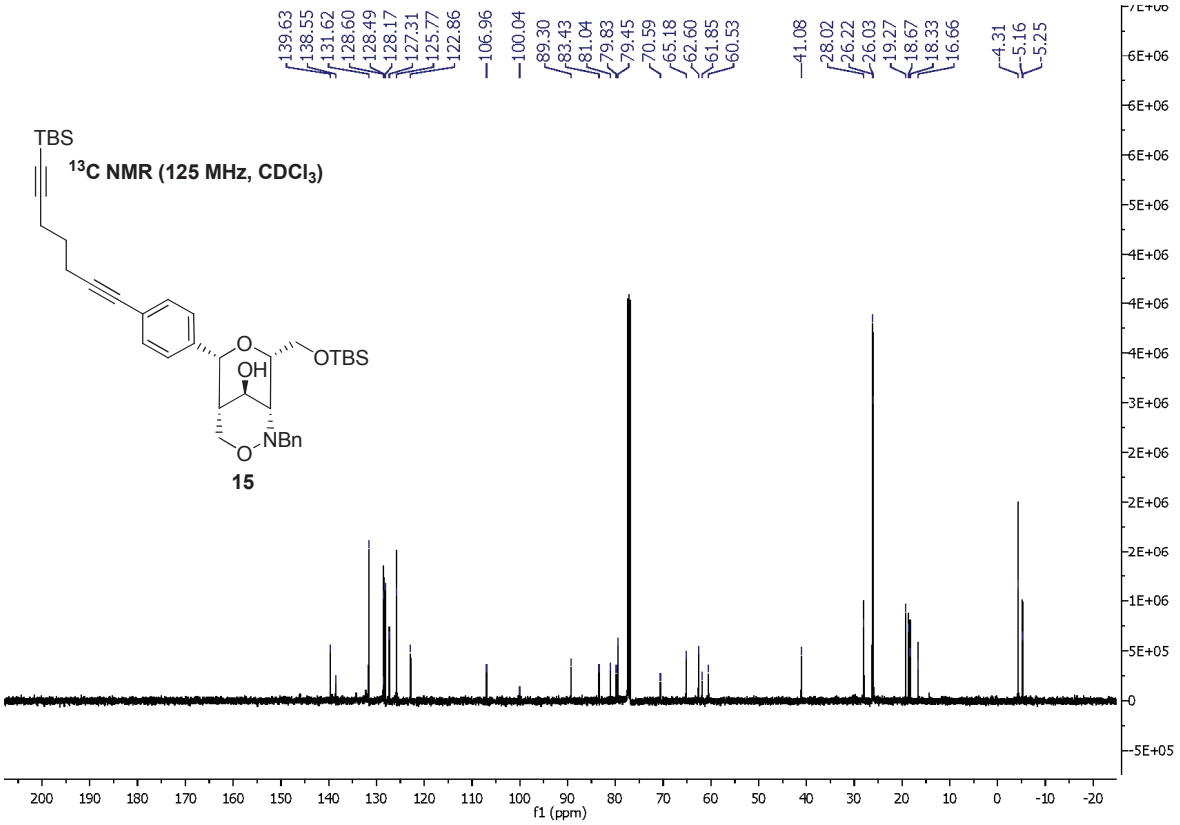

$^1$H NMR (700 MHz, CD$_3$OD)
O
OH
HO
NHBn
OH
12
Methanol-d4
7.44
7.43
7.40
7.38
7.36
7.35
7.17
7.15
4.87
4.77
4.77
4.49
4.48
4.34
4.32
4.12
4.11
3.91
3.91
3.76
3.74
3.67
3.63
3.63
3.62
3.62
3.39
2.23
1.62
1.33
0.91
f1 (ppm)

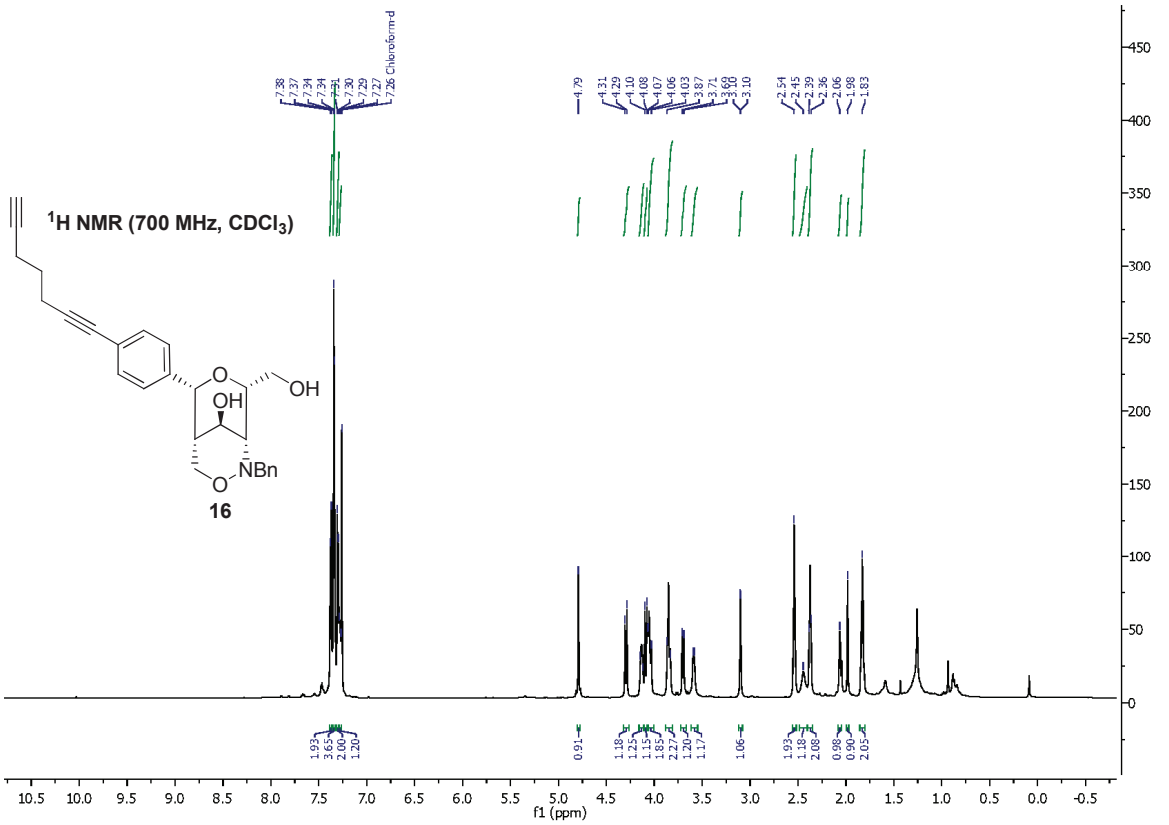

$^{13}$C NMR (175 MHz, CD$_3$OD)
O
OH
HO
NHBn
OH
12
142.79
138.32
129.98
129.86
129.09
129.01
126.96
82.57
79.08
73.80
64.55
59.33
56.47
54.71
49.00 Methanol-d4
47.03
36.60
32.87
32.69
30.77
29.98
23.67
14.40
f1 (ppm)

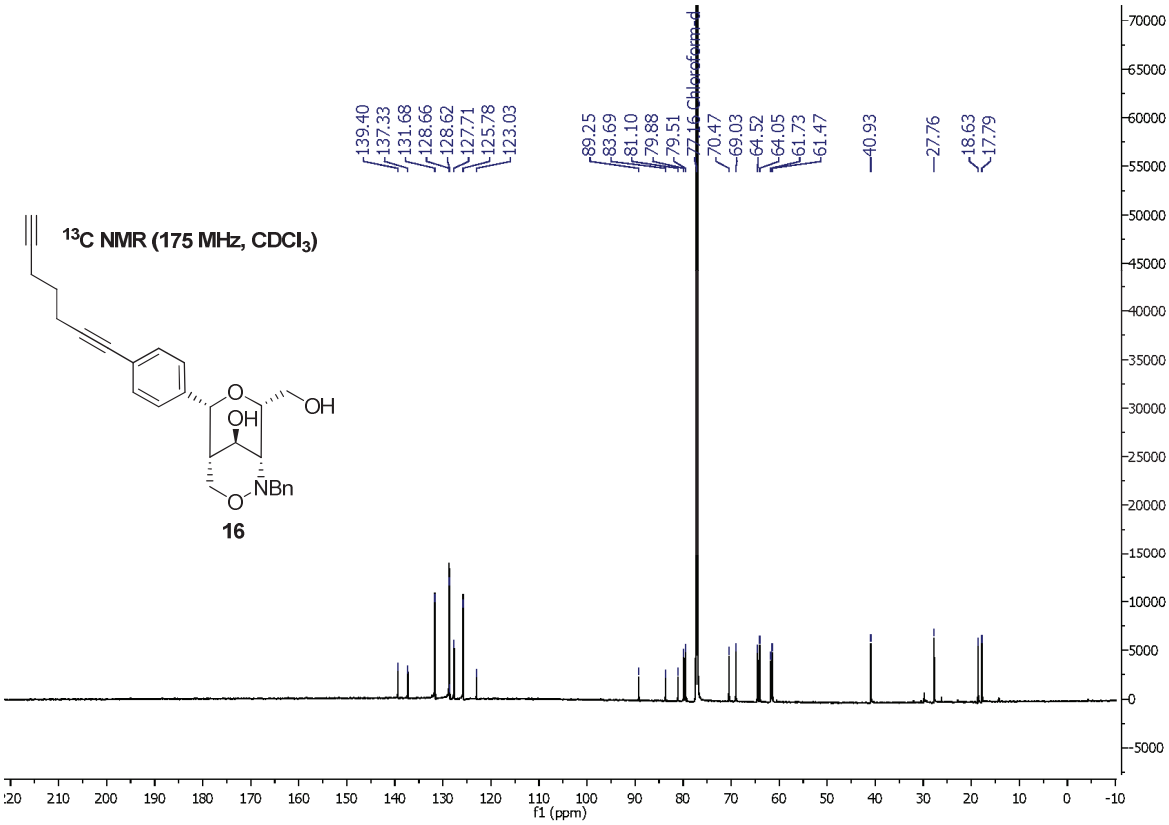

7.37
7.36
7.16
7.15
4.67
4.67
4.29
4.29
3.85
3.75
3.74
3.65
3.65
3.64
3.63
3.63
3.55
3.54
3.53
3.27
3.26
3.26
2.61
2.60
2.13
2.13
1.65
1.64
1.53
1.38
HO
$^{1}$H NMR (700 MHz, CD$_3$OD)
O
OH
HO
NH$_2$
OH
13
1.90
2.11
0.91
0.88
0.95
1.08
1.80
2.46
0.70
0.92
2.36
0.89
2.78
2.66
5.42
f1 (ppm)

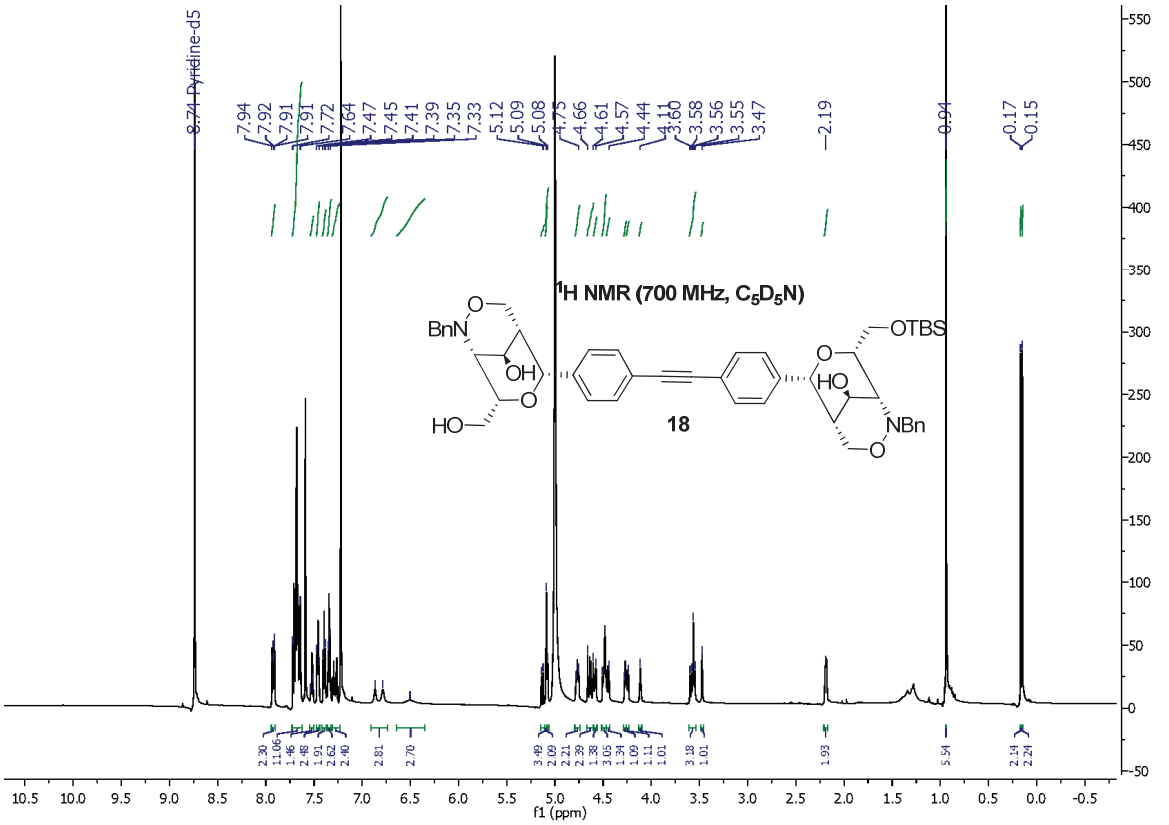

142.49
138.70
128.94
126.98
81.98
80.20
72.90
63.09
62.93
56.22
50.79
47.18
36.50
33.56
32.66
30.09
26.75
HO
$^{13}$C NMR (175 MHz, CD$_3$OD)
O
OH
HO
NH$_2$
OH
13
f1 (ppm)

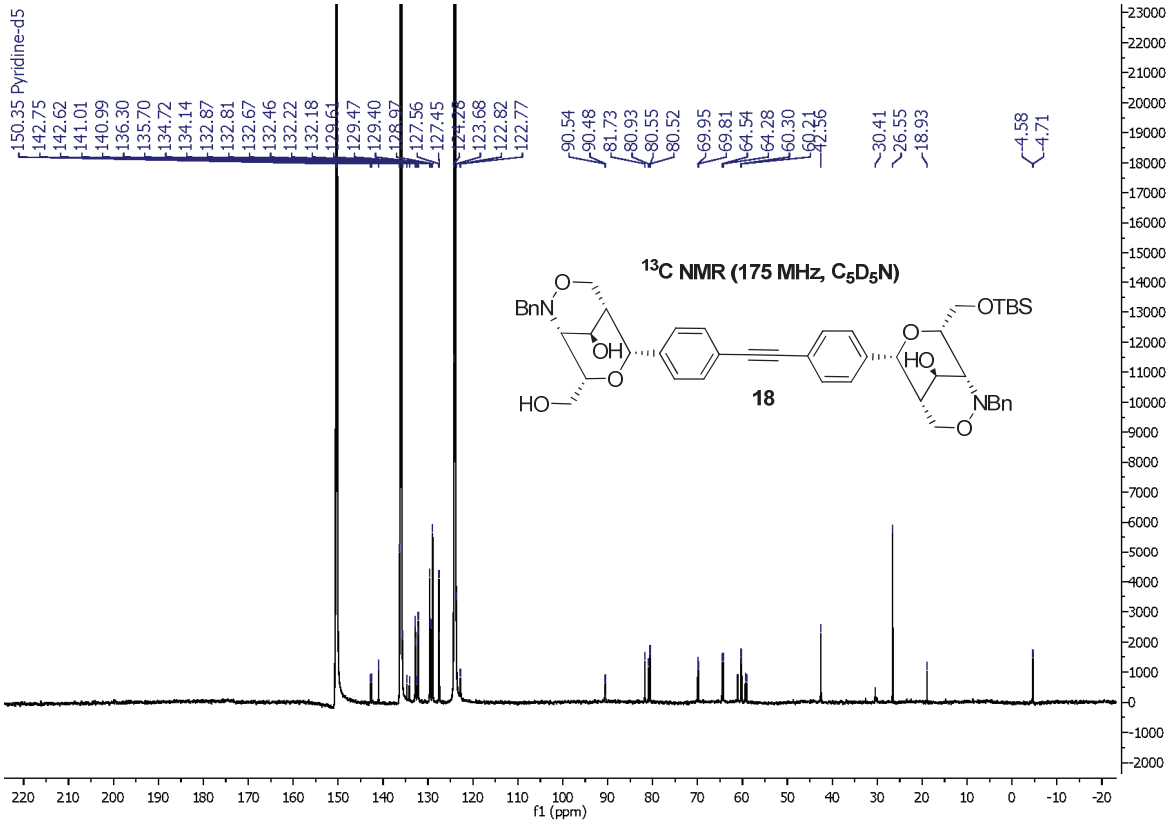

TBS
$^{1}$H NMR (500 MHz, $CDCl_3$)
OTBS
OH
NBn
15
f1 (ppm)

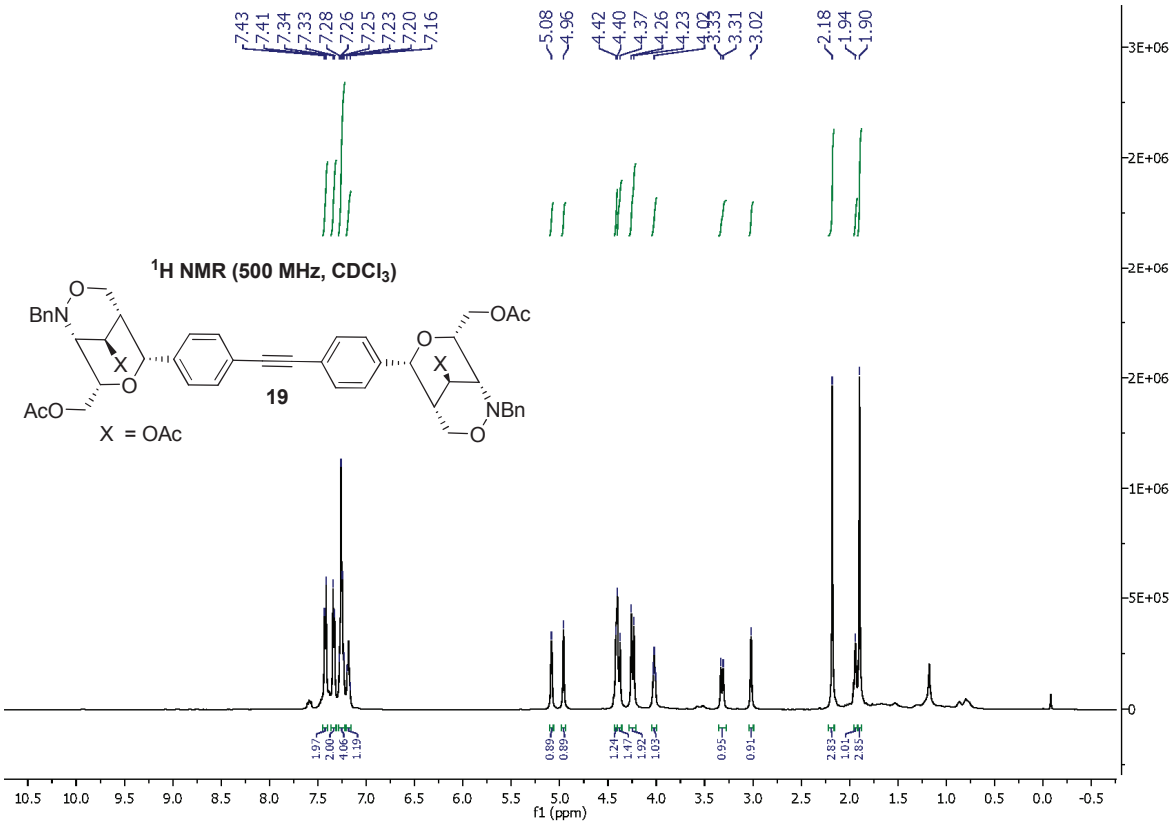

TBS
$^{13}$C NMR (125 MHz, $CDCl_3$)
OTBS
OH
NBn
15
f1 (ppm)

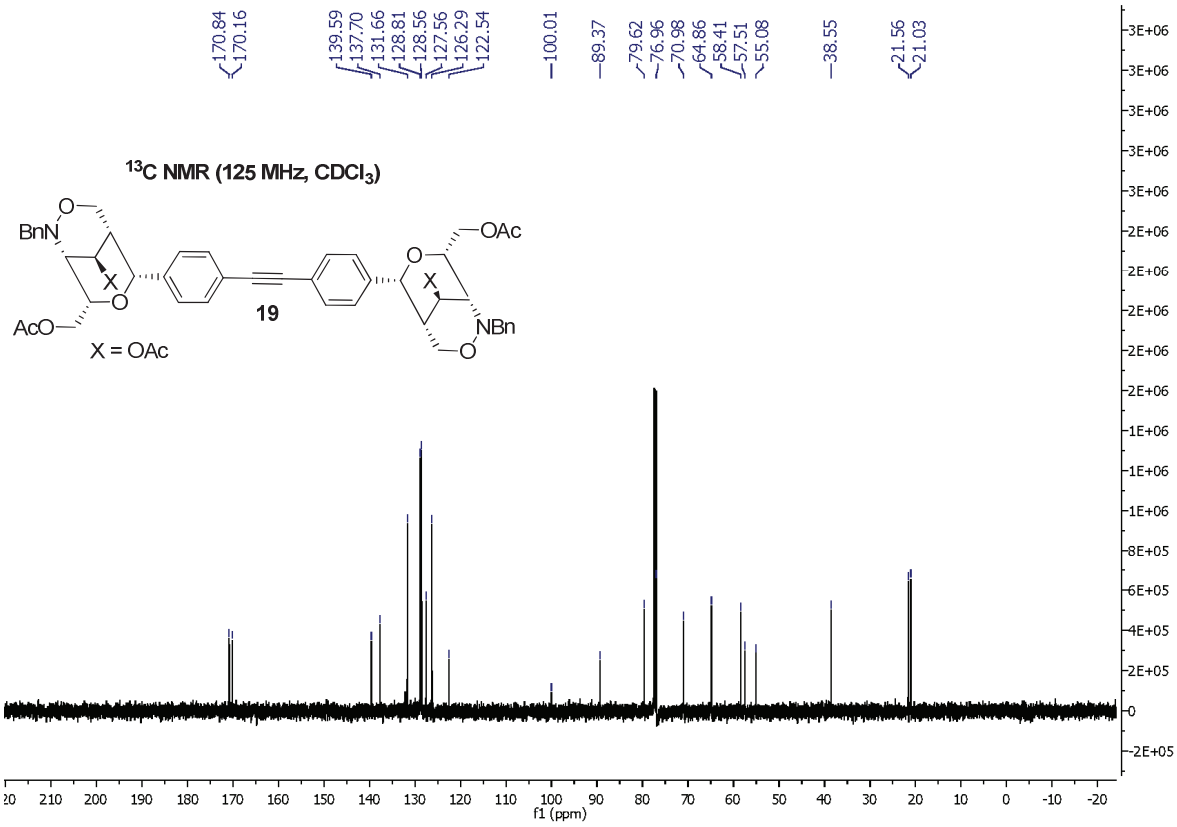

$^{1}$H NMR (700 MHz, $CDCl_3$)
OH
OH
NBn
16
f1 (ppm)

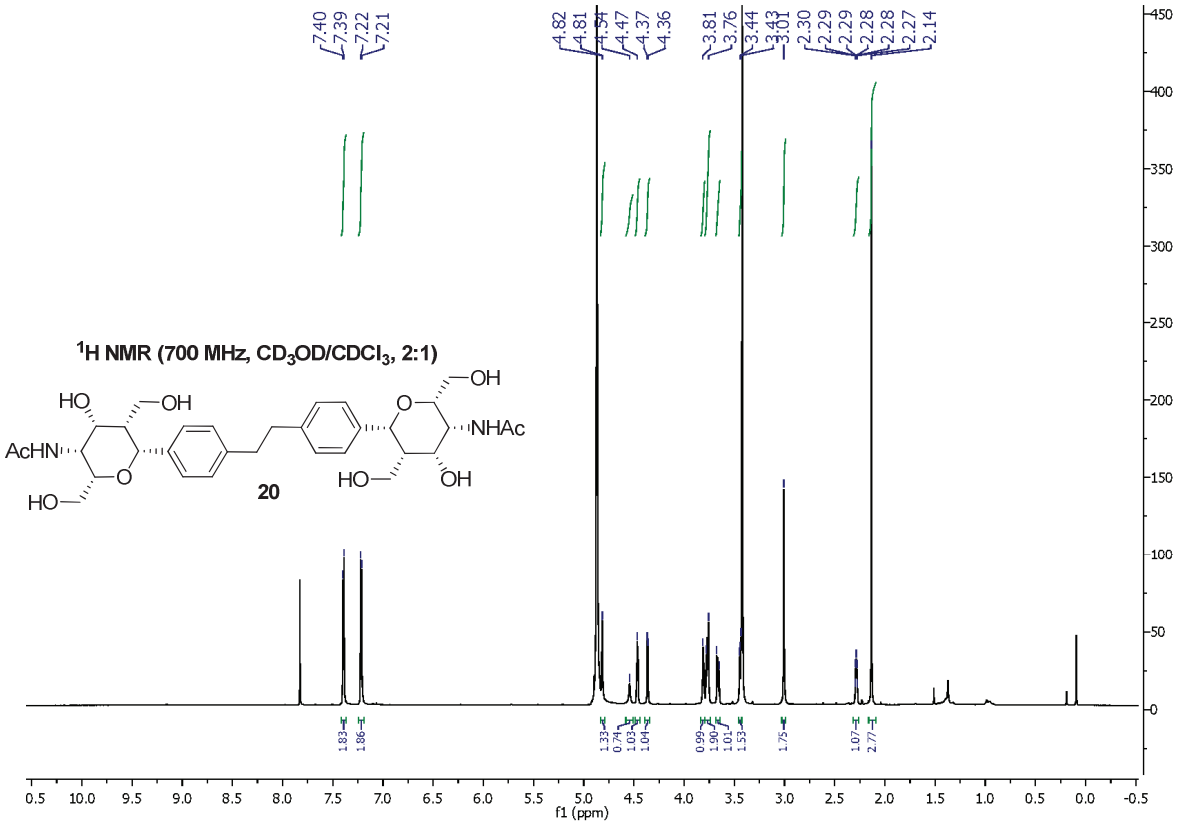

$^{13}$C NMR (175 MHz, $CDCl_3$)
OH
OH
NBn
16
f1 (ppm)


$^{1}$H NMR (700 MHz, $C_5D_5N$)
18
f1 (ppm)


$^{13}$C NMR (175 MHz, $C_5D_5N$)
18
f1 (ppm)


7.43
7.41
7.34
7.33
7.28
7.26
7.25
7.23
7.20
7.16
5.08
4.96
4.42
4.40
4.37
4.26
4.23
4.02
3.33
3.31
3.02
2.18
1.94
1.90
1H NMR (500 MHz, CDCl3)
BnN
AcO
X = OAc
19
OAc
NBn
f1 (ppm)

