A Short Synthesis of Polyhydroxylated Piperidines by Aldol Reaction of Chelated Amino Acid Ester Enolates☆

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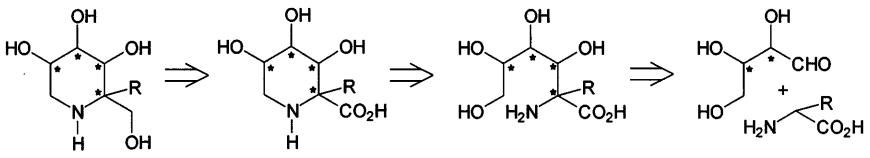
Aldol reactions of a chelated glycine ester enolate with a chiral aldehyde gives rise to the corresponding polyhydroxylated amino acid with excellent induced diastereoselectivity. These oxygenated amino acids can be converted into polyhydroxylated pipecolinic acids and azasugars by cyclization using the Mitsunobu reaction. An interesting epimerization was observed during the cyclization. The potential glycosidase inhibitor 1-deoxyaltronojirimycin (**8b**) was synthesized by this approach in a highly stereoselective fashion.

Introduction

Based on their structural relationship to sugars, polyhydroxylated piperidines and pipecolinic acid derivatives are interesting candidates for the inhibition of various glycosidases. In their protonated form they can act as transition-state analogues of these enzymes.[1] Deoxynojirimycin,[2] isolated from Bacillus strains,[3] and Deoxymannojirimycin[4] from *Lonchocarpus* sp.[5] are specific inhibitors of glucosidases,[2] mannosidases,[6] as well as fucosidases.[7] (2*S*,3*R*,4*R*,5*S*)-Trihydroxypipecolinic acid,[8] isolated from *Baphia racemosa*,[9] acts as glucoronidase and fucosidase inhibitor.[10] This biological activity is important for the therapy of diabetes,[11] cancer[12] and viral infections.[13]

In the meanwhile several interesting syntheses of natural as well as synthetical deoxyazasugars[4][14] and related pipecolinic acid derivatives[8][15] were described. The interesting properties of these compounds encouraged us to develop an own approach to their synthesis, based on asymmetric aldol reactions of chelated ester enolates.[16] The retrosynthetical analysis of these piperidine alkaloids (Scheme 1) leads to the corresponding pipecolinic acid derivatives, which can be obtained from acyclic polyhydroxylated α-amino acids. These are accessible by aldol reaction of amino acid ester enolates and chiral polyhydroxylated aldehydes.[17]

Scheme 1



For some time, our group has been interested in reactions of metal-chelated enolates of *N*-protected amino acid esters.[18] Besides chelate enolate Claisen rearrangements, aldol reactions give especially good results.[19] A very high simple diastereoselectivity of > 95% is obtained in the reactions of *N*-sulfonylated amino acid esters in the presence of 2.5 equiv. of $SnCl_2$ with both, aliphatic as well as aromatic aldehydes.[20] At least 2 equiv. of metal salt are necesarry for good selectivities. Probably one equiv. is involved in the formation of the chelate complex, and the second one is responsible for the activation of the aldehyde.[19b] This protocol can be applied to various types of amino acids, and the selectivities observed are nearly independent of the sulfonyl protecting group used. In cases where the tosyl group is difficult to remove, the easier cleavable 2-(trimethylsilyl)-ethanesulfonyl (SES) protecting group, developed by Weinreb et al.,[21] can be used.

In aldol reactions of chiral α-alkoxy or α-siloxy aldehydes, an induction on the newly formed chiral centers is observed, and two aldol products, out of the four possible stereoisomers, were formed preferentially. In general the induced diastereoselectivity is very high (≥ 95% ds), independent of the amino acid ester used.[17] The formation of the 3,4-*anti* diastereomer as the mayor isomer is in accordance with the Felkin-Ahn model.[22] Also good simple diastereoselectivities were obtained with esters of most amino acids except glycine. In this case, the chiral α center is formed as a nearly 1:1 mixture.

This loss of selectivity may have two different reasons. First, the attack of the glycine ester enolate, in contrast to other amino acid ester enolates, proceeds unselective, what

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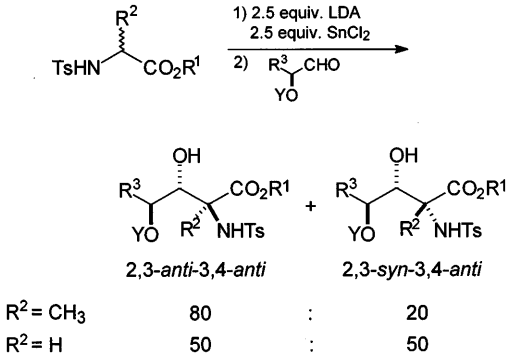
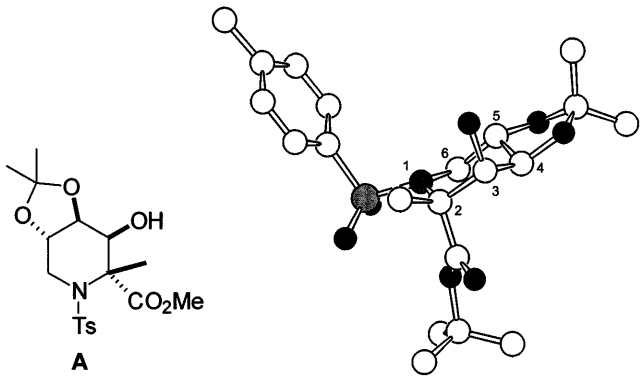
Scheme 2



is not very rational. Second, the attack of the glycine ester enolate occurs with comparable selectivity like the enolates of the other amino acid esters, and the aldol product subsequently epimerizes under the reaction conditions used. The configurational lability of the tosylated amino acid esters may result from an acidification of the α position by the strong electron-withdrawing sulfonyl protecting group. On the first view this effect limits the applicability of this aldol approach. On the other hand we were interested to see, if it is possible to use this epimerization effect also in a positive sense, to control the configuration of this labile center, e.g. in cyclic derivatives like piperidines.

During our studies towards the synthesis of α-alkylated pipecolinic acids we were able to obtain crystals of an α-methylated derivative **A**, suitable for X-ray crystal structure analysis (Figure 1).[17] The pseudo planar environment of the nitrogen atom leads to a close orientation of the sulfonyl group and the methyl substituent at C2. The expectable interactions between these two groups results in a enlarged bond angle (S−N−C2) at the nitrogen atom of approximately 121°. Similar interactions obviously also occur in solution, as indicated by a strong NOE between the α-methyl substituent and the aromatic protons of the tosyl group.

