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A Proline and 4-Hydroxyproline Based Approach to Enantiopure Pyrrolidin-2-yl-Substituted Pyridine and Pyrimidine Derivatives

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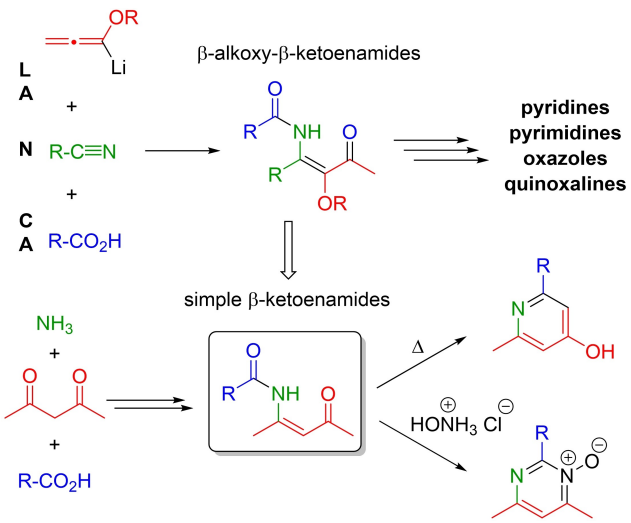
Dedicated to the memory of Professor Klaus Hafner.

The optimized coupling of N-protected (*S*)-proline and (2*S*,4*R*)-4-hydroxyproline derivatives with (*Z*)-4-aminopent-3-en-2-one provided the expected β-ketoenamides in good to excellent yields. The subsequent intramolecular cyclizations afforded enantiopure pyridin-4-one derivatives with pyrrolidin-2-yl substituents. The nonaflates generated from these intermediates were excellent precursors for typical palladium-catalyzed coupling reactions. Oxidation with *m*-chloroperbenzoic acid gave pyrrolidine *N*-oxides whose subsequent reactions were investigated. The condensation of β-ketoenamides with hydroxylamine hydrochloride furnished the corresponding enantiopure pyrimidine *N*-oxides in good yields. The subsequent Boekelheide rearrangement provided hydroxymethyl-substituted pyrimidine derivatives together with minor components. Overall, this study nicely demonstrates the potential of (*S*)-proline- or (2*S*,4*R*)-4-hydroxyproline-derived β-ketoenamides to approach a library of novel chiral pool-derived enantiopure functionalized pyridine and pyrimidine derivatives.

Introduction

Specifically substituted pyridine and pyrimidine derivatives are compounds of particular importance as biologically active compounds, but also as components of functional materials and catalysts.[1,2] The two classes of six-membered heterocycles are also often integral parts of chiral catalysts, either as organocatalysts or as ligands of metal complexes.[3] New and flexible methods to prepare novel pyridine or pyrimidine derivatives bearing substituents with stereogenic centers are therefore a permanent challenge. Our group investigated in great detail a new and versatile three-component reaction which employed lithiated alkoxyallenes, nitriles and carboxylic acids (LANCA process) to deliver β-alkoxy-β-ketoenamides as key compounds (Scheme 1, upper part).[4] Under specific conditions, these intermediates undergo subsequent cyclization reactions to furnish highly substituted pyridine,[5] pyrimidine,[6] oxazole,[7] and quinoxaline[8] derivatives. Their substitution pattern allowed a variety of subsequent reactions leading to comprehensive libraries of heterocycles.[9] The successful application of β-alkoxy-β-ketoenamides for the synthesis of hundreds of new compounds motivated our group to study the behavior of simple β-ketoenamides (Scheme 1, lower part) which are very easily available in two steps from ammonia, 1,3-diketones and carboxylic acids. Analogous cyclization reactions led indeed to formation of pyridine, bipyridine, terpyridine and pyrimidine derivatives in good yields. This approach is less flexible and most compounds obtained bear methyl substitu-



Scheme 1. Approach to β-ketoenamides by two three-component reactions and their subsequent cyclizations to heterocycles such as pyridine and pyrimidine derivatives.

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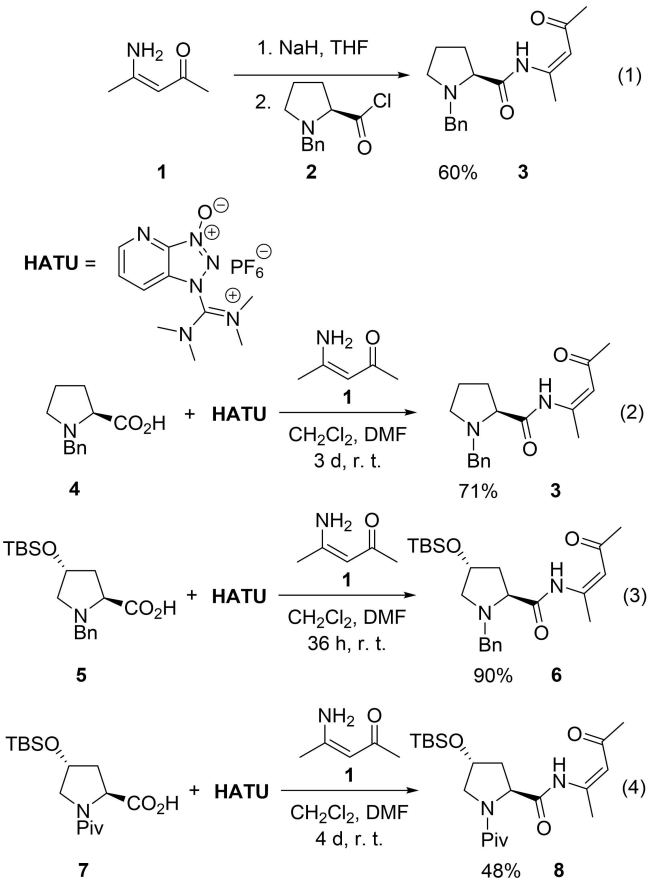
ents, but the products are still sufficiently functionalized to allow further applications.[10]

Both approaches to pyridines and pyrimidines have already been used to prepare enantiopure compounds. For the LANCA process, enantiopure nitriles and/or carboxylic acids gave pyridine and pyrimidine derivatives bearing substituents with stereogenic centers.[11] Likewise, first experiments were undertaken to use enantiopure carboxylic acid derivatives (mostly derived from chiral pool α-hydroxy carboxylic acids or amino acids) to prepare simple β-ketoenamides which were cyclized to pyridines with chiral substituents.[12] In the current investigation we extend this approach to (*S*)-proline and (2*S*,4*R*)-4-hydroxyproline derivatives as starting materials, which are more challenging than simple amino acids due to the higher steric hindrance exerted by the secondary amino acid moiety. The obtained β-ketoenamides were subsequently cyclized to pyridine and pyrimidine *N*-oxide derivatives. Their subsequent synthetic elaboration demonstrates the value of this new approach to enantiopure pyrrolidin-2-yl-substituted heterocycles.

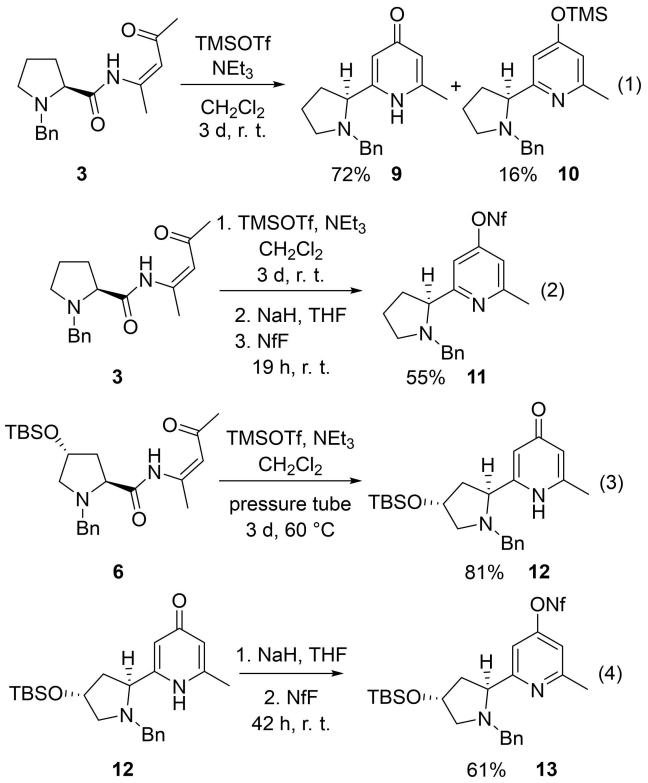
Results and Discussion

In our previous study of amino acid derivatives we already included one experiment employing *N*-benzyl-substituted (*S*)-proline and we were able to synthesize the corresponding β-ketoenamide **3** in 60% yield (Scheme 2, equation 1).[12a] However, an excess of the sodium salt of (*Z*)-4-aminopent-3-en-2-one (**1**)[13] and a generation of the acid chloride **2** at low temperature were required, making this method quite inconvenient. A more practical and simple approach is described in equation 2: *N*-benzyl (*S*)-proline **4** was in situ activated by **HATU** (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]-pyridinium 3-oxide hexafluorophosphate)[14] followed by addition of β-ketoenamine **1**. All steps occur at room temperature and after three days, aqueous work up and chromatographic purification provided the desired β-ketoenamide **3** in satisfying 71% yield. Similarly, β-ketoenamide **6** was prepared in excellent 90% yield starting from *tert*-butyldimethylsilyl-protected (2*S*,4*R*)-hydroxyproline derivative **5**,[15] **HATU** and **1** (equation 3). The method employing the acid chloride derived from **5** and the sodium salt of **1** furnished **6** only in 55% yield. The related *N*-pivaloyl-substituted compounds are sterically even more demanding. Here, the acid chloride method gave the desired β-ketoenamide **8** in only 8% yield, whereas the **HATU**-activated amino acid **7**[16] and β-ketoenamine **1** furnished at least 48% of product **8** (equation 4). Alternative coupling reagents (e.g. benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, propanephosphonic acid anhydride, or carbodiimide-based compounds) provided less satisfying results. The developed **HATU** activation of carboxylic acids seems to be particularly suitable for the generation of amide bonds starting from amines with relatively low nucleophilicity as given for β-ketoenamines such as **1**. It is important to note, that β-ketoenamides **6** and **8** were formed as diastereomerically pure compounds, an observation which indicates that no epimerization at C-2 of the pyrrolidin-2-yl moiety has occurred under the chosen reaction conditions.

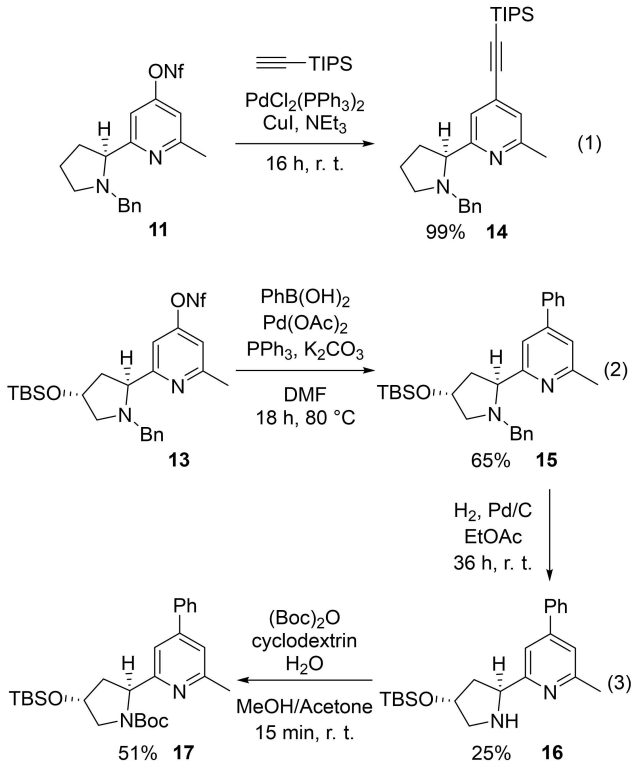


Scheme 2. Synthesis of β-ketoenamides **3**, **6** and **8** from β-ketoenamine **1** and the *N*- and *O*-protected (*S*)-proline and (2*S*,4*R*)-hydroxyproline derivatives **4**, **5** and **7**.