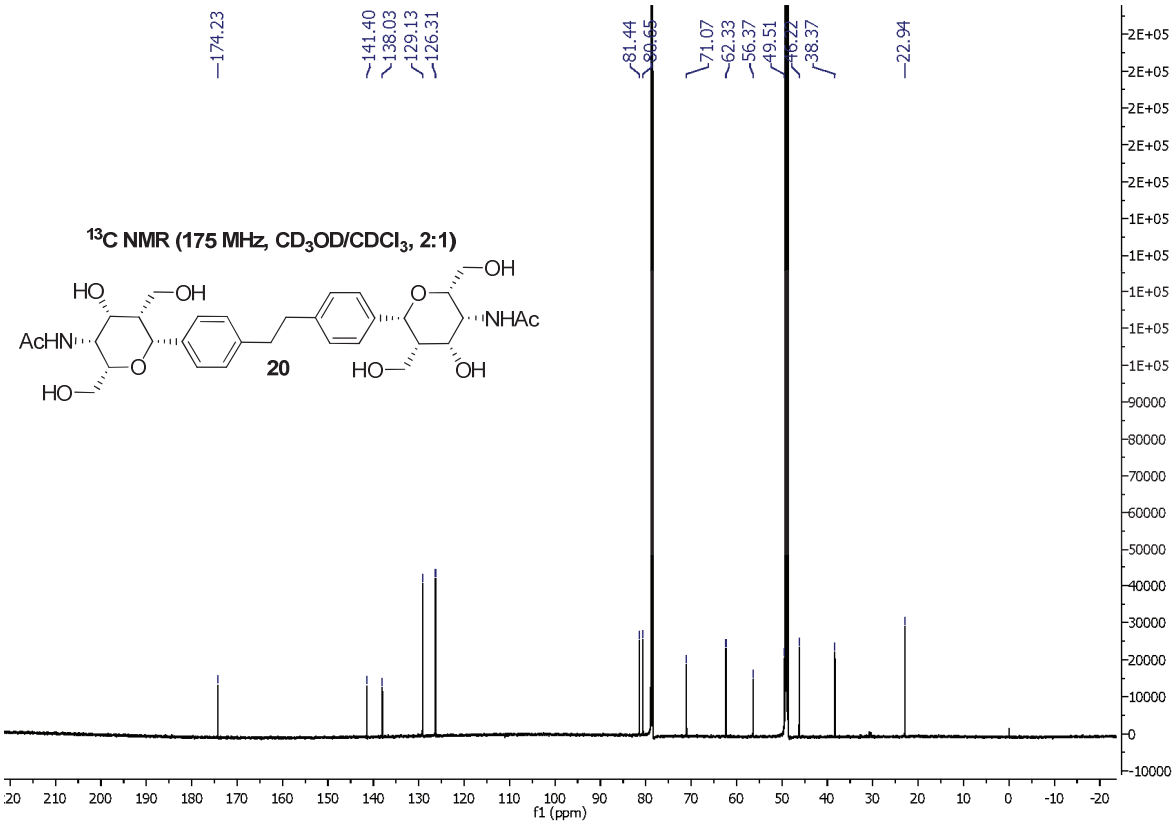

170.84
170.16
139.59
137.70
131.66
128.81
128.56
127.56
126.29
122.54
100.01
89.37
79.62
76.96
70.98
64.86
58.41
57.51
55.08
38.55
21.56
21.03
13C NMR (125 MHz, CDCl3)
BnN
AcO
X = OAc
19
OAc
NBn
f1 (ppm)




$^{1}$H NMR (700 MHz, $CD_3OD/CDCl_3$, 2:1)



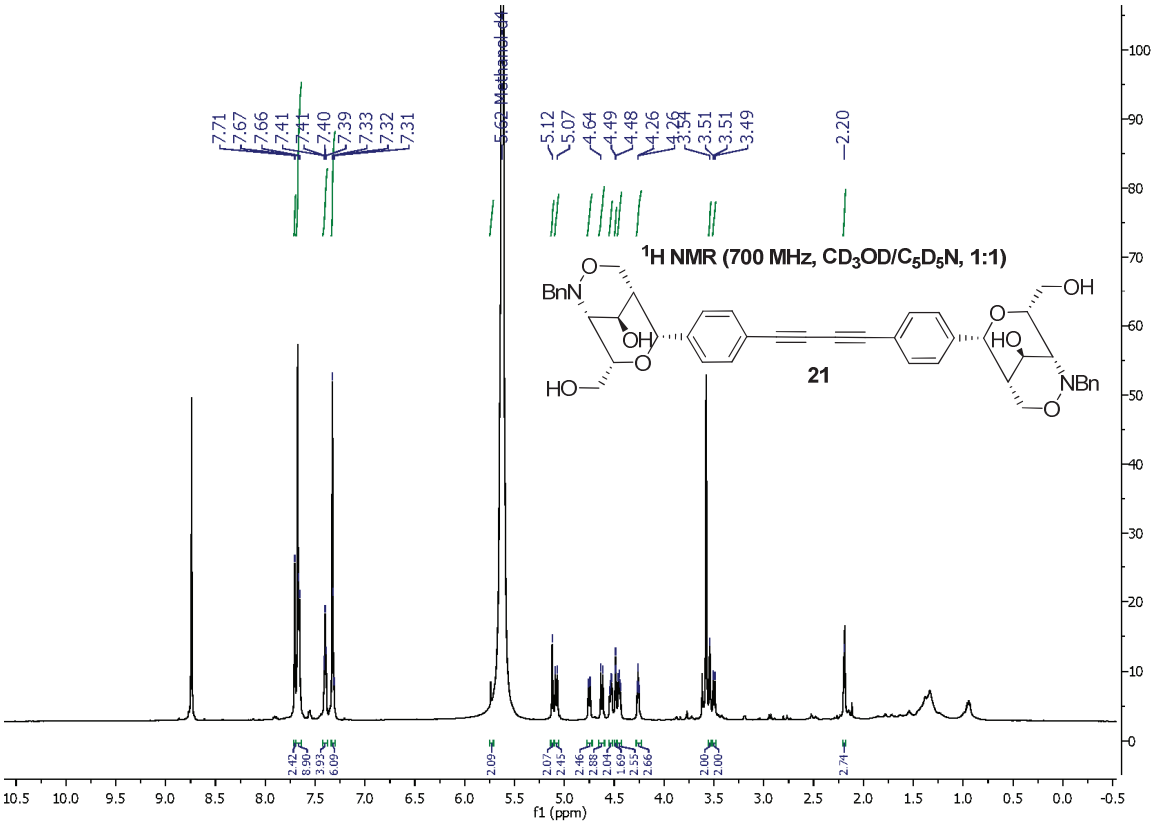

**20**




$^{13}$C NMR (175 MHz, $CD_3OD/CDCl_3$, 2:1)



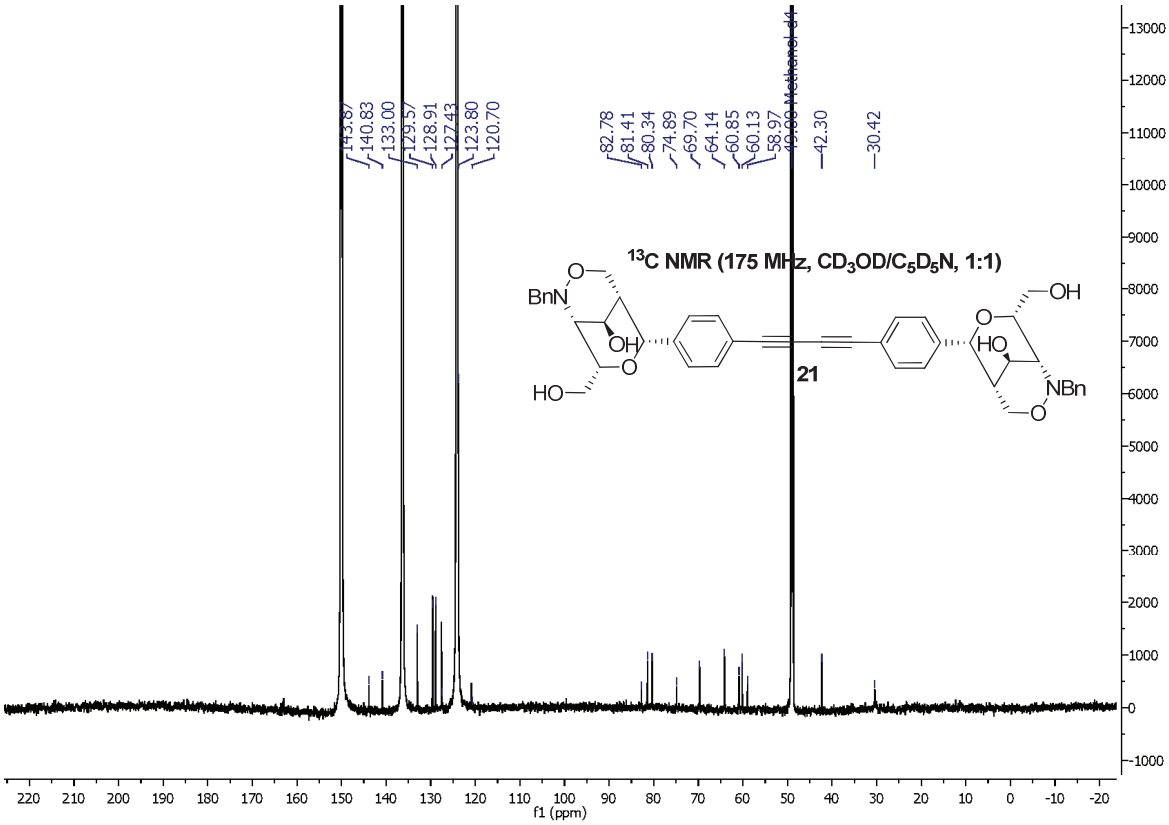

**20**




$^{1}$H NMR (700 MHz, $CD_3OD/C_5D_5N$, 1:1)



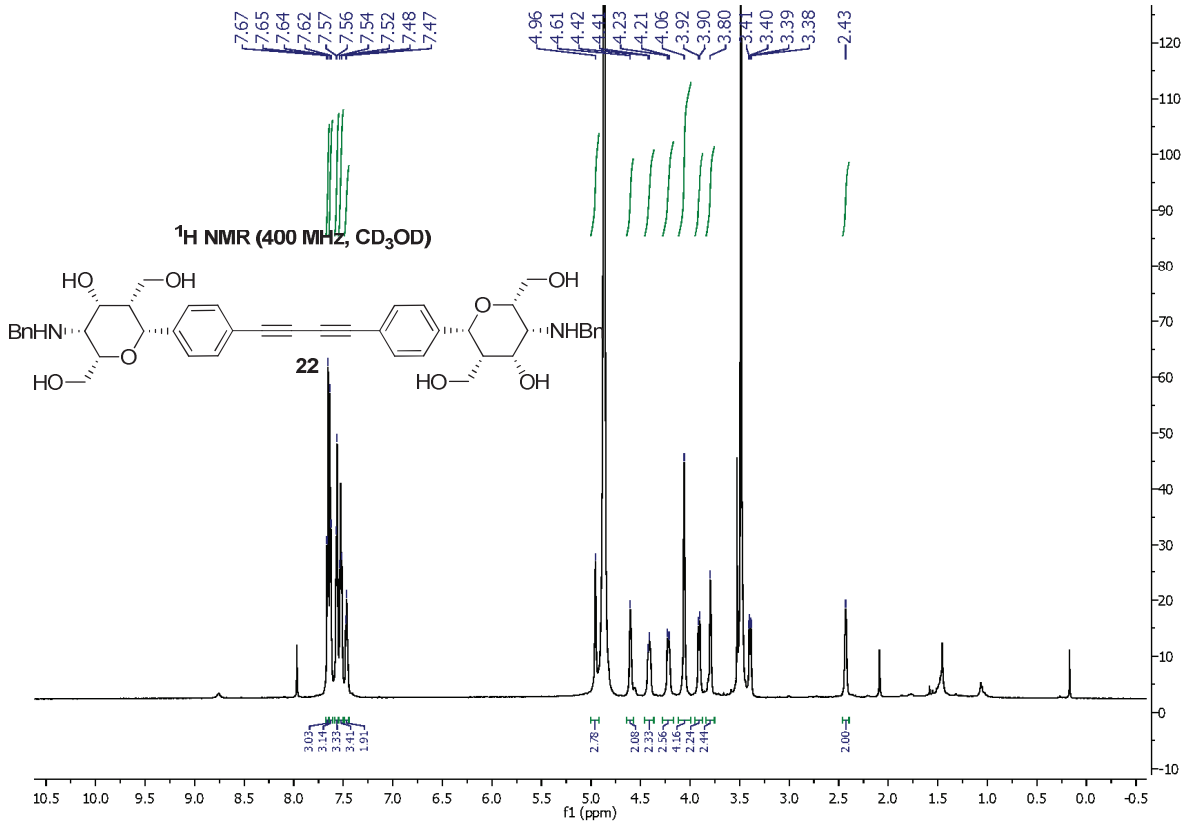

21

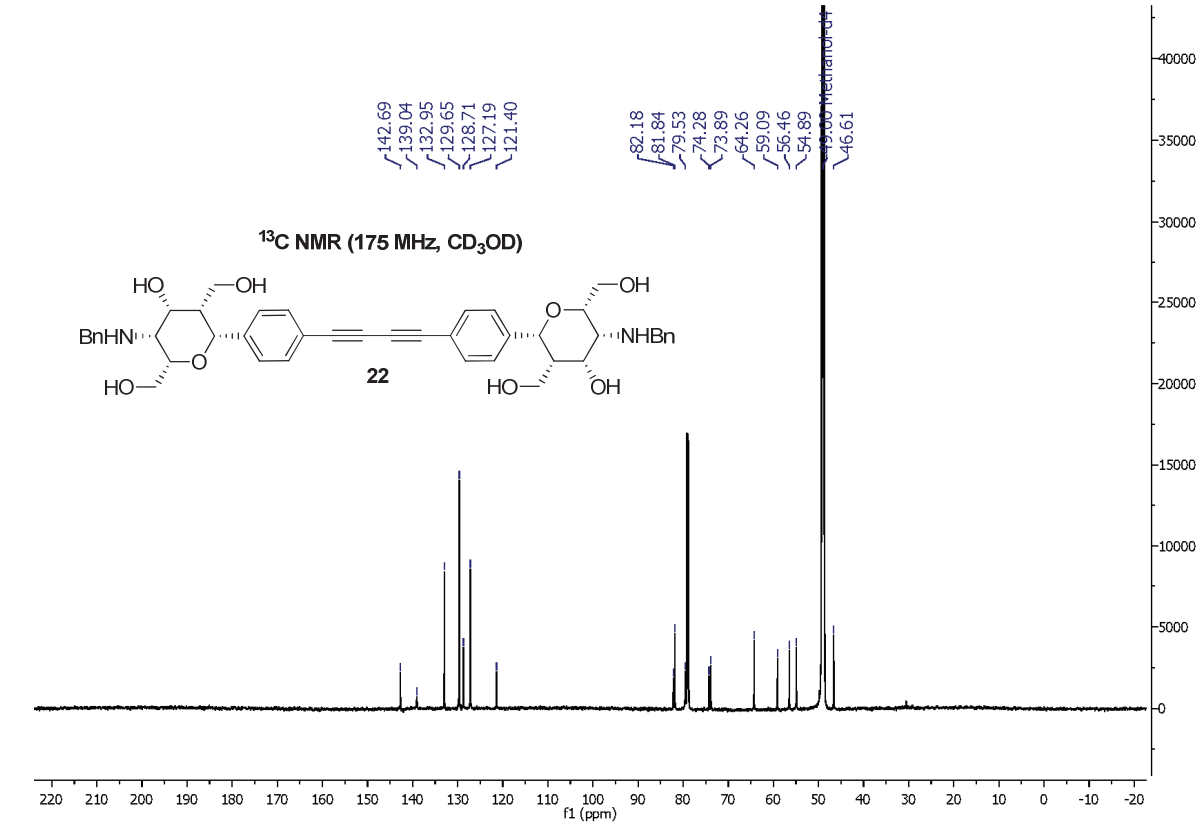


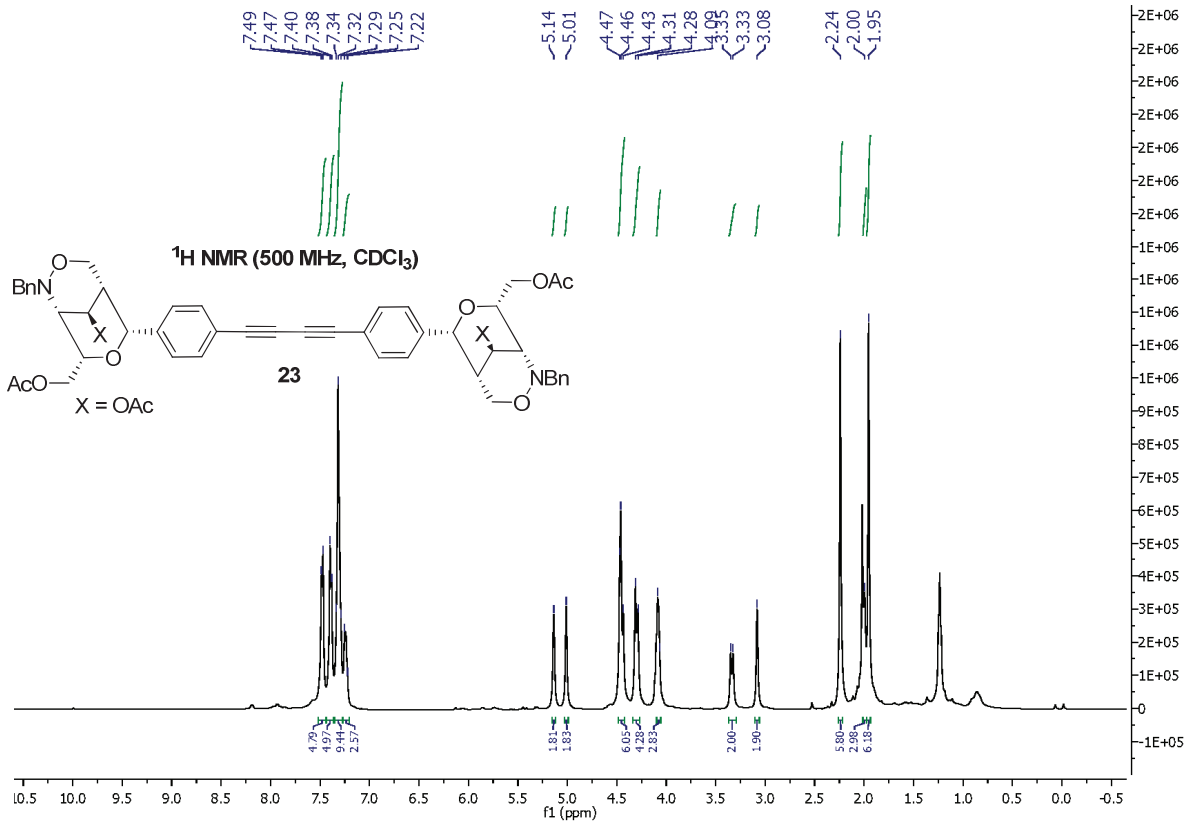

$^{13}$C NMR (175 MHz, $CD_3OD/C_5D_5N$, 1:1)

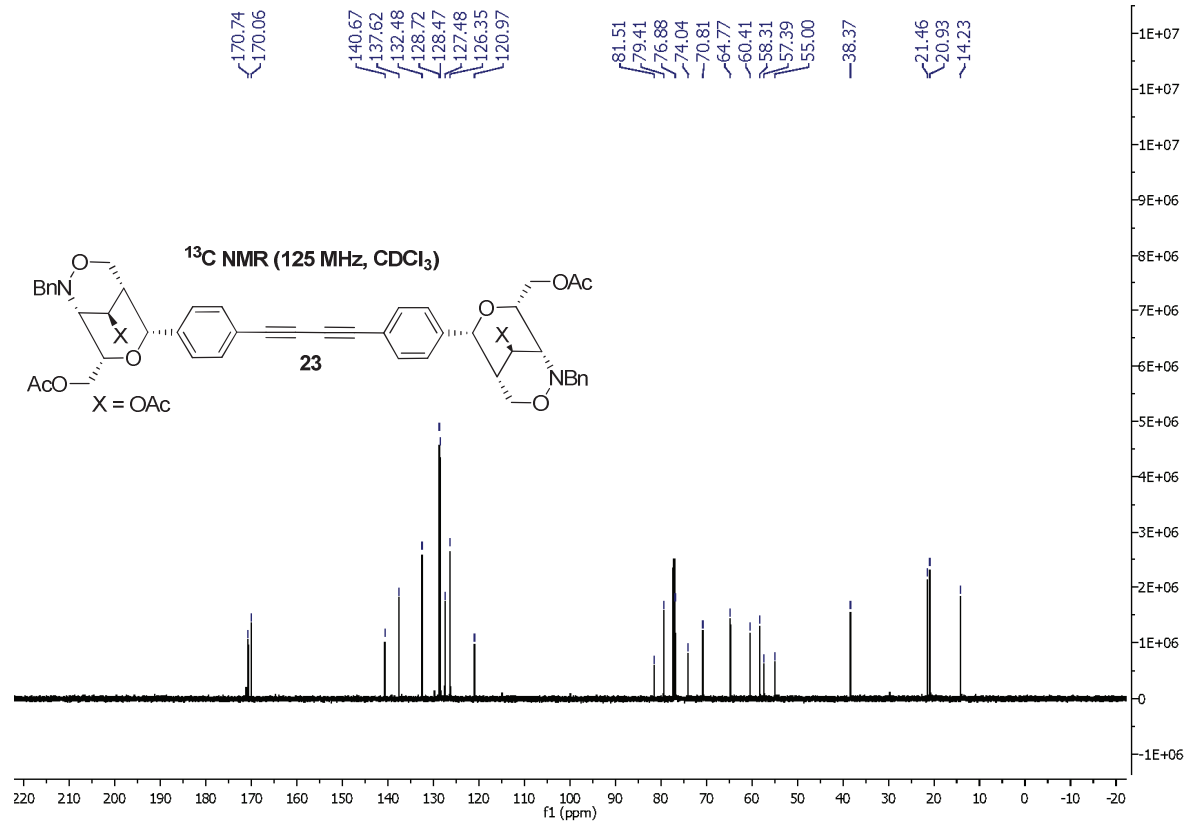


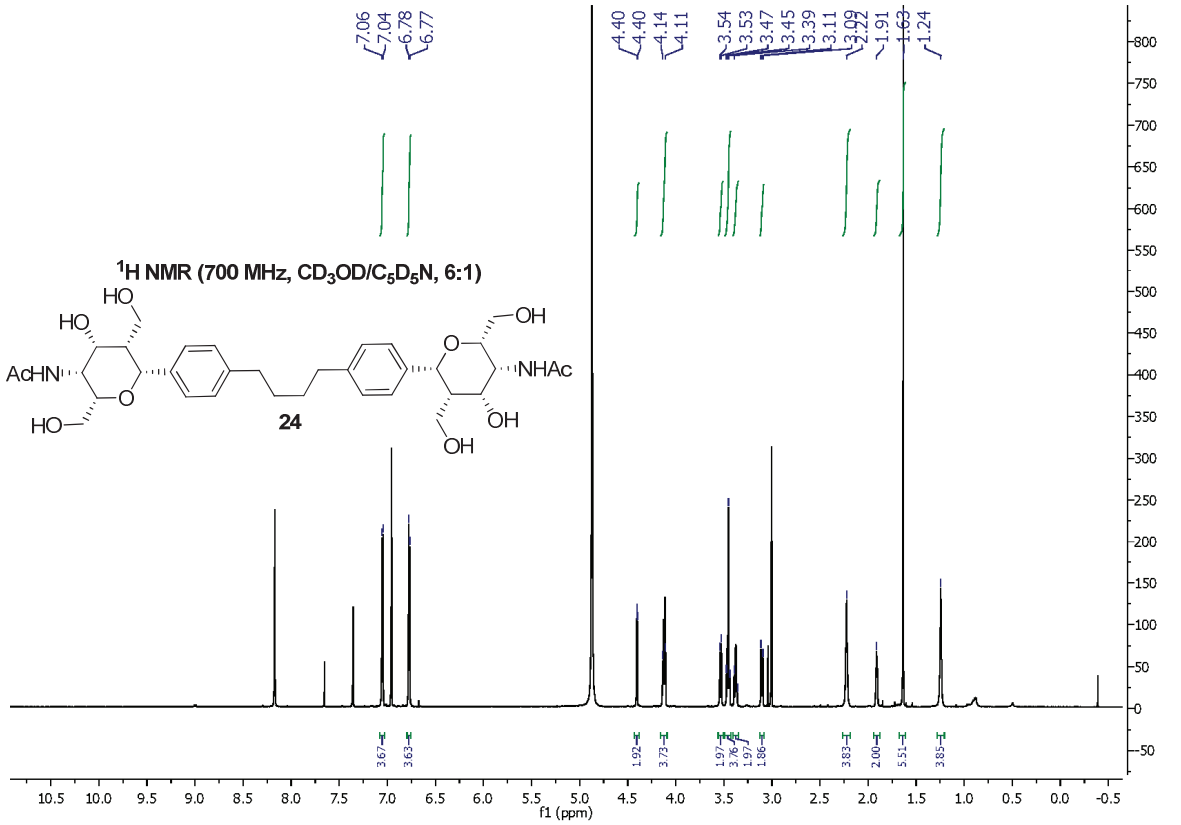

21

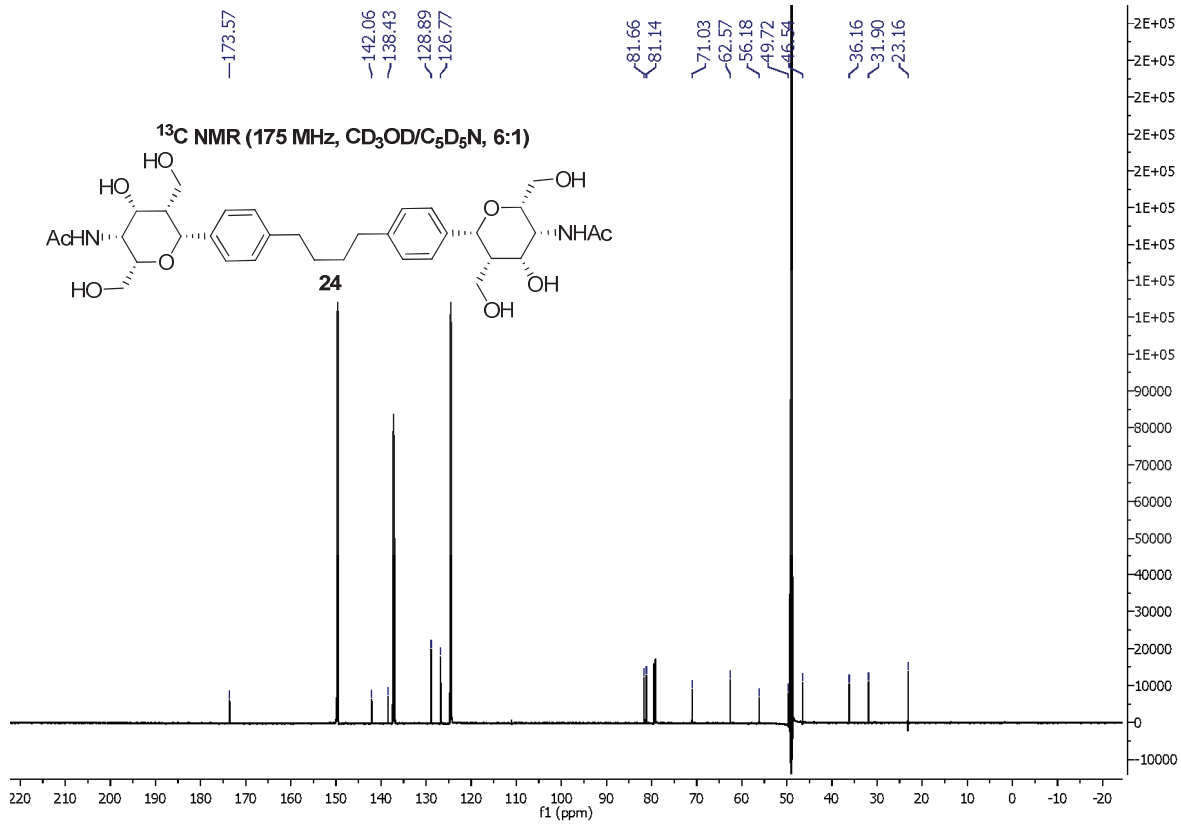

7.67
7.65
7.64
7.62
7.57
7.56
7.54
7.52
7.48
7.47
4.96
4.61
4.42
4.41
4.23
4.21
4.06
3.92
3.90
3.80
3.41
3.40
3.39
3.38
2.43
$^1$H NMR (400 MHz, CD$_3$OD)
HO
OH
BnHN
O
HO
22
OH
O
NHBn
HO
OH
3.03
3.14
3.33
3.41
1.91
2.78
2.08
2.33
2.56
4.16
2.24
2.44
2.00
f1 (ppm)