Figure 1. Crystal structure of α-methylated pipecolinic acid derivative **A**

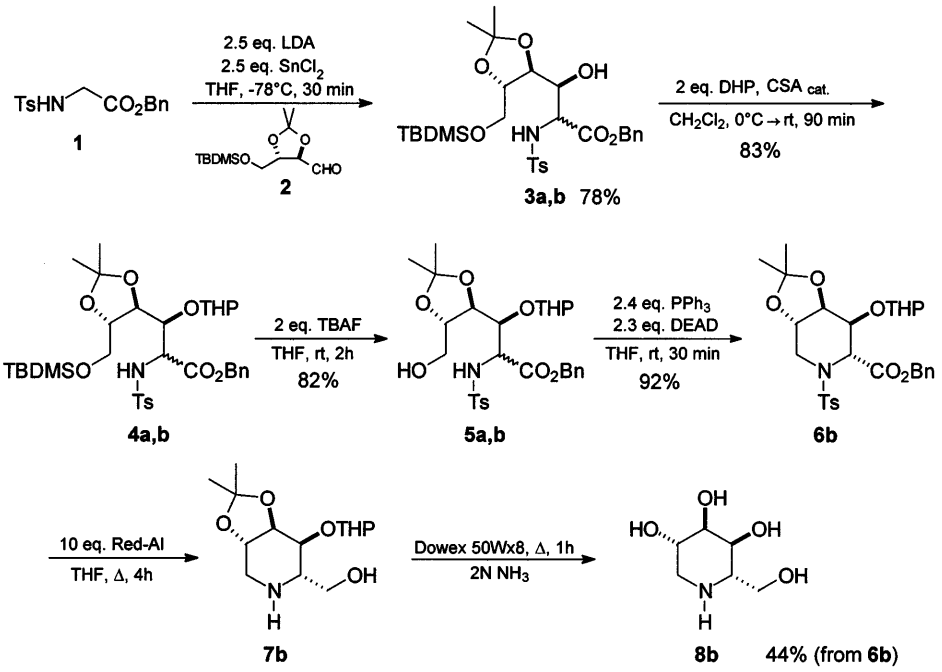


Our intention for the investigations described here, results from the question, if these sterical interactions can be used as a stereocontrolling element for the synthesis of piperidines, if configurationally labile derivatives like the glycine esters are used.

Results and Discussion

Starting from tosylated glycine ester **1**[23] the aldol reaction with chiral aldehyd **2**[24] in the presence of 2.5 equiv. of $SnCl_2$ gave the corresponding aldol product **3** with excellent induced diastereoselectivity (> 95% ds), while the α center gave a nearly 1:1 epimeric mixture (**a**, **b**) (Scheme 3). This mixture was directly used for the following piperidine syn-

Scheme 3

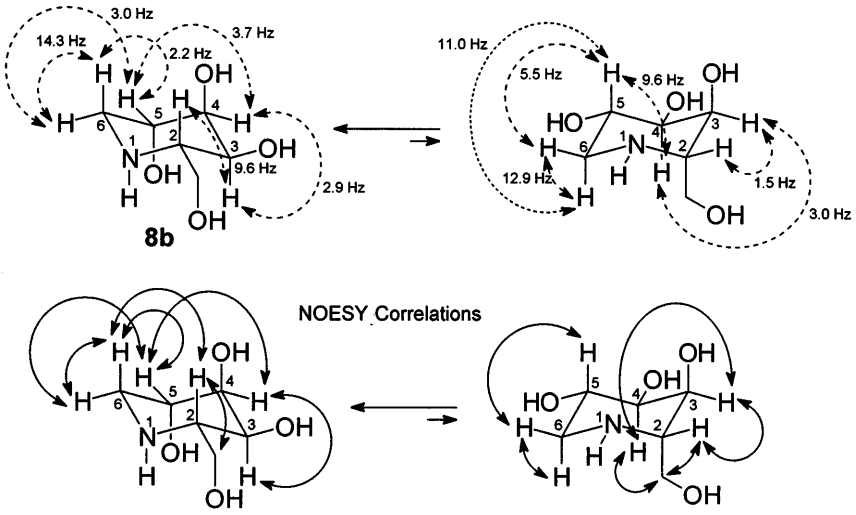


thesis, with the hope, that the configuration of the labile α position can be controlled in the six-membered ring system. Protection of the β-OH group was necessary to avoid their elimination (Scheme 7) during the subsequent Mitsunobu reaction,[25] which was used in the cyclization step. The THP protecting group was especially suitable for this purpose and the epimeric mixture of **4** was obtained in 83% yield.[26] Cleavage of the silyl protecting group with TBAF gave rise to alcohols **5a**, **b**, which was cyclized in the presence of an excess of Mitsunobu reagents producing *only one* diastereomer[26] of the pipecolinic acid derivative **6b** in 92% yield. Addition of an excess Red-Al resulted in a simultaneous cleavage of the *N*-tosyl protecting group and reduction of the ester moiety.[27] Removal of the acid-labile groups with Dowex 50W×8 gave rise to 1-deoxyaltronojirimycin (**8b**)

Cyclization of **5a** and **5b** with a stoichiometrical amount of PPh_3/DEAD (method a) gave the corresponding pipecolinic acid derivatives **6a** and **6b**, respectively, without epimerization (Scheme 4). If an excess of Mitsunobu reagents was used (method b), **5a** as well as **5b** provided the pipecolinic acid derivative **6b** with the axially oriented ester moiety. In the synthesis of **6b** from **5a** both PPh_3 as well as DEAD had to be used in excess. Excess of only one of the reagents produced **6a**, and no epimerization was observed.

Also no epimerization occurred when pipecolinic acid derivative **6a** was treated with various amounts of Mitsunobu reagents. Obviously, basic intermediates formed during the Mitsunobu reaction are responsible for the deprotonation and epimerization of the linear amino acid ester **5**. The cyclization then occurs under kinetically controlled conditions from a rapid epimerization equilibrium. Cyclization

Figure 2. Coupling constants and NOESY correlations in **8b**

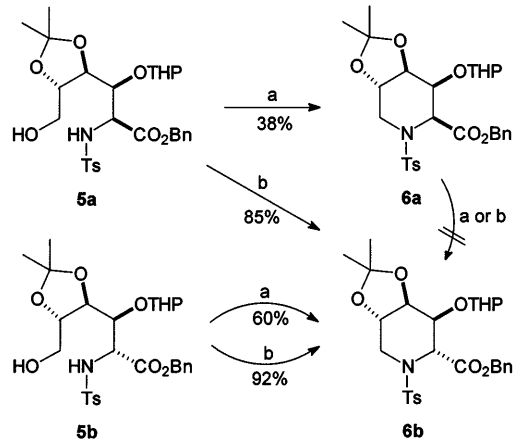


The configuration of **8b** was determined by NOESY and NMR experiments (Figure 2). In solution **8b** exists as a mixture of two conformers in a ratio of 9:1.