With sufficient amounts of starting materials in hand, their cyclization reactions could be investigated. The standard method for the generation of pyridine derivatives applies trimethylsilyl trifluoromethanesulfonate in the presence of triethylamine under gentle heating for extended times. These approved conditions induce the intramolecular aldol condensation of the moderately reactive amide carbonyl group with the terminal methyl group.[10] With this procedure, β-ketoenamide **3** was efficiently converted into a mixture of pyrrolidin-2-yl-substituted pyridin-4-one derivative **9** (72%) and 4-(trimethylsiloxy)pyridine **10** (16%) (Scheme 3, equation 1). We assume that during the condensation of **3** only **10** is generated by the present excess of the silylating agent, but during work-up and purification the labile trimethylsiloxy group is almost completely hydrolyzed to the requested pyridin-4-one derivative **9**. The observed ratio of pyridin-4-ones and its 4-hydroxypyridine tautomer is strongly dependent on the substitution pattern of the respective compound and on the solvents used for their spectroscopic characterization.[5,10] The first example of Scheme 3 demonstrates the high efficiency of the condensation reaction even in the presence of the sterically demanding *N*-



Scheme 3. Condensation reactions transforming β-ketoenamides **3** and **6** into pyridin-4-one derivatives **9** and **12**, respectively, followed by conversion into enantiopure pyridin-4-yl nonaflates **11** and **13** (NfF = $C_4F_9SO_2F$).



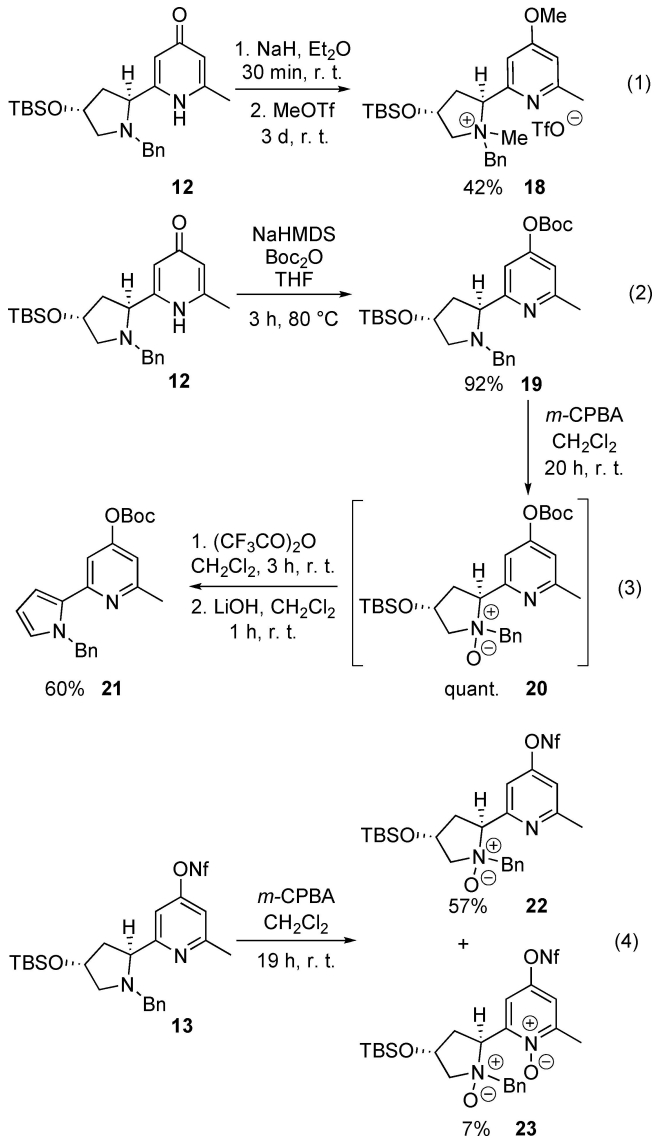
Scheme 4. Palladium-catalyzed transformations of pyridin-4-yl nonaflates **11** and **13** leading to alkynyl- or phenyl-substituted pyridine derivatives **14** and **15**, respectively, and hydrogenolysis of **15**.

benzyl-pyrrolidine moiety. In equation 2, a one-pot generation of the corresponding pyridin-4-yl nonaflate **11** is illustrated. For this purpose, the condensation step was performed as usual, but instead of aqueous work up all volatile components were removed and the crude product mixture was directly used in the same flask for the deprotonation with sodium hydride in tetrahydrofuran and treatment with nonafluorobutanesulfonyl fluoride. This one-pot/two-stage protocol furnished the pyrrolidin-2-yl-substituted pyridin-4-yl nonaflate **11** in 55% yield.

The related nonaflate **13** was prepared in two separate steps with purified intermediate **12** (Scheme 3, equations 3 and 4). First, the condensation reaction of 4-hydroxyproline-derived β-ketoenamide **6** under standard conditions efficiently produced compound **12**.[17] The formation of 4-hydroxypyrrolidin-2-yl-substituted pyridin-4-yl nonaflate **13** under approved conditions proceeded reasonably in 61% yield. Compounds **12** and **13** are diastereomerically pure, demonstrating their configurational persistence under the reaction conditions employed.

Two typical reactions of the pyridin-4-yl nonaflates **11** and **13** demonstrate the potential of this product class for further synthetic elaboration by palladium-catalyzed coupling reactions.[5,10,18] As first example, the Sonogashira reaction of **11** with triisopropylsilylacetylene under approved conditions smoothly provided the 4-alkynyl-substituted pyridine derivative **14** almost quantitatively (Scheme 4, equation 1). In a second exemplary transformation, the 4-hydroxyproline-derived compound **13** was converted by a Suzuki coupling with phenylboronic acid into the 4-phenyl-substituted pyridine derivative **15** in 65% yield (equation 2). With this compound we examined the possibility to selectively remove the *N*-benzyl group by palladium-catalyzed hydrogenolysis. After 36 hours the sluggish reaction reached only a conversion of approximately 50% (47% of **15** were re-isolated) and 25% of the desired compound **16** were obtained after chromatographic separation (equation 3).[19] For full characterization this secondary amine was converted into the *N*-Boc protected compound **17** employing a cyclodextrin-promoted method.[20] An attempt to reductively remove the nonafloxy and *N*-benzyl moieties of pyridin-4-yl nonaflate **13** gave a mixture of compounds that could not be fully identified.

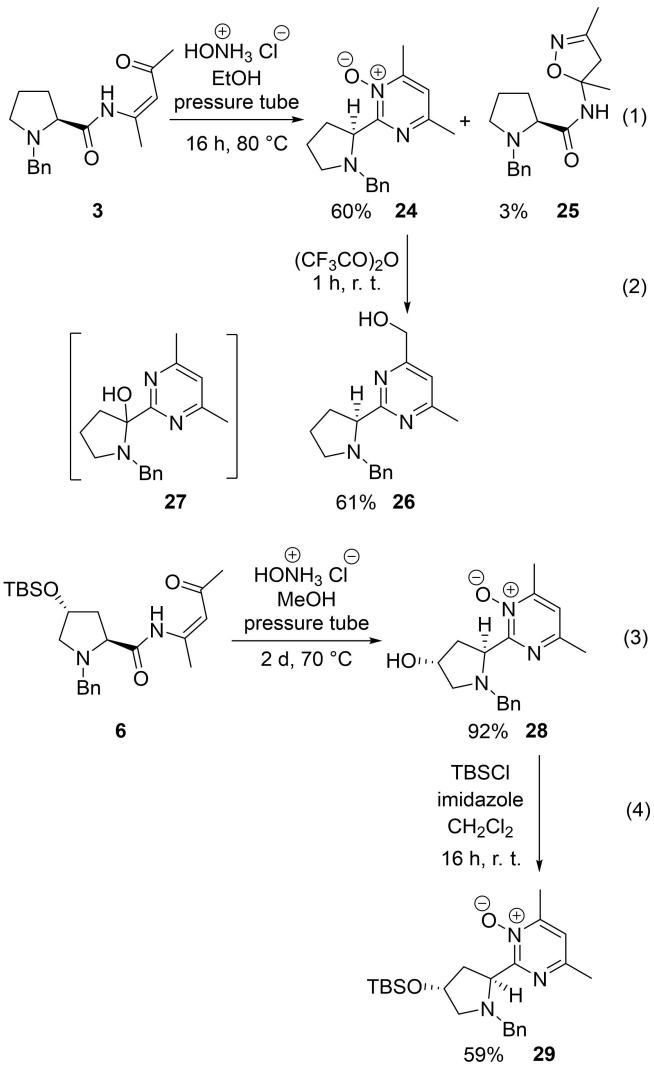
Other functional group transformations of pyridin-4-one **12** and nonaflate **13** are summarized in Scheme 5. An attempt to *O*-alkylate **12** with methyl triflate (1.5 equivalents) gave a mixture of compounds from which only the 4-methoxypyridine derivative **18** bearing a quaternary ammonium moiety could be cleanly isolated and characterized (equation 1). On the other hand, conversion of **12** into the *O*-Boc derivative **19** occurred smoothly under approved conditions (equation 2). Oxidation of this *O*-Boc-protected pyridine derivative with *m*-chloroperbenzoic acid (*m*-CPBA, 1.4 equivalents) quantitatively furnished *N*-oxide **20** which was subsequently treated with trifluoroacetic anhydride to promote a Polonovski-Potier reaction.[21] Addition of lithium hydroxide to the mixture furnished pyrrol-2-yl-substituted pyridine derivative **21** in moderate overall yield (for



Scheme 5. *O*-Functionalizations of pyridin-4-one **12** and *m*-CPBA oxidations of compounds **19** and **13**.

three steps), which is the result of two elimination processes (equation 3).[22] It is known that pyridin-4-yl nonaflates are oxidized fairly sluggishly at the pyridine nitrogen atom to the corresponding *N*-oxides.[23] This experience was confirmed by the oxidation of nonaflate **13** with two equivalents of *m*-CPBA, which gave the pyrrolidine *N*-oxide derivative **22** as major product (57% yield) and the *N,N'*-dioxide **23** as minor component (7%). Heating of *N*-oxide **22** with acetic anhydride led to an unidentifiable mixture of compounds; the considerably milder method employing trifluoroacetic anhydride was not investigated.

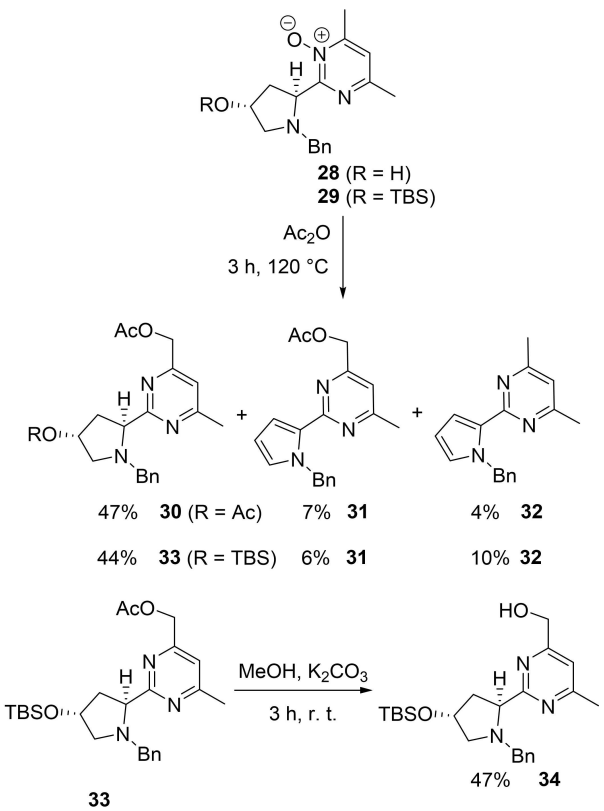
The condensation of β-alkoxy-β-ketoenamides and simple β-ketoenamides with ammonium salts leads to pyrimidine derivatives.[6a] The closely related reaction with hydroxylamine hydrochloride occurs under considerably milder conditions and provides the corresponding pyrimidine *N*-oxides, generally in very good yields.[6b,c] The *N*-oxide moiety of the products allows very useful subsequent reactions such as the Boekelheide rearrangement which converts the adjacent alkyl group into a hydroxyalkyl group.[24] It was therefore self-evident to check these transformations with the enantiopure β-ketoenamides of this study. Precursor **3** was treated with hydroxylamine hydrochloride under heating and afforded a mixture of the desired pyrimidine *N*-oxide **24** together with a small amount of dihydrooxazole derivative **25** (Scheme 6, equation 1); the yield for **24** of 60% could not be improved by using microwave irradiation. The Boekelheide rearrangement of *N*-oxide **24** was executed under particular mild conditions employing trifluoroacetic anhydride at room temperature for 1 h.[25] We exclusively isolated the hydroxymethyl-substituted compound **26**, but due to the low mass balance we cannot exclude the formation of regioisomer **27** (equation 2). This compound may be fairly instable and decompose during the reaction or the work up procedure and hence we cannot claim full regioselectivity of the rearrangement in this case. Hydroxymethyl-substituted



Scheme 6. Synthesis of β-ketoenamide-derived enantiopure pyrimidine *N*-oxides **24**, **28** and **29** and Boekelheide rearrangement of compound **24**.

pyrimidine **26** was subsequently converted into a Mosher ester to prove its enantiomeric purity. Only one set of signals could be observed by ^{1}H-, ^{13}C- and ^{19}F-NMR spectroscopy, which indicates that the ester is diastereomerically pure and that precursor **26** is also a compound with high enantiomeric purity. The 4-hydroxyproline-derived β-ketoenamide **6** was converted into pyrimidine *N*-oxide **28** under similar reaction conditions in excellent yield (equation 3), but the acidic medium and long reaction time caused full desilylation of the hydroxyl group of the pyrrolidine moiety. Unpurified **28** was cleanly silylated again giving the *tert*-butyldimethylsiloxy-protected compound **29** in 59% yield (equation 4).