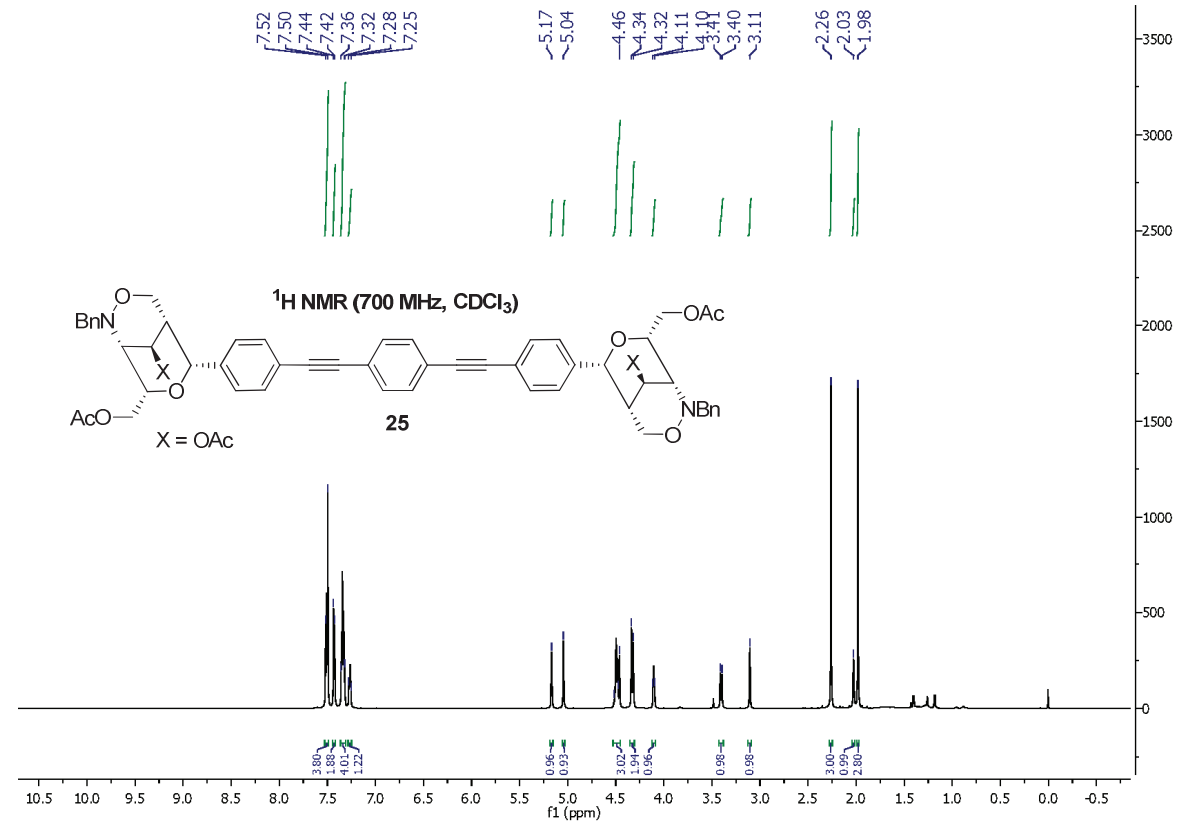

142.69
139.04
132.95
129.65
128.71
127.19
121.40
82.18
81.84
79.53
74.28
73.89
64.26
59.09
56.46
54.89
49.00 Methanol-d4
46.61
$^{13}$C NMR (175 MHz, CD$_3$OD)
HO
OH
BnHN
O
HO
22
OH
O
NHBn
HO
OH
f1 (ppm)


7.49
7.47
7.40
7.38
7.34
7.32
7.29
7.25
7.22
5.14
5.01
4.47
4.46
4.43
4.31
4.28
4.09
3.35
3.33
3.08
2.24
2.00
1.95
$^1$H NMR (500 MHz, CDCl$_3$)
BnN
AcO
X = OAc
23
OAc
NBn
f1 (ppm)


170.74
170.06
140.67
137.62
132.48
128.72
128.47
127.48
126.35
120.97
81.51
79.41
76.88
74.04
70.81
64.77
60.41
58.31
57.39
55.00
38.37
21.46
20.93
14.23
$^{13}$C NMR (125 MHz, CDCl$_3$)
BnN
AcO
X = OAc
23
OAc
NBn
f1 (ppm)


7.06
7.04
6.78
6.77
4.40
4.40
4.14
4.11
3.54
3.53
3.47
3.45
3.39
3.11
3.09
2.22
1.91
1.63
1.24
$^1$H NMR (700 MHz, CD$_3$OD/C$_5$D$_5$N, 6:1)
HO
HO
AcHN
O
HO
24
OH
O
NHAc
OH
OH
f1 (ppm)


173.57
142.06
138.43
128.89
126.77
81.66
81.14
71.03
62.57
56.18
49.72
46.54
36.16
31.90
23.16
$^{13}$C NMR (175 MHz, CD$_3$OD/C$_5$D$_5$N, 6:1)
HO
HO
AcHN
O
HO
24
OH
O
NHAc
OH
OH
f1 (ppm)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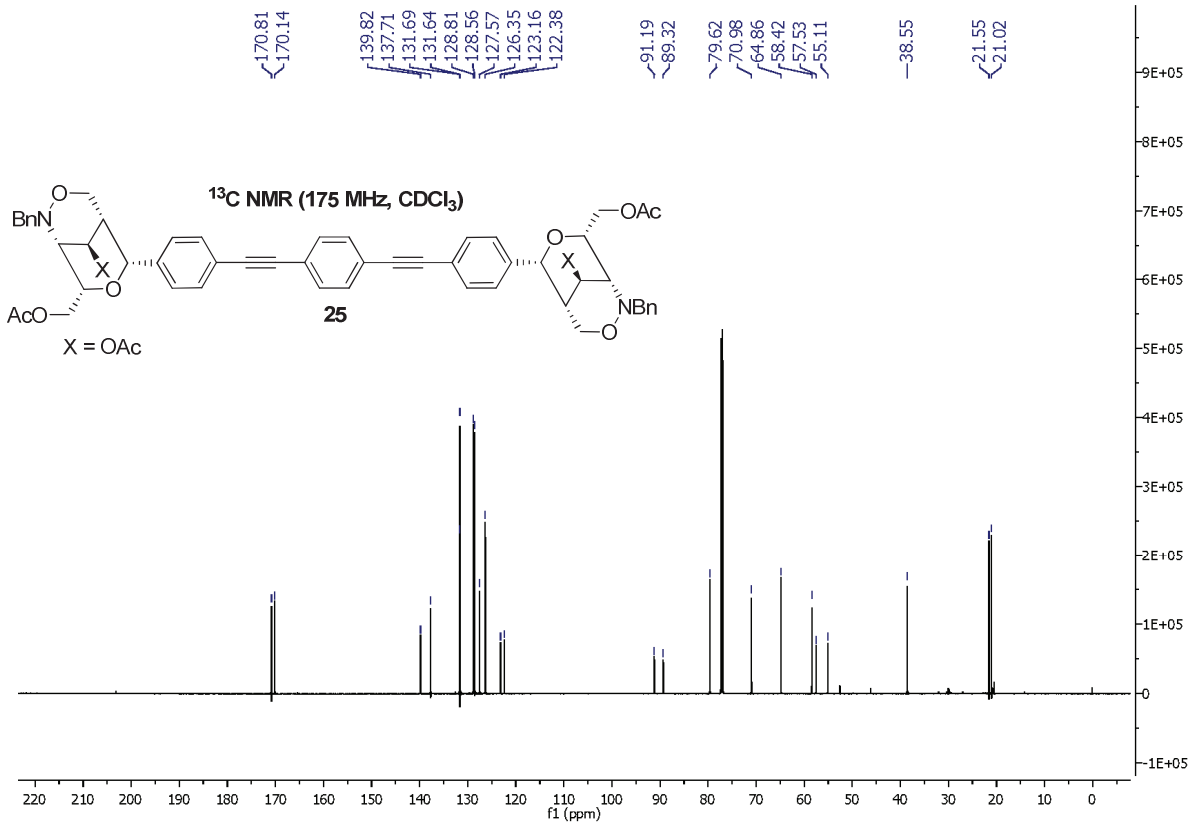
7.50
7.44
7.42
7.36
7.32
7.28
7.25
5.17
5.04
4.46
4.34
4.32
4.11
4.10
3.41
3.40
3.11
2.26
2.03
1.98
$^1$H NMR (700 MHz, CDCl$_3$)
BnN
AcO
X = OAc
25
OAc
NBn
f1 (ppm)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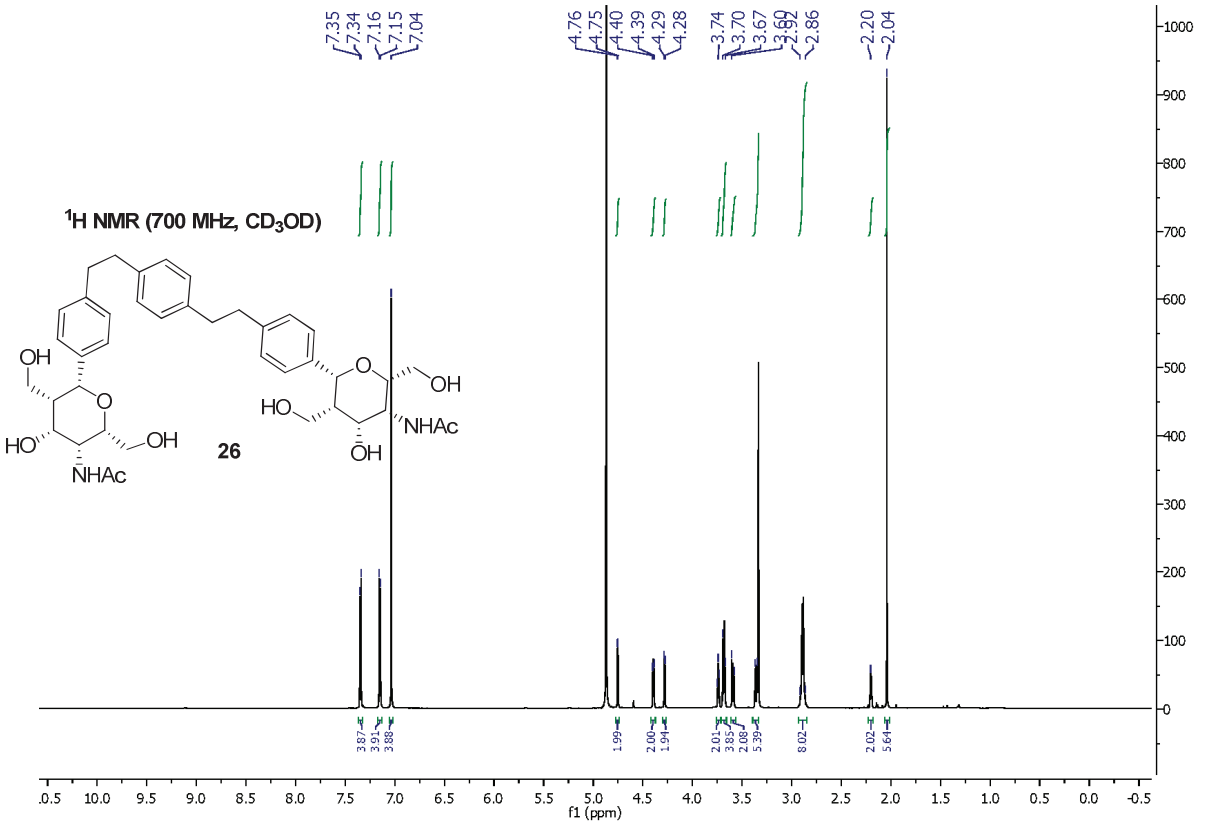
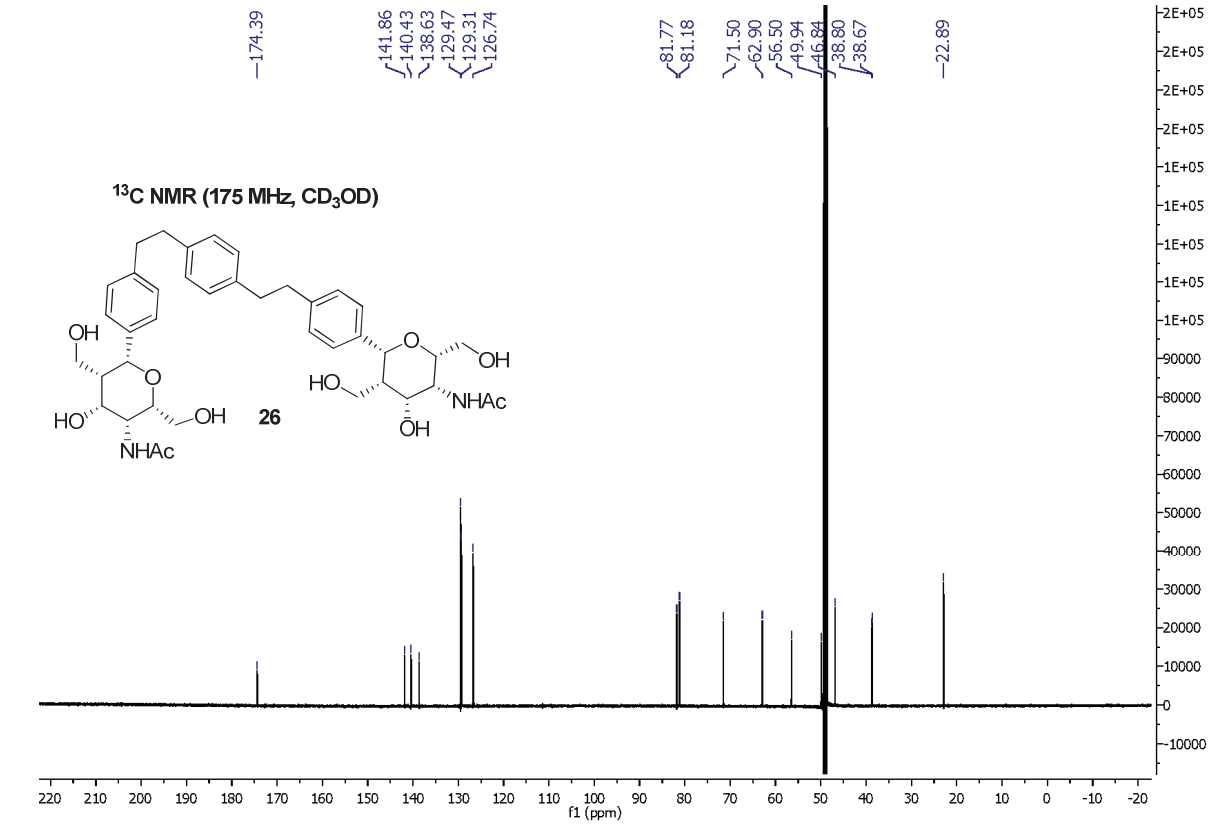
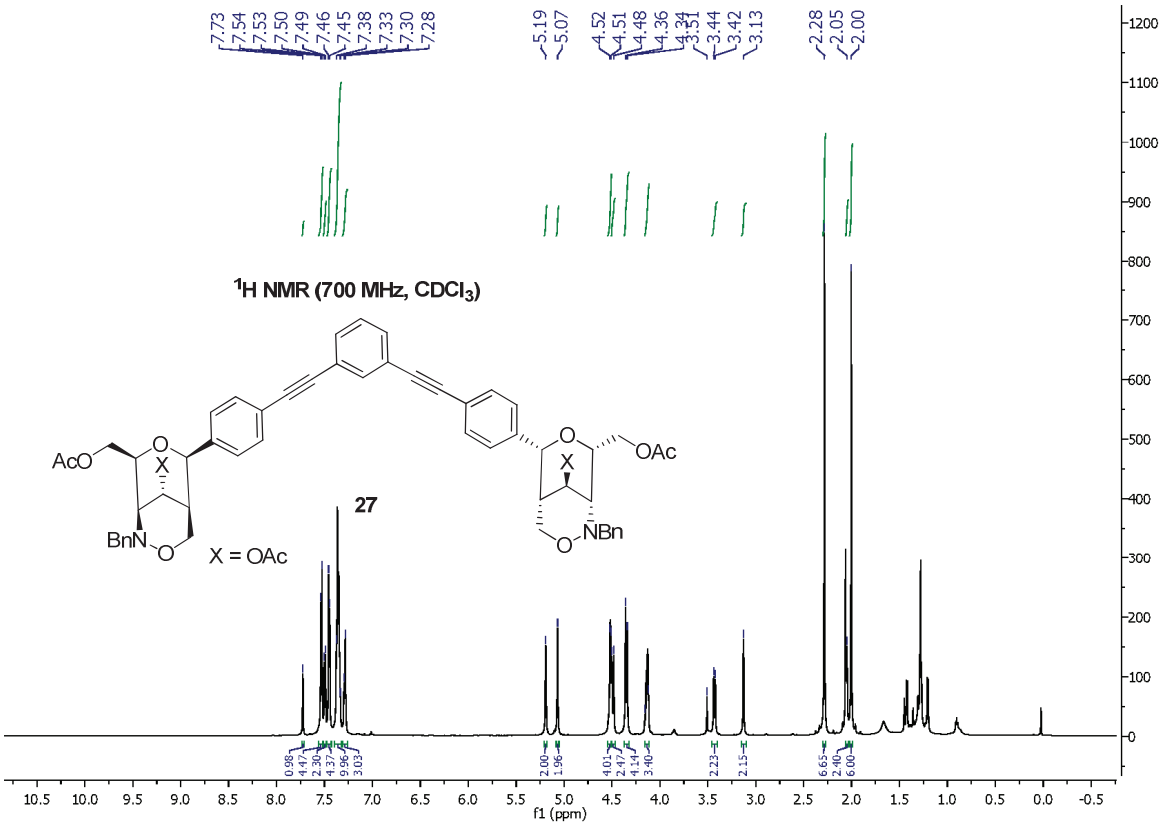
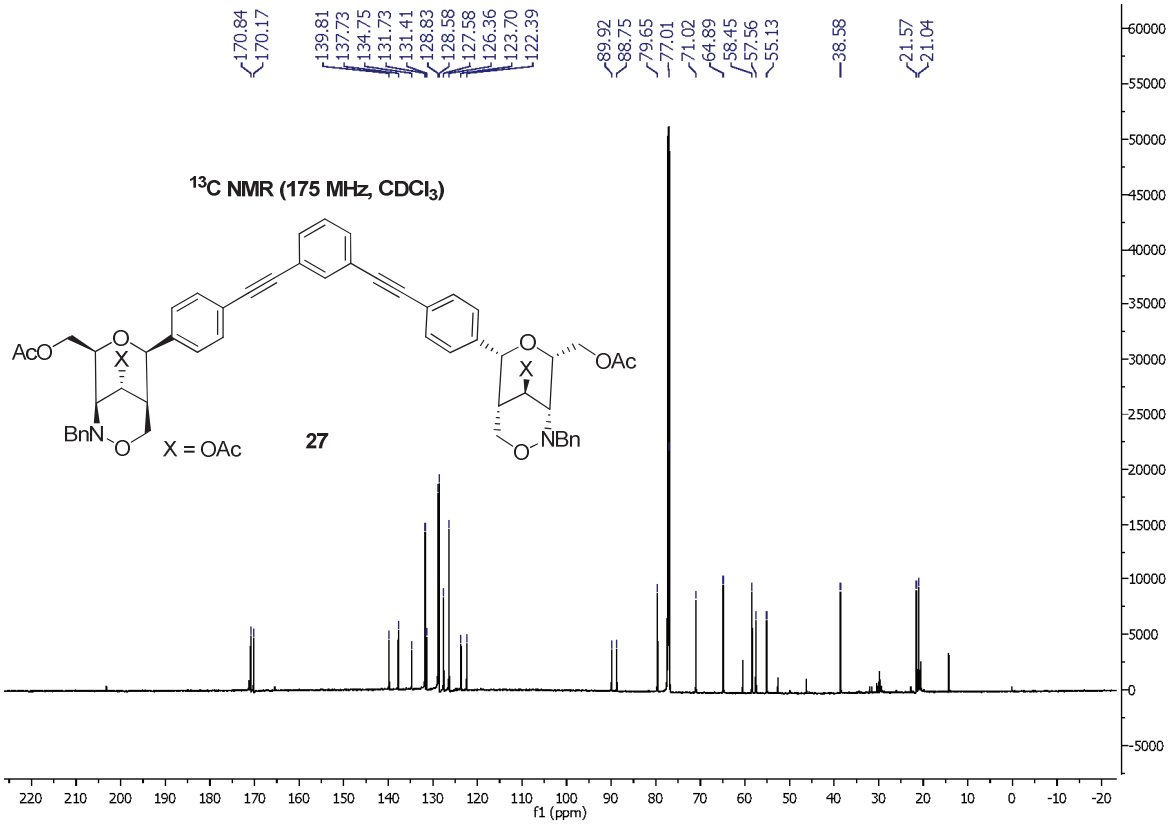
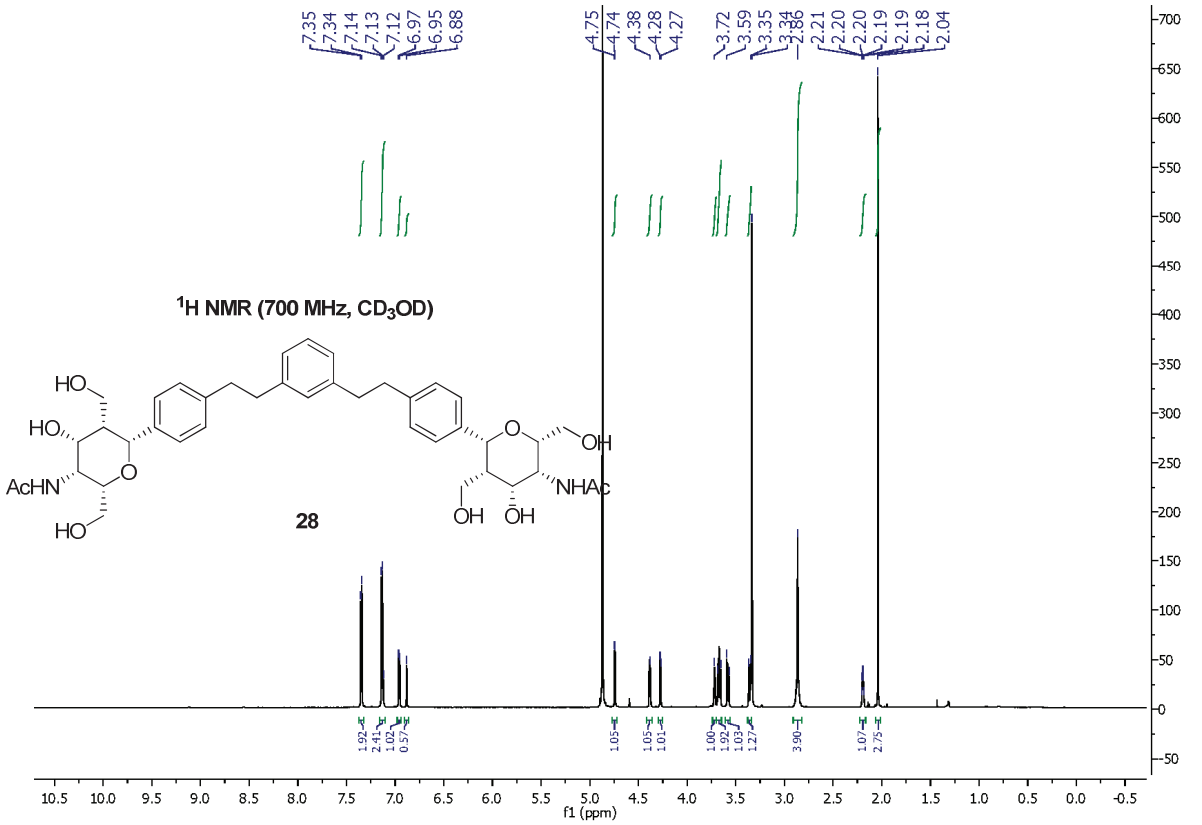
170.14
139.82
137.71
131.69
131.64
128.81
128.56
127.57
126.35
123.16
122.38
91.19
89.32
79.62
70.98
64.86
58.42
57.53
55.11
38.55
21.55
21.02
$^{13}$C NMR (175 MHz, CDCl$_3$)
BnN
AcO
X = OAc
25
OAc
NBn
f1 (ppm)

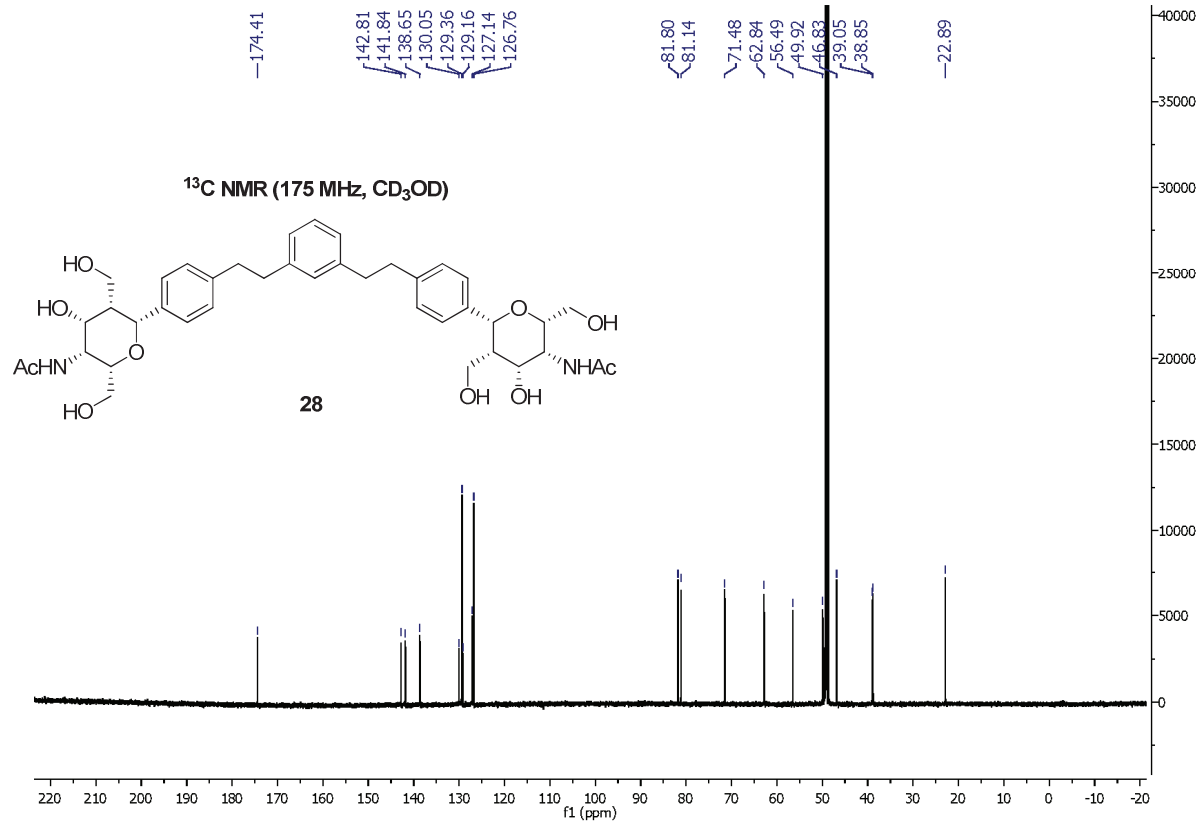

$^1$H NMR (700 MHz, $CD_3OD$)
26
7.35
7.34
7.16
7.15
7.04
4.76
4.75
4.40
4.39
4.29
4.28
3.74
3.70
3.67
2.92
2.86
2.20
2.04
f1 (ppm)

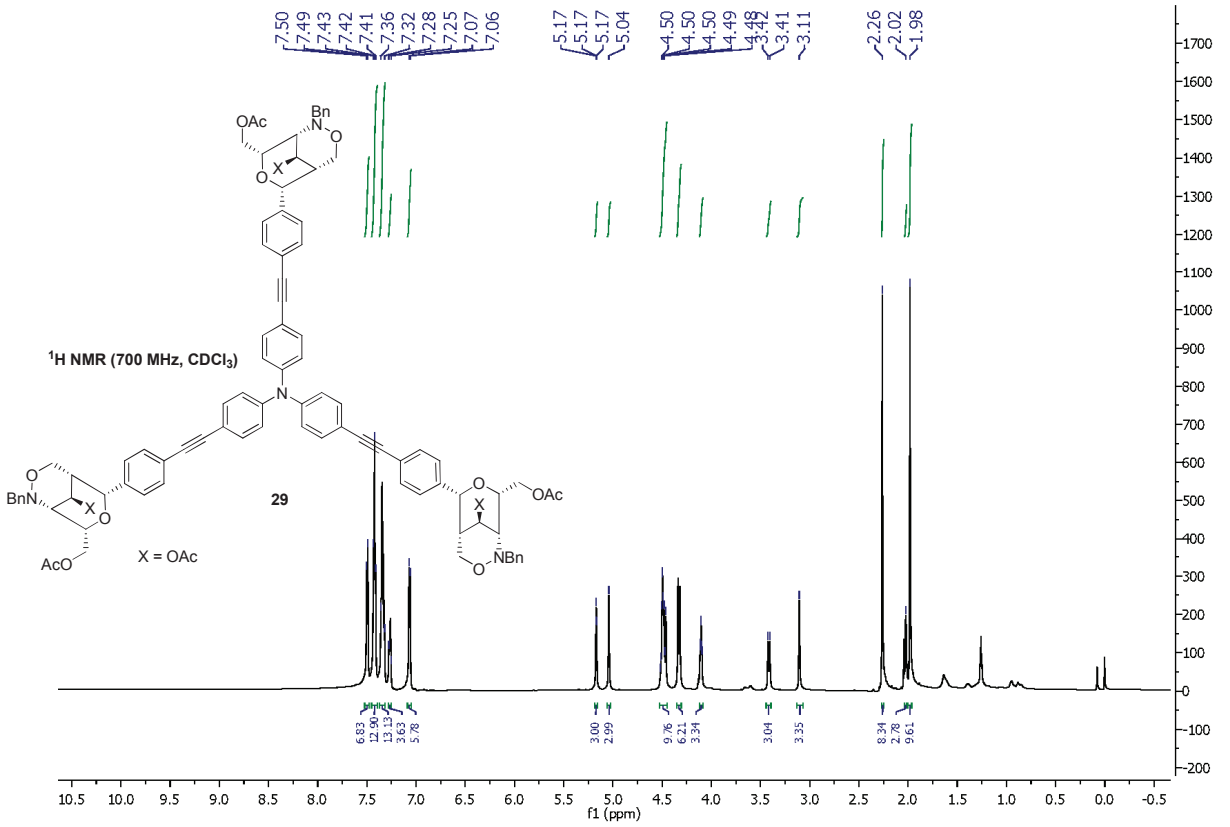

$^{13}$C NMR (175 MHz, $CD_3OD$)
26
174.39
141.86
140.43
138.63
129.47
129.31
126.74
81.77
81.18
71.50
62.90
56.50
49.94
46.84
38.80
38.67
22.89
f1 (ppm)