In the major isomer the conformation the α-hydroxymethyl group (C2) and the β-hydroxy group (C3) both are in equatorial positions. The large coupling constant (9.6 Hz) between the α-H and β-H, as well as the missing NOESY correlation between these axial atoms are characteristic for this conformation.

The formation of the diastereomerically pure cyclic product **6b** out of the epimeric mixture of the linear precursor **5a**, **b** in nearly quantitative yield (no removal of the second diastereomer!) is quite astonishing. Although we hoped to find such an epimerization, because of the sterical interactions discussed above, the very clean and smooth conversion nevertheless was surprising. Obviously, the epimerization already occurs during the Mitsunobu cyclization. Therefore, we had a closer look at this interesting phenomenon, and we investigated the cyclization of the pure diastereomers **5a** and **5b**. These could be obtained after formation of the THP ether and removal of the silyl group from the alcohols **3a** and **3b**, which could be separated by MPLC. of epimer **5b** with the axial ester moiety obviously is faster than that of epimer **5a** with the equatorial ester moiety. The

Scheme 4

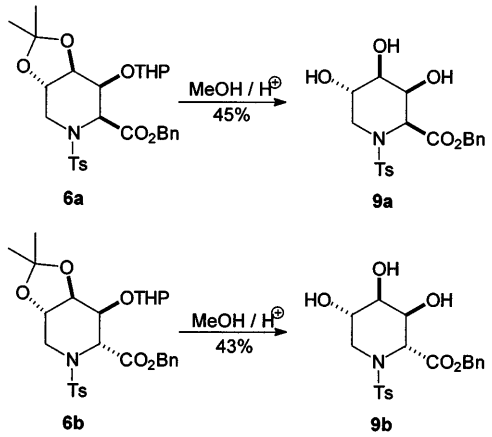


Reaction conditions: a: 1.0 equiv. PPh_3, 0.95 equiv. DEAD; b: 2.5 equiv. PPh_3, 2.4 equiv. DEAD.

expected sterical interactions between the sulfonyl group and the ester moiety may be the reason for this effect.

The configuration of pipecolinic acid derivatives **6a** and **6b** and the aldol products **3a** and **3b** as well, was confirmed by NMR using the deprotected triols **9a** and **9b** respectively. These were obtained by treatment of **6a** and **6b** with catalytic amounts of acid (Scheme 5).

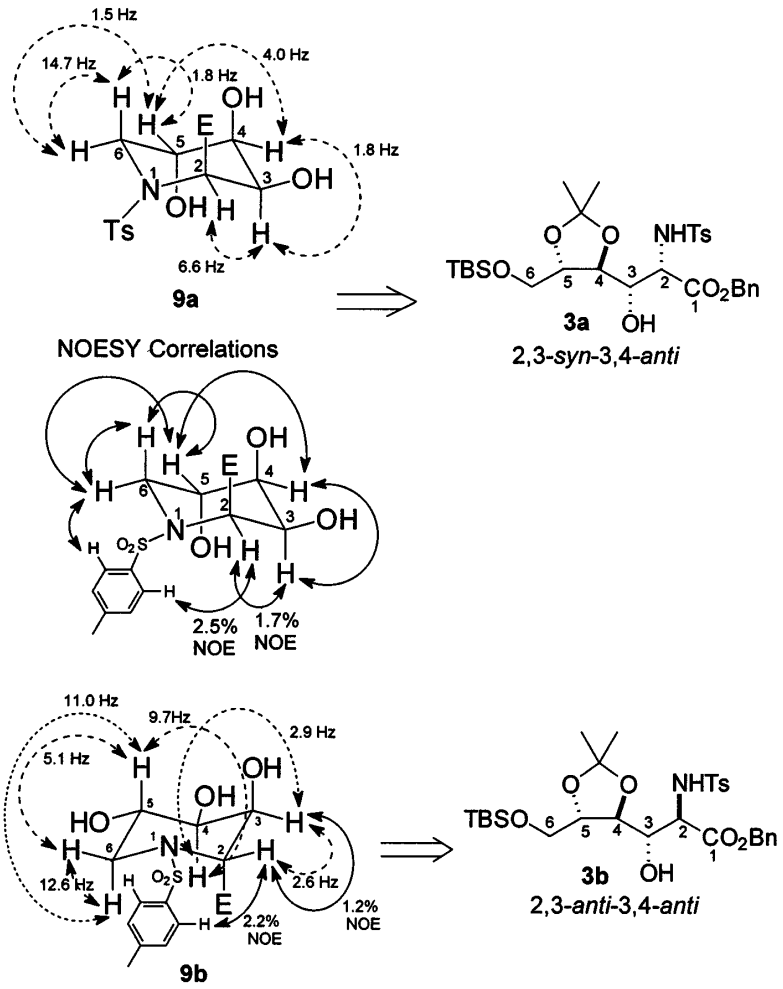
Scheme 5



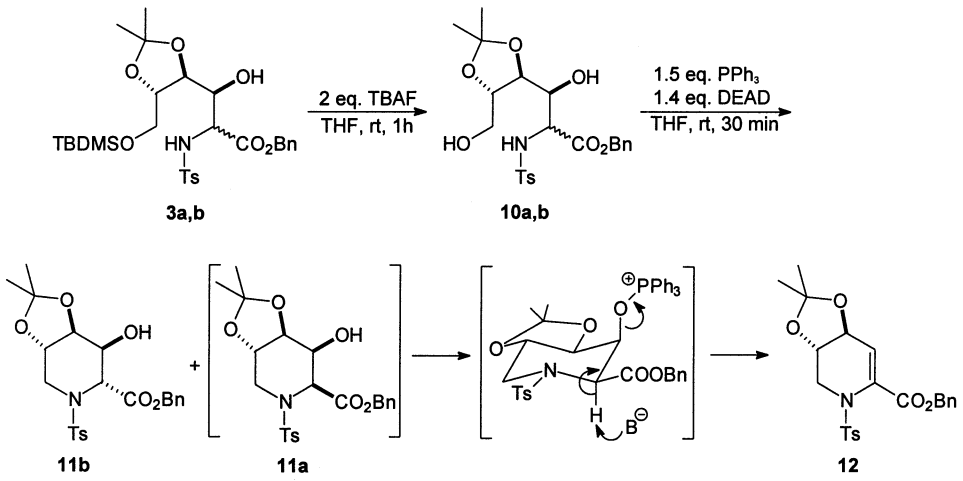
NOE and NMR experiments clearly indicate that in both isomers **9a** and **9b** the ester moiety is in the axial position (Scheme 6). For derivative **9b** this is not surprising, but for **9a** a conformation with an equatorial orientation of most of the substituents should be expected. Obviously, the steric interactions between the sulfonyl group and the ester functionality in **9a** are extremely strong, and therefore the conformation shown is the only one observed. Because of the configurations determined for these pipecolinic acid derivatives the aldol product **3a** can be assigned as the 2,3-*syn*-3,4-*anti* isomer, while aldol product **3b** is the 2,3-*anti*-3,4-*anti* isomer.