The subsequent Boekelheide rearrangement of **28** was performed under standard conditions by heating the compound with acetic anhydride without solvent (Scheme 7). After aqueous work up and purification by chromatography three products could be identified: the expected acetoxymethyl-substituted pyrimidine derivative **30** and the two pyrrole derivatives **31** and **32**. Not surprisingly, the hydroxyl group of the pyrrolidine moiety was acylated under these conditions. Pyrrole derivative **31** could be formed from **30** by elimination and subsequent oxidation of the resulting dihydropyrrole intermediate. Formation of compound **32** could be explained by the intermediacy of a regioisomeric rearrangement product (analogous to **27**) and twofold elimination.[26] The Boekelheide rearrangement of *O*-silylated *N*-oxide **29** with acetic anhydride under slightly harsher conditions provided a product mixture



Scheme 7. Boekelheide rearrangement of pyrimidine *N*-oxides **28** and **29** with acetic anhydride leading to compounds **30** and **33** as major products.

which is very similar to that generated from **28**. The major component was acetoxymethyl-substituted compound **33** and the two pyrrole derivatives **31** and **32** were isolated in 6% and 10%, respectively. The ester **33** was subsequently saponified by potassium carbonate in methanol to furnish the primary alcohol **34** in 47% yield. Preliminary experiments to oxidize this compound to the corresponding aldehyde and to use the resulting intermediate for reductive aminations were studied but provided only low yields. Nevertheless, these attempts clearly demonstrate the potential of this route to prepare libraries of enantiopure pyrimidine derivatives with pyrrolidin-2-yl moieties. All 4-hydroxproline-derived pyrimidine derivatives characterized are diastereomerically pure, hence we can assume that the enantiopurity of the precursor compounds was fully transferred to the final products.

Conclusion

Employing the coupling reagent **HATU**, we could optimize the amide bond formation of the moderately nucleophilic β-ketoenamine **1** with *N*-protected (*S*)-proline and (2*S*,4*R*)-4-hydroxyproline derivatives. The resulting β-ketoenamides **3** and **6** are excellent precursors for the synthesis of enantiopure pyrrolidin-2-yl-substituted heterocycles. Aldol type cyclization efficiently provided the two pyridin-4-ones **9** and **12** which were subsequently converted into the corresponding pyridin-4-yl nonaflates **11** and **13**. These pyridine derivatives were examined in two exemplarily palladium-catalyzed coupling reactions to smoothly deliver new enantiopure pyridine derivatives **14** and **15**. The oxidation of pyridine derivatives with *m*-chloroperbenzoic acid was also studied and subsequent reactions were investigated. Alternatively, condensation of β-ketoenamides **3** and **6** with hydroxylamine hydrochloride furnished pyrimidine *N*-oxides **24** and **28** in good to excellent yields. Boekelheide rearrangement provided the expected hydroxymethyl-substituted pyrimidine derivatives **26**, **30** and **33**, in part under formation of minor amounts of side-products. Overall, our study demonstrates the high potential of β-ketoenamides such as **3** and **6** for the synthesis of chiral pool-derived pyrrolidin-2-yl-substituted pyridine and pyrimidine derivatives. Their substitution pattern allows interesting subsequent reactions leading to a library of enantiopure products. Compounds such as **16** could be examined as organocatalyst[27] and other pyridine or pyrimidine derivatives of this study are possibly interesting ligands of chiral catalysts.[3,28] As particular attractive feature, the 4-hydroxyproline derived heterocycles offer the option of immobilization of these catalysts at a polymeric support.[29]

Experimental Section

If not stated otherwise, all reactions were carried out under argon. The solvents used were purified by distillation using common drying agents and procedures and were transferred under argon. Chromatography was performed with Merck silica gel 60 (230–400 mesh). NMR spectra were recorded with BRUKER (AV 500, AV 700) and JEOL (ECX 400, ECP 500) instruments in the solvents

indicated; chemical shifts (δ) are given in ppm relative to residual solvent peaks, coupling constants (*J*) are given in Hz. IR spectra were recorded with a Nicolet-FT-IR spectrometer or 5 SXC spectrometer. Mass spectra were recorded with Ionspec QFT-7 (ESI-FT ICRMS) (Varian) and Agilent 6210 (ESI-TOF, 4 μL/min, 1.0 bar, 4 kV) instruments. Melting points: Thermovar (Reichert) melting point apparatus (not corrected). Elemental analyses: Elemental Analyzer (Perkin-Elmer), Vario EL elemental analysis system. All commercially available compounds (Acros, Lancaster, Fluka, Aldrich, TCI Europe) were used as received unless stated otherwise.

(2*S*,*Z*)-1-Benzyl-*N*-(4-oxopent-2-en-2-yl)pyrrolidine-2-carboxamide (3): In a flame-dried Schlenk tube, (*S*)-1-benzylproline **4** (2.00 g, 9.75 mmol) was dissolved in dichloromethane (40 mL) and dimethylformamide (10 mL). Enaminoketone **1** (6.77 g, 68.2 mmol) and (1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (**HATU**) (4.08 g, 10.7 mmol) were added to the mixture. The mixture was stirred at room temperature for 3 d and then quenched with water (15 mL). The aqueous phase was extracted with diethyl ether (4×20 mL) and the combined organic phases were dried (Na_2SO_4) and filtrated. The solvent was removed under reduced pressure to provide the crude product (8.95 g) as yellow oil. Purification by column chromatography (silica gel, hexanes/ethyl acetate, 7:3) afforded **3** (1.98 g, 71%) as colorless oil. $[\alpha]^{20}_D = -177.9$ ($c = 1.2$, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76–1.89, 2.20–2.23 (2 m, 3 H, 1 H, 3'-H, 4'-H), 2.16 (s, 3 H, 5-H), 2.24 (d, $J = 1.0$ Hz, 3 H, 1-H), 2.37–2.43 (m, 1 H, 5'-H), 3.15 (dd, $J = 10.4$, 4.5 Hz, 1 H, 5'-H), 3.27 (t, $J = 7.4$ Hz, 1 H, 2'-H), 3.66, 3.81 (AB system, $J_{AB} = 12.9$ Hz, 1 H each, CH_2Ph), 5.30 (s, 1 H, 3-H), 7.17–7.27, 7.35–7.38 (2 m, 3 H, 2 H, Ph), 12.81 (s_{br}, 1 H, N–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8 (q, C-1), 24.0 (t, C-4'), 30.6 (q, C-5), 31.2 (t, C-3'), 54.1 (t, C-5'), 59.7 (t, CH_2Ph), 68.6 (d, C-2'), 106.3 (d, C-3), 127.1, 128.2, 129.4, 138.1 (3 d, s, Ph), 153.7 (s, C-2), 175.9 (s, C=O), 198.5 (s, C-4) ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{17}H_{23}N_2O_2$: 287.1754; found: 287.1767; *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{22}N_2NaO_2$: 309.1573; found: 309.1582; $C_{17}H_{22}N_2O_2$ (286.4): calcd. C 71.30, H 7.74, N 9.78; found: C 71.30, H 7.67, N 9.81. Analytical data match those reported in the literature.[12a]

(2*S*,4*R*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)-*N*-[(*Z*)-4-oxopent-2-en-2-yl]pyrrolidine-2-carboxamide (6): Carboxylic acid derivative **5** (2.00 g, 5.96 mmol) was suspended in dichloromethane (30 mL) and dimethylformamide (8 mL). After addition of **HATU** (2.49 g, 6.56 mmol) and enaminoketone **1** (2.96 g, 29.8 mmol, dissolved in 5 mL of dichloromethane), the mixture was stirred at room temperature for 36 h. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and dichloromethane (20 mL). After separation of the phases, the aqueous phase was extracted with dichloromethane (2×20 mL). The combined organic phases were concentrated under reduced pressure, ethyl acetate (40 mL) and water (30 mL) were added to the residue and after separation of the phases the aqueous layer was extracted with ethyl acetate (3× 30 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). Filtration and removal of the solvent under reduced pressure gave the crude product as yellow oil. Purification by column chromatography (silica gel, hexanes/ethyl acetate, 8:1) provided of **6** (2.24 g, 90%) as colorless oil. $[\alpha]^{20}_D = -95.8$ ($c = 1.0$, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01, 0.02 (2 s, 3 H each, $SiMe_2$), 0.86 (s, 9 H, Si*t*Bu), 1.96–2.02, 2.14–2.19 (2 m, 1 H each, 3'-H), 2.15 (s, 3 H, 5-H), 2.25 (d, $J = 1.0$ Hz, 3 H, 1-H), 2.46 (dd, $J = 10.3$, 4.6 Hz, 1 H, 5'-H), 3.42 (dd, $J = 10.3$, 5.1 Hz, 1 H, 5-H'), 3.47 (t, $J = 8.4$ Hz, 1 H, 2'-H), 3.69, 3.87 (AB system, $J_{AB} = 12.9$ Hz, 2 H, CH_2Ph), 4.36–4.41 (m, 1 H, 4'-H), 5.30 (s, 1 H, 3-H), 7.18–7.39 (m, 5 H, Ph), 12.8 (s_{br}, 1 H, N–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.70, −4.75 (2 q, $SiMe_2$), 18.0, 25.9 (s, q, Si*t*Bu), 21.9 (q, C-1), 30.6 (q, C-5), 41.1 (t, C-3'), 60.7 (t, CH_2Ph), 61.9 (t, C-5'), 68.2 (d, C-2'), 71.1 (d, C-4'), 106.4 (d, C-3), 127.2, 128.3, 129.8, 138.1 (3 d, s, Ph), 153.7 (s, C-2), 175.3 (s, C=O), 198.6 (s, C-4) ppm; IR (ATR): ν = 3125 (N–H), 3060, 3030 (=C–H), 2955–2800 (C–H), 1650 (C=O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{23}H_{37}N_2O_3Si$: 417.2568; found: 417.2588; *m/z* $[M+Na]^+$ calcd. for $C_{23}H_{36}NaN_2O_3Si$: 439.2387; found: 439.2392; $C_{23}H_{36}N_2O_3Si$ (416.6): calcd. C 66.31, H 8.71, N 6.72; found: C 66.12, H 8.28, N 6.40.