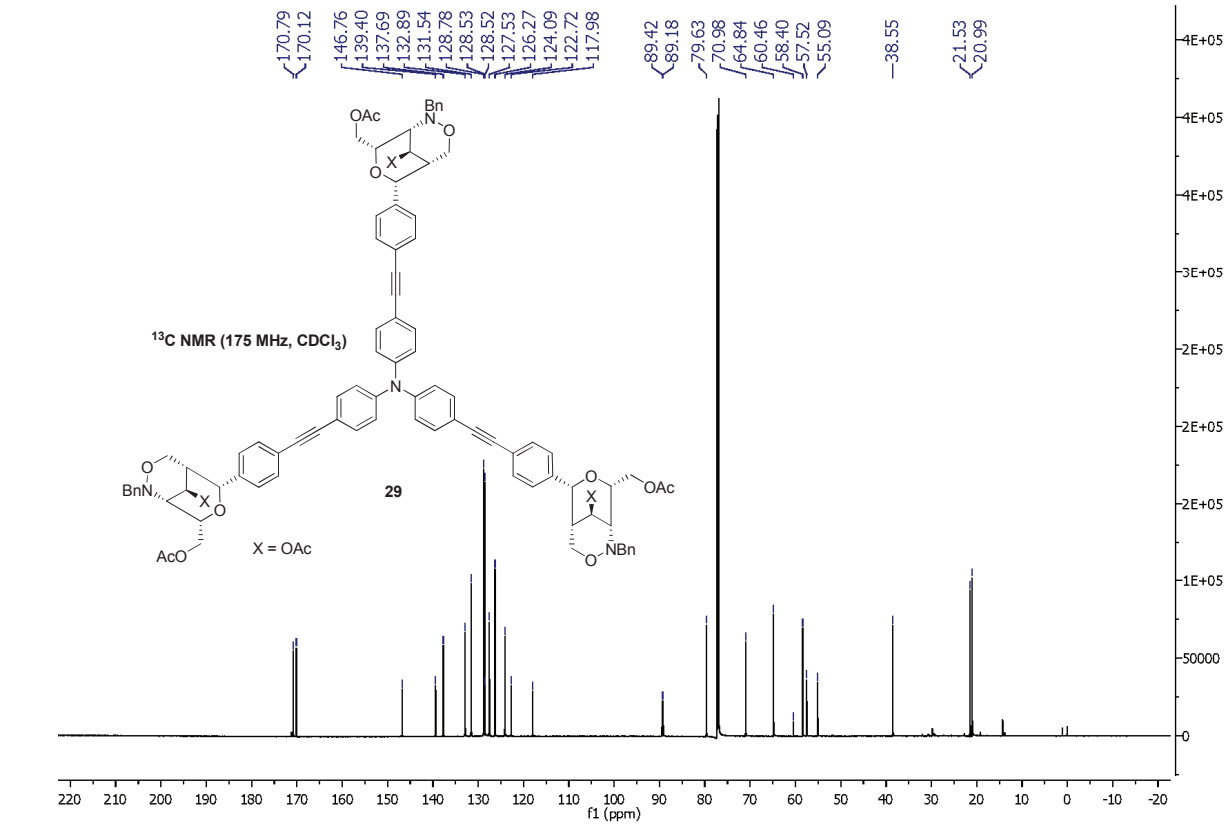

7.73
7.54
7.53
7.50
7.49
7.46
7.45
7.38
7.33
7.30
7.28
5.19
5.07
4.52
4.51
4.48
4.36
4.34
3.51
3.44
3.42
3.13
2.28
2.05
2.00
1H NMR (700 MHz, CDCl3)
AcO
OAc
BnN
NBn
X = OAc
27
f1 (ppm)

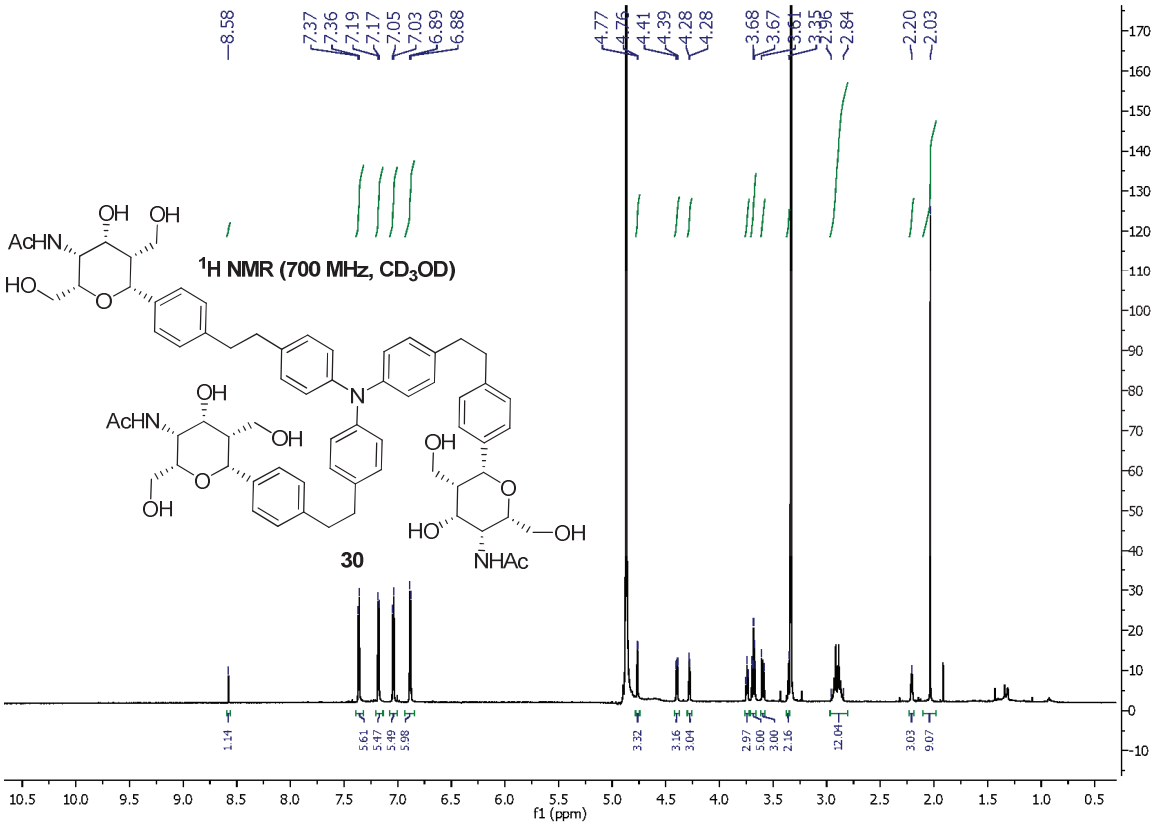

170.84
170.17
139.81
137.73
134.75
131.73
131.41
128.83
128.58
127.58
126.36
123.70
122.39
89.92
88.75
79.65
77.01
71.02
64.89
58.45
57.56
55.13
38.58
21.57
21.04
13C NMR (175 MHz, CDCl3)
AcO
OAc
BnN
NBn
X = OAc
27
f1 (ppm)

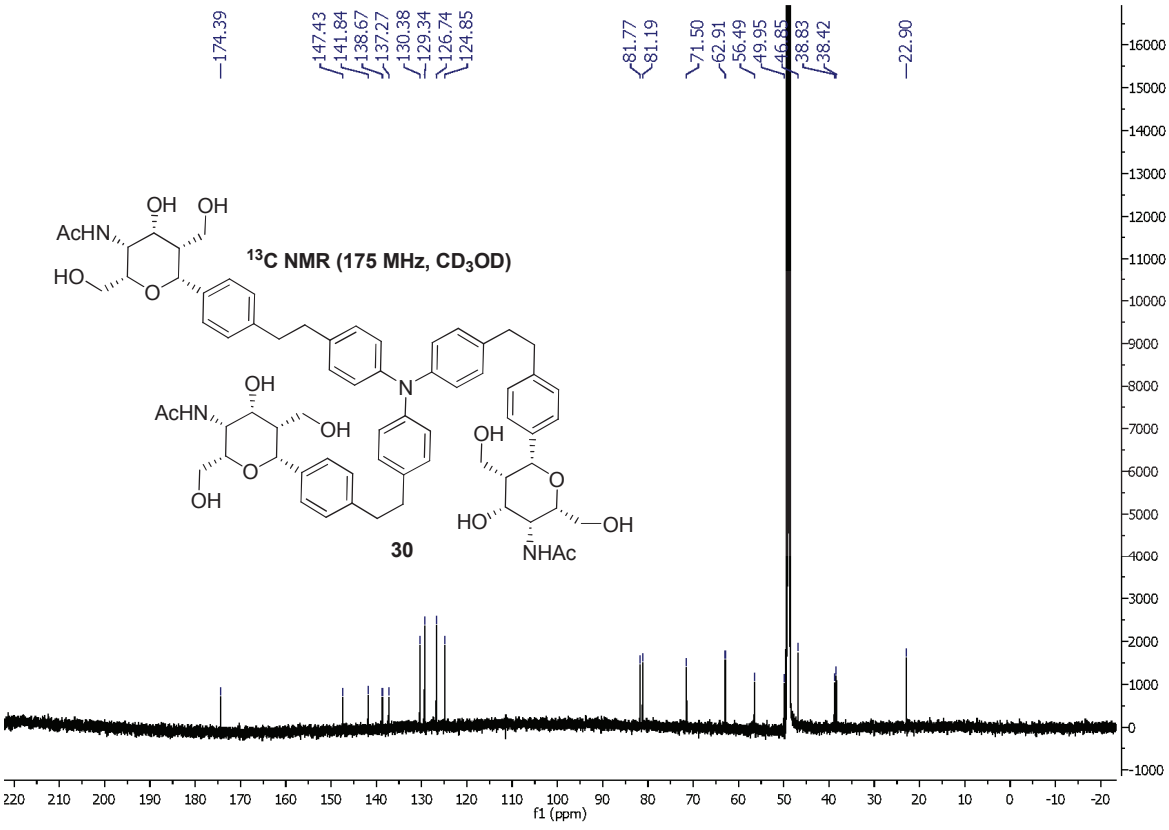

7.35
7.34
7.14
7.13
7.12
6.97
6.95
6.88
4.75
4.74
4.38
4.28
4.27
3.72
3.59
3.35
3.34
2.86
2.21
2.20
2.20
2.19
2.19
2.18
2.04
1H NMR (700 MHz, CD3OD)
HO
HO
AcHN
O
HO
O
OH
NHAc
OH
OH
28
1.92
2.41
1.02
0.57
1.05
1.05
1.01
1.00
1.92
1.03
1.27
3.90
1.07
2.75
f1 (ppm)


174.41
142.81
141.84
138.65
130.05
129.36
129.16
127.14
126.76
81.80
81.14
71.48
62.84
56.49
49.92
46.83
39.05
38.85
22.89
13C NMR (175 MHz, CD3OD)
HO
HO
AcHN
O
HO
O
OH
NHAc
OH
OH
28
f1 (ppm)


7.50
7.49
7.43
7.42
7.41
7.36
7.32
7.28
7.25
7.07
7.06
5.17
5.17
5.17
5.04
4.50
4.50
4.50
4.49
4.48
3.42
3.41
3.11
2.26
2.02
1.98
OAc
Bn
N
O
X
O
BnN
AcO
X = OAc
29
OAc
NBn
$^1$H NMR (700 MHz, CDCl$_3$)
6.83
12.90
13.13
3.63
5.78
3.00
2.99
9.76
6.21
3.34
3.04
3.35
8.34
2.78
9.61
f1 (ppm)


170.79
170.12
146.76
139.40
137.69
132.89
131.54
128.78
128.53
128.52
127.53
126.27
124.09
122.72
117.98
89.42
89.18
79.63
70.98
64.84
60.46
58.40
57.52
55.09
38.55
21.53
20.99
OAc
Bn
N
O
X
O
BnN
AcO
X = OAc
29
OAc
NBn
$^{13}$C NMR (175 MHz, CDCl$_3$)
f1 (ppm)


8.58
7.37
7.36
7.19
7.17
7.05
7.03
6.89
6.88
4.77
4.76
4.41
4.39
4.28
4.28
3.68
3.67
3.61
3.35
2.96
2.84
2.20
2.03
1H NMR (700 MHz, CD3OD)
30
f1 (ppm)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147.43
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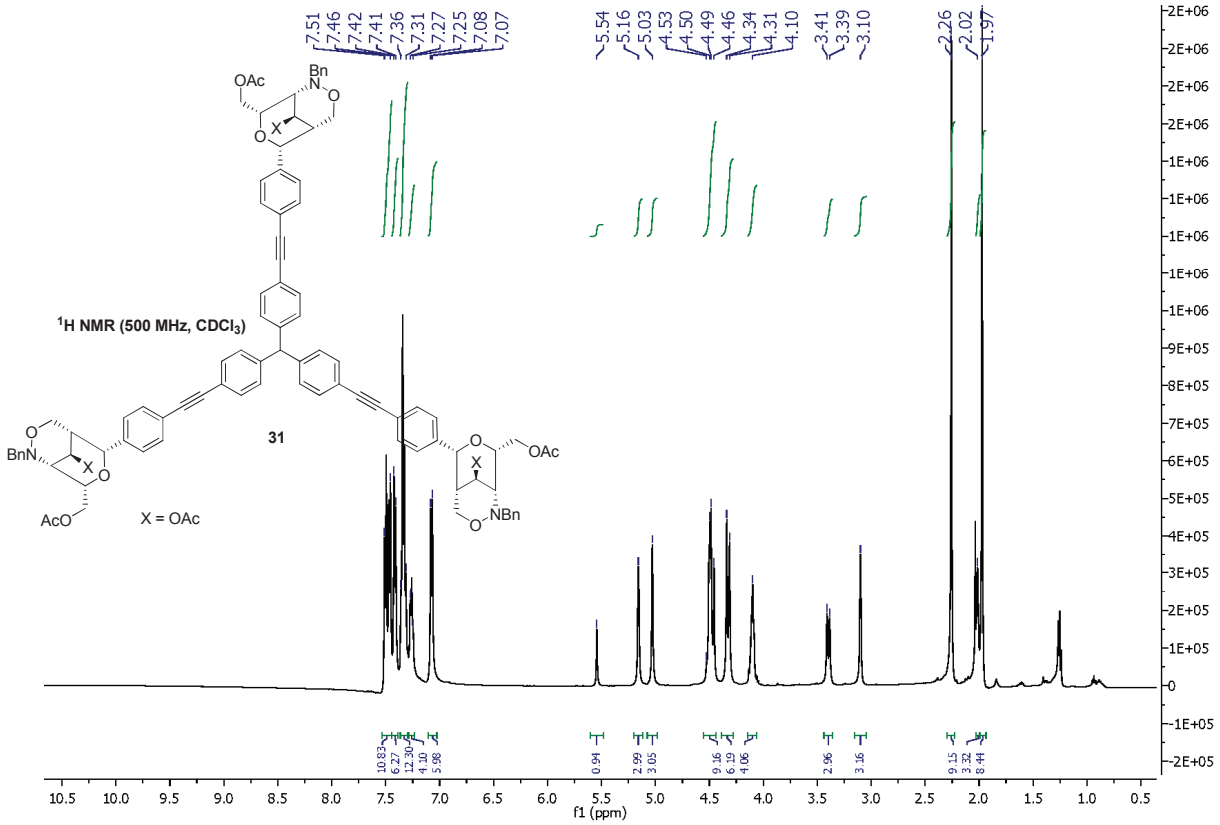
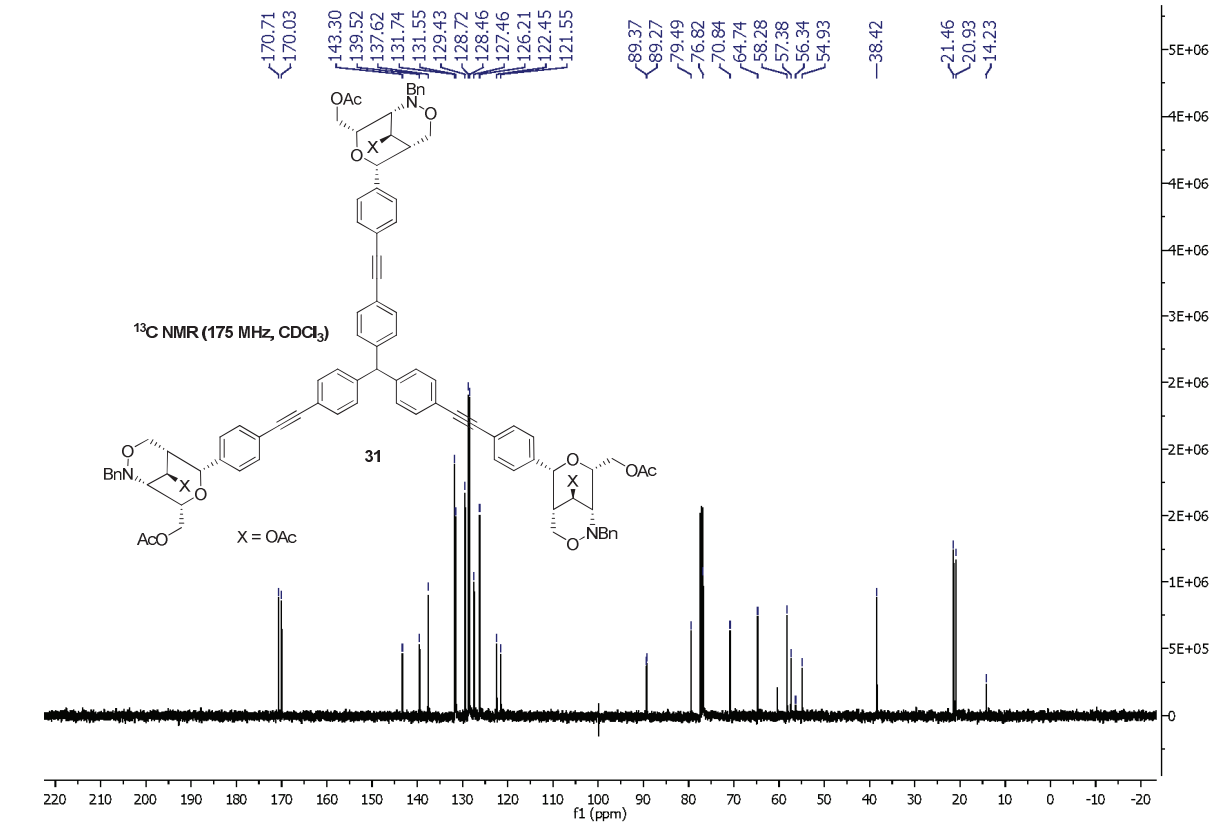
138.67
137.27
130.38
129.34
126.74
124.85
81.77
81.19
71.50
62.91
56.49
49.95
46.85
38.83
38.42
22.90
13C NMR (175 MHz, CD3OD)
30
f1 (ppm)


7.51
7.46
7.42
7.41
7.36
7.31
7.27
7.25
7.08
7.07
5.54
5.16
5.03
4.53
4.50
4.49
4.46
4.34
4.31
4.10
3.41
3.39
3.10
2.26
2.02
1.97
OAc
Bn
N
O
X
O
$^1$H NMR (500 MHz, CDCl$_3$)
31
BnN
AcO
X = OAc
NBn
f1 (ppm)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170.03
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139.52
137.62
131.74
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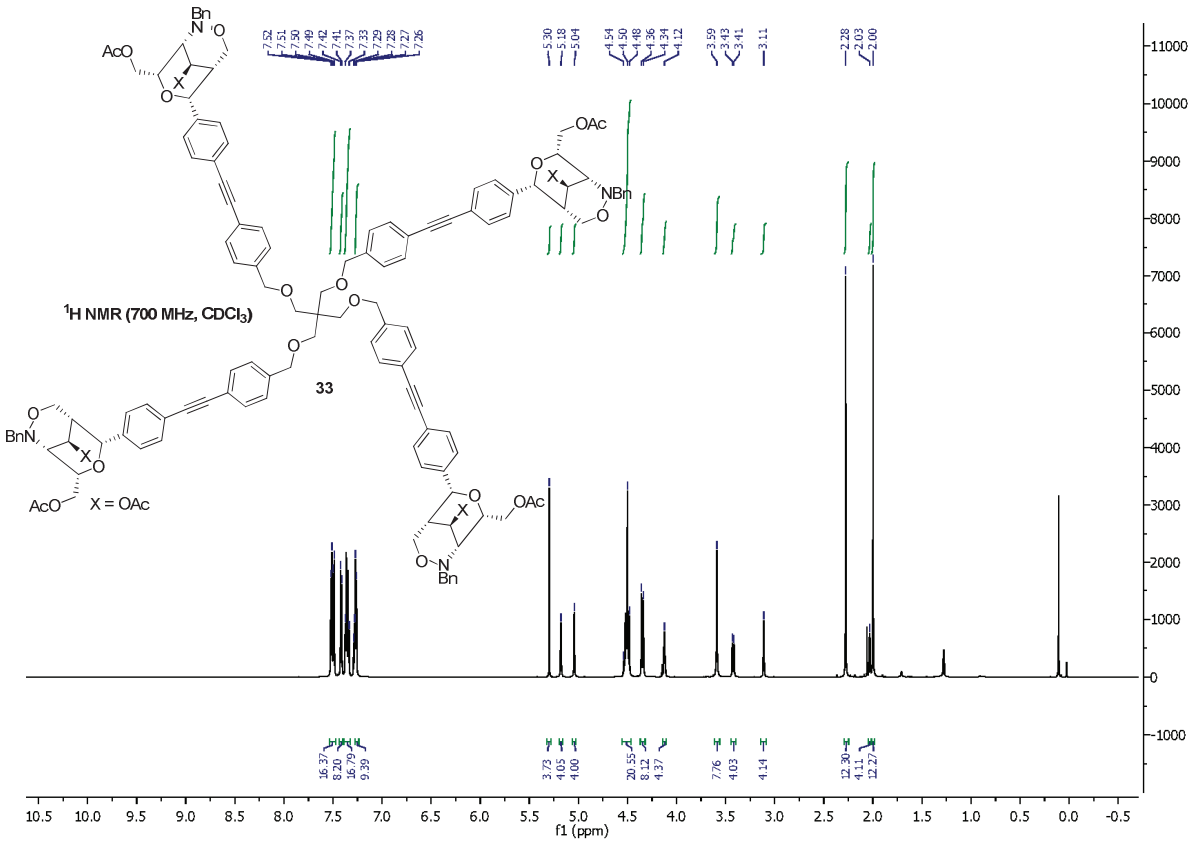
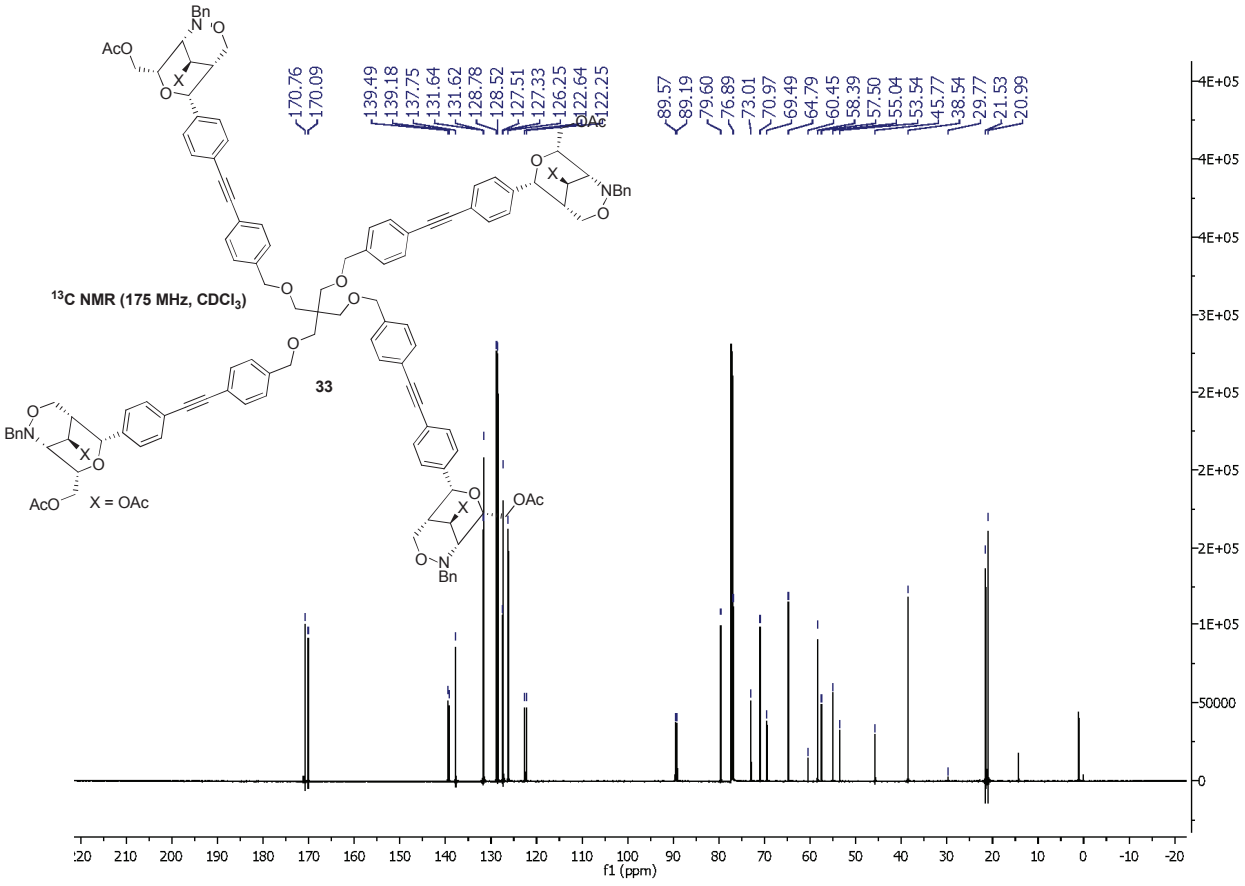
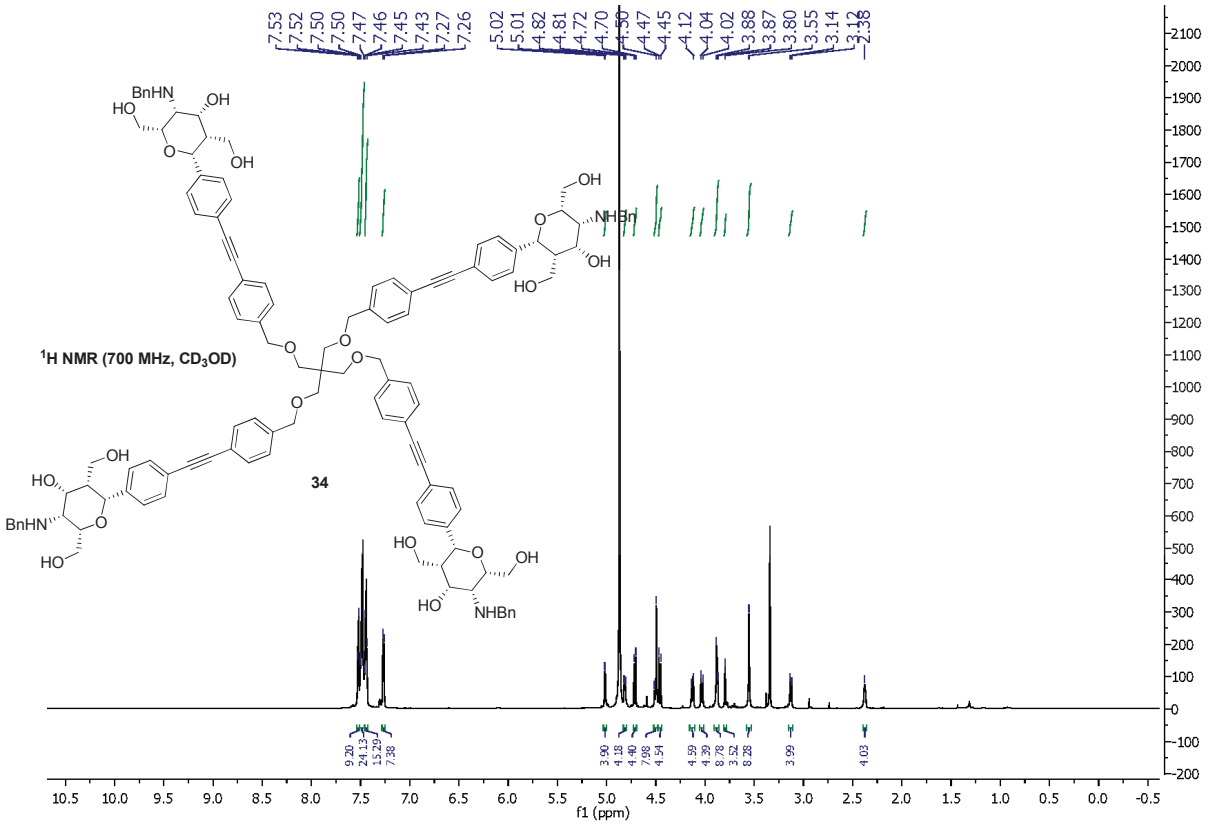
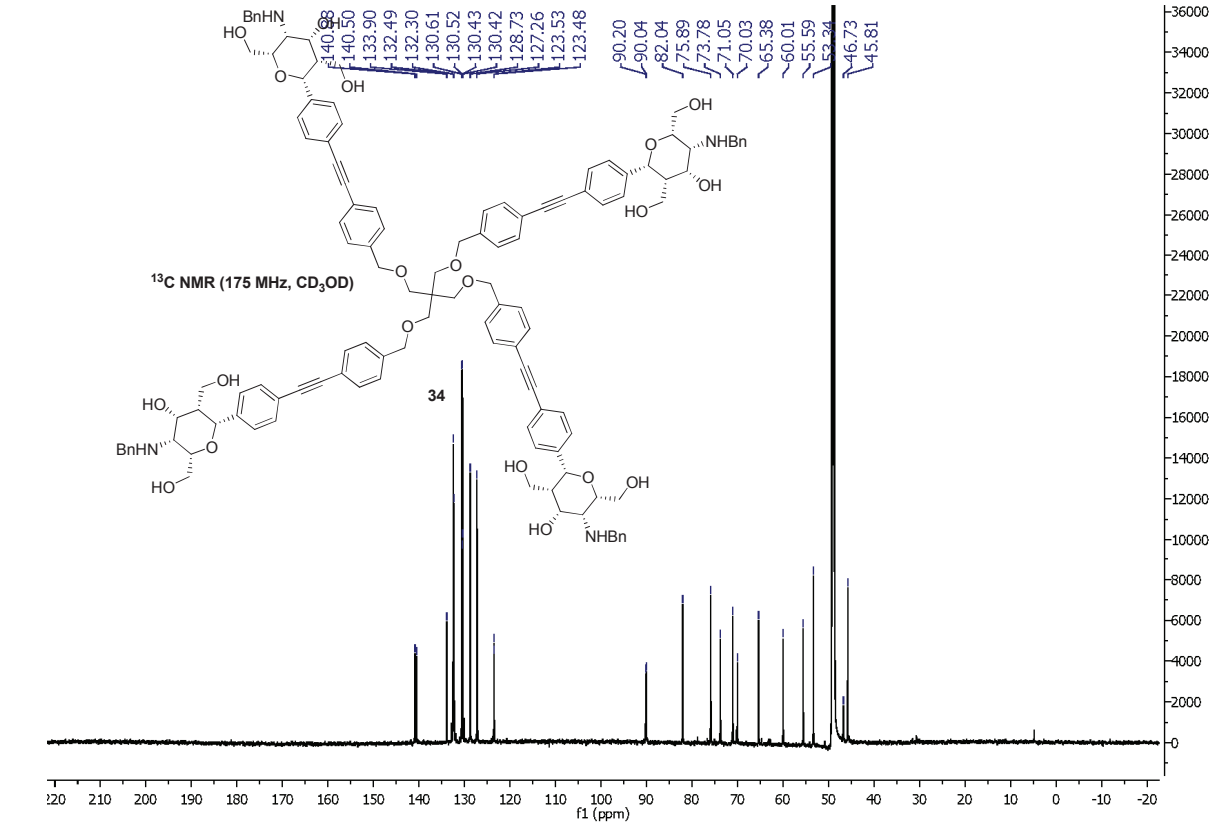
129.43
128.72
128.46
127.46
126.21
122.45
121.55
89.37
89.27
79.49
76.82
70.84
64.74
58.28
57.38
56.34
54.93
38.42
21.46
20.93
14.23
OAc
Bn
N
O
X
O
$^{13}$C NMR (175 MHz, CDCl$_3$)
31
BnN
AcO
X = OAc
NBn
f1 (ppm)