Attempts to perform the Mitsunobu cyclization with the unprotected diol **10**, obtained by desilylation from **3**, also gave the diastereomerically pure pipecolinic acid derivative **11b**, although in only 40% yield (Scheme 7). The major side product (30%) was the didehydro amino acid **12,** probably obtained from the epimeric pipecolinic acid ester **11a**, and elimination of the β-OH group under the assistance of some basic intermediates (B^-) formed during the Mitsunobu reaction. In contrast, no elimination was observed when **11b**, with an axially oriented ester functionality, was treated with Mitsunobu reagents.

Scheme 6



Scheme 7



In conclusion we have shown, that polyhydroxylated piperidines and pipecolinic acid derivatives can easily be obtained by aldol reaction of chelated enolates. Sterical interactions can be used to control the configuration of the labile α position in tosylated amino acid esters.

We thank Prof. Dr. *G. Helmchen* for his generous support of this work. Financial support by the *Graduiertenkolleg*, the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* is gratefully acknowledged.

Experimental Section

All reactions were carried out in oven-dried glassware (100°C) under argon. All solvents were dried before use. THF was distilled from sodium benzophenone, dichloromethane from calcium hydride. Dowex 50W×8 was purchased from Aldrich. LDA solutions were prepared from freshly distilled diisopropylamine and commercially available *n*-butyllithium solution (15% in hexane) in THF at −20°C directly before use. All other solvents were reagent-grade quality and used as received. The starting materials and the products were purified by flash chromatography on silica gel (32−63 μm). Mixtures of ethyl acetate and hexanes were used as eluents. − TLC: Commercially precoated Polygram© SIL G/UV_{254} plates (Macherey-Nagel). Visualization was accomplished with UV light, iodine, and potassium permanganate solution. − ^1H and ^{13}C NMR: Bruker AC-300 spectrometer. − Analytical HPLC: Daicel "Chiralcel OD-H" column (flow: 0.5 ml/min), Knauer UV detector. − Optical rotations: Perkin-Elmer 241 polarimeter.

Benzyl (2RS,3S,4S,5S)-6-tert-Butyldimethylsilyloxy-3-hydroxy-4,5-isopropylidenedioxy-2-[(4-toluenesulfonyl)amino]hexanoate (**3a**, **b**): A solution of 4 mmol of LDA in anhydrous THF (10 ml) was added at −78°C under argon to a solution of *N*-tosylated benzyl glycinate **1**[22] (512 mg, 1.6 mmol) and $SnCl_2$ (760 mg, 4.0 mmol) in 8 ml of THF. After 10 min, a solution of aldehyde **2**[23] (527 mg, 1.92 mmol) in 3 ml of THF was added. After 30 min at −78°C, the reaction was quenched by adding phosphate buffer pH = 7 (20 ml). The mixture was diluted with diethyl ether (20 ml) and was allowed to warm to room temp. After filtration of the mixture through a pad of Celite, the aqueous phase was extracted twice with diethyl ether (20 ml each). The combined organic layers were washed with brine, dried with Na_2SO_4, and the solvent was evaporated in vacuo. The crude aldol product was purified by flash chromatography (hexanes/ethyl acetate, 8:2) giving rise to **3** (743 mg, 78%) as a colorless oil and a mixture of diastereomers (**3a**/**3b**, 54:46). − HPLC (*n*-hexane/2-propanol, 8:2): t_R(**3b**) = 11.50 min; t_R(**3a**) = 13.54. − HRMS (FAB); $C_{29}H_{43}NO_8SSiNa$ [M^+ + Na]: calcd. 616.2376, found 616.2385. − The diastereomers could be separated by MPLC.

3a (2*S* isomer): Colorless oil. − $[\alpha]_D^{20}$ = +21.5 (*c* = 0.8, $CHCl_3$). − ^1H NMR ($CDCl_3$): δ = 0.10 (s, 3 H), 0.11 (s, 3 H), 0.89 (s, 9 H), 1.28 (s, 3 H), 1.37 (s, 3 H), 2.38 (s, 3 H), 3.52 (dd, *J* = 9.2, 9.1 Hz, 1 H), 3.77 (dd, *J* = 8.6, 7.7 Hz, 1 H), 3.85 (ddd, *J* = 9.0, 7.7, 3.9 Hz, 1 H), 3.94 (ddd, *J* = 8.5, 1.6, 1.5 Hz, 1 H), 3.95 (dd, *J* = 9.2, 3.8 Hz, 1 H), 4.22 (d, *J* = 1.6 Hz, 1 H), 4.36 (dd, *J* = 10.5, 1.5 Hz, 1 H), 4.94 (d, *J* = 12.5 Hz, 1 H), 5.07 (d, *J* = 12.4 Hz, 1 H), 5.39 (d, *J* = 10.5 Hz, 1 H), 7.19 (d, *J* = 8.3 Hz, 2 H), 7.23−7.33 (m, 5 H), 7.72 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR ($CDCl_3$): δ = −5.64, −5.61, 18.29, 21.48, 25.79, 26.49, 26.72, 57.50, 64.24, 67.16, 73.37, 79.37, 79.71, 109.55, 127.24, 127.84, 128.20, 128.45, 129.38, 135.33, 137.59, 143.15, 170.14. − $C_{29}H_{43}NO_8SSi$ (593.82): calcd. C 58.66, H 7.30, N 2.36; found C 58.64, H 7.47, N 2.28.

3b (2*R* isomer): Colorless oil. − $[\alpha]_D^{20}$ = −26.4 (*c* = 0.8, $CHCl_3$). − ^1H NMR ($CDCl_3$): δ = 0.07 (s, 3 H), 0.08 (s, 3 H), 0.88 (s, 9 H), 1.28 (s, 6 H), 2.40 (s, 3 H), 3.53 (m_c, 1 H), 3.71 (dd, *J* = 9.0, 7.3 Hz, 1 H), 3.78−3.88 (m, 3 H), 3.93 (ddd, *J* = 9.0, 4.0, 2.4 Hz, 1 H), 4.29 (dd, *J* = 8.9, 2.3 Hz, 1 H), 4.93 (d, *J* = 12.4 Hz, 1 H), 4.99 (d, *J* = 12.3 Hz, 1 H), 5.64 (d, *J* = 8.9 Hz, 1 H), 7.21−7.33 (m, 7 H), 7.72 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR ($CDCl_3$): δ = −5.55, 18.32, 21.52, 25.84, 26.64, 26.69, 58.75, 64.07, 67.32, 74.81, 79.24, 80.73, 109.68, 127.35, 127.87, 128.12, 128.22, 128.42, 128.52, 128.58, 129.59, 134.98, 136.85, 143.51, 168.39. − $C_{29}H_{43}NO_8SSi$ (593.82): calcd. C 58.66, H 7.30, N 2.36; found C 58.74, H 7.57, N 2.26.