(2'*S*,4'*R*)-4'-(*tert*-Butyldimethylsiloxy)-*N*-[(*Z*)-4-oxopent-2-en-2-yl)]-1'-pivaloylpyrrolidine-2'-carboxamide (8): The carboxylic acid derivative **7** (100 mg, 0.30 mmol) was suspended in dichloromethane (4 mL) and dimethylformamide (0.8 mL). After addition of **HATU** (138 mg, 0.36 mmol) and enaminoketone **1** (164 mg, 1.66 mmol, dissolved in 1 mL of dichloromethane), the mixture was stirred at room temperature for 4 d. The solvents were removed under reduced pressure and water (10 mL) and ethyl acetate (10 mL) were added. The aqueous phase was extracted with ethyl acetate (2× 10 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), filtrated and concentrated under reduced pressure to give a yellow oil as crude product. Purification by column chromatography (silica gel, ethyl acetate/hexanes, 1:1) provided β-ketoenamide **8** (59 mg, 48%) as a pale yellow solid. M. p. 59–61 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.04, 0.05 (2 s, 3 H each, $SiMe_2$), 0.85 (s, 9 H, Si*t*Bu), 1.28 (s, 9 H, *t*Bu), 1.90 (ddd, $J = 13.1$, 8.9, 4.3 Hz, 1 H, 3'-H), 2.09 (s, 3 H, 5-H), 2.15–2.19 (m, 1 H, 3'-H), 2.35 (d, $J = 1.0$ Hz, 3 H, 1-H), 3.75–3.85 (m, 1 H, 5'-H), 3.89 (dd, $J = 10.8$, 3.8 Hz, 1 H, 5'-H), 4.43–4.52 (m, 1 H, 4'-H), 4.54 (t, $J \approx 8.4$ Hz, 1 H, 2'-H), 5.31 (d, $J = 1.0$ Hz, 1 H, 3-H), 12.44 (s, 1 H, N–H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = −4.9, −4.6 (2 q, $SiMe_2$), 18.0, 25.8 (s, q, Si*t*Bu), 21.9 (q, C-5), 27.4 (q, CMe_3), 30.5 (q, C-1), 37.6 (t, C-3), 38.9 (s, CMe_3), 57.2 (t, C-5'), 63.2 (d, C-2'), 71.5 (d, C-4'), 105.9 (d, C-3), 155.5 (s, C-2), 172.6 (s, C=O), 178.1 (s, C=O), 199.4 (s, C-4) ppm; IR (ATR): ν = 3780 (N–H), 2960, 2930 (C–H), 1705 (C=O), 1510 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd. $C_{21}H_{38}N_2NaO_4Si$: 433.2499; found: 433.2519.

(*S*)-2-(1'-Benzylpyrrolidin-2'-yl)-6-methylpyridin-4-one (9): β-Ketoenamide **3** (136 mg, 0.475 mmol) was dissolved in dichloromethane (9 mL) and triethylamine (0.20 mL, 1.43 mmol) was added. Trimethylsilyl trifluoromethanesulfonate (0.27 mL, 1.43 mmol) was added dropwise and the tube was flushed with argon. The mixture was stirred at room temperature for 3 d and then quenched by addition of water (30 mL). The organic phase was separated, the aqueous phase was extracted with dichloromethane (4×40 mL) and the combined organic phases were dried (Na_2SO_4). Filtration and concentration under reduced pressure provided the crude product (247 mg) as brown oil. Purification by column chromatography (silica gel, dichloromethane/methanol, 19:1) afforded **9** (92 mg, 72%) as brownish oil and by-product **10** (26 mg, 16%) as yellow oil. $[\alpha]^{20}_D = -14.6$ ($c = 0.79$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.69–1.83 (m, 4 H, 3'-H, 4'-H), 2.33 (s, 3 H, Me), 2.35–2.43 (m, 1 H, 5'-H), 3.11–3.16 (m, 1 H, 5'-H), 3.60–3.65 (m, 1 H, 2'-H), 3.45, 3.74 (AB system, $J_{AB} = 13.0$ Hz, 2 H, CH_2Ph), 6.28 (d, $J = 2.0$ Hz, 1 H, 5-H), 6.55 (d, $J = 2.0$ Hz, 1 H, 3-H), 7.17–7.28 (m, 5 H, Ph) ppm; the N–H signal could not be identified unambiguously; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 19.4 (t, C-3'), 23.3 (q, Me), 33.8 (t, C-4'), 54.0 (t, C-5'), 59.0 (t, CH_2Ph), 65.0 (d, C-2'), 111.7 (d, C-5), 115.0 (d, C-3), 127.4, 128.6, 128.8, 138.2 (3 d, s, Ph), 148.0 (s, C-6), 154.2 (s, C-2), 179.0 (s, C-4) ppm; IR (ATR): ν = 3020 (=C–H), 2925, 2850 (C–H), 1735 (C=O), 1630, 1515 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{17}H_{21}N_2O$ 269.1648; found: 269.1669; *m/z* $[M+Na]^+$ calcd for $C_{17}H_{20}N_2NaO$: 291.1468; found 291.1481.

(*S*)-2-(1'-Benzylpyrrolidin-2'-yl)-6-methyl-4-(trimethylsiloxy)-pyridine (10): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.31 (s, 9 H, $SiMe_3$), 1.60–1.89 (m, 4 H, 3'-H, 4'-H), 2.16 (s, 3 H, Me), 2.45–2.53 (m, 1 H, 5'-H), 3.18 (t_{br}, $J = 7.6$ Hz, 1 H, 5'-H), 3.54, 3.73 (AB system, $J_{AB} = 13.2$ Hz, 2 H, CH_2Ph), 3.83 (dd, $J = 10.0$, 5.6 Hz, 1 H, 2'-H), 5.98 (d, $J = 1.2$ Hz, 1 H, 5-H), 7.16–7.22, 7.22–7.35 (2 m, 1 H, 4 H, Ph), 7.19 (d, $J =$

1.2 Hz, 1 H, 3-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.2 (q, $SiMe_3$), 21.1 (q, Me), 35.0 (t, C-4'), 41.9 (t, C-5'), 54.3 (t, *C*H_2Ph), 59.2 (d, C-2'), 119.0 (d, C-5), 121.0 (d, C-3), 127.9, 128.6, 129.0, 137.3 (3 d, s, Ph), 154.2 (s, C-6), 171.5 (s, C-2), 187.0 (s, C-4) ppm.

2-[(2'*S*)-1'-Benzylpyrrolidin-2'-yl]-6-methylpyridin-4-yl Nonaflate (11): β-Ketoenamide **3** (200 mg, 0.700 mmol) was dissolved in dichloromethane (13 mL) and triethylamine (0.29 mL, 2.09 mmol). The tube was flushed with argon, trimethylsilyl trifluoromethanesulfonate (0.40 mL, 2.09 mmol) was added dropwise, and the mixture was stirred at room temperature for 3 d. The volatile components were then removed under reduced pressure providing a brown oil (779 mg) which was dissolved in THF and added to a flask containing sodium hydride (60% in mineral oil, 212 mg, 5.29 mmol). The mixture was stirred under argon at room temperature for 30 min, then nonafluorobutanesulfonyl fluoride (0.93 mL, 5.29 mmol) was added and stirring was continued for 19 h. The reaction was quenched by slow addition of methanol (60 mL). All volatile components were evaporated, and the crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate, 4:1) to provide **11** (213 mg, 55%) as yellow oil. $[\alpha]^{20}_D$ = −46.9 (*c* = 1.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65–1.77, 1.77–1.95, 2.28–2.40 (3 m, 1 H, 2 H, 2 H, 3'-H, 4'-H, 5'-H), 2.59 (s, 3 H, Me), 3.07–3.18 (m, 1 H, 5'-H), 3.29, 3.81 (AB system, J_{AB} = 12.7 Hz, 2 H, C*H*$_2$Ph), 3.64–3.77 (m, 1 H, 2'-H), 6.93 (d, *J* = 2.0 Hz, 1 H, 5-H), 7.16–7.35 (m, 5 H, Ph), 7.46 (d, *J* = 2.0 Hz, 1 H, 3-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.9 (t, C-3'), 24.6 (q, Me), 34.0 (t, C-4'), 53.7 (d, C-2'), 58.9 (t, *C*H_2Ph), 70.2 (t, C-5'), 110.0 (d, C-5), 113.5 (d, C-3), 126.9, 128.2, 128.7, 138.2 (3 d, s, Ph), 157.7 (s, C-6), 160.8 (s, C-2), 168.4 (s, C-4) ppm; signals of the C_4F_9 group were not assigned; IR (ATR): ν = 3020 (=C–H), 2955–2850 (C–H), 1730, 1590 (C=C, C=N), 1240, 1215 (C–F) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{21}H_{20}F_9N_2O_3S$: 551.1021; found: 551.1056.

[(2*S*,4*S*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)pyrrolidin-2-yl]-6-methylpyridin-4-one (12): In an ACE pressure tube, β-ketoenamide **6** (350 mg, 0.84 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.35 mL, 2.50 mmol). Trimethylsilyl trifluoromethanesulfonate (0.45 mL, 2.68 mmol) was added and the tube was flushed with argon. The mixture was heated for 3 d to 60 °C, which led to formation of a brownish solution. After quenching by addition of water (10 mL), the organic phase was separated, the aqueous phase was extracted with dichloromethane (3 × 20 mL) and the combined organic phases were dried (Na_2SO_4). Filtration and evaporation provided the crude product (572 mg). Purification by column chromatography (silica gel, ethyl acetate/methanol, 12:1, then dichloromethane/methanol, 4:1) afforded **12** (268 mg, 81%) as light brown solid. M. p. 70–72 °C; $[\alpha]^{20}_D$ = −27.2 (*c* = 0.58, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.05, 0.06 (2 s, 3 H each, $SiMe_2$), 0.89 (s, 9 H, Si*t*Bu), 1.94–2.02, 2.10–2.15 (2 m, 1 H each, 3'-H), 2.30 (s, 3 H, 6-Me), 2.41 (dd, *J* = 10.4, 4.1 Hz, 1 H, 5'-H), 3.39 (dd, *J* = 10.4, 5.3 Hz, 1 H, 5'-H), 3.54, 3.74 (AB system, J_{AB} = 12.9 Hz, 1 H each, C*H*$_2$Ph), 3.80 (dd, *J* = 9.1, 7.7 Hz, 1 H, 2'-H), 4.45–4.49 (m, 1 H, 4'-H), 6.13 (d, *J* = 1.7 Hz, 1 H, 5-H), 6.39 (d, *J* ≈ 2.3 Hz, 1 H, 3-H), 7.16–7.26 (m, 5 H, Ph) ppm; ^{13}C NMR (126 MHz, CD_3OD): δ = −3.7 (q, $SiMe_2$), 19.8, 27.3 (s, q, Si*t*Bu), 20.0 (q, 6-Me), 45.9 (t, C-3'), 61.3 (t, *C*H_2Ph), 64.6 (t, C-5'), 66.9 (d, C-2'), 72.8 (d, C-4'), 114.6 (d, C-5), 116.9 (d, C-3), 129.3, 130.3, 131.0, 140.5 (3 d, s, Ph), 151.9 (s, C-6), 156.6 (s, C-2), 183.0 (s, C-4) ppm; IR (ATR): ν = 3260 (N–H), 3135–3020 (=C–H), 2950–2795 (C–H), 1625 (C=O), 1520 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{23}H_{35}N_2O_2Si$: 399.2468; found: 399.2471.

2-[(2'*S*,4'*R*)-1'-Benzyl-4'-(*tert*-butyldimethylsiloxy)pyrrolidin-2'-yl]-6-methylpyridin-4-yl Nonaflate (13): Under an atmosphere of argon, pyridine-4-one **12** (248 mg, 0.62 mmol) was dissolved in THF (10 mL) and sodium hydride (60% in mineral oil, 38 mg, 0.93 mmol) was added. The mixture was stirred at room temperature for 30 min and nonafluorobutanesulfonyl fluoride (0.17 mL, 281 mg, 0.93 mmol) were added. After stirring for 42 h at room temperature methanol (5 mL) was slowly added and all volatile components were removed under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate, 1:1, then methanol) to provide **13** (258 mg, 61%) as pale yellow oil. $[\alpha]^{20}_D$ = −28.1 (*c* = 0.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00, 0.02 (2 s, 3 H each, $SiMe_2$), 0.86 (s, 9 H, Si*t*Bu), 1.92 (ddd, *J* = 13.0, 8.6, 7.3 Hz, 1 H, 3'-H), 2.24 (ddd, *J* = 13.0, 7.8, 3.4 Hz, 1 H, 3'-H), 2.35 (dd, *J* = 9.9, 5.2 Hz, 1 H, 5'-H), 2.60 (s, 3 H, 6-Me), 3.35 (dd, *J* = 9.9, 5.8 Hz, 1 H, 5'-H), 3.37, 3.79 (AB system, J_{AB} = 13.0 Hz, 1 H each, C*H*$_2$Ph), 4.04 (t, *J* = 8.3 Hz, 1 H, 2'-H), 4.36–4.42 (m, 1 H, 4'-H), 6.92 (d, *J* = 2.1 Hz, 1 H, 5-H), 7.16–7.30 (m, 5 H, Ph), 7.41 (d, *J* = 2.1 Hz, 1 H, 3-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = −4.8, −4.7 (2 q, $SiMe_2$), 18.1, 25.9 (s, q, Si*t*Bu), 24.7 (q, 6-Me), 44.6 (t, C-3'), 59.2 (t, *C*H_2Ph), 62.4 (t, C-5'), 68.9 (d, C-2'), 70.5 (d, C-4'), 110.4 (d, C-3), 113.7 (d, C-5), 127.1, 128.3, 128.7, 138.9 (3 d, s, Ph), 157.8 (s, C-6), 161.2 (s, C-2), 168.9 (s, C-4) ppm; signals of the C_4F_9 group were not assigned; IR (ATR): ν = 3060, 3025 (=C–H), 2955–2800 (C–H), 1600, 1575 (C=C, C=N), 1235–1200 (C–F) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{27}H_{34}F_9N_2O_4SSi$: 681.1860; found: 681.1866.