$^1$H NMR (700 MHz, CDCl$_3$)
33
X = OAc
f1 (ppm)


$^{13}$C NMR (175 MHz, CDCl$_3$)
33
X = OAc
f1 (ppm)


$^1$H NMR (700 MHz, CD$_3$OD)
34
f1 (ppm)


$^{13}$C NMR (175 MHz, CD$_3$OD)
34
f1 (ppm)

[1] M. Kandziora, H.-U. Reissig, *Beilstein J. Org. Chem.* **2014**, *10*, 1749-1758.

[2] M. Schelper, O. Buisine, S. Kozhushkov, C. Aubert, A. de Meijere, M. Malacria, *Eur. J. Org. Chem.* **2005**, 3000-3007.

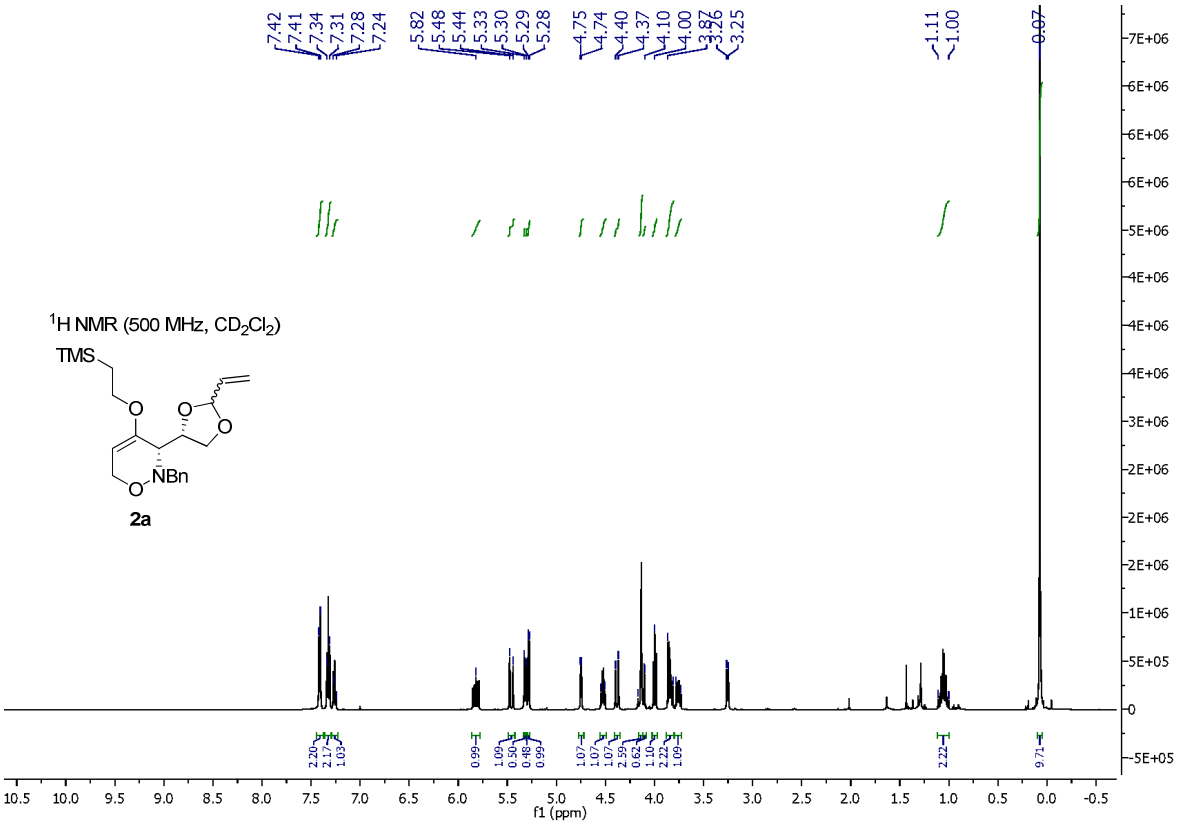
[3] B. Liu, R. Roy, *Tetrahedron* **2001**, *57*, 6909-6913.

## 7.3 Spektrenanhang zur Publikation:

### Syntheses of Mono- and Divalent *C*-Aminoglycosides Based on 1,2-Oxazine Chemistry and on Olefin-Metathesis

Die Publikation wurde im Kapitel 3.3 vorgestellt und in der folgenden Zeitschrift publiziert:

M. Kandziora, E. Mucha, S. P. Zucker, H.-U. Reissig, *Synlett* **2014**, *im Druck.*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7.41
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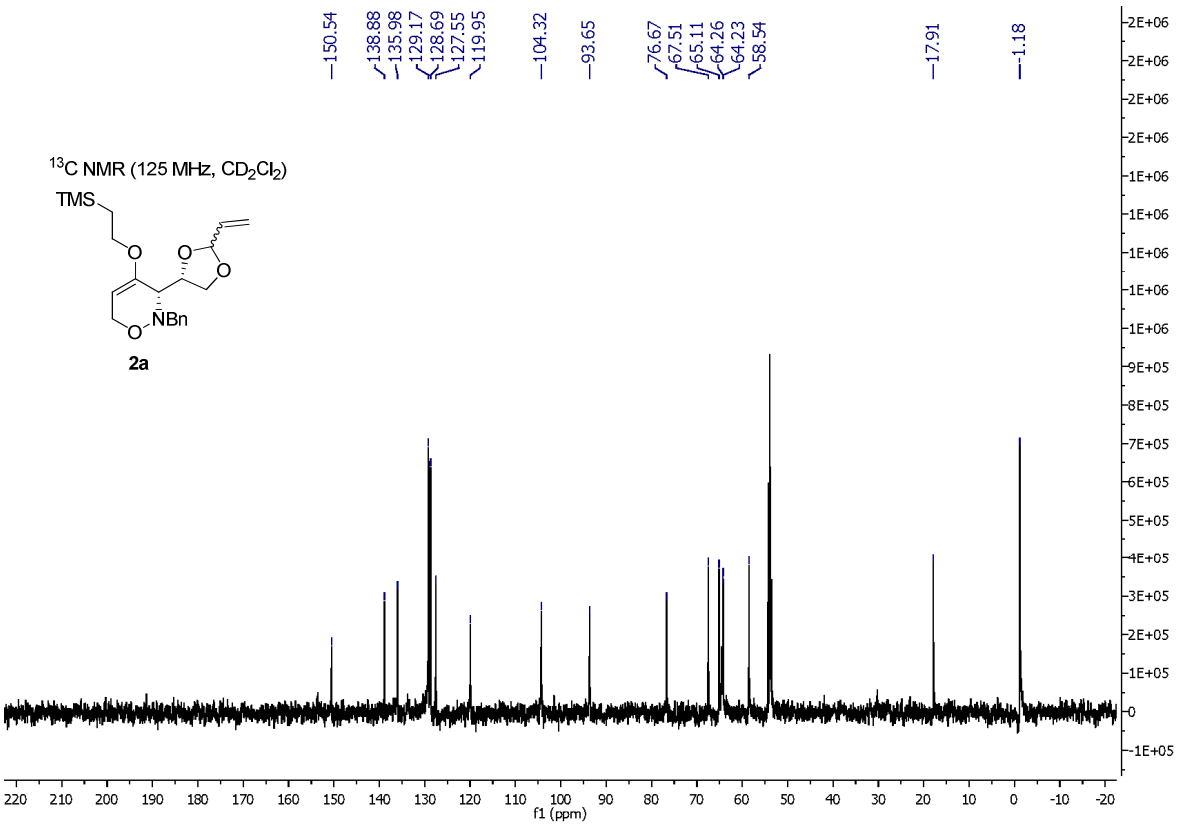
5.48
5.44
5.33
5.30
5.29
5.28
4.75
4.74
4.40
4.37
4.10
4.00
3.87
3.26
3.25
1.11
1.00
0.07
$^1$H NMR (500 MHz, $CD_2Cl_2$)
TMS
O
O
O
NBn
O
2a
f1 (ppm)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138.88
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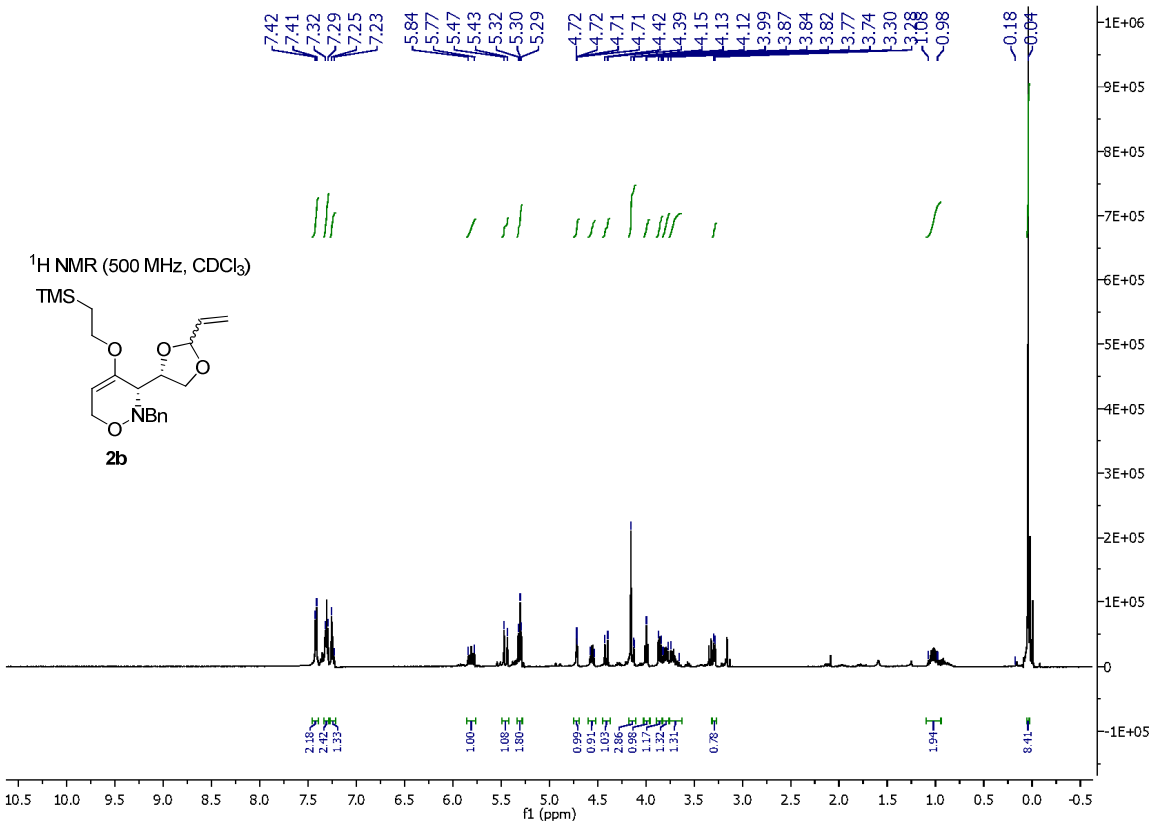
127.55
119.95
104.32
93.65
76.67
67.51
65.11
64.26
64.23
58.54
17.91
1.18
$^{13}$C NMR (125 MHz, $CD_2Cl_2$)
TMS
O
O
O
NBn
O
2a
f1 (ppm)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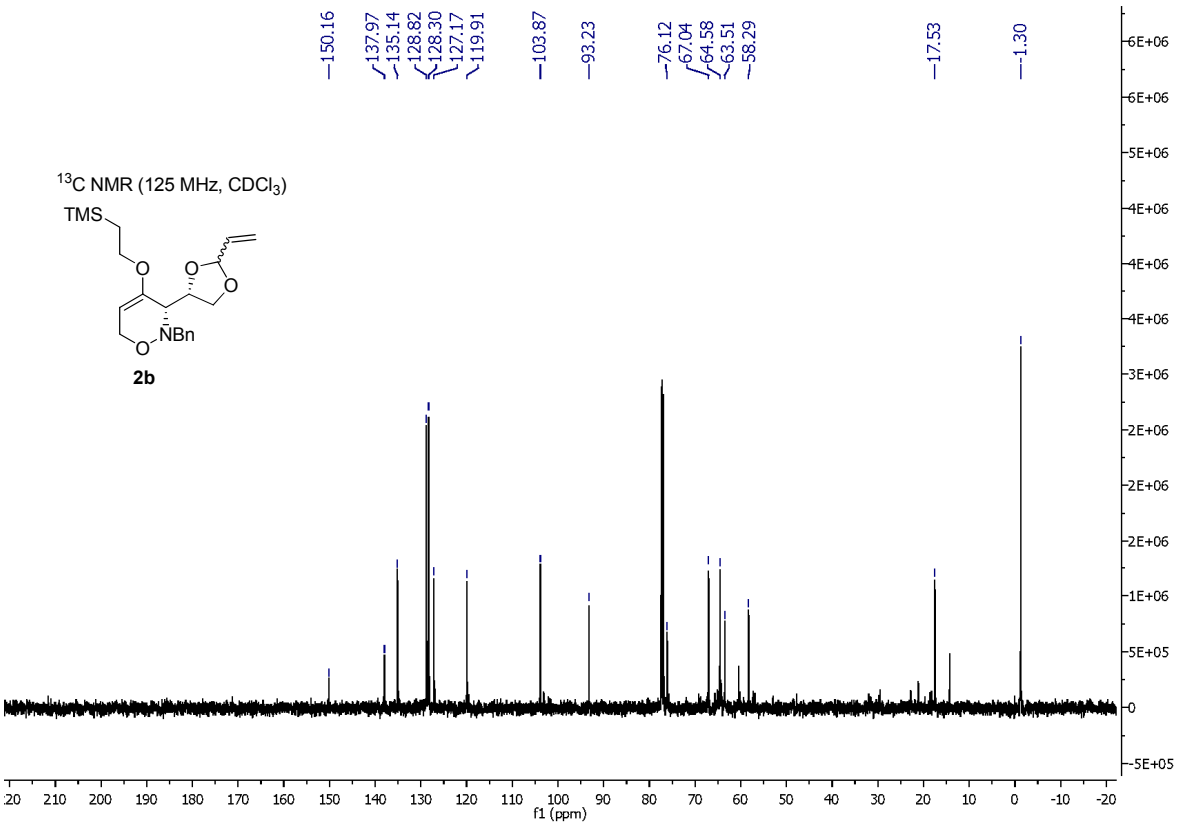
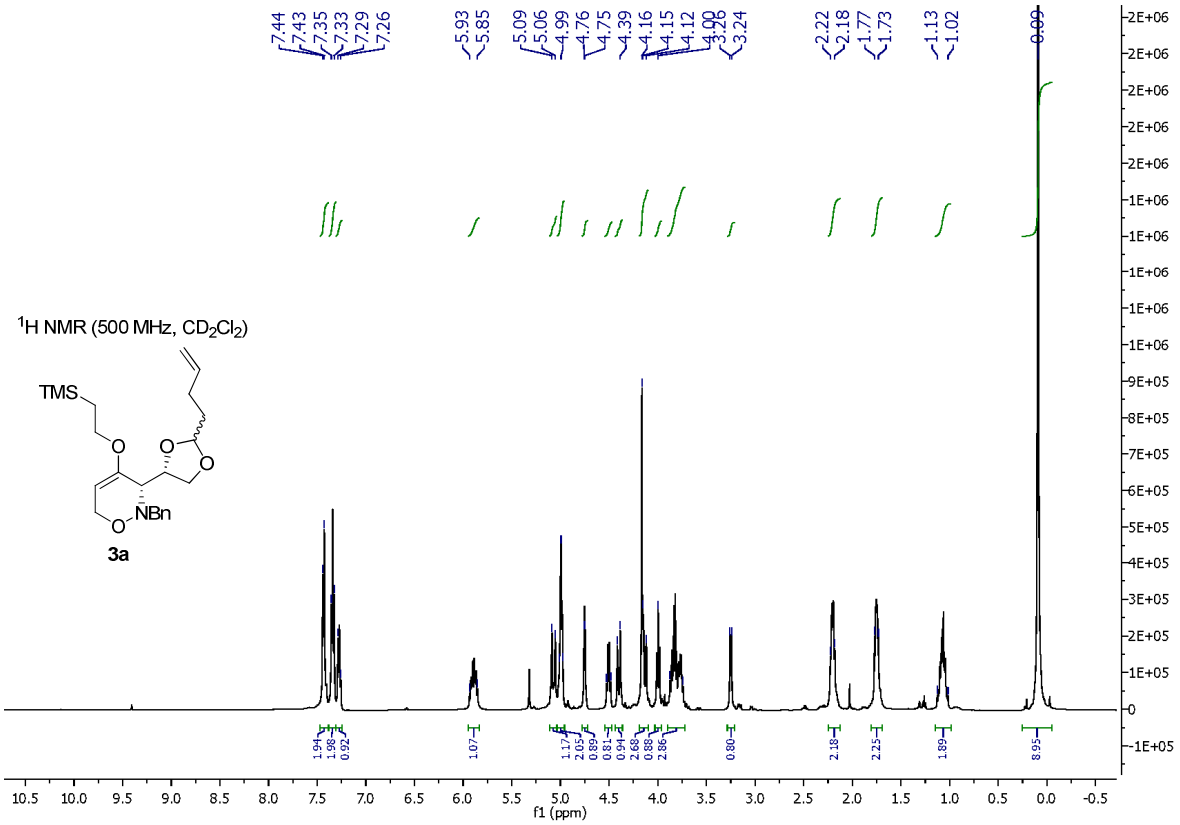
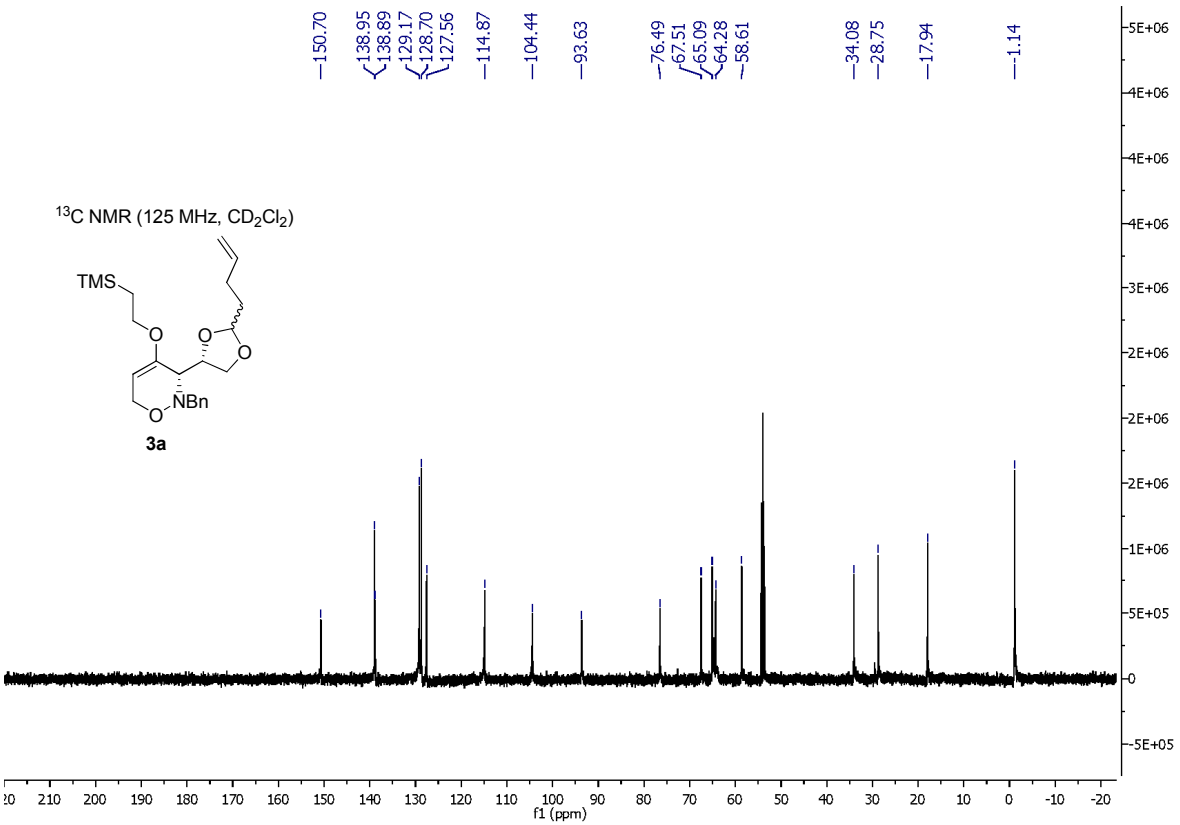
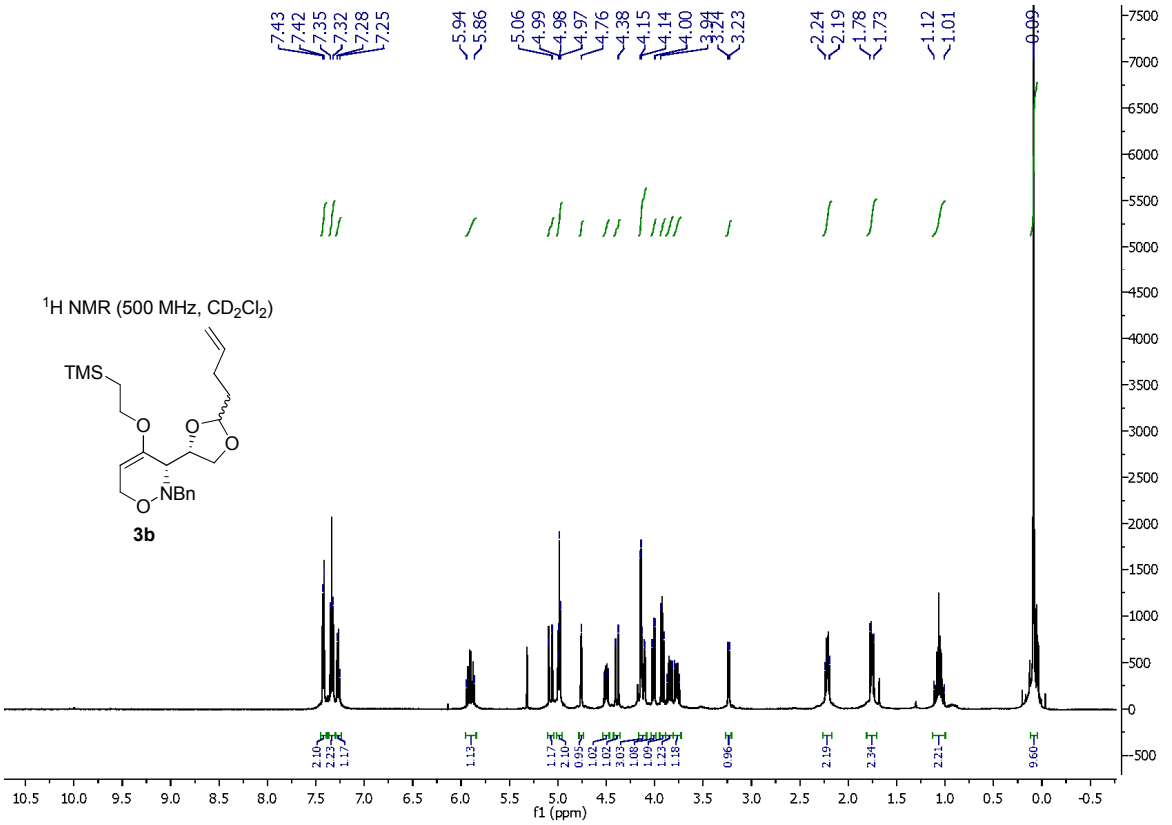
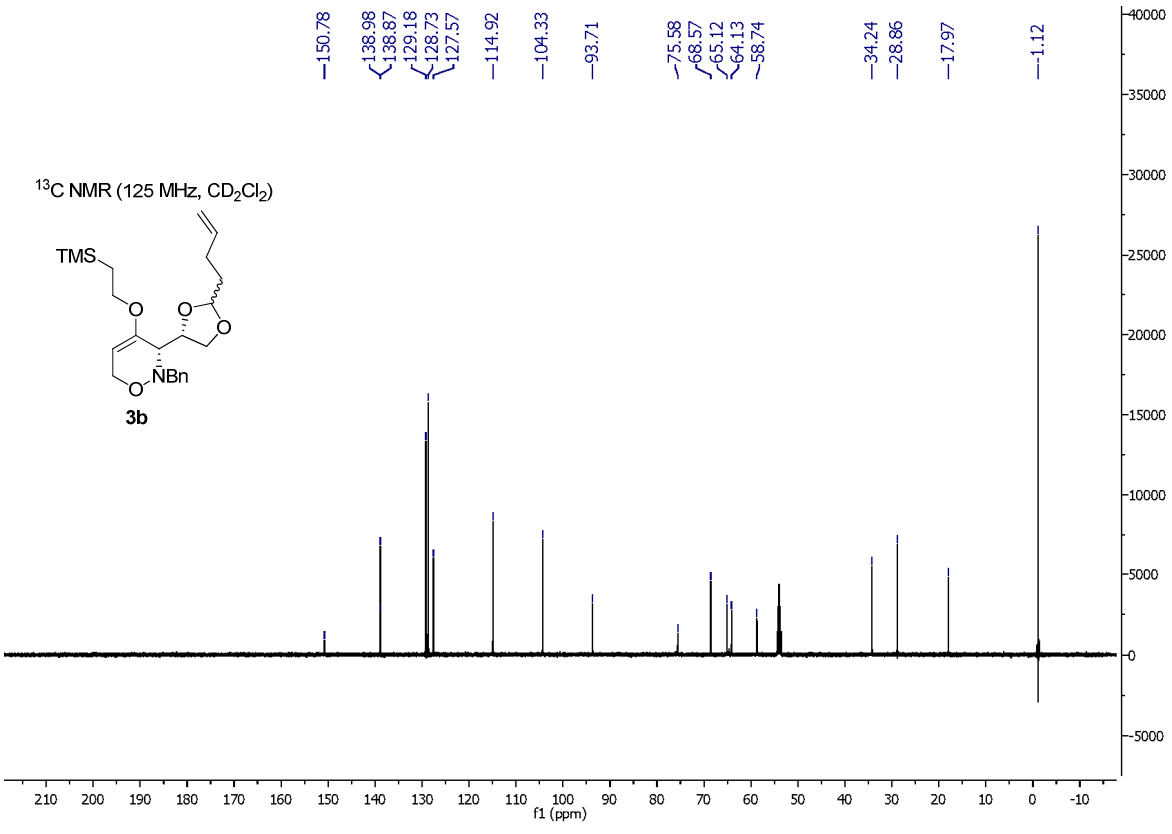
7.41
7.32
7.29
7.25
7.23
5.84
5.77
5.47
5.43
5.32
5.30
5.29
4.72
4.72
4.71
4.71
4.42
4.39
4.15
4.13
4.12
3.99
3.87
3.84
3.82
3.77
3.74
3.30
3.08
1.08
0.98
0.18
0.04
1H NMR (500 MHz, CDCl3)
TMS
O
O
O
O
NBn
2b
2.18
2.42
1.33
1.00
1.08
1.80
0.99
0.91
1.03
2.86
0.98
1.17
1.32
1.31
0.78
1.94
8.41
f1 (ppm)