Benzyl (2S,3S,4S,5S)-6-tert-Butyldimethylsilyloxy-4,5-isopropylidenedioxy-3-(R/S)-tetrahydropyranyloxy-2-[(4-toluenesulfonyl)amino]hexanoate (**4a**): To a solution of aldol product **3a** (650 mg, 1.10 mmol) and 2,3-dihydro-2*H*-pyrane (200 μl, 2.19 mmol) in dichloromethane (5 ml) a catalytic amount of *dl*-10-camphorsulfonic acid (5 mg) was added at 0°C under argon. After stirring at this temp. for 30 min and 1 h at room temp., sodium bicarbonate (10 mg) was added. After filtration, the solvent was evaporated in vacuo, and the crude product was purified by flash chromatography [hexanes/ethyl acetate (2% NEt_3), 9:1, 85:15] to give **4a** as a colorless oil (517 mg, 70%). − $[\alpha]_D^{20}$ = −0.9 (*c* = 4.4, $CHCl_3$). − HPLC

(*n*-hexane/2-propanol, 9:1): t_R(**4a**) = 13.96 min; t_R(**4a′**) = 14.78 min. − ^{1}H NMR ($CDCl_3$): δ = 0.00, 0.01 (2 s, 6 H), 0.84, 0.85 (2 s, 9 H), 1.23, 1.31, 1.33, 1.35 (4 s, 6 H), 1.51−1.75 (m, 5.5 H), 2.34, 2.37 (2 s, 3 H), 3.10 (m_c, 0.5 H), 3.45−3.81 (m, 5 H), 3.91−4.15 (m, 2.5 H), 4.27−4.57 (m, 1.5 H), 4.92 (d, *J* = 12.5 Hz, 0.5 H), 4.98 (d, *J* = 12.0 Hz, 0.5 H), 5.02 (d, *J* = 12.3 Hz, 0.5 H), 5.03 (d, *J* = 12.0 Hz, 0.5 H), 5.33 (d, *J* = 10.0 Hz, 0.5 H), 5.51 (d, *J* = 10.0 Hz, 0.5 H), 7.14 (d, *J* = 8.3 Hz, 1 H), 7.20 (d, *J* = 8.3 Hz, 1 H), 7.24−7.32 (m, 5 H), 7.71 (d, *J* = 8.3 Hz, 1 H), 7.72 (d, *J* = 8.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = −5.33, −5.29, 18.40, 20.83, 21.10, 21.49, 24.71, 24,81, 25.97, 27.07, 27.22, 27.38, 30.77, 30.96, 56.58, 57.21, 63.70, 64.26, 64.81, 67.21, 67.35, 73.59, 74.51, 78.10, 80.88, 81.00, 81.24, 99.74, 102.35, 109.50, 109.72, 127.22, 127.99, 128.19, 128.45, 128.56, 128.62, 128.69, 129.27, 129.43, 134.97, 135.55, 137.65, 138.22, 142.89, 143.25, 170.07, 170.64. − HRMS (FAB) $C_{34}H_{51}NO_9SSi$ [M^+]: calcd. 677.3054; found 677.3052. − $C_{34}H_{51}NO_9SSi$ (677.95): calcd. C 60.24, H 7.58. N 2.07; found: C 59.98, H 7.44, N 1.89.

Benzyl (2R,3S,4S,5S)-6-tert-Butyldimethylsilyloxy-4,5-isopropylidenedioxy-3-(R/S)-tetrahydropyranyloxy-2-[(4-toluenesulfonyl)amino]hexanoate (**4b**): According to the synthesis of **4a** the reaction of aldol product **3b** (160 mg, 0.28 mmol) and 2,3-dihydro-2*H*-pyrane (50 µl, 0.54 mmol) yielded after flash chromatography [hexanes/ethyl acetate (2% NEt_3), 9:1, 85:15] a colorless oil (130 mg, 71%). − $[\alpha]_D^{20}$ = −19.6 (*c* = 0.3, $CHCl_3$). − HPLC (*n*-hexane/2-propanol, 9:1): t_R(**4b**) = 13.53 min; t_R(**4b′**) = 15.99 min. − ^{1}H NMR ($CDCl_3$): δ = 0.00, 0.04 (2 s, 6 H), 0.84, 0.87 (2 s, 9 H), 1.22, 1.27, 1.30, 1.33 (4 s, 6 H), 1.40−1.70 (m, 5 H), 2.36, 2.37 (2 s, 3 H), 3.40−3.55 (m, 2 H), 3.60−3.79 (m, 2 H), 3.75−4.10 (m, 3.5 H), 4.22 (dd, *J* = 9.2, 2.6 Hz, 0.5 H), 4.33 (dd, *J* = 8.8, 2.6 Hz, 0.5 H), 4.43 (m_c, 0.5 H), 4.53 (dd, *J* = 10.7, 1.8 Hz, 0.5 H), 4.67 (m_c, 0.5 H), 4.84 (d, *J* = 12.3 Hz, 0.5 H), 4.88 (d, *J* = 12.4 Hz, 0.5 H), 5.02 (d, *J* = 12.5 Hz, 0.5 H), 5.03 (d, *J* = 12.3 Hz, 0.5 H), 5.44 (d, *J* = 8.6 Hz, 0.5 H), 6.60 (d, *J* = 10.4 Hz, 0.5 H), 7.10−7.20 (m, 2 H), 7.20−7.30 (m, 5 H), 7.67 (d, *J* = 8.3 Hz, 1 H), 7.68 (d, *J* = 8.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = −5.69, −5.34, −5.28, −5.22, 18.41, 18.47, 20.11, 20.30, 21.52, 24.79, 25.17, 25.83, 25.92, 26.89, 27.15, 27.30, 27.35, 30.46, 30.93, 56.90, 57.31, 64.00, 64.29, 64.39, 66.84, 67.43, 74.43, 75.02, 81.76, 81.91, 85.79, 97.61, 102.19, 109.74, 110.04, 127.17, 127.23, 127.98, 128.15, 128.36, 128.50, 129.41, 129.51, 135.01, 135.37, 137.02, 137.95, 143.02, 143.38, 168.12, 168.84. − HRMS (FAB) $C_{34}H_{51}NO_9SSiNa$ [M^+ + Na]: calcd. 700.2952; found 700.2952. − MS (FAB); *m/z* (%): 700 [M^+ + Na] (12), 677 [M^+] (1), 594 (43), 536 (100). − $C_{34}H_{51}NO_9SSi$ (677.95): calcd. C 60.24, H 7.58. N 2.07; found: C 59.78, H 7.34, N 1.87.