2-[(2'*S*)-1'-Benzylpyrrolidin-2'-yl]-6-methyl-4-[(triisopropylsilyl)-ethynyl]pyridine (14): In an argon flushed Schlenk tube, nonaflate **11** (152 mg, 0.276 mmol) was dissolved in triethylamine (3.4 mL). Triisopropylsilylacetylene (171 mg, 0.94 mmol), bis(triphenylphosphine)palladium(II) dichloride (9.6 mg, 0.014 mmol) and copper(I) iodide (3.2 mg, 0.017 mmol) were added and the mixture was stirred for 16 h at room temperature. Dichloromethane (5 mL) was added to the mixture which was concentrated under reduced pressure. Purification of the crude product (378 mg) by column chromatography (silica gel, hexanes/ethyl acetate, 19:1) afforded **14** (120 mg, 99%) as yellow oil. $[\alpha]^{20}_D$ = −82.9 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (s_{br}, 21 H, TIPS), 1.70–1.90 (m, 3 H, 3'-H, 4'-H), 2.24–2.34 (m, 2 H, 4'-H, 5'-H), 2.53 (s, 3 H, Me), 3.11 (td, *J* = 7.5, 2.5 Hz, 1 H, 5'-H), 3.60 (t, *J* = 8.5 Hz, 1 H, 2'-H), 3.21, 3.84 (AB system, J_{AB} = 13.0 Hz, 2 H, C*H*$_2$Ph), 7.06 (d, *J* = 1.0 Hz, 1 H, 5-H), 7.19–7.32 (m, 5 H, Ph), 7.54 (d, *J* = 1.0 Hz, 1 H, 3-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 11.3, 18.7 (d, q, $SiCHMe_2$), 22.8 (t, C-3'), 24.3 (q, Me), 33.9 (t, C-4'), 53.7 (t, *C*H_2Ph), 58.9 (t, C-5'), 70.7 (d, C-2'), 95.2, 105.1 (2 s, C≡C), 120.5 (d, C-5), 123.7 (d, C-3), 126.9, 128.2, 128.9, 132.2 (3 d, s, Ph) 139.6 (s, C-6), 157.6 (s, C-2), 164.0 (s, C-4) ppm; IR (ATR): ν = 3050, 3020 (=C–H), 2940–2860 (C–H), 2210 (C≡C), 1590, 1550 (C=C, C=N) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{28}H_{40}N_2Si$: 433.3034; found: 433.3052.

2-[(2'*S*,4'*R*)-1'-Benzyl-4'-(*tert*-butyldimethylsiloxy)pyrrolidin-2'-yl]-6-methyl-4-phenylpyridine (15): Under an atmosphere of argon, nonaflate **13** (688 mg, 1.01 mmol) was dissolved in dimethylformamide (6 mL) and phenylboronic acid (123 mg, 1.01 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), PPh_3 (52 mg, 0.20 mmol) and K_2CO_3 (143 mg, 1.01 mmol) were added. The mixture was heated to 80 °C for 18 h and then filtrated. Ethyl acetate and brine (40 mL/10 mL) were added to the filtrate. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine/water (1:1, 3 × 30 mL), dried (Na_2SO_4), filtrated and concentrated under reduced pressure. The crude product (796 mg) was purified by column chromatography (silica gel, hexanes/ethyl acetate, 4:1) to furnish **15** (302 mg, 65%) as pale yellow oil. $[\alpha]^{20}_D$ = −58.3 (*c* = 0.74, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = −0.05, −0.04 (2 s, 3 H each, $SiMe_2$), 0.82 (s, 9 H, Si*t*Bu), 1.87–1.97 (m, 1 H, 3'-H), 2.07–2.17 (m, 1 H, 3'-H), 2.30 (dd, *J* = 9.9, 4.8 Hz, 1 H, 5'-H), 2.50 (s, 3 H, 6-Me), 3.29, 3.71 (AB system, J_{AB} = 13.2 Hz, 1 H each, C*H*$_2$Ph), 3.31 (dd, *J* = 9.9. 5.9 Hz, 1 H, 5'-H), 3.93 (dd, *J* = 9.3, 7.5 Hz, 1 H, 2'-H), 4.34–4.40 (m, 1 H, 4'-H), 7.04–7.20 (m, 5 H, Ph), 7.24 (d, *J* = 1.3 Hz, 1 H, 3-H or 5-H), 7.29–7.40, 7.53–7.58 (2 m, 5 H, 4-Ph), 7.63 (d, *J* = 1.3 Hz, 1 H, 5-H or 3-H) ppm; ^{13}C NMR (126 MHz, CD_3OD): δ = −3.52, −3.49 (2 q, $SiMe_2$), 19.8, 27.4

(s, q, Si*t*Bu), 24.9 (q, 6-Me), 46.7 (t, C-3'), 60.9 (t, C-5'), 64.7 (t, *C*H$_2$Ph), 70.9 (d, C-2'), 72.7 (d, C-4'), 118.4, 122.0 (2 d, C-3, C-5), 128.98, 129.02, 130.2, 130.7, 131.12, 131.15, 140.4, 141.0 (6 d, 2 s, Ph), 152.3 (s, C-4), 160.1 (s, C-6), 165.4 (s, C-2) ppm; IR (ATR): ν = 3055, 3025 (=C–H), 2950–2780 (C–H), 1595, 1555 (C=C, C=N) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{29}H_{39}N_2OSi$: 459.2827; found: 459.2823.

2-[(2'*S*,4'*R*)-4'-(*tert*-Butyldimethylsiloxy)pyrrolidin-2'-yl]-6-methyl-4-phenylpyridine (16): Palladium on charcoal (10% Pd, 152 mg) was suspended in ethyl acetate (10 mL) and saturated with hydrogen for 20 min. Pyridine derivative **15** (253 mg, 0.545 mmol, dissolved in 20 mL of ethyl acetate) was added and the mixture was stirred under an atmosphere of hydrogen at room temperature for 36 h. Filtration through a pad of Celite and careful washing with methanol provided a solution of the crude products. The solvents were removed under reduced pressure and the resulting residue (201 mg) was purified by column chromatography (silica gel, ethyl acetate, then dichloromethane/methanol 4:1) to furnish **16** (51 mg, 25%) as yellow-orange resin. In addition, starting material **15** was recovered (119 mg, 47%). $[\alpha]^{20}_D = -14.8$ ($c = 0.45$, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 0.182, 0.188 (2 s, 3 H each, $SiMe_2$), 0.99 (s, 9 H, Si*t*Bu), 2.11 (ddd, $J = 13.3$, 10.5, 4.9 Hz, 1 H, 3'-H), 2.41 (dd, $J = 13.3$, 6.7 Hz, 1 H, 3'-H), 2.63 (s, 3 H, 6-Me), 3.15 (d, $J \approx 11.9$ Hz, 1 H, 5'-H), 3.57 (dd, $J = 11.9$, 4.5 Hz, 1 H, 5'-H) 4.73 (m_c, 1 H, 4'-H), 4.82 (dd, $J = 10.5$, 6.7 Hz, 1 H, 2'-H), 7.20–7.57, 7.60–7.79 (2 m, 7 H, Ph, 3-H, 5-H) ppm; ^{13}C NMR (126 MHz, CD_3OD): δ = −3.9, −3.8 (2 q, $SiMe_2$), 19.8, 27.2 (s, q, Si*t*Bu), 25.1 (q, 6-Me), 45.1 (t, C-3'), 57.3 (t, C-5'), 63.8 (d, C-2'), 75.0 (d, C-4'), 118.8, 122.6 (2 d, C-3, C-5), 129.0, 131.1, 131.3, 140.0 (3 d, s, Ph), 152.5 (s, C-4), 160.3 (s, C-6), 161.1 (s, C-2) ppm. A complete analytical characterization was done at the stage of subsequent product **17** (see below).

***tert*-Butyl (2'*S*,4'*R*)-4'-(*tert*-Butyldimethylsiloxy)-2'-(6-methyl-4-phenylpyridin-2-yl)pyrrolidin-1'-carboxylate (17)**: β-Cyclodextrin (11 mg, 0.01 mmol) was dissolved in water (10 mL) and a solution of **16** (39 mg, 0.11 mmol, methanol/acetone 1:1, 4 mL) was added. Di-*tert*-butyl dicarbonate (24.0 μL, 0.11 mmol) was added dropwise by syringe, the mixture was stirred at room temperature for 15 min and then extracted with ethyl acetate (3×10 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), filtrated and concentrated under reduced pressure. The resulting crude product (145 mg) was purified by column chromatography (silica gel, hexanes/ethyl acetate, 3:1) to provide **17** (26 mg, 51%) as colorless oil. $[\alpha]^{20}_D = -47.5$ ($c = 1.14$, MeOH); ^{1}H NMR (400 MHz, CD_3OD, rotamer ratio ≈2:1): δ = 0.13 (s_{br}, 6 H, $SiMe_2$), 0.90 (s, 9 H, Si*t*Bu), 1.13, 1.45 (2 s, 6 H, 3 H, O*t*Bu), 2.00–2.15 (m, 1 H, 3'-H), 2.35–2.47 (m, 1 H, 3'-H), 2.60 (s, 3 H, 6-Me), 3.60–3.65, 3.71–3.82 (2 m, 2 H, 5'-H), 4.51–4.57 (m, 1 H, 2'-H), 4.94–5.07 (m, 1 H, 4'-H), 7.32, 7.34, 7.36–7.52, 7.57–7.73 (2 s, 2 m, 0.33 H, 1 H, 3.67 H, 2 H, Ph, 3-H, 5-H) ppm; IR (ATR): ν = 3055, 3030 (=C–H), 2950–2860 (C–H), 1700 (C=O), 1600, 1550 (C=C, C=N) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd. for $C_{27}H_{40}N_2NaO_3Si$ 491.2700; found: 491.2706.