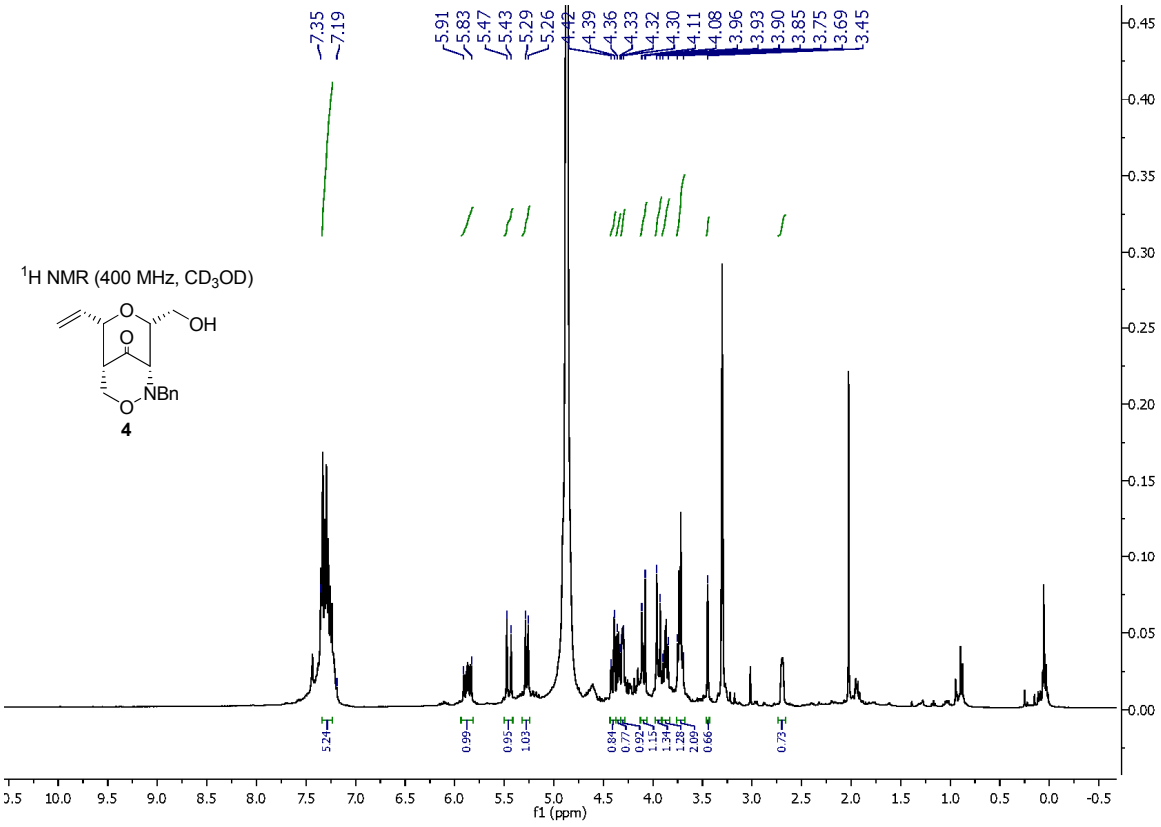

150.16
137.97
135.14
128.82
128.30
127.17
119.91
103.87
93.23
76.12
67.04
64.58
63.51
58.29
17.53
1.30
13C NMR (125 MHz, CDCl3)
TMS
O
O
O
O
NBn
2b
f1 (ppm)

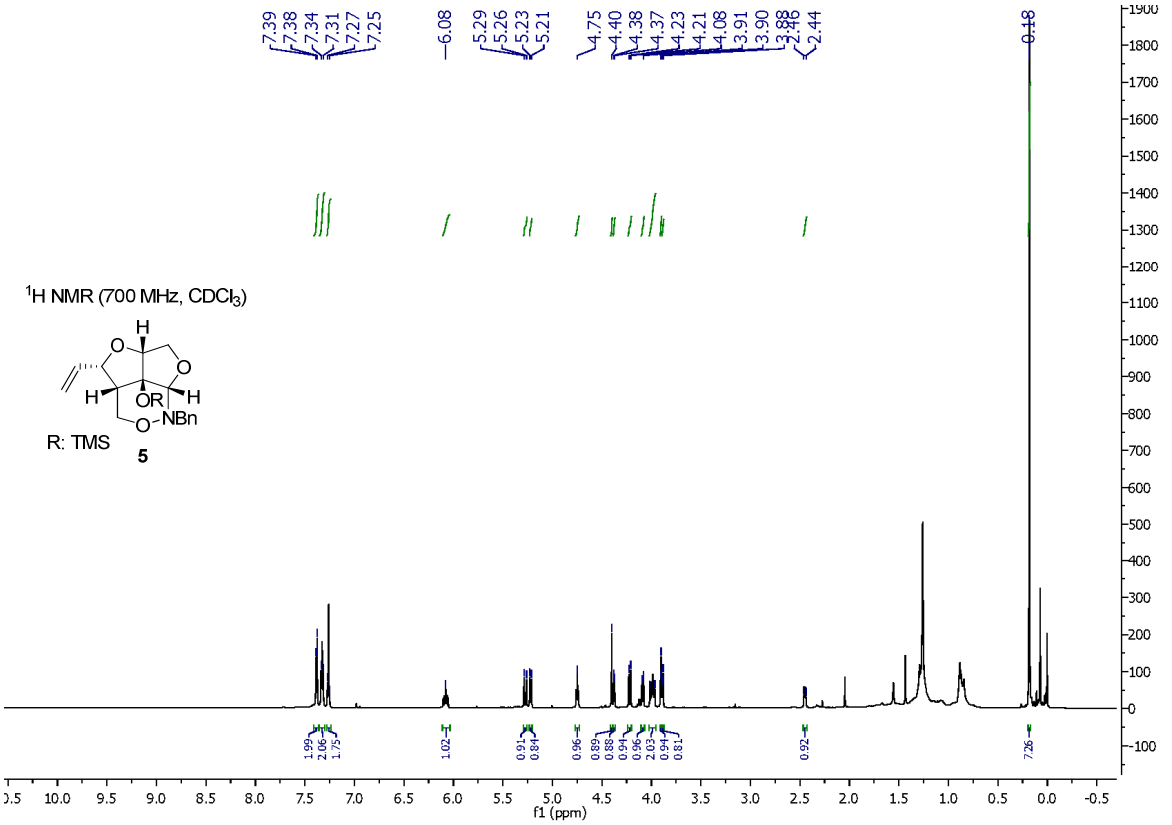

7.44
7.43
7.35
7.33
7.29
7.26
5.93
5.85
5.09
5.06
4.99
4.76
4.75
4.39
4.16
4.15
4.12
4.00
3.26
3.24
2.22
2.18
1.77
1.73
1.13
1.02
0.09
1H NMR (500 MHz, CD2Cl2)
TMS
O
O
O
O
NBn
3a
f1 (ppm)


150.70
138.95
138.89
129.17
128.70
127.56
114.87
104.44
93.63
76.49
67.51
65.09
64.28
58.61
34.08
28.75
17.94
1.14
13C NMR (125 MHz, CD2Cl2)
TMS
O
O
O
O
NBn
3a
f1 (ppm)


7.43
7.42
7.35
7.32
7.28
7.25
5.94
5.86
5.06
4.99
4.98
4.97
4.76
4.38
4.15
4.14
4.00
3.94
3.24
3.23
2.24
2.19
1.78
1.73
1.12
1.01
0.09
$^1$H NMR (500 MHz, $CD_2Cl_2$)
TMS
O
O
O
O
NBn
3b
f1 (ppm)


150.78
138.98
138.87
129.18
128.73
127.57
114.92
104.33
93.71
75.58
68.57
65.12
64.13
58.74
34.24
28.86
17.97
1.12
$^{13}$C NMR (125 MHz, $CD_2Cl_2$)
TMS
O
O
O
O
NBn
3b
f1 (ppm)


7.35
7.19
5.91
5.83
5.47
5.43
5.29
5.26
4.42
4.39
4.36
4.33
4.32
4.30
4.11
4.08
3.96
3.93
3.90
3.85
3.75
3.69
3.45
1H NMR (400 MHz, CD3OD)
O
OH
O
NBn
O
4
5.24
0.99
0.95
1.03
0.84
0.77
0.92
1.15
1.34
1.28
2.09
0.66
0.73
f1 (ppm)

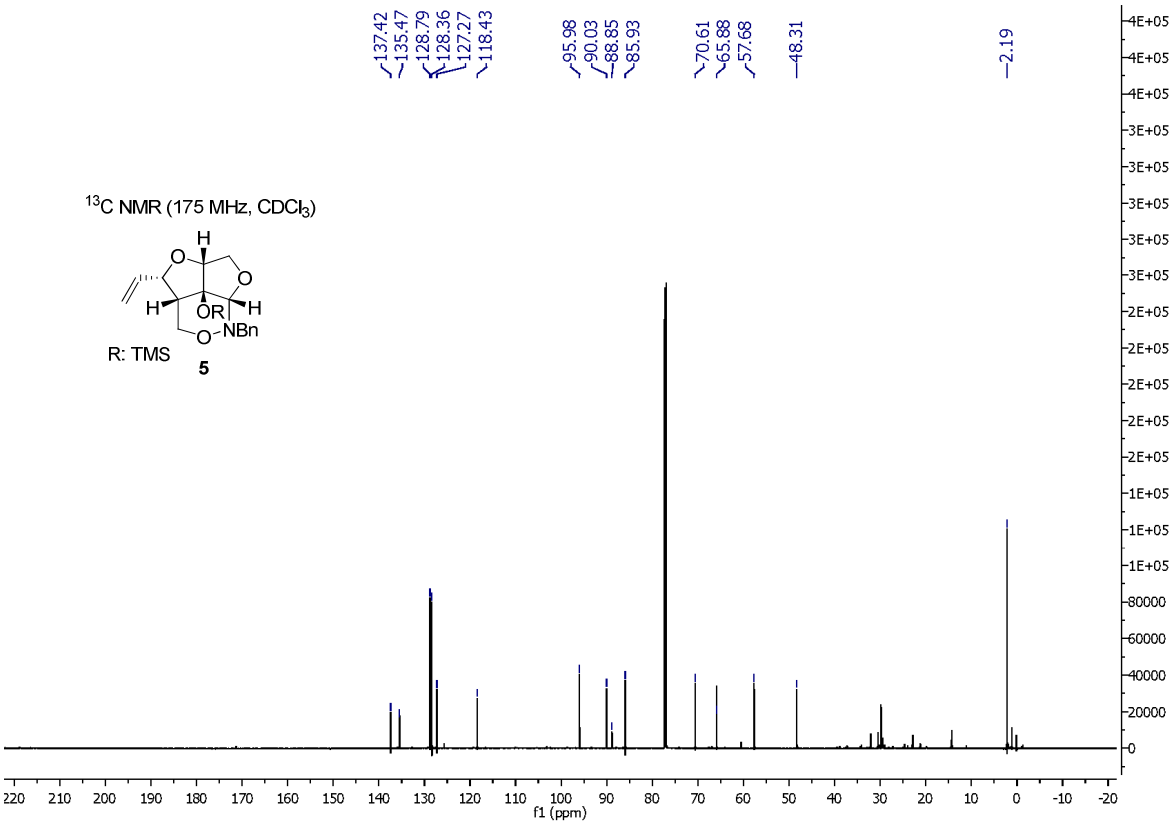



$^{1}$H NMR (700 MHz, $CDCl_3$)



R: TMS

**5**

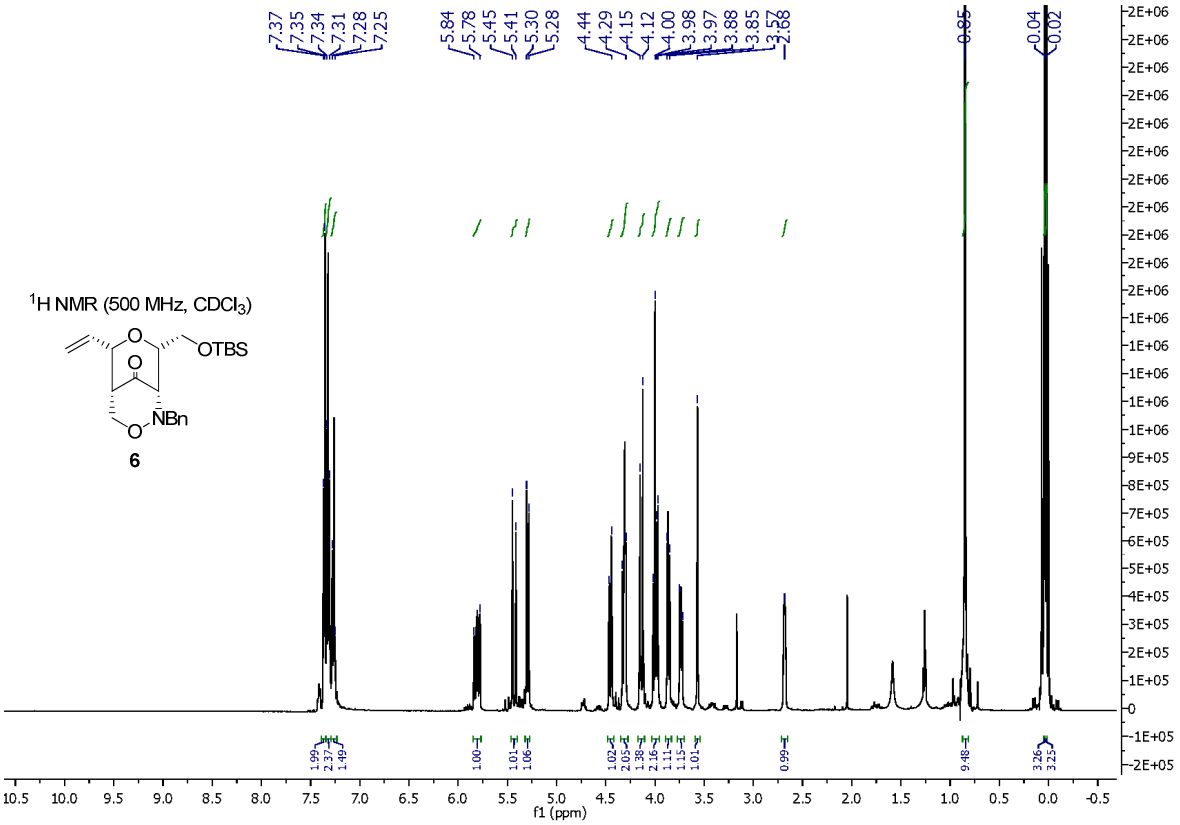



$^{13}$C NMR (175 MHz, $CDCl_3$)



R: TMS

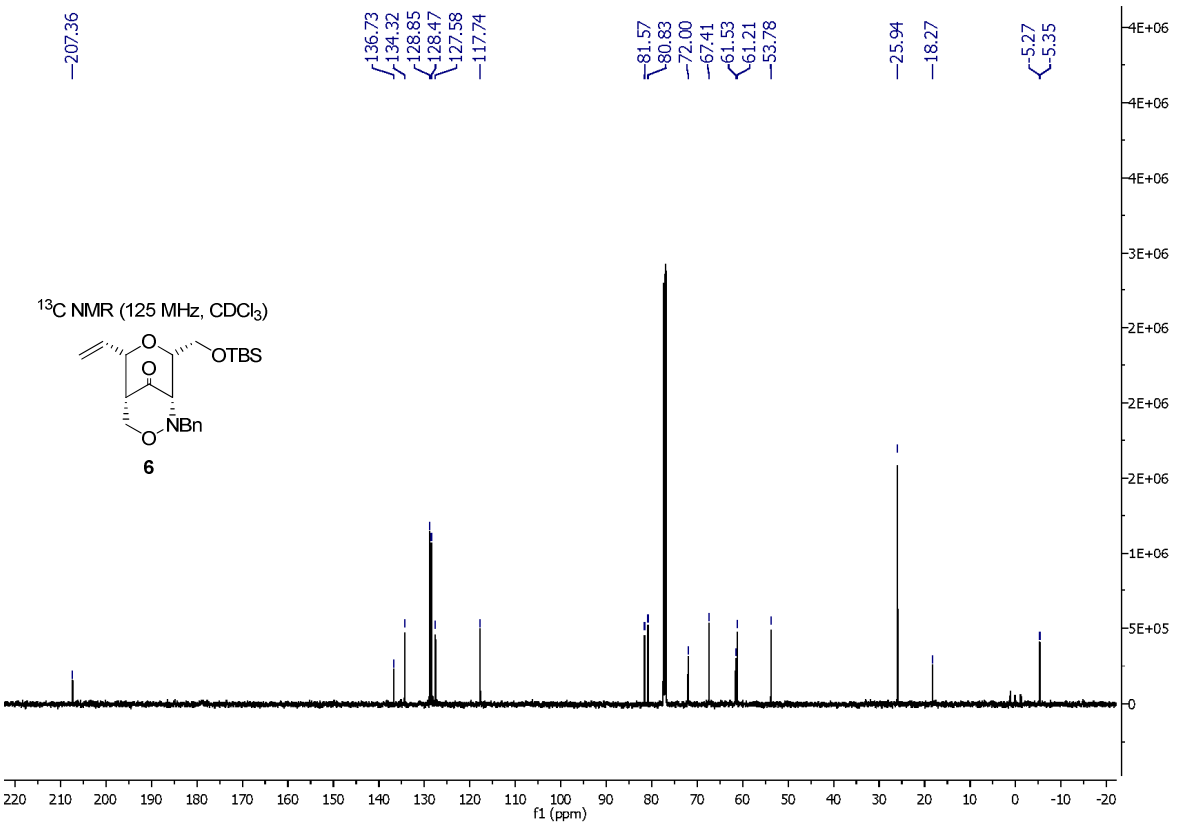
**5**




$^{1}$H NMR (500 MHz, $CDCl_3$)



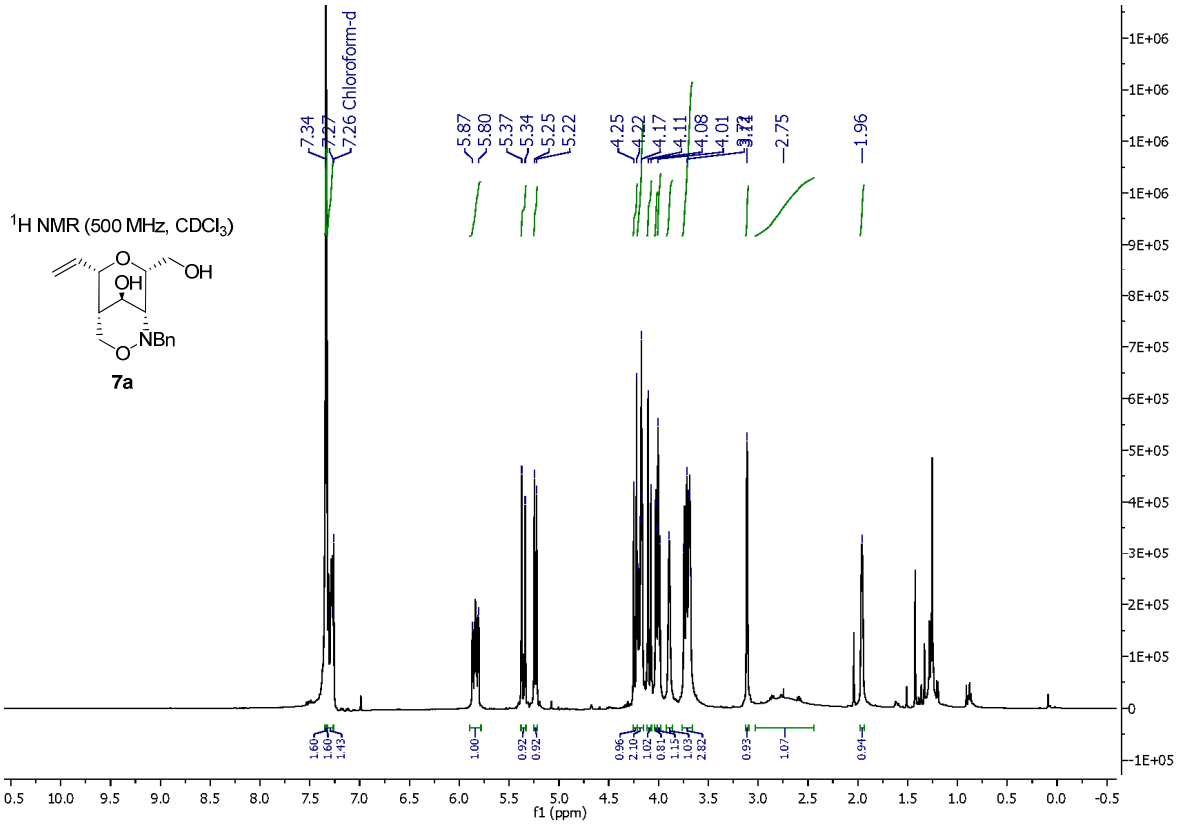

**6**

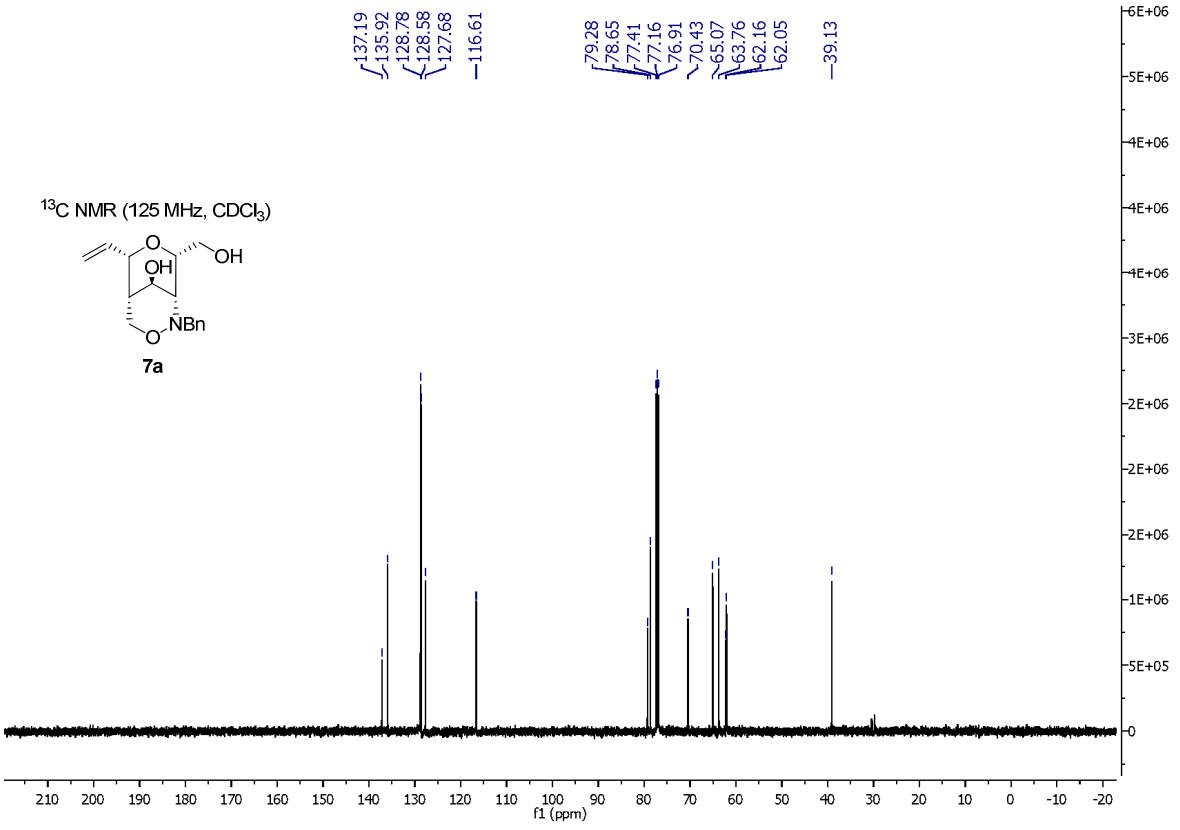


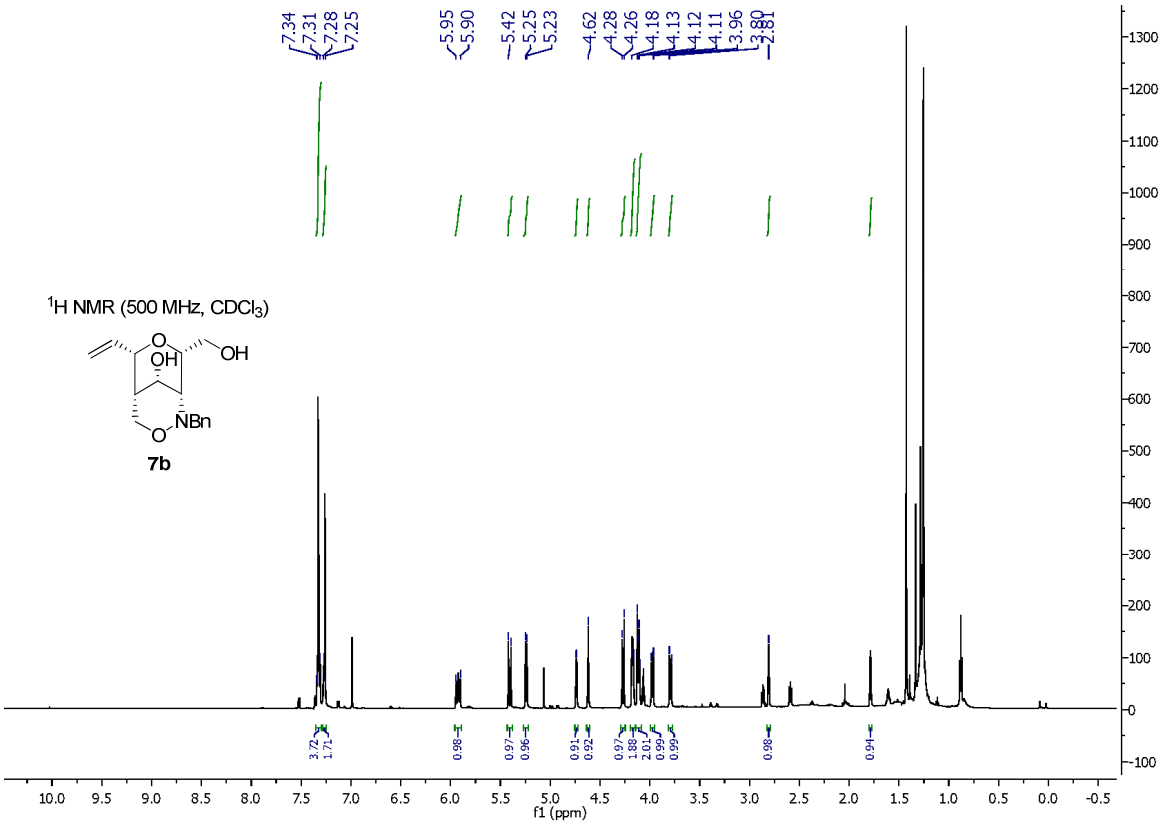

$^{13}$C NMR (125 MHz, $CDCl_3$)