Benzyl (2S,3S,4S,5S)-6-Hydroxy-4,5-isopropylidenedioxy-3-(R/S)-tetrahydropyranyloxy-2-[(4-toluenesulfonyl)amino]-hexanoate (**5a**): To a solution of **4a** (517 mg, 0.76 mmol) in 3 ml of THF a solution of TBAF (1 M in THF, 1.3 ml) was added at room temp. After 2 h, the reaction mixture was diluted with diethyl ether (20 ml) and was washed with saturated $NaHCO_3$ and brine (20 ml each). The organic layer was dried with Na_2SO_4, and the solvent was evaporated in vacuo. After flash chromatography [hexanes/ethyl acetate (2% NEt_3), 7:3, 1:1], **5a** was obtained as a colorless oil (271 mg, 63%). − $[\alpha]_D^{20}$ = +1.8 (*c* = 2.7, $CHCl_3$). − HPLC (*n*-hexane/2-propanol, 7:3): t_R(**5a,a′**) = 11.74 min. − ^{1}H NMR ($CDCl_3$): δ = 1.23, 1.31, 1.34, 1.35 (4 s, 6 H), 1.20−1.80 (m, 6 H), 2.00 (m_c, 1 H), 2.35, 2.37 (2 s, 3 H), 3.00−3.20 (m, 1 H), 3.50−3.80 (m, 4 H), 3.85−4.05 (m, 2 H), 4.05−4.20 (m, 1 H), 4.30−4.40 (m, 1 H), 4.93 (d, *J* = 12.4 Hz, 0.5 H), 5.00 (s, 1 H), 5.02 (d, *J* = 12.4 Hz, 0.5 H), 5.34 (d, *J* = 10.7 Hz, 0.5 H), 5.55 (d, *J* = 9.9 Hz, 0.5 H), 7.15 (d, *J* = 8.3 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1 H), 7.24−7.34 (m, 5 H), 7.71 (d, *J* = 8.3 Hz, 1 H), 7.72 (d, *J* = 8.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 21.01, 21.16, 21.50, 24.63, 24.71, 26.90, 27.00, 30.81, 30.88, 56.62, 57.12, 63.37, 63.73, 64.96, 65.32, 67.30, 67.42, 74.66, 75.32, 78.24, 80.46, 80.51, 80.58, 100.22, 102.50, 109.39, 109.60, 127.23, 128.03, 128.27, 128.47, 128.65, 128.77, 129.30, 129.43, 134.87, 135.23, 137.43, 137.83, 143.08, 143.38, 169.90, 170.37. − HRMS (FAB) $C_{28}H_{37}NO_9S$ [M^+]: calcd. 563.2189; found 563.2203. − MS (FAB); *m/z* (%): 586 [M^+ + Na] (29), 563 [M^+] (1), 547 (27), 503 (26), 480 (100), 422 (84).

Benzyl (2R,3S,4S,5S)-6-Hydroxy-4,5-isopropylidenedioxy-3-(R/S)-tetrahydropyranyloxy-2-[(4-toluenesulfonyl)amino]hexanoate (**5b**): According to the synthesis of **5a** treatment of **4b** (74 mg, 0.11 mmol) with TBAF (1 M in THF, 186 µl) yielded after flash chromatography [hexanes/ethyl acetate (2% NEt_3), 7:3, 1:1] **5b** as a colorless oil (46 mg, 75%). − $[\alpha]_D^{20}$ = −15.5 (*c* = 1.2, $CHCl_3$). − HPLC (hexane/2-propanol, 7:3): t_R(**5b**) = 10.78 min; t_R(**5b′**) = 12.70 min. − ^{1}H NMR ($CDCl_3$): δ = 1.23, 1.29, 1.32 (3 s, 6 H), 1.30−1.80 (m, 6 H), 2.00 (m_c, 1 H), 2.37 (s, 1.5 H), 2.38 (s, 1.5 H), 3.45−3.55 (m, 1.5 H), 3.60−3.70 (m, 1 H), 3.70−4.00 (m, 3.5 H), 4.05−4.15 (m, 0.5 H), 4.24 (dd, *J* = 9.2, 2.2 Hz, 0.5 H), 4.30−4.40 (m, 0.5 H), 4.45−4.55 (m, 1 H), 4.68 (dd, *J* = 6.6, 2.2 Hz, 0.5 H), 4.90 (d, *J* = 12.2 Hz, 0.5 H), 4.96 (s, 1 H), 5.01 (d, *J* = 12.2 Hz, 0.5 H), 5.40−5.50 (m, 0.5 H), 6.57 (d, *J* = 9.9 Hz, 0.5 H), 7.15−7.35 (m, 7 H), 7.68 (d, *J* = 8.4 Hz, 1 H), 7.69 (d, *J* = 8.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 20.04, 20.55, 21.51, 24.71, 25.05, 26.58, 26.95, 27.01, 27.08, 30.55, 30.84, 56.99, 57.31, 63.35, 63.71, 64.46, 64.56, 66.98, 67.58, 75.45, 75.56, 78.26, 81.22, 85.75, 98.35, 102.25, 109.65, 110.00, 127.15, 127.21, 128.17, 128.25, 128.40, 128.49, 128.52, 129.45, 129.56, 134.78, 135.25, 136.88, 137.82, 143.13, 143.53, 167.97, 168.61. − HRMS (FAB) $C_{28}H_{37}NO_9SNa$ [M^+ + Na]: calcd. 586.2087; found 586.2083. − MS (FAB); *m/z* (%): 586 [M^+ + Na] (4), 563 [M^+] (1), 547 (42), 503 (38), 480 (22), 459 (30), 422 (30), 415 (22).