(2*S*,4*R*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)-2-(4-methoxy-6-methylpyridin-2-yl)-1-methylpyrrolidinium Triflate (18): Pyridin-4-one **12** (120 mg, 0.30 mmol) was dissolved in diethyl ether (5 mL) and sodium hydride (60% in mineral oil, 20 mg, 0.45 mmol) were added. The mixture was stirred for 30 min at room temperature and methyl triflate (0.05 mL, 0.45 mmol) was added. After stirring for 72 h at room temperature, the volatile components were removed under reduced pressure and the residue was dissolved in dichloromethane (20 mL). Water (10 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (3×10 mL) and the combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtrated and concentrated under reduced pressure. The resulting brownish oil was purified by chromatography (silica gel, ethyl acetate, then dichloromethane, then gradient to dichloromethane/methanol 6:1) affording **18** (52 mg, 42%) as yellowish oil. $[\alpha]^{20}_D = -10.0$ ($c = 0.05$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, CD_3OD): δ = −0.03, −0.02 (2 s, 3 H each, $SiMe_2$), 0.74 (s, 9 H, Si*t*Bu), 2.23 (ddd, $J = 13.1$, 8.7, 4.6 Hz, 1 H, 3-H'), 2.38–2.46 (m, 1 H, 3-H'), 2.51 (s, 3 H, 6-Me), 2.90–2.98, 3.26–3.36 (2 m, 1 H each, 5-H'), 3.69 (s, 3 H, NMe), 4.18–4.30 (m, 1 H, 4-H'), 3.87 (s, 3 H, OMe), 4.79, 4.87 (AB system, $J_{AB} = 12.6$ Hz, 1 H, *C*H$_2$Ph), 5.21 (t, $J \approx 7.5$ Hz, 1 H, 2-H'), 6.57 (d, $J = 2.1$ Hz, 1 H, 3-H), 6.89 (d, $J = 2.1$ Hz, 1 H, 5-H), 7.29–7.40, 7.45–7.51 (2 m, 5 H, Ph) ppm; ^{13}C NMR (126 MHz, $CDCl_3$, CD_3OD): δ = −5.4, −5.2 (2 q, $SiMe_2$), 17.6, 25.4 (s, q, Si*t*Bu), 24.2 (q, 6-Me), 38.7 (t, C-3'), 55.4 (q, NMe), 57.0 (q, OMe), 68.3 (d, C-4'), 68.8 (t, C-5'), 69.8 (t, *C*H$_2$Ph), 76.7 (d, C-2'), 109.8 (d, C-3), 110.4 (d, C-5), 127.8, 128.3, 129.1, 130.8 (3 d, s, Ph), 151.9 (s, C-6), 160.8 (s, C-4), 167.1 (s, C-2) ppm; the CF_3-signal could not be identified; ^{19}F NMR (376 MHz, $CDCl_3$, CD_3OD): δ = −78.2 ppm; IR (ATR): ν = 3370 (R_4N^+), 2960, 2930, 2855 (C–H), 1595 (C=C), 1050 (SO_2) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M]^+$ calcd. for $C_{26}H_{39}N_2O_2Si$: 427.2776; found: 427.2790.

g(2'*S*,4'*R*)-1-Benzyl-4'-(*tert*-butyldimethylsiloxy)pyrrolin-2'-yl]-6-methylpyridin-4-yl *tert*-butyl-carbonate (19): A solution of **12** (82 mg, 0.21 mmol) in THF (10 mL) was treated with sodium hexamethyldisilazane (2 M in THF, 0.11 mL, 0.22 mmol) and stirred at room temperature for 10 min. After addition of di-*tert*-butyl dicarbonate (90 mg, 0.42 mmol) the mixture was heated at 80 °C for 3 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue dissolved in dichloromethane (20 mL). After addition of water (10 mL) and separation of the phases, the aqueous phase was extracted with dichloromethane (2×10 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), filtrated and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexanes, then gradient to hexanes/ethyl acetate, 8:1) provided **19** (95 mg, 92%) as colorless oil. $[\alpha]^{20}_D = -9.6$ ($c = 0.05$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.01, 0.01 (2 s, 3 H each, $SiMe_2$), 0.86 (s, 9 H, Si*t*Bu), 1.57 (s, 9 H, *t*Bu), 1.93–2.07 (m, 1 H, 3'-H), 2.21 (ddd, $J = 13.2$, 7.8, 3.4 Hz, 1 H, 3'-H), 2.30 (dd, $J = 9.7$, 5.4 Hz, 1 H, 5'-H), 2.55 (s, 3 H, 6-Me), 3.30 (d, $J = 13.5$ Hz, 1 H, C*H*$_2$Ph), 3.30–3.38 (m, 1 H, 5'-H), 3.85 (d, $J = 13.5$ Hz, 1 H, C*H*$_2$Ph), 3.98 (t, $J \approx 7.8$ Hz, 1 H, 2'-H), 4.34–4.45 (m, 1 H, 4'-H), 6.90 (d, $J = 1.9$ Hz, 1 H, 5-H), 7.17–7.34 (m, 5 H, Ph), 7.32 (d, $J = 1.9$ Hz, 1 H, 3-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = −4.7, −4.6 (2 q, $SiMe_2$), 18.1, 26.0 (s, q, Si*t*Bu), 24.7 (q, 6-Me), 27.8 (q, O*CMe*$_3$), 44.4 (t, C-3'), 58.8 (t, *C*H$_2$Ph), 62.4 (t, C-5'), 69.1 (d, C-2'), 70.4 (d, C-4'), 84.3 (s, O*C*Me$_3$), 110.7 (d, C-3), 114.0 (d, C-5), 126.9, 128.3, 128.9, 139.3 (3 d, s, Ph), 150.6 (s, C=O), 156.1 (s, C-6), 159.1 (s, C-2), 159.8 (s, C-4) ppm; IR (ATR): ν = 2950 (C–H), 1765 (C=O), 1590 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{28}H_{43}N_2O_4Si$: 499.2992; found 499.2994; $C_{28}H_{42}N_2O_4Si$ (498.7): calcd. C 67.43, H 8.49, N 5.62; found: C 67.42, H 8.35, N 5.72.

Oxidation of 19: A solution of **19** (150 mg, 0.30 mmol) and *m*-chloroperbenzoic acid (75 mg, 0.42 mmol) in dichloromethane (10 mL) was stirred at room temperature for 20 h. The solvent was removed to provide crude **20** (230 mg) as pale yellow oil which was directly used for the next step. ^{1}H NMR (400 MHz, CD_3OD): δ = −0.03, 0.01 (2 s, 3 H each, $SiMe_2$), 0.76 (s, 9 H, Si*t*Bu), 1.55 (s, 9 H, *t*Bu), 2.19 (dd, $J = 13.8$, 7.2 Hz, 1 H, 3'-H), 2.63 (s, 3 H, 6-Me), 3.10 (ddd, $J \approx 13.1$, 11.6, 6.7 Hz, 1 H, 3'-H), 3.56 (dd, $J = 12.7$, 4.2 Hz, 1 H, 5'-H), 4.59 (dd, $J \approx 12.7$, 6.4 Hz, 1 H, 5'-H), 4.71 (d, $J = 13.0$ Hz, 1 H, C*H*$_2$Ph), 4.84–4.90 (m, 1 H, 2'-H), 5.08 (d, $J = 13.0$ Hz, 1 H, C*H*$_2$Ph), 5.11–5.17 (m, 1 H, 4'-H), 7.13 (d, $J = 2.0$ Hz, 1 H, 5-H), 7.43–7.47 (m, 5 H, Ph), 7.56 (d, $J = 2.0$ Hz, 1 H, 3-H) ppm; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{28}H_{43}N_2O_5Si$: 515.2941; found: 515.2958.

2-(1-Benzyl-1*H*-pyrrol-2-yl)-6-methylpyridinyl-4-*tert*-butyl Carbonate (21): A solution of crude **20** (140 mg, 0.27 mmol) in dichloromethane (3 mL) was treated with trifluoroacetic anhydride (0.15 mL, 0.82 mmol) and under stirred argon at room temperature

for 3 h. All volatile components were removed under reduced pressure and dichloromethane (3 mL), water (3 mL) and lithium hydroxide (33 mg, 1.36 mmol) were added. The mixture was stirred for 1 h and dichloromethane (20 mL) and water (10 mL) were added. The phases were separated and the aqueous phase was extracted with dichloromethane (2×20 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), filtrated and concentrated under reduced pressure to give the crude product as yellow oil. Purification by column chromatography (silica gel, hexanes, then gradient to hexanes/ethyl acetate, 10:1) afforded **21** (59 mg, 60% for two steps) as pale yellow oil (fast colorization to brownish). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65 (s, 9 H, *t*Bu), 2.56 (s, 3 H, 6-Me), 5.84 (s, 2 H, C*H*$_2$Ph), 6.31 (dd, *J* = 3.8, 2.7 Hz, 1 H, 4'-H), 6.71 (dd, *J* ≈ 3.8, 1.8 Hz, 1 H, 3'-H), 6.85–6.90 (m, 2 H, 5-H, 5'-H), 7.11–7.17 (m, 2 H, 3-H, Ph), 7.27–7.35 (m, 4 H, Ph) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.6 (q, 6-Me), 27.8 (q, OC*Me*$_3$), 52.3 (t, *C*H$_2$Ph), 84.3 (s, O*C*Me$_3$), 108.5 (d, C-4'), 110.6 (d, C-3'), 111.8 (d, C-3), 112.3 (d, C-5), 126.3 (d, C-5'), 126.9, 127.0, 128.5, 139.6 (3 d, s, Ph), 150.6 (s, C=O), 153.7 (s, C-2), 158.5 (s, C-6), 159.3 (s, C-4) ppm; the C-2' cannot be assigned unambiguously; IR (ATR): ν = 2920 (C–H), 1760 (C=O), 1585 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{22}H_{25}N_2O_3$: 365.1865; found: 365.1844; $C_{22}H_{24}N_2O_3$ (364.4): calcd. C 72.50, H 6.64, N 7.69; found: C 72.51, H 6.68, N 7.75.

(2'*S*,4'*R*)-1'-Benzyl-4'-(*tert*-butyldimethylsiloxy)-2'-[6-methyl-4-(nonaflyl)pyridin-2-yl]-pyrrolidine 1-Oxide (22): A solution of **13** (258 mg, 0.38 mmol) and *m*-chloroperbenzoic acid (183 mg, 0.76 mmol) in dichloromethane (10 mL) was stirred at room temperature for 19 h. After addition of water (5 mL) and dichloromethane (10 mL), the organic phase was separated and the aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (3×20 mL), dried (Na_2SO_4), filtrated and concentrated under reduced pressure. The crude product (222 mg) was purified by column chromatography (silica gel, ethyl acetate, then ethyl acetate/methanol, 10:1, then dichloromethane/methanol, 4:1) to afford **22** (150 mg, 57%) and **23** (18 mg, 7%) as light brownish resins. $[\alpha]^{20}_D = -10.8$ (*c* = 0.85, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = −0.04, −0.01 (2 s, 3 H each, SiMe$_2$), 0.76 (s, 9 H, Si*t*Bu), 2.08–2.15 (m, 1 H, 3'-H), 2.64 (s, 3 H, 6-Me), 3.02 (m$_c$, 1 H, 3'-H), 3.47 (dd, *J* = 11.9, 4.6 Hz, 1 H, 5'-H), 3.82 (dd, *J* = 11.9, 6.4 Hz, 1 H, 5'-H), 4.37, 4.43 (AB system, J_{AB} = 12.9 Hz, 1 H each, C*H*$_2$Ph), 4.82 (m$_c$, 1 H, 4'-H), 5.03 (dd, *J* = 11.7, 6.9 Hz, 1 H, 2'-H), 7.10 (d, *J* = 2.0 Hz, 1 H, 3-H), 7.28–7.47, 7.69–7.73 (2 m, 5 H, Ph), 7.67 (d, *J* = 2.0 Hz, 1 H, 5-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = −5.0, −4.9 (2 q, SiMe$_2$), 17.8, 25.7 (s, q, Si*t*Bu), 24.6 (q, 6-Me), 39.0 (t, C-3'), 68.5 (d, C-4'), 70.5 (t, *C*H$_2$Ph), 74.7 (t, C-5'), 75.9 (d, C-2'), 115.8 (d, C-3), 116.7 (d, C-5), 128.8, 129.8, 130.5, 132.8 (3 d, s, Ph), 155.9 (s, C-2), 156.7 (s, C-6), 160.7 (s, C-4) ppm; the signals of the C_4F_9 group were not assigned; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −125.7 (2 F, *C*F$_2$CF$_3$), −120.8 (2 F, SO$_2$CF$_2$*C*F$_2$), −108.6 (2 F, SO$_2$CF$_2$), −80.5 (3 F, CF$_3$) ppm; IR (ATR): ν = 2950–2850 (C–H), 1590, 1580 (C=C, C=N), 1230–1120 (C–F) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{27}H_{34}F_9N_2O_5SSi$: 697.1809; found: 697.1821.

(2'*S*,4'*R*)-1'-Benzyl-4'-(*tert*-butyldimethylsiloxy)-2'-[6-methyl-1-oxido-4-(nonaflyl)pyridin-2-yl]-pyrrolidine 1-Oxide (23): $[\alpha]^{20}_D$ = 20.1 (*c* = 0.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02, 0.04 (2 s, 3 H each, SiMe$_2$), 0.85 (s, 9 H, Si*t*Bu), 2.21–2.26 (m, 1 H, 3'-H), 2.52 (s, 3 H, 6-Me), 2.82–2.90 (m, 1 H, 3'-H), 3.48 (dd, *J* = 11.5, 4.9 Hz, 1 H, 5'-H), 3.73 (dd, *J* = 11.5, 6.5 Hz, 1 H, 5'-H), 4.28, 4.62 (AB system, J_{AB} = 12.6 Hz, 1 H each, C*H*$_2$Ph), 4.87 (m$_c$, 1 H, 4'-H), 6.13 (dd, *J* = 12.1, 7.4 Hz, 1 H, 2'-H), 7.17 (d, *J* = 3.4 Hz, 1 H, 3-H), 7.25–7.53 (m, 5 H, Ph), 8.18 (d, *J* = 3.4 Hz, 1 H, 5-H) ppm; IR (ATR): ν = 3100 (=C–H), 2950–2860 (C–H), 1235–1130 (C–F) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{27}H_{34}F_9N_2O_6SSi$: 713.1758; found: 713.1714.