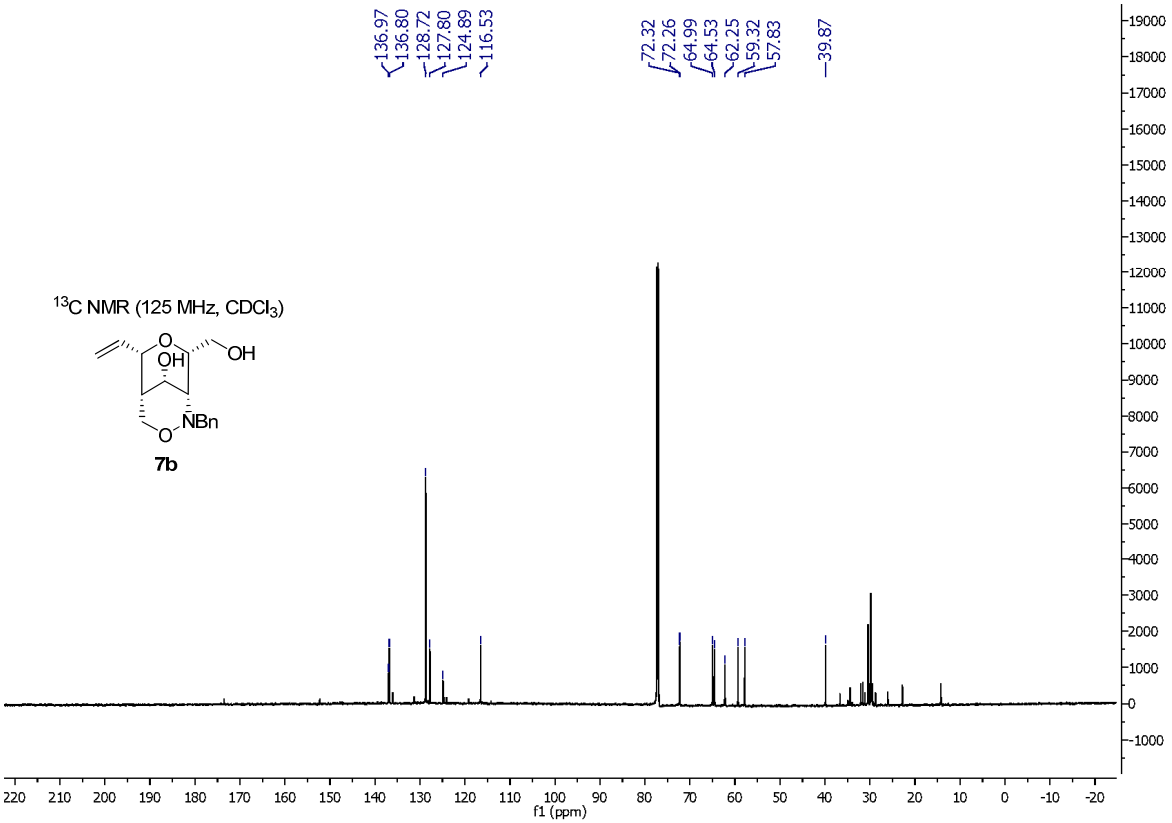


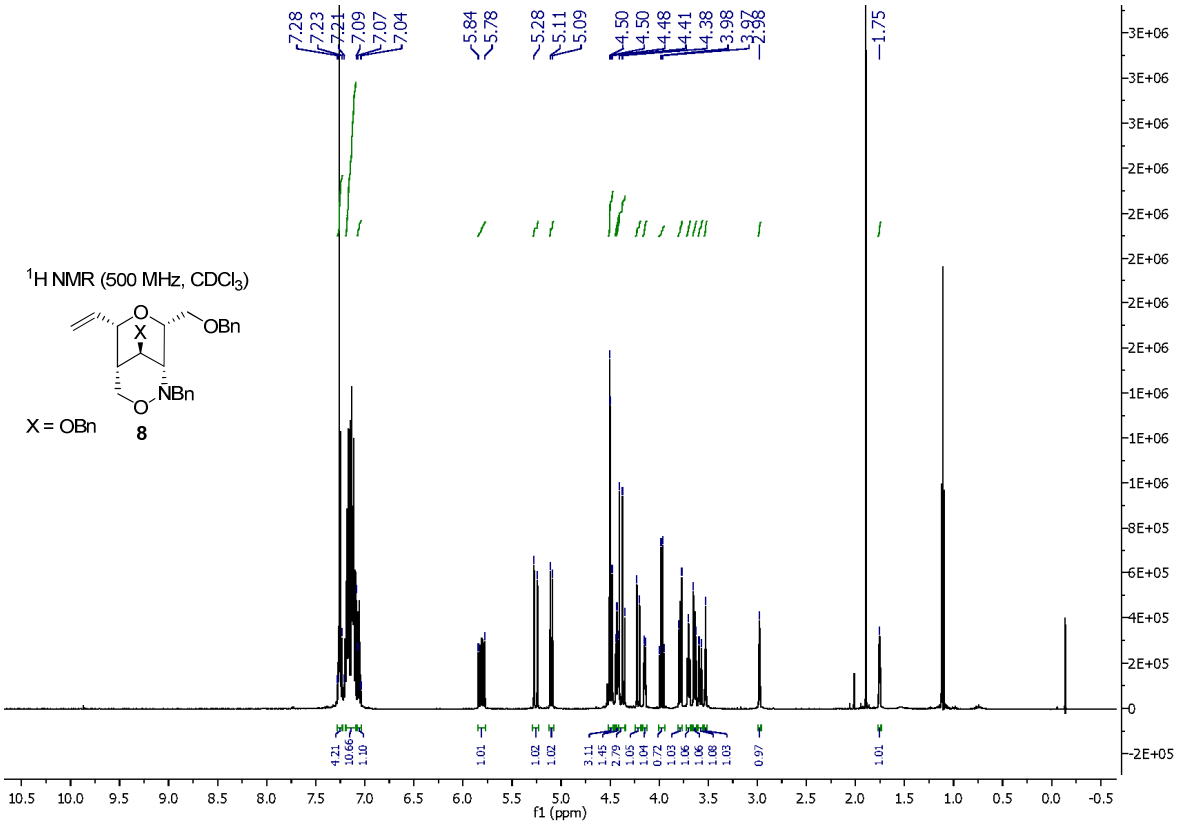

**6**

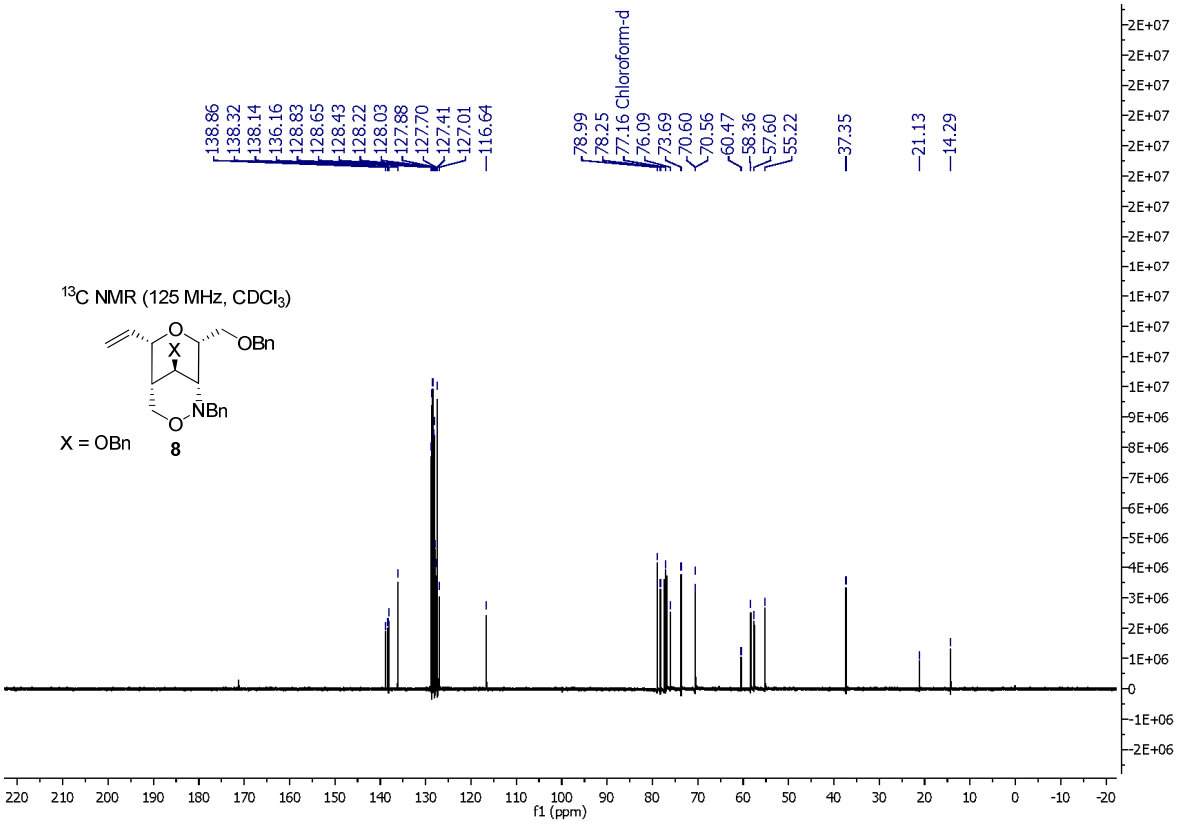

$^1$H NMR (500 MHz, CDCl$_3$)
OH
OH
NBn
O
O
7a
7.34
7.27
7.26 Chloroform-d
5.87
5.80
5.37
5.34
5.25
5.22
4.25
4.22
4.17
4.11
4.08
4.01
2.75
1.96
f1 (ppm)

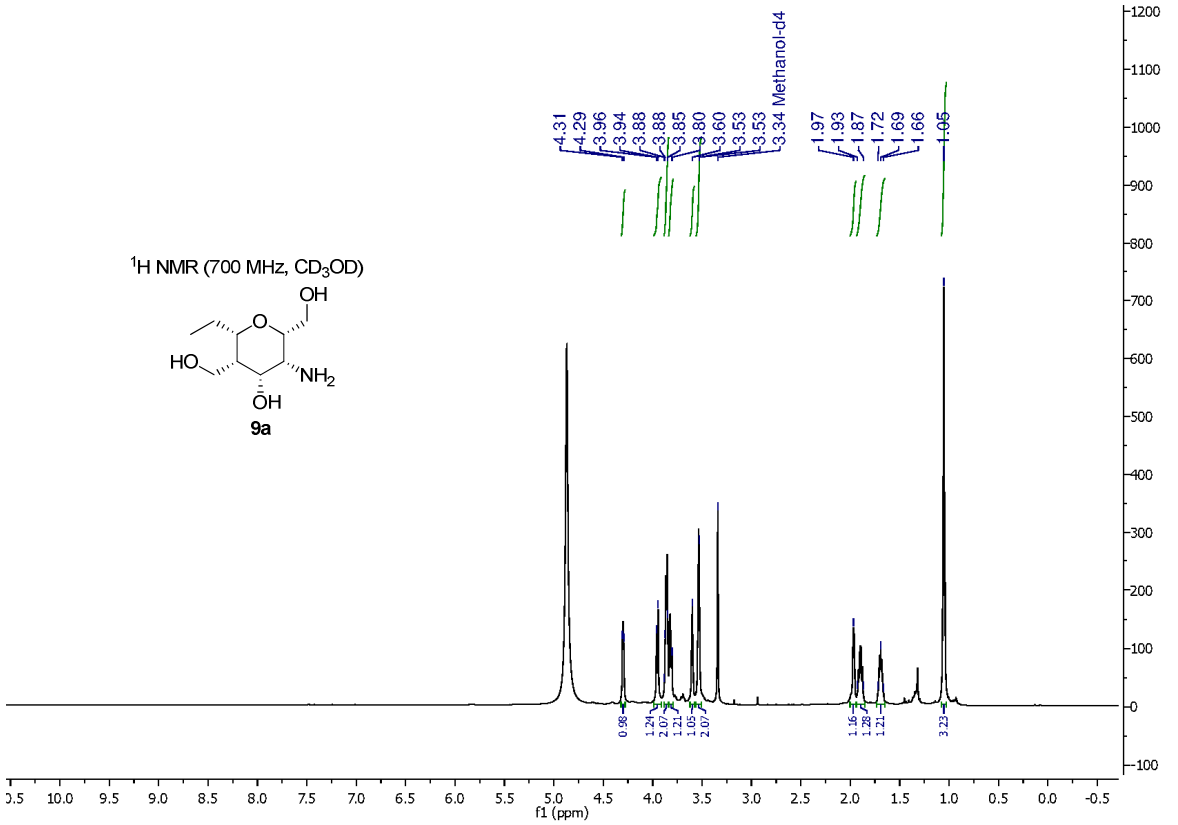

$^{13}$C NMR (125 MHz, CDCl$_3$)
OH
OH
NBn
O
O
7a
137.19
135.92
128.78
128.58
127.68
116.61
79.28
78.65
77.41
77.16
76.91
70.43
65.07
63.76
62.16
62.05
39.13
f1 (ppm)

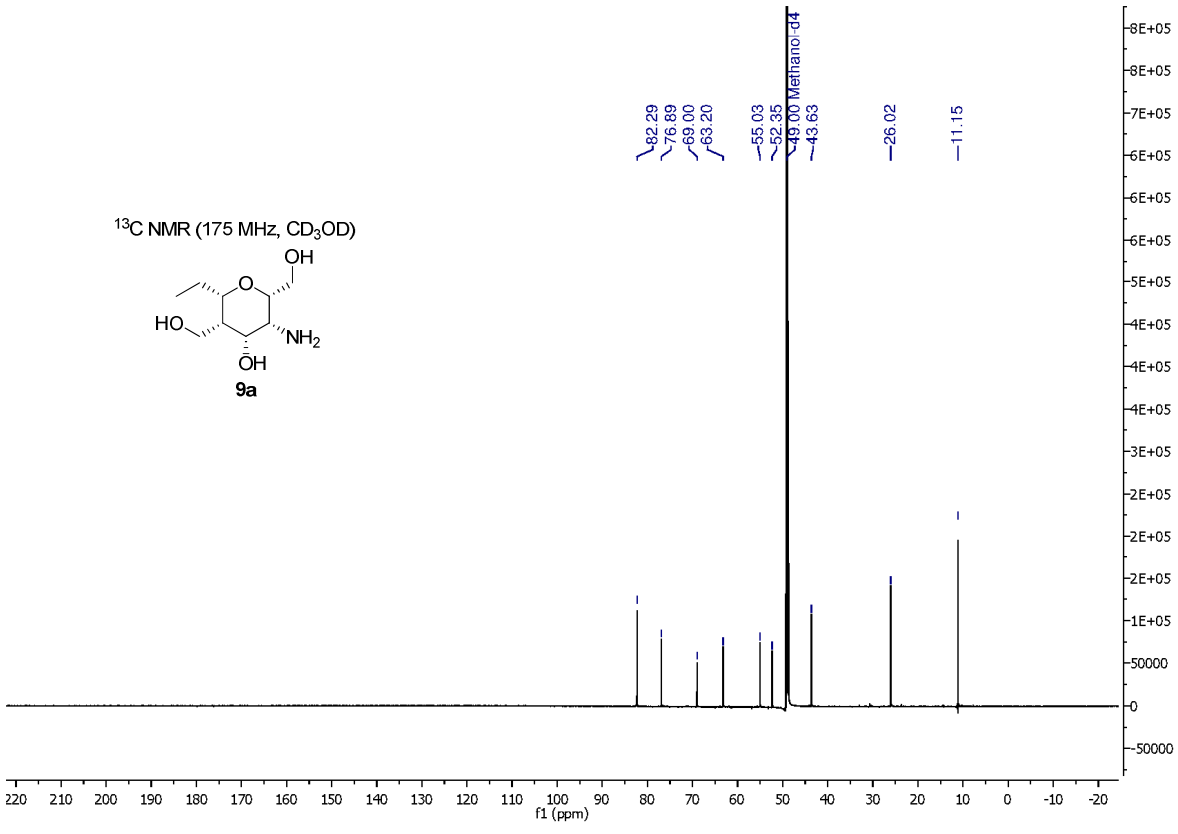

7.34
7.31
7.28
7.25
5.95
5.90
5.42
5.25
5.23
4.62
4.28
4.26
4.18
4.13
4.12
4.11
3.96
3.80
2.81
$^1$H NMR (500 MHz, CDCl$_3$)
OH
OH
NBn
O
7b
f1 (ppm)


136.97
136.80
128.72
127.80
124.89
116.53
72.32
72.26
64.99
64.53
62.25
59.32
57.83
39.87
$^{13}$C NMR (125 MHz, CDCl$_3$)
OH
OH
NBn
O
7b
f1 (ppm)

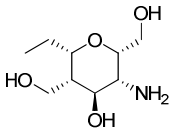

7.28
7.23
7.21
7.09
7.07
7.04
5.84
5.78
5.28
5.11
5.09
4.50
4.50
4.48
4.41
4.38
3.98
3.97
2.98
1.75
$^1$H NMR (500 MHz, CDCl$_3$)
OBn
NBn
X = OBn
8
f1 (ppm)


138.86
138.32
138.14
136.16
128.83
128.65
128.43
128.22
128.03
127.88
127.70
127.41
127.01
116.64
78.99
78.25
77.16 Chloroform-d
76.09
73.69
70.60
70.56
60.47
58.36
57.60
55.22
37.35
21.13
14.29
$^{13}$C NMR (125 MHz, CDCl$_3$)
OBn
NBn
X = OBn
8
f1 (ppm)


$^1$H NMR (700 MHz, $CD_3OD$)
OH
O
HO
NH$_2$
OH
9a
4.31
4.29
3.96
3.94
3.88
3.88
3.85
3.80
3.60
3.53
3.53
3.34 Methanol-d4
1.97
1.93
1.87
1.72
1.69
1.66
1.05
f1 (ppm)


$^{13}$C NMR (175 MHz, $CD_3OD$)
OH
O
HO
NH$_2$
OH
9a
82.29
76.89
69.00
63.20
55.03
52.35
49.00 Methanol-d4
43.63
26.02
11.15
f1 (ppm)

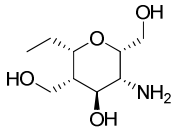
$^{1}$H NMR (700 MHz, $CD_3OD$)



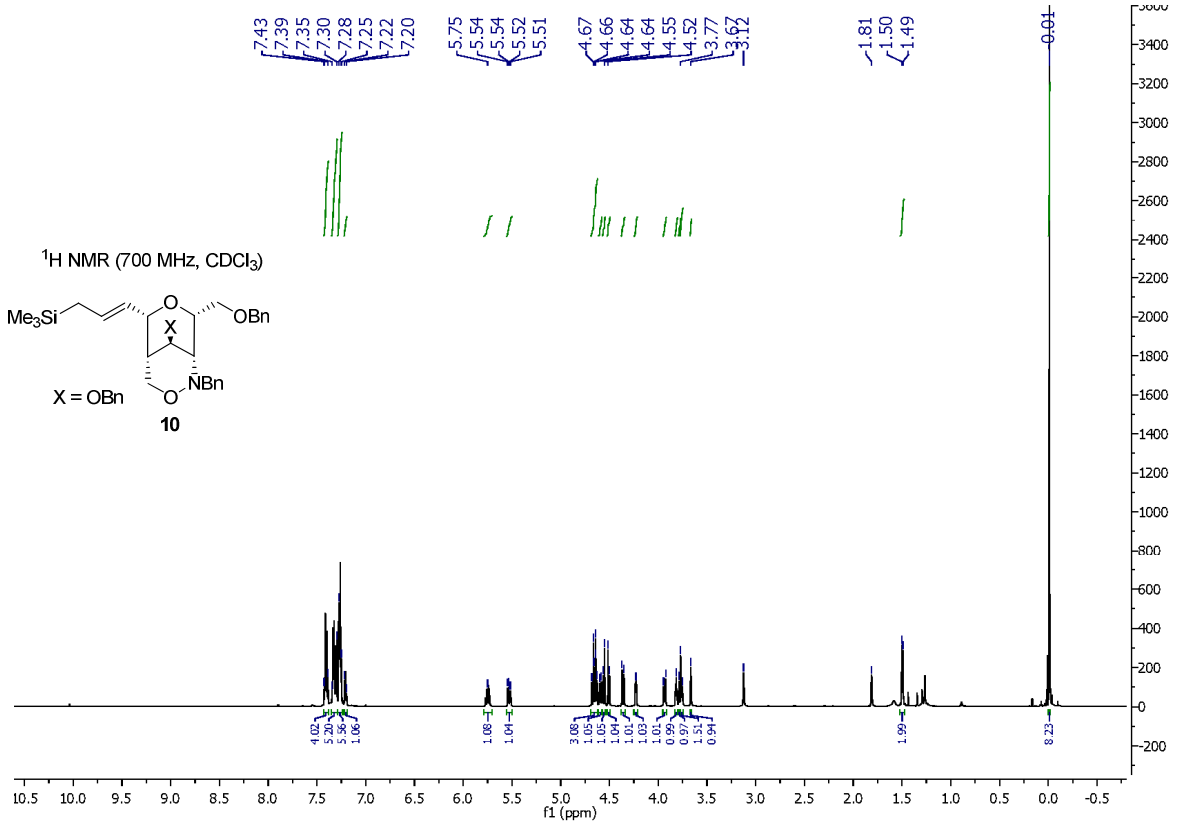

**9b**




$^{13}$C NMR (175 MHz, $CD_3OD$)



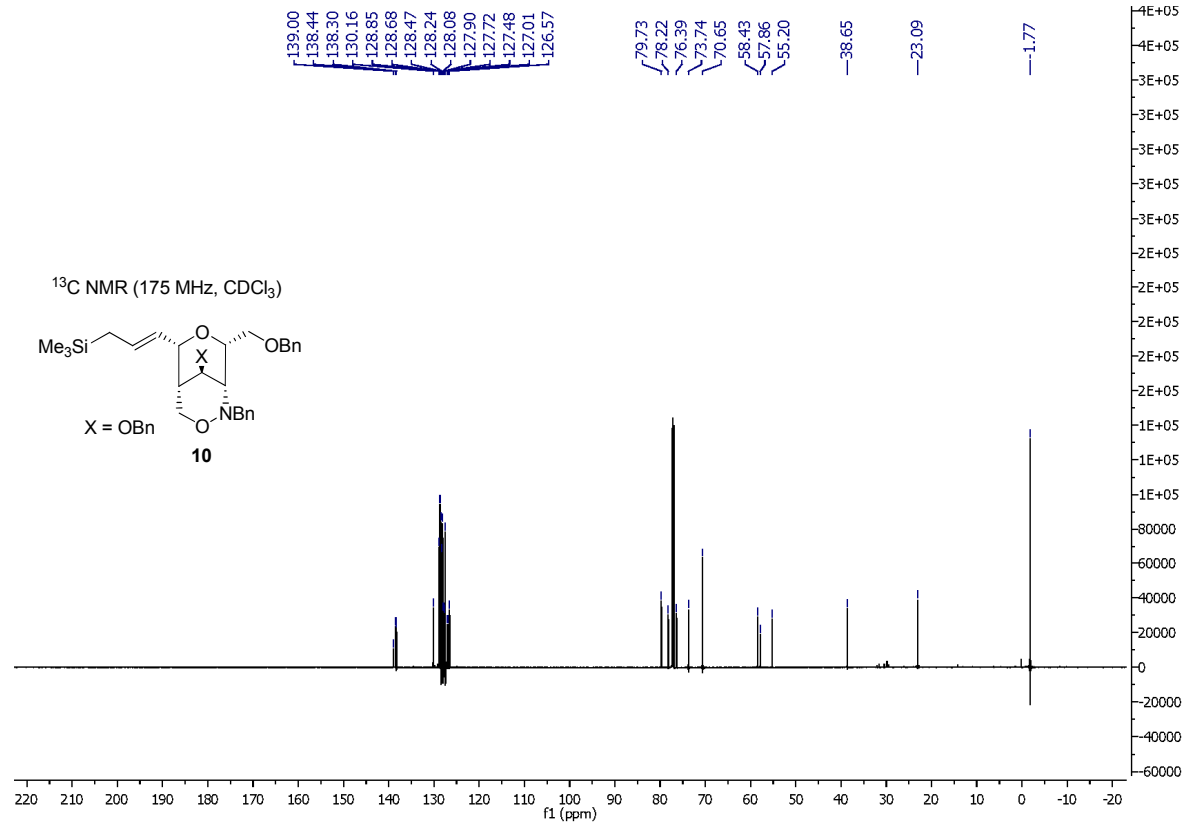

**9b**




$^1$H NMR (700 MHz, $CDCl_3$)