Benzyl (2S,3S,4S,5S)-4,5-Isopropylidenedioxy-3-(R/S)-tetrahydropyranyloxy-N-(4-toluenesulfonyl)pipecolate (**6a**): PPh_3 (46 mg, 0.18 mmol) was added at room temp. to a solution of **5a** (100 mg, 0.18 mmol) in 10 ml of THF. Subsequently, DEAD (25 µl, 0.16 mmol) was added dropwise as slow as possible. After complete addition, the mixture was stirred for 30 min, before the solvent was evaporated in vacuo. The residue was stirred with hexanes/ethyl acetate (9:1) and the residue was filtered off. After flash chromatography [hexanes/ethyl acetate (2% NEt_3), 8:2], **6** (37 mg, 38%) was obtained as a colorless oil. − $[\alpha]_D^{20}$ = +27.8 (*c* = 0.3, $CHCl_3$). − HPLC (*n*-hexane/2-propanol, 85:15): t_R(**6a**) = 15.64 min; t_R(**6a′**) = 21.15 min. − ^{1}H NMR ($CDCl_3$): δ = 1.32, 1.38, 1.39, 1.54 (4 s, 6 H), 1.30−1.70 (m, 5.5 H), 2.38 (s, 3 H), 3.35−3.65 (m, 3.5 H), 3.78 (m_c, 0.5 H), 3.85−4.00 (m, 1 H), 4.15 (m_c, 0.5 H), 4.25−4.30 (m, 1 H), 4.70−4.85 (m, 3 H), 4.85−4.95 (m, 0.5 H), 5.00−5.10 (m, 1.5 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 7.20−7.40 (m, 5 H), 7.62 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 17.81, 18.03, 21.58, 25.22, 25.31, 26.58, 26.66, 27.08, 27.15, 29.80, 48.35, 48.64, 59.20, 60.78, 60.78, 61.75, 65.57, 66.99, 67.21, 67.82, 68.89, 77.46, 78.15, 97.23, 97.94, 112.25, 127.36, 127.30, 128.17, 128.25, 128.52, 128.62, 129.65, 134.90, 135.04, 137.05, 143.83, 167.94, 168.31. − HRMS (FAB) $C_{28}H_{35}NO_8SNa$ [M^+ + Na]: calcd. 568.1981; found 568.1994. − MS (FAB); *m/z* (%): 568 [M^+ + Na] (13), 546 [M^+] (2), 462 (26), 404 (75), 281 (31), 207 (30).

Benzyl (2R,3S,4S,5S)-4,5-Isopropylidenedioxy-3-(R/S)-tetrahydropyranyloxy-N-(4-toluenesulfonyl)pipecolate (**6b**): According to the synthesis of **6a**, stereoisomer **5b** and the epimeric mixture **5a**, **b** as well (710 mg, 1.26 mmol each) were treated with PPh_3 (761 mg, 2.90 mmol) and DEAD (436 µl, 2.77 mmol). After flash chro-

matography [hexanes/ethyl acetate (2% NEt_3), 7:2], **6b** (633 mg, 92%) was obtained as a colorless oil. − $[\alpha]_D^{20}$ = +42.6 (*c* = 0.7, $CHCl_3$). − HPLC (*n*-hexane/2-propanol, 85:15): t_R(**6b**) = 19.42 min; t_R(**6b′**) = 20.51 min. − ^{1}H NMR ($CDCl_3$): δ = 1.28, 1.31, 1.32, 1.39 (4 s, 6 H), 1.45−1.90 (m, 6 H), 2.38, 2.39 (2 s, 3 H), 3.15−3.30 (m, 2 H), 3.45−3.60 (m, 1 H), 3.75−3.85 (m, 0.5 H), 3.85−4.00 (m, 0.5 H), 3.95−4.10 (m, 2 H), 4.75−4.85 (m, 1 H), 4.85−4.95 (m, 1 H), 4.95−5.05 (m, 1 H), 5.05−5.20 (m, 2 H), 7.20−7.40 (m, 7 H), 7.66 (d, *J* = 8.3 Hz, 1 H), 7.75 (d, *J* = 8.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 18.28, 18.89, 21.48, 25.35, 25.38, 26.35, 26.39, 26.51, 26.63, 30.05, 30.30, 46.55, 58.85, 60.99, 61.61, 62.38, 67.49, 68.94, 69.02, 70.09, 71.52, 78.37, 79.12, 95.27, 99.58, 110.64, 110.67, 127.19, 127.50, 128.13, 128.27, 128.49, 128.58, 128.63, 129.37, 129.49, 134.88, 135.04, 137.11, 143.36, 143.42, 168.51, 168.65. − HRMS (FAB) $C_{28}H_{36}NO_8S$ [M^+ + H]: calcd. 546.2162; found 546.2164. − $C_{28}H_{35}NO_8S$ (545.65): calcd. C 61.63, H 6.46, N, 2.57; found: C 61.48, H 6.46, N 2.51.

(2S,3S,4R,5S)-3,4,5-Trihydroxy-2-(hydroxymethyl)piperidine (**8b**): A solution of **6b** (120 mg, 0.22 mmol) and Red-Al© (70% in toluene, 0.77g, 2.66 mmol)) in 3 ml of THF was refluxed for 4 h. The solution was cooled to 0°C, before 2 ml of 15% NaOH was added carefully. The aqueous phase was extracted twice with diethyl ether (5 ml each). The combined organic extracts were washed with brine (5 ml), dried with Na_2SO_4, and the solvent was evaporated in vacuo. To a solution of the resulting yellow oil in 5 ml of methanol Dowex 50W×8 (50 mg) was added. After refluxing and stirring for 1 h, the resin was washed with methanol and water. Subsequently, the product was eluted from the resin with 2 N NH_4OH. The aqueous solution was concentrated in vacuo, before toluene was added. The solution was concentrated to dryness, giving rise to **8b** (16 mg, 44%) as a colorless oil. − $[\alpha]_D^{20}$ = −34.6 (*c* = 0.3, H_2O). − ^{1}H NMR (D_2O): δ = 2.71 (dd, *J* = 14.3, 3.0 Hz, 1 H), 2.76 (ddd, *J* = 9.6, 4.8, 4.4 Hz, 1 H), 2.89 (dd, *J* = 14.0, 2.2 Hz, 1 H), 3.67 (dd, *J* = 9.2, 4.8 Hz, 1 H), 3.69 (dd, *J* = 9.0, 4.4 Hz, 1 H), 3.75 (dd, *J* = 9.6, 2.9 Hz, 1 H), 3.82 (ddd, *J* = 3.7, 2.9, 2.2 Hz, 1 H), 3.86 (dd, *J* = 3.7, 3.3 Hz, 1 H), 4.75 (s, 5H). − ^{13}C NMR (D_2O): δ = 45.47, 56.54, 61.75, 67.08, 70.29, 71.58. − HRMS (FAB) for $C_6H_{13}NO_4$ [M^+ + H]: calcd. 164.0923; found 164.0937. − MS (FAB); *m/z* (%): 164 [M^+] (100), 136 (16).