(*S*)-2-(1-Benzylpyrrolidin-2-yl)-4,6-dimethylpyrimidine 1-Oxide (24): In a sealed pressure tube, β-ketoenamide **3** (306 mg, 1.06 mmol) was dissolved in ethanol (2 mL) and hydroxylamine hydrochloride (1.10 g, 15.9 mmol) was added. The mixture was heated to 80 °C for 16 h. After cooling to room temperature, water (10 mL) was added followed by 2.5 M aqueous sodium hydroxide solution until the pH reached 10. After extraction of the aqueous phase with dichloromethane (4×15 mL), the combined organic phases were dried (Na_2SO_4), filtrated and concentrated under reduced pressure furnishing the crude product (924 mg) as colorless oil. Purification by column chromatography (silica gel, ethyl acetate, then ethyl acetate/methanol, 9:1) gave **24** (181 mg, 60%) as a violet oil and **25** (10 mg, 3%) as a colorless oil. $[\alpha]^{20}_D = +17.0$ (*c* = 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79–1.99, 2.41–2.47 (2 m, 2 H each, 3'-H, 4'-H), 2.57–2.64 (m, 1 H, 5'-H$_a$), 2.48, 2.50 (2 s, 3 H each, 4-Me, 6-Me), 3.21 (ddd, *J* = 9.3, 7.4, 1.7 Hz, 1 H, 5'-H$_b$), 3.46, 3.85 (AB system, J_{AB} = 12.4 Hz, 2 H, C*H*$_2$Ph), 4.51 (t, *J* = 8.2 Hz, 1 H, 2'-H), 6.96 (s, 1 H, 5-H), 7.17–7.37 (m, 5 H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6 (q, 4-Me), 22.7 (q, 6-Me), 23.5 (t, C-4'), 29.7 (t, C-3'), 54.3 (t, C-5'), 59.7 (t, *C*H$_2$Ph), 62.8 (d, C-2'), 119.4 (d, C-5), 127.0, 128.0, 129.4, 138.9 (3 d, s, Ph), 153.3 (s, C-4) 155.0 (s, C-6), 161.6 (s, C-2) ppm; IR (ATR): ν = 2960 (C–H), 1610 (C=C), 1450, 1420, 1240 (N–O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{17}H_{22}N_3O$: 284.1757; found: 284.1731; $C_{17}H_{21}N_3O$ (283.4) + 1.25 H_2O: calcd. C 66.75, H 7.74, N 13.73; found: C 66.99, H 8.05, N 13.57.

(2*S*)-1-Benzyl-*N*-(3,5-dimethyl-4,5-dihydroisoxazol-5-yl)-pyrrolidine-2-carboxamide (25): (ratio of diastereoisomers = 1:1); $[\alpha]^{20}_D = -77.5$ (*c* = 1.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53, 1.67 (2 s, 1.5 H each, 5-Me), 1.71–1.87 (m, 3 H, 3'-H, 4'-H), 1.94, 1.96 (2 s, 1.5 H each, 3-Me), 2.13–2.23 (m, 1 H, 4'-H), 2.33–2.42 (m, 1 H, 5'-H$_a$), 2.74 (dd, *J* = 17.6, 1.2 Hz, 0.5 H, 4-H), 2.83 (dd, *J* = 17.6, 1.0 Hz, 0.5 H, 4-H), 2.99–3.11 (m, 2 H, 5'-H$_b$, 2'-H), 3.29, 3.33 (2 d$_{br}$, *J* = 17.6 Hz, 0.5 H each, 4-H), 3.48, 3.56, 3.73, 3.75 (4 d, *J* = 12.8 Hz, 0.5 H each, C*H*$_2$Ph), 7.23–7.34 (m, 5 H, Ph), 7.77, 7.89 (2 s$_{br}$, 0.5 H each, N–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 13.4 (2 q, 5-Me), 24.1, 20.2 (2 q, 3-Me), 25.3, 25.5 (2 t, C-4'), 30.7, 30.8 (2 t, C-3'), 48.47, 48.49 (2 t, C-4), 54.2, 54.6 (2 t, C-5'), 60.1, 60.3 (2 t, *C*H$_2$Ph), 67.4, 67.6 (2 d, C-2'), 92.5, 92.9 (2 s, C-5), 127.4, 127.5, 128.7, 129.0, 136.9, 137.4 (4 d, 2 s, Ph), 156.9, 157.2 (2 s, C-3), 174.4 (s, C=O) ppm; IR (ATR): ν = 3320 (O–H), 2930, 2830 (C–H), 1670 (C=N, C=C), 1500, 1020 (N–O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{17}H_{24}N_3O_2$: 302.1863; found: 302.1844; *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{23}N_3NaO_2$: 324.1682; found: 324.1707; *m/z* $[M+K]^+$ calcd. for $C_{17}H_{23}KN_3O_2$: 340.1422; found: 340.1418; $C_{17}H_{23}N_3O_2$ (301.4) + 0.25 H_2O: calcd. C 66.75, H 7.74, N 13.74; found: C 66.49, H 7.98, N 13.97.

(*S*)-[2-(1-Benzylpyrrolidin-2-yl)-6-methylpyrimidin-4-yl]methanol (26): Trifluoroacetic anhydride (4 mL) was added to **24** (180 mg, 0.635 mmol) and the mixture was stirred at room temperature for 1 h. All volatile compounds were removed under reduced pressure, dichloromethane (15 mL) was added and the organic phase was washed with saturated aqueous $NaHCO_3$ solution (20 mL). The organic phase was dried (Na_2SO_4), filtrated and the solvent was removed under reduced pressure to give the crude product (295 mg) as black oil. Purification by column chromatography (silica gel, ethyl acetate/methanol/triethylamine, 100:10:1) provided **26** (109 mg, 61%) as a yellow oil. $[\alpha]^{20}_D = -4.7$ (*c* = 1.06, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83–1.88, 2.02–2.13 (2 m, 1 H, 2 H, 3'-H, 4'-H$_a$), 2.29–2.33 (m, 1 H, 4'-H$_b$), 2.44 (m$_c$, 1 H, 5'-H$_a$), 2.53 (s, 3 H, 6-Me), 3.25 (m$_c$, 1 H, 5'-H$_b$), 3.50, 3.83 (2 d, *J* = 12.8 Hz, 1 H each, C*H*$_2$Ph), 3.76 (t, *J* = 8.2 Hz, 1 H, 2'-H), 4.70 (s, 2 H, 4-CH$_2$O), 7.00 (s, 1 H, 5-H), 7.18–7.30 (m, 5 H, Ph) ppm; the OH signal could not be assigned due to overlap with pyrrolidine signals; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6 (t, C-4'), 24.2 (q, 6-Me), 31.9 (t, C-3'), 54.1 (t, C-5'), 58.6 (t, *C*H$_2$Ph), 63.7 (t, CH$_2$O), 70.3 (d, C-2'), 115.3 (d, C-5), 127.7, 128.3, 130.0, 138.2 (3 d, s, Ph), 153.9 (s, C-6), 167.6 (s, C-4), 168.6 (s,

C-2) ppm; IR (ATR): ν = 3340 (O–H), 2960 (C–H), 1450 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{17}H_{22}N_3O$: 284.1757; found: 284.1760.

[2-((*S*)-1-Benzylpyrrolidin-2-yl)-6-methylpyrimidin-4-yl]methyl (*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate: To a solution of **26** (22 mg, 0.077 mmol) in dichloromethane (0.4 mL) and dry pyridine (0.4 mL), (*S*)-Mosher acid chloride (27.5 mg, 0.11 mmol) was added and the mixture was stirred at room temperature for 16 h. The mixture was diluted with dichloromethane (5 mL) and successively washed with saturated aqueous $NaHCO_3$ solution (5 mL) and water (5 mL). The organic phase was dried (Na_2SO_4), filtrated and concentrated under reduced pressure to afford the crude product (28 mg) as a dark oil. ^{1}H-, ^{13}C- and ^{19}F-NMR spectroscopy reveal that the sample is diastereomerically pure. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79–1.84, 1.95–2.04, 2.20–2.23 (3 m, 1 H, 2 H, 1 H, 3'-H, 4'- H), 2.36–2.39 (m, 1 H, 5'-H), 2.42 (s, 3 H, 6-Me), 3.22 (m_c, 1 H, 5'-H), 3.44 (d, *J* = 12.7 Hz, 1 H, C*H*$_2$Ph), 3.60 (s, 3 H, OMe), 3.67 (t, *J* = 8.2 Hz, 1 H, 2'-H), 3.76 (d, *J* = 12.7 Hz, 1 H, C*H*$_2$Ph), 5.29, 5.43 (2 dd, *J* = 15.1, 0.7 Hz, 1 H each, 4-CH_2O), 6.71 (s, 1 H, 5-H), 7.13–7.22, 7.41–7.44 (2 m, 5 H each, 2 Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4 (q, 6-Me), 24.2 (t, C-4'), 32.1 (t, C-3'), 54.1 (t, C-5'), 55.6 (q, OMe), 59.0 (t, *C*H$_2$Ph), 66.5 (d, C-2'), 70.7 (t, 4-CH_2O), 114.7 (d, C-5), 126.8, 127.3, 127.9, 128.5, 129.4, 129.8, 131.8, 138.3 (6 d, 2 s, Ph), 163.1, 166.0, 168.1 (3 s, C-4, C-6, C-2), 170.9 (s, C=O) ppm; the signal of the quaternary C was not observed; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −71.2 (s, CF_3) ppm.

2-[(2'*S*,4'*R*)-1-Benzyl-4'-hydroxypyrrolidin-2'-yl]-4,6-dimethylpyrimidine 1-Oxide (28): A solution of β-ketoenamide **6** (112 mg, 0.268 mmol) in methanol (1 mL) was transferred into a sealed pressure tube and hydroxylamine hydrochloride (280 mg, 4.03 mmol) was added. The mixture was stirred at 70 °C for 2 d. After cooling to room temperature, a first extraction was performed with dichloromethane (10 mL). To the aqueous phase was added 1 M aqueous sodium hydroxide solution until pH 10 was reached and then extracted with dichloromethane (5 × 30 mL). The combined organic phases from the basified aqueous phase was dried (Na_2SO_4), filtrated and the solvent was removed under reduced pressure giving **28** (74 mg, 92%) as a colorless oil which was used without further purification in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74 (m, 2 H, 3'-H), 2.36–2.43 (m, 1 H, 5'-H), 2.44, 2.46 (2 s, 3 H each, 4-Me, 6-Me), 2.52 (m, 1 H, 5'-H), 3.21 (ddd, *J* = 9.5, 7.6, 2.3 Hz, 1 H, 4'-H), 3.41, 3.80 (AB system, J_{AB} = 12.4 Hz, 1 H each, C*H*$_2$Ph), 4.46 (t, *J* = 8.2 Hz, 1 H, 2'-H), 6.91 (s, 1 H, 5-H), 7.14–7.33 (m, 5 H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (q, 4-Me), 23.5 (q, 6-Me), 40.3 (t, C-3'), 59.6 (t, *C*H$_2$Ph), 61.5 (d, C-2'), 62.6 (t, C-5), 69.9 (d, C-4'), 119.7 (d, C-5), 127.1, 128.1, 129.3, 138.5 (3 d, s, Ph), 154.1 (s, C-4), 155.3 (s, C-6), 161.0 (s, C-2) ppm; IR (ATR): ν = 3350 (O–H), 2920, 2800 (C–H), 1610 (C=C), 1540, 1450, 1230 (N–O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{17}H_{22}N_3O_2$: 300.1707; found: 300.1712; *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{21}N_3NaO_2$: 322.1526; found: 322.1514; $C_{17}H_{21}N_3O_2$ (299.4): calcd. C 68.20; H 7.07; N 14.04; found: C 68.34; H 7.21; N 13.63.