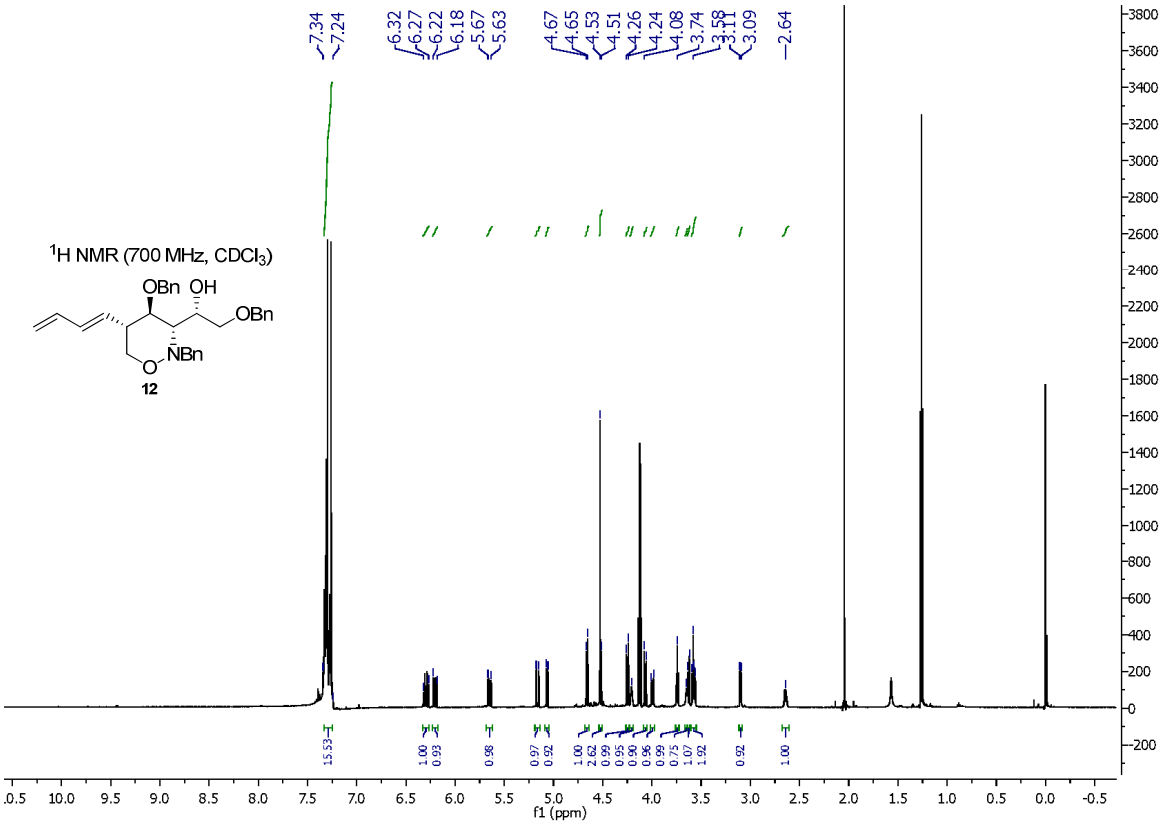

**10**

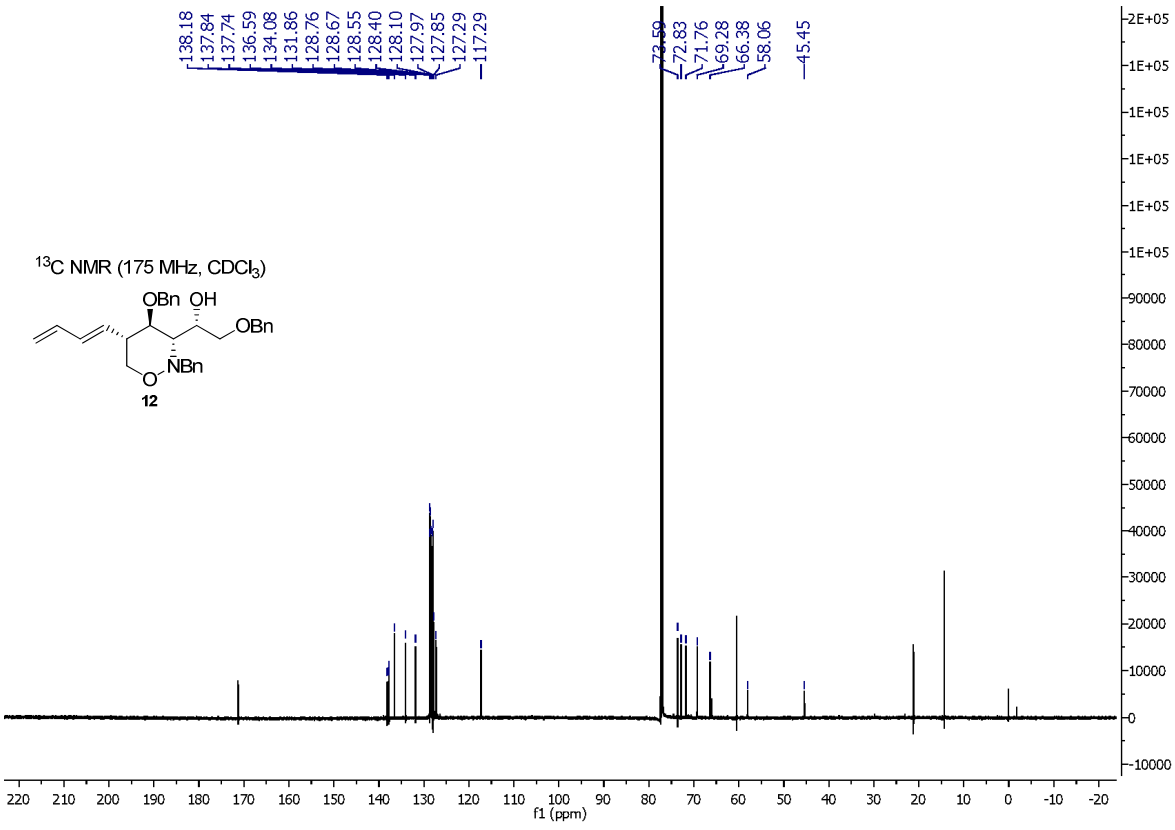


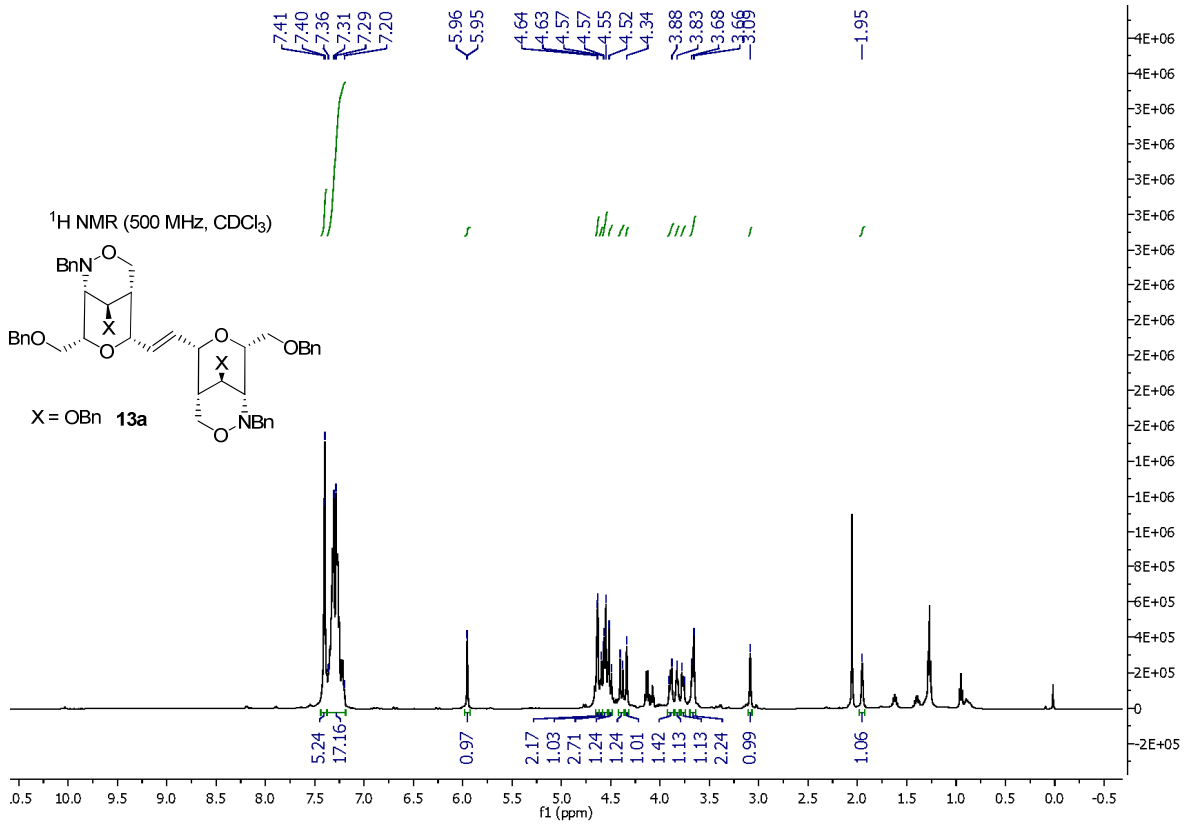

$^{13}$C NMR (175 MHz, $CDCl_3$)

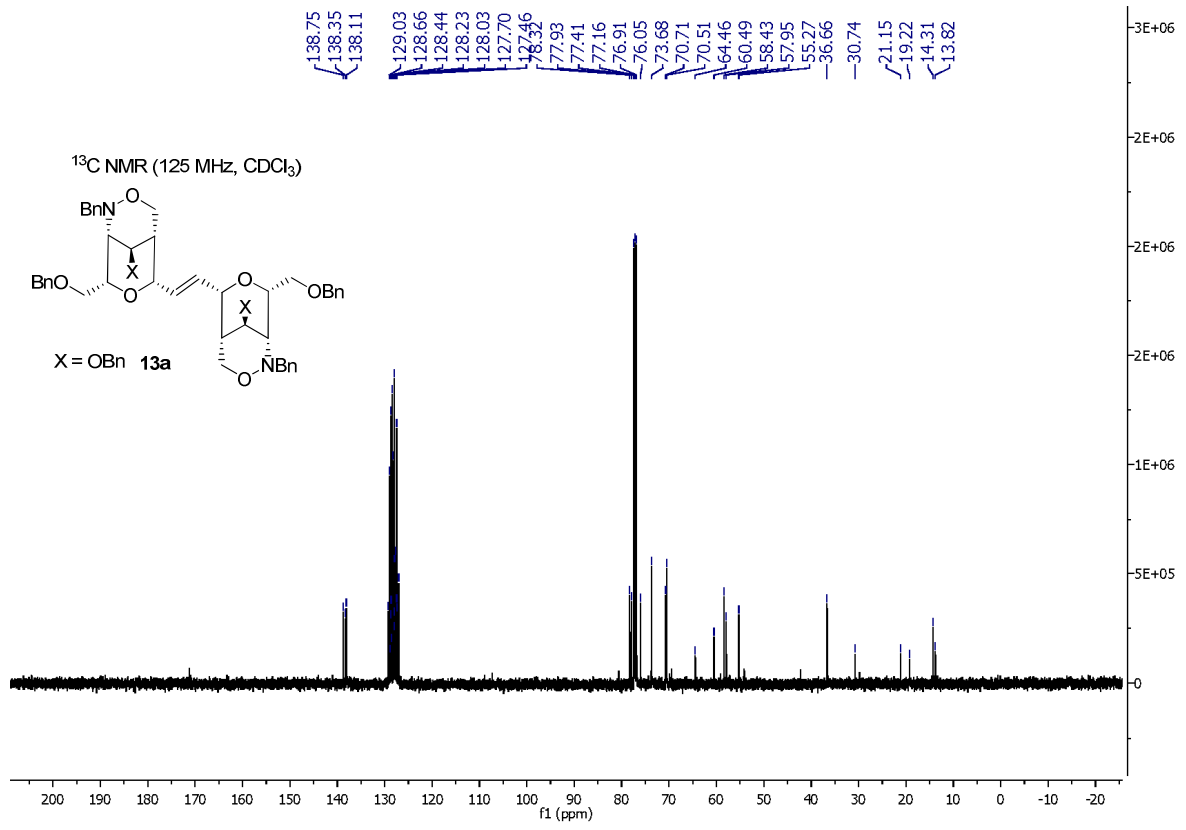


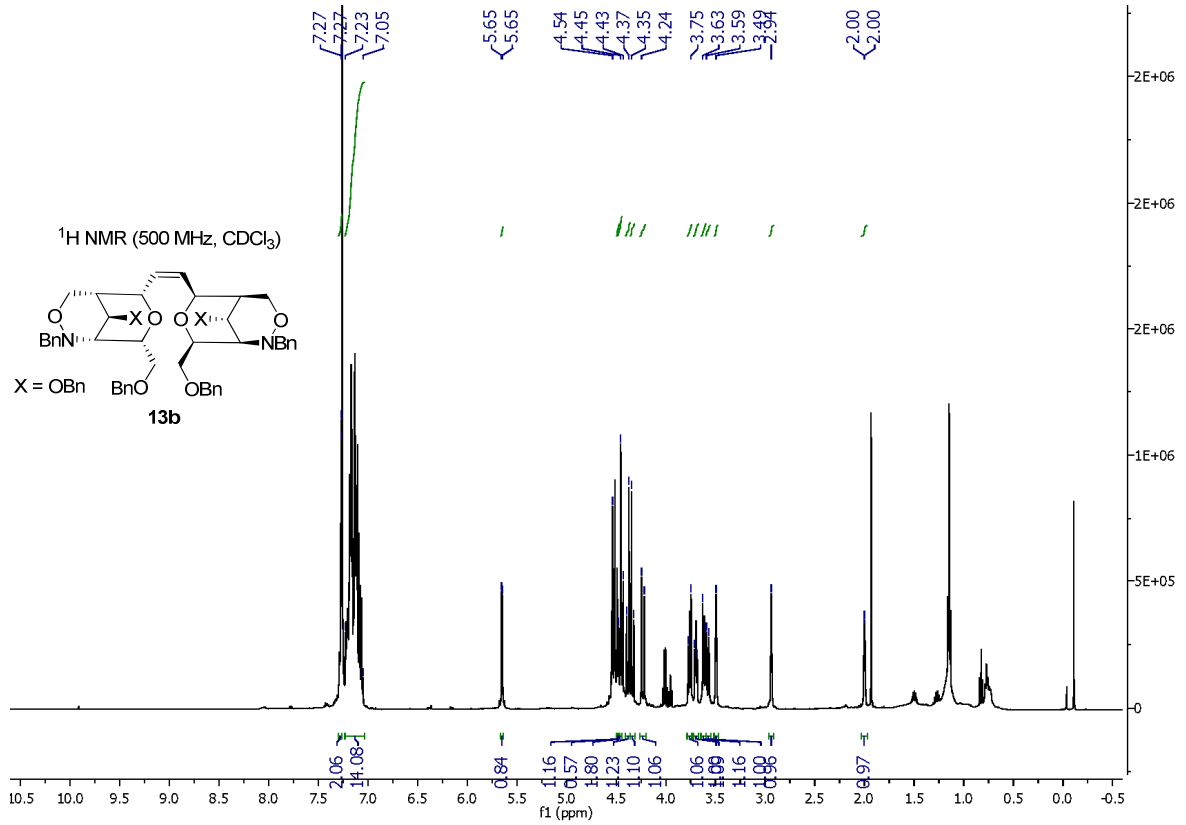

**10**

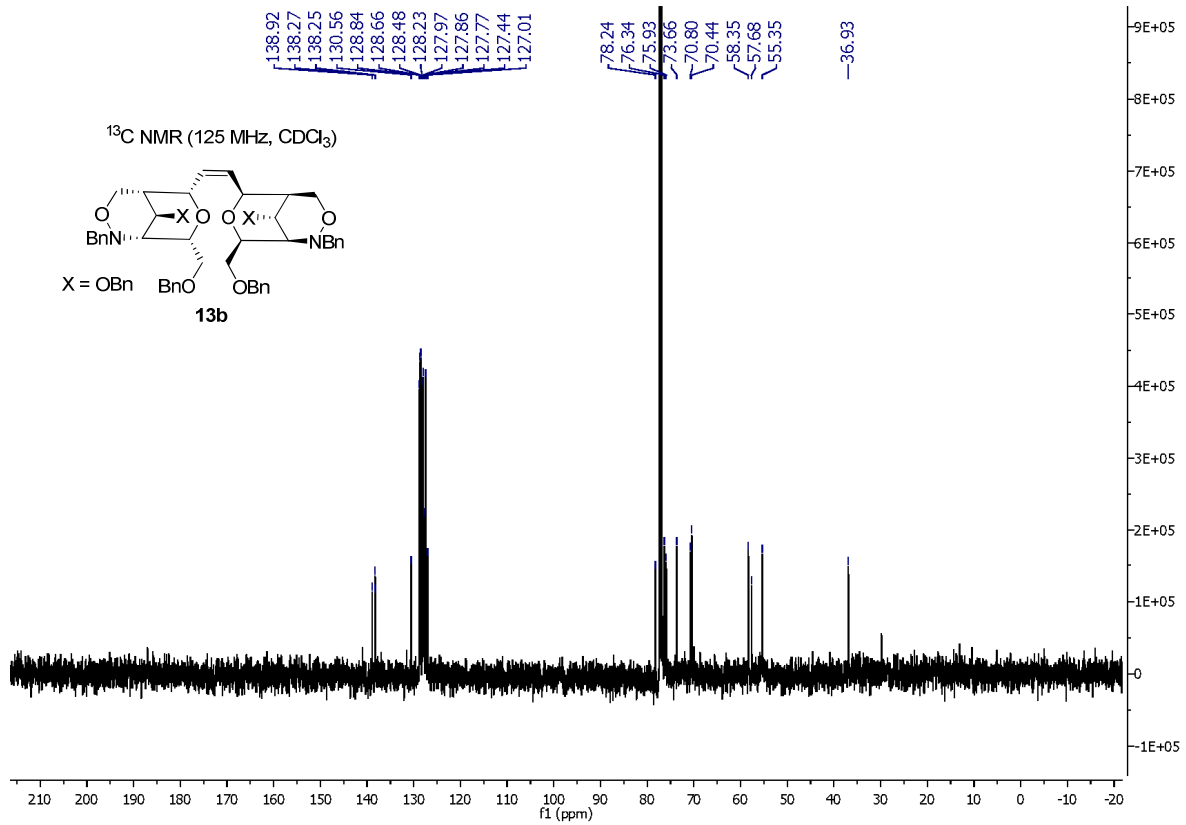

7.34
7.24
6.32
6.27
6.22
6.18
5.67
5.63
4.67
4.65
4.53
4.51
4.26
4.24
4.08
3.74
3.58
3.11
3.09
2.64
1H NMR (700 MHz, CDCl3)
OBn OH
OBn
NBn
O
12
f1 (ppm)

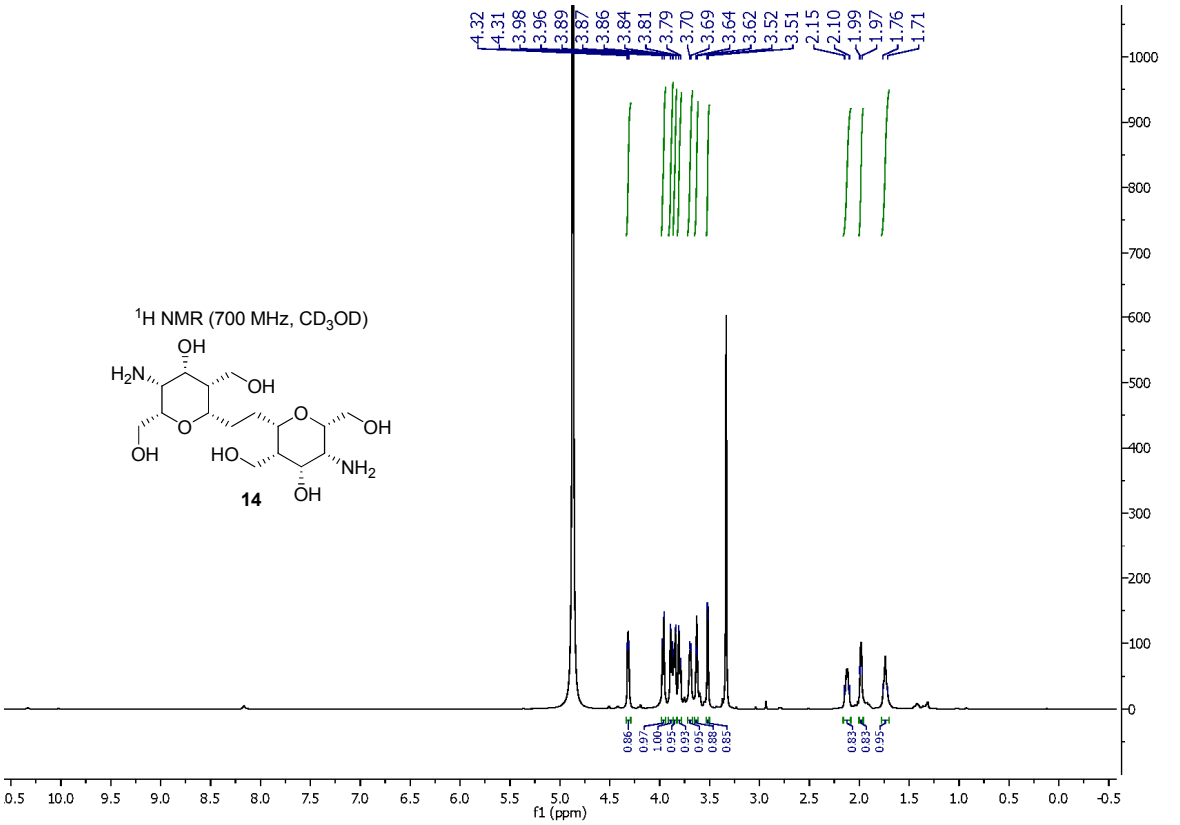

138.18
137.84
137.74
136.59
134.08
131.86
128.76
128.67
128.55
128.40
128.10
127.97
127.85
127.29
117.29
73.59
72.83
71.76
69.28
66.38
58.06
45.45
13C NMR (175 MHz, CDCl3)
OBn OH
OBn
NBn
O
12
f1 (ppm)

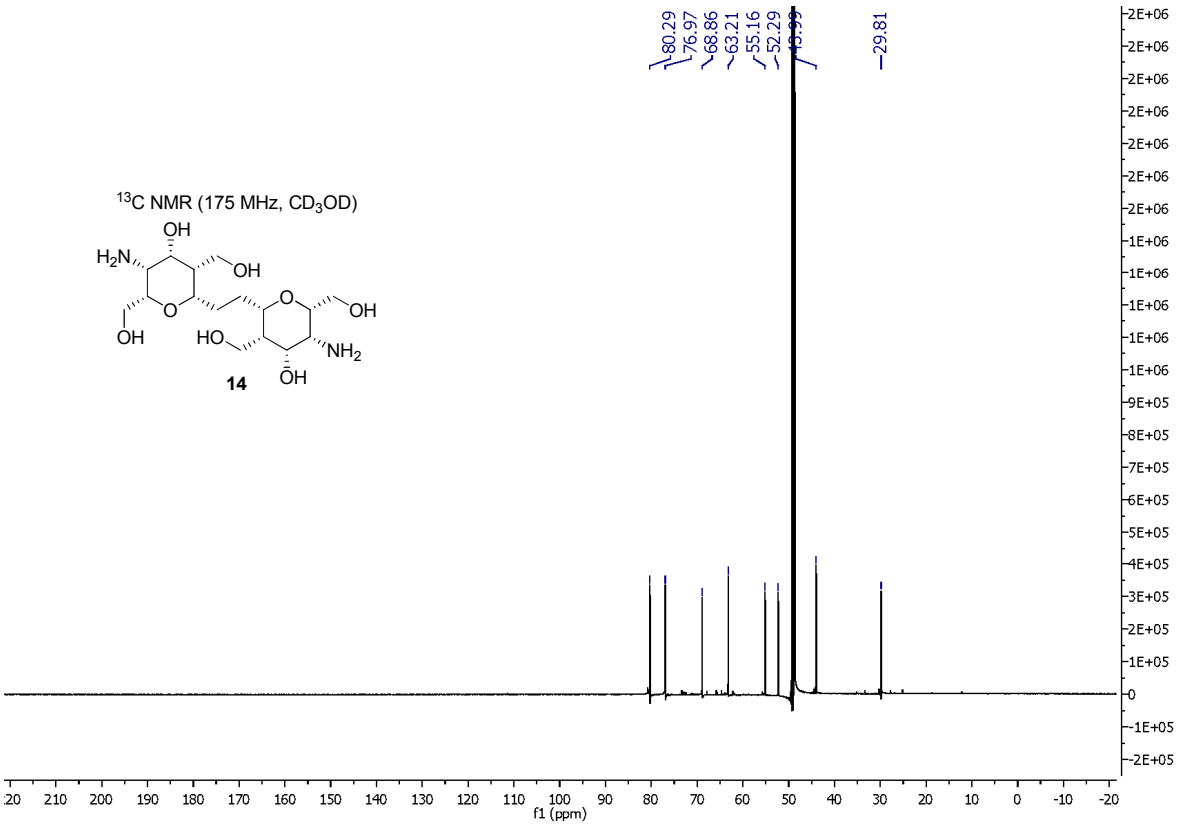

7.41
7.40
7.36
7.31
7.29
7.20
5.96
5.95
4.64
4.63
4.57
4.57
4.55
4.52
4.34
3.88
3.83
3.68
3.66
3.65
1.95
$^1$H NMR (500 MHz, $CDCl_3$)
BnO
BnN
OBn
NBn
X = OBn 13a
5.24
17.16
0.97
2.17
1.03
2.71
1.24
1.24
1.01
1.42
1.13
1.13
2.24
0.99
1.06
f1 (ppm)


138.75
138.35
138.11
129.03
128.66
128.44
128.23
128.03
127.70
127.46
78.32
77.93
77.41
77.16
76.91
76.05
73.68
70.71
70.51
64.46
60.49
58.43
57.95
55.27
36.66
30.74
21.15
19.22
14.31
13.82
$^{13}$C NMR (125 MHz, $CDCl_3$)
BnO
BnN
OBn
NBn
X = OBn 13a
f1 (ppm)


$^1$H NMR (500 MHz, $CDCl_3$)
X = OBn
13b
f1 (ppm)


$^{13}$C NMR (125 MHz, $CDCl_3$)
X = OBn
13b
f1 (ppm)


4.32
4.31
3.98
3.96
3.89
3.87
3.86
3.84
3.81
3.79
3.70
3.69
3.64
3.62
3.52
3.51
2.15
2.10
1.99
1.97
1.76
1.71
1H NMR (700 MHz, CD3OD)
OH
H2N
OH
O
OH
O
OH
HO
NH2
OH
14
f1 (ppm)


80.29
76.97
68.86
63.21
55.16
52.29
49.99
29.81
13C NMR (175 MHz, CD3OD)
OH
H2N
OH
O
OH
O
OH
HO
NH2
OH
14
f1 (ppm)

## 7.4 Daten zu Röntgenstrukturanalyse von (1*S*,2*R*,4*S*,5*R*,8*S*)-6-Benzyl-2-(4-bromphenyl)-4-(hydroxymethyl)-3-oxa-6-azabicyclo[3.2.1]-octan-8-ol (28)

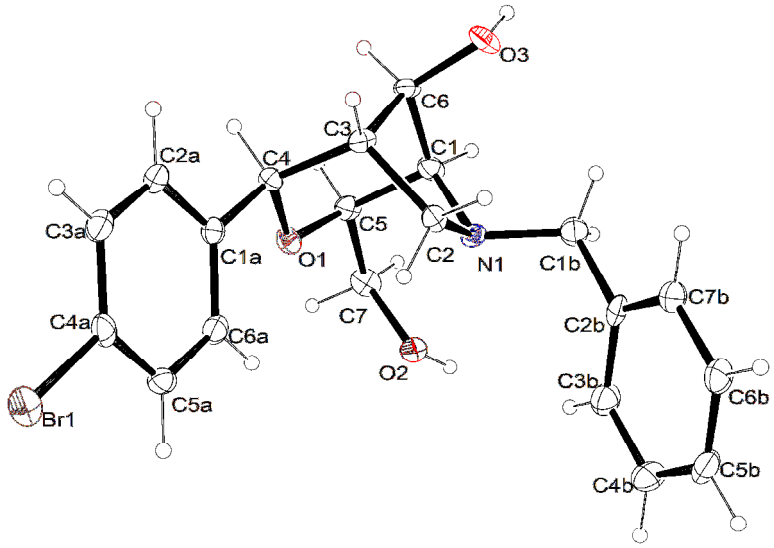



Abbildung 17: Kristallstruktur vom bicyclischen 1,2-Oxazin **28**.

**Kristallographische Daten:**

| | |
|---|---|
| Empirische Summenformel: | $C_{20}H_{22}BrNO_3$ |
| Molekulargewicht: | 404.3 g/mol |
| Farbe: | farblos |
| Kristalldimension: | 0.80 x 0.30 x 0.02 $mm^3$ |
| Kristallsystem: | monoklines |
| Raumgruppe: | C 2 |
| Gitterkonstante: | a = 17.672(6) Å |
| | b = 6.855(3) Å |
| | c = 15.436(6) Å |
| | α = 90° |
| | β = 104.30(8)° |
| | γ = 90° |
| Anzahl der Formeleinheiten: | Z = 4 |
| Berechnete Dichte: | 1.482 $g/cm^3$ |
| Wellenlänge der Strahlung: | 0.71073 Å |
| Temperatur: | 100(2) K |
| Messbereich: | 1.36 bis 30.54° |

| | |
|---|---|
| Gemessener Bereich des reziproken Raums: | -22 ≤ h ≤25 |
| | -8 ≤ k ≤ 9 |
| | -22 ≤ l ≤13 |
| Zahl der gemessenen Reflexe: | 5325 |
| Zahl der unabhängigen Reflexe: | 4123 |
| F(000): | 832.0 |
| Absorptionskoeffizient: | 2.29 $mm^{-1}$ |
| Anzahl der verfeinerten Parameter: | 228 |
| Verfeinerungsmethode: | Kleinste-Quadrate-Formalismus |
| $R_1$: | 0.0648 |
| $wR_2$: | 0.1429 |
| GooF: | 1.075 |

Tabelle 3: Atomkoordinaten (x $10^4$) und äquivalente isotrope Auslenkungsparameter $U_{eq}$.

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| Br(1) | 4387(1) | 12756(1) | 3131(1) | 21(1) |
| C(1) | 3491(3) | 7054(7) | 7772(4) | 16(1) |
| C(2) | 4517(2) | 7805(11) | 7088(3) | 14(1) |
| C(3) | 3850(2) | 6721(6) | 6445(4) | 14(1) |
| C(4) | 3204(2) | 8097(6) | 5958(3) | 14(1) |
| C(5) | 2843(3) | 8510(7) | 7355(4) | 16(1) |
| C(6) | 3530(2) | 5472(6) | 7094(4) | 14(1) |
| C(7) | 2760(3) | 10154(8) | 7985(4) | 20(1) |
| C(1A) | 3447(3) | 9308(7) | 5261(3) | 15(1) |
| C(2A) | 3436(3) | 8469(8) | 4439(3) | 19(1) |
| C(3A) | 3709(3) | 9492(8) | 3792(4) | 18(1) |
| C(4A) | 3984(3) | 11367(7) | 3981(4) | 17(1) |
| C(5A) | 3987(3) | 12245(7) | 4785(4) | 16(1) |
| C(6A) | 3721(3) | 11203(7) | 5427(4) | 16(1) |
| C(1B) | 4846(3) | 7376(7) | 8730(4) | 18(1) |
| C(2B) | 5569(3) | 8612(8) | 8907(3) | 16(1) |
| C(3B) | 5548(3) | 10554(8) | 9171(4) | 22(1) |
| C(4B) | 6221(3) | 11694(8) | 9359(4) | 24(1) |
| C(5B) | 6924(3) | 10888(8) | 9276(4) | 21(1) |
| C(6B) | 6954(3) | 8979(8) | 9002(4) | 23(1) |
| C(7B) | 6277(2) | 7842(10) | 8822(3) | 20(1) |
| N(1) | 4258(2) | 8084(6) | 7928(3) | 13(1) |
| O(1) | 2987(2) | 9409(5) | 6581(2) | 16(1) |
| O(2) | 3483(2) | 11170(5) | 8302(3) | 19(1) |
| O(3) | 4073(2) | 3993(5) | 7447(3) | 19(1) |

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# Lebenslauf

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