2-[(2'*S*,4'*R*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)pyrrolidin-2'-yl]-4,6-dimethylpyrimidine 1-Oxide (29): To a solution of crude **28** (166 mg, 0.555 mmol) in dichloromethane (1 mL) were added imidazole (76 mg, 1.11 mmol) and *tert*-butyldimethylsilyl chloride (101 mg, 0.666 mmol) and the mixture was stirred at room temperature for 16 h. After addition of water (10 mL), the aqueous phase was extracted with dichloromethane (3 × 15 mL), the combined organic phases were dried (Na_2SO_4), filtrated and concentrated under reduced pressure. The crude product (203 mg) was purified by column chromatography (alumina, hexanes/ethyl acetate, 4:1) to furnish **29** (135 mg, 59%). $[\alpha]^{20}_D$ = −12.8 (*c* = 0.6, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00, 0.01 (2 s, 3 H each, $SiMe_2$), 0.85 (s, 9 H, Si*t*Bu), 2.07–2.11, 2.39–2.44 (2 m, 1 H, 2 H, 3'-H, 5'-H), 2.46, 2.47 (2 s, 3 H each, 4-Me, 6-Me), 3.38 (dd, *J* = 9.3, 6.1 Hz, 1 H, 5'-H), 3.49, 3.82 (2 d, *J* = 12.4 Hz, 1 H each, C*H*$_2$Ph), 4.48 (m_c, 1 H, 4'-H), 4.78 (t, *J* = 8.4 Hz, 1 H, 2'-H), 6.93 (s, 1 H, 5-H), 7.15–7.33 (m, 5 H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.77, −4.73 (2 q, $SiMe_2$), 17.6 (q, 4-Me), 18.1, 25.9 (s, q, Si*t*Bu), 23.5 (q, 6-Me), 39.8 (t, C-3'), 59.8 (t, *C*H$_2$Ph), 61.6 (d, C-2'), 62.3 (t, C-5'), 70.4 (d, C-4'), 119.5 (d, C-5), 127.0, 128.0, 129.3, 138.6 (3 d, s, Ph), 153.0 (s, C-4), 155.0 (s, C-6), 161.2 (s, C-2) ppm; IR (ATR): ν = 2950, 2930, 2855 (C–H), 1610 (C=C, C=N), 1536, 1450, 1250 (N–O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{23}H_{36}N_3O_2Si$: 414.2571; found: 414.2562; $C_{23}H_{35}N_3O_2Si$ (413.6) + 0.5 H_2O: calcd. C 65.36, H 8.59, N 9.94; found: C 65.20, H 8.54, N 10.22.

2-[(2'*S*,4'*R*)-4'-Acetoxy-1'-benzylpyrrolidin-2'-yl]-6-methylpyrimidin-4-yl}methyl Acetate (30): In a sealed tube, **28** (81 mg, 0.270 mmol) and acetic anhydride (3 mL) were heated to 120 °C for 3 h. After cooling to room temperature, the solvent was removed at reduced pressure yielding a dark brown oil which was purified by chromatography (silica gel, hexanes/ethyl acetate, 4:1, then 1:1) providing **30** (49 mg, 47%) as pale yellow oil, **31** (6 mg, 7%) as colorless oil and **32** (3 mg, 4%) as colorless solid. $[\alpha]^{20}_D$ = −43.8 (*c* = 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04, 2.20 (2 s, 3 H each, 2 Ac), 2.27 (dd, *J* = 9.0, 7.0 Hz, 1 H, 3'-H), 2.37–2.53 (m, 3 H, 3'-H, 5'-H), 2.55 (s, 3 H, Me), 3.54, 3.78 (AB system, J_{AB} = 12.0 Hz, 1 H each, C*H*$_2$Ph), 3.65–3.68 (m, 1 H, 5'-H), 5.18 (s, 2 H, C*H*$_2$OAc), 5.31 (m_c, 1 H, 4'-H), 7.03 (s, 1 H, 5-H), 7.15–7.25 (m, 5 H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 21.2 (2 q, 2 CO*Me*), 24.4 (q, 6-Me), 39.5 (t, C-3'), 58.2 (d, C-2'), 59.5 (t, *C*H$_2$Ph), 65.5 (t, C-5'), 68.7 (t, CH_2O), 73.0 (d, C-4'), 115.5 (d, C-5), 127.0, 128.1, 129.3, 138.0 (3 d, s, Ph), 164.5 (s, C-6), 168.1 (s, C-4), 169.5 (s, C-2), 170.4, 170.8 (2 s, 2 C=O) ppm; IR (ATR): ν = 2950, 2925, 2860 (C–H), 1735, 1705 (C=O), 1590, 1460 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+K]^+$ calcd. $C_{21}H_{25}KN_3O_4$: 422.1482; found: 422.1513.

[2-(1-Benzyl-1*H*-pyrrol-2-yl)-6-methylpyrimidin-4-yl]methyl Acetate (31): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33, 2.43 (2 s, 3 H each, 6-Me, CO*Me*), 5.04 (s, 2 H, C*H*$_2$OAc), 5.82 (s_{br}, 2 H, C*H*$_2$Ph), 6.26 (dd, *J* = 3.8, 2.6 Hz, 1 H, 3'-H), 6.83 (m_c, 1 H, 4'-H), 7.04 (m_c, 2 H, 5-H, 5'-H), 7.16–7.24 (m, 5 H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1 (q, CO*Me*), 24.5 (q, 6-Me), 52.9 (t, *C*H$_2$Ph), 65.7 (t, 4-CH_2), 108.8 (d, C-4'), 112.8, 115.5 (2 d, C-3', C-5'), 116.1 (d, C-5), 126.5, 126.9, 128.5, 138.9 (3 d, s, Ph), 138.9. 141.0 (2 s, C-6, C-4), 166.3 (s, C-2), 178.1 (s, C=O) ppm; IR (ATR): ν = 2920, 2850 (C–H), 1730 (C=O), 1580 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{20}N_3O_2$: 322.1550; found: 322.1552; *m/z* $[M+Na]^+$ calcd. for $C_{19}H_{19}N_3NaO_2$: 344.1369; found: 344.1359; $C_{19}H_{19}N_3O_2$ (321.4): calcd. C 71.01, H 5.96, N 13.08; found: C 71.03, H 6.44, N 12.92.

2-(1-Benzyl-1*H*-pyrrol-2-yl)-4,6-dimethylpyrimidine (32): M. p. 83–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 6 H, Me), 5.87 (s, 2 H, C*H*$_2$Ph), 6.25 (dd, *J* = 3.9, 2.6 Hz, 1 H, 3'-H), 6.65 (s, 1 H, 5-H), 6.85 (dd, *J* = 2.6, 1.9 Hz, 1 H, 4'-H), 7.03 (m_c, 1 H, 5'-H), 7.05–7.20 (m, 5 H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1 (q, Me), 52.8 (t, *C*H$_2$Ph), 108.6 (d, C-4'), 115.35, 115.4 (2 d, C-2', C-5), 115.9 (d, C-3'), 126.6 (d, C-5'), 126.8, 127.8, 128.4, 139.9 (3 d, s, Ph), 140.0 (s, C-6, C-4), 166.1 (s, C-2) ppm; IR (ATR): ν = 3030, 2925 (C–H), 1580, 1540 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{17}H_{18}N_3$: 264.1495; found: 264.1491; *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{17}N_3Na$: 286.1315; found: 286.1302; $C_{17}H_{17}N_3$ (263.3): calcd. C 77.54, H 6.51, N 15.96; found: C 77.58; H 7.35; N 15.92.

2-[(2'*S*,4'*R*)-1'-Benzyl-4'-(*tert*-butyldimethylsiloxy)pyrrolidin-2'-yl]-6-methylpyrimidin-4-yl}methyl Acetate (33): In a sealed tube, **29** (136 mg, 0.329 mmol) and acetic anhydride (2 mL) were heated to 120 °C for 3 h. After cooling to room temperature, the solvent was removed at reduced pressure yielding a black oil which was purified by chromatography (silica gel, hexanes/ethyl acetate, 20:1, then 6:1, 3:1, 2:1, ethyl acetate) providing **33** (64 mg, 44%) as yellow oil, **31** (7 mg, 6%) as colorless oil and **32** (9 mg, 10%) as colorless

solid. $[\alpha]^{20}_D = -21.5$ ($c = 1.18$, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.00, 0.01 (2 s, 3 H each, $SiMe_2$), 0.85 (s, 9 H, Si*t*Bu), 2.06–2.13 (m, 2 H, 3'-H), 2.41–2.46, 3.39–3.48 (2 m, 1 H, 3 H, 5'-H, CH_2Ph, CH_2OAc), 3.46, 3.79, 3.81 (3 d, $J = 12.7$ Hz, 1 H each, CH_2Ph, CH_2OAc), 3.99 (m_c, 1 H, 2'-H), 4.51 (m_c, 1 H, 4'-H), 6.96 (s, 1 H, 5-H), 7.14–7.22 (m, 5 H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.72$, -4.71 (2 q, $SiMe_2$), 18.1, 25.9 (s, q, Si*t*Bu), 20.9 (q, CO*Me*), 24.5 (q, 6-Me), 42.6 (t, C-3'), 59.1 (t, CH_2Ph), 60.4 (d, C-2'), 62.9 (t, C-5'), 66.6 (t, CH_2O), 70.4 (d, C-4'), 115.2 (d, C-5), 126.9, 128.0, 129.4, 138.5 (3 d, s, Ph), 159.2 (s, C-6), 164.5 (s, C- 4), 168.0 (s, C-2), 170.5 (s, C=O) ppm; IR (ATR): $\nu =$ 2950, 2930, 2850 (C–H), 1750, 1700 (C=O), 1590, 1440 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. $C_{25}H_{37}N_3O_3Si$: 456.2682; found: 456.2689; $C_{25}H_{37}N_3O_3Si$ (455.7): calcd. C 65.90, H 8.18, N 9.22; found: C 66.53, H 8.32, N: 9.00.

{2-[(2*S*,4*R*)-1-Benzyl-4-(*tert*-butyldimethylsiloxy)pyrrolidin-2-yl]-6-methylpyrimidin-4-yl}methanol (34): Compound **33** (60 mg, 0.13 mmol) was stirred with K_2CO_3 (73 mg, 0.53 mmol) in MeOH (5 mL) at room temperature for 3 h. Filtration and purification of the crude product by chromatography (silica gel, ethyl acetate) yielded 25 mg (47%) of **34** as a yellow oil. $[\alpha]^{20}_D = +11.0$ ($c = 2.0$, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.00$, 0.01 (2 s, 3 H each, $SiMe_2$), 0.87 (s, 9 H, Si*t*Bu), 2.11–2.15 (m, 1 H, 3'-H), 2.32–2.41 (m, 2 H, 3'-H, 5'-H), 2.50 (s, 3 H, 6-Me), 3.41 (dd, $J = 9.6$, 6.1 Hz, 1 H, 5'-H), 3.47, 3.78 (2 d, $J = 12.8$ Hz, 1 H each, CH_2Ph), 4.04 (t, $J = 8.0$ Hz, 1 H, 2'-H), 4.52 (m_c, 1 H, 4'-H), 4.67 (s, 2 H, CH_2O), 6.96 (s, 1 H, 5-H), 7.16–7.25 (m, 5 H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.73$, -4.70 (2 q, $SiMe_2$), 18.1, 25.9 (s, q, Si*t*Bu), 24.3 (q, 6-Me), 42.6 (t, C-3'), 59.3 (t, CH_2Ph), 62.9 (t, C-2'), 63.6 (t, C-5'), 69.3 (t, 4-CH_2), 70.5 (d, C-4'), 115.0 (d, C-5), 127.1, 128.1, 129.5, 138.0 (3 d, s, Ph), 166.8, 167.5 (s, C-4, C-6), 168.0 (s, C-2) ppm; IR (ATR): $\nu = 3340$ (O–H), 2960 (C–H), 1450 cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{23}H_{35}N_3O_2Si$: 414.2571; found: 414.2574; $C_{23}H_{35}N_3O_2Si$ (413.6) + 0.75 H_2O: calcd. C 64.67, H 8.61, N 9.84; found: C 64.48, H 8.57, N 10.03.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Amino acids · Chiral pool · Cyclization of β-ketoenamides · Pyridines · Pyrimidines

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