Benzyl (2S,3S,4S,5S)-3,4,5-Trihydroxy-N-(4-toluenesulfonyl)pipecolate (**9a**): To a solution of **6a** (37 mg, 0.07 mmol) in 2 ml of methanol a catalytic amount of 4-toluenesulfonic acid was added. After stirring for 24 h, $NaHCO_3$ was added. The solution was filtered and the solvent was evaporated in vacuo. Flash chromatography [hexanes/ethyl acetate, 2:8] afforded **9a** (13 mg, 45%) as a colorless oil. − $[\alpha]_D^{20}$ = −14.5 (*c* = 0.4, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 2.38 (s, 3 H), 3.54 (dd, *J* = 14.7, 1.5 Hz, 1 H), 3.60 (dd, *J* = 14.3, 1.8 Hz, 1 H), 3.93 (ddd, *J* = 4.0, 1.8, 1.5 Hz, 1 H), 3.96 (dd, *J* = 4.0, 1.8 Hz, 1 H), 4.28 (dd, *J* = 6.6, 1.8 Hz, 1 H), 4.85 (d, *J* = 6.6 Hz, 1 H), 4.98 (d, *J* = 12.1 Hz, 1 H), 5.09 (d, *J* = 12.1 Hz, 1 H), 7.13 (d, *J* = 8.1 Hz, 2 H), 7.16−7.20 (m, 2 H), 7.30−7.32 (m, 3 H), 7.62 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 21.52, 43.49, 55.08, 67.73, 67.76, 68.62, 71.23, 127.28, 127.91, 128.36, 128.57, 128.66, 129.55, 134.49, 136.45, 143.65, 170.78. − HRMS (FAB) $C_{20}H_{24}NO_7S$ [M^+ + H]: calcd. 422.1273; found 422.1321. − MS (FAB); *m/z* (%): 444 [M^+ + Na] (5), 422 [M^+ + H] (10), 391 (25), 384 (9), 286 (66), 147 (100).

Benzyl (2R,3S,4S,5S)-3,4,5-Trihydroxy-N-(4-toluenesulfonyl)pipecolate (**9b**): According to the synthesis of **9a**, **6b** (100 mg, 0.19 mmol) was treated with 4-toluenesulfonic acid. Flash chromatography [hexanes/ethyl acetate, 2:8] afforded **9b** (34 mg, 43%) as a colorless oil. − $[\alpha]_D^{20}$ = +29.0 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 2.29 (s, 3 H), 2.89 (dd, *J* = 12.6, 11.0 Hz, 1 H), 3.44 (dd, *J* = 9.7, 2.9 Hz, 1 H), 3.79 (dd, *J* = 12.1, 5.1 Hz, 1 H), 3.95 (ddd, *J* = 11.0, 9.7, 5.1 Hz, 1 H), 4.49 (dd, *J* = 2.9, 2.6 Hz, 1 H), 4.86 (d, *J* = 12.1 Hz, 1 H), 4.92−4.94 (m, 1 H), 5.00 (d, *J* = 12.1 Hz, 1 H), 7.04 (d, *J* = 8.5 Hz, 2 H), 7.10−7.18 (m, 2 H), 7.21−7.28 (m, 3 H), 7.60 (d, *J* = 8.5 Hz, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 21.47, 46.45, 61.04, 66.37, 67.50, 69.51, 73.00, 127.27, 127.43, 128.21, 128.39, 128.54, 129.43, 134.86, 136.33, 143.40, 168.13. − HRMS (FAB) $C_{20}H_{24}NO_7S$ [M^+ + H]: calcd. 422.1273, found 422.1255. − MS (FAB); *m/z* (%): 444 [M^+ + Na] (6), 422 [M^+ + H] (33), 286 (23), 138 (100).

Benzyl (2RS,3S,4S,5S)-3,6-Dihydroxy-4,5-isopropylidenedioxy-2-[(4-toluenesulfonyl)amino]hexanoate (**10a**, **b**): A solution of TBAF (1 M in THF, 0.96 ml, 0.96 mmol) was added to a solution of **3a**, **b** (284 mg, 0.48 mmol) in 5 ml of THF. After complete cleavage of the protecting group (2−3 h), the reaction mixture was diluted with diethyl ether (20 ml) and was washed with sat. $NaHCO_3$ solution and brine (30 ml each). The organic layer was dried with Na_2SO_4, and the solvent was evaporated in vacuo. After flash chromatography [hexanes/ethyl acetate, 3:7], a pale yellow oil (163 mg, 77%) was obtained as a mixture of diastereomers. −^{1}H NMR ($CDCl_3$): δ = 1.23, 1.25, 1.29, 1.35 (4 s, 6 H), 2.38 (s, 1.5 H), 2.40 (s, 1.5 H), 3.63−3.88 (m, 3 H), 3.90−4.10 (m, 2 H), 4.18 (d, *J* = 2.4 Hz, 0.5 H), 4.34 (d, *J* = 1.8 Hz, 0.5 H), 4.93 (d, *J* = 12.2 Hz, 0.5 H), 4.94 (d, *J* = 12.1 Hz, 0.5 H), 5.00 (d, *J* = 12.2 Hz, 0.5 H), 5.06 (d, *J* = 12.1 Hz, 0.5 H), 7.17−7.26 (m, 4 H), 7.32−7.34 (m, 3 H), 7.71 (d, *J* = 8.4 Hz, 1 H), 7.72 (d, *J* = 8.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 21.54, 21.60, 26.61, 26.72, 26.84, 57.82, 58.95, 62.98, 67.52, 67.73, 73.67, 74.40, 77.10, 77.70, 79.78, 81.04, 109.62, 109.66, 127.28, 127.37, 128.11, 128.21, 128.44, 128.57, 128.61, 129.50, 129.80, 134.64, 135.03, 135.83, 137.20, 143.42, 144.02, 168.20, 170.41. − HRMS (FAB) $C_{23}H_{30}NO_8S$ [M^+ + H]: calcd. 480.1692, found 480.1709. − MS (FAB); *m/z* (%): 502 [M^+ + Na] (16), 480 [M^+ + H] (36), 459 (17), 422 (33), 415 (29), 371 (29).

Pipecolinic Acid Derivatives **11b** *and* **12**: According to the synthesis of **6a** the epimeric mixture **10a**, **b** (150 mg, 0.31 mmol) was treated with PPh_3 (122 mg, 0.47 mmol) and DEAD (70 µl, 0.44 mmol). A mixture of the pipecolinic acid derivatives **11b** and **12** was obtained, which could easily be separated by flash chromatography [hexanes/ethyl acetate 8:2].

11b: Yield 57 mg (40%), colorless oil. − $[\alpha]_D^{20}$ = +28.1 (*c* = 2.2, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 3 H), 1.38 (s, 3 H), 2.40 (s, 3 H), 2.49 (bs, 1 H), 3.21 (dd, *J* = 9.4, 2.2 Hz, 1 H), 3.26 (dd, *J* = 11.8, 11.0 Hz, 1 H), 3.81 (ddd, *J* = 11.0, 9.6, 4.8 Hz, 1 H), 4.11 (dd, *J* = 11.8, 4.8 Hz, 1 H), 4.80 (dd, *J* = 2.2, 1.9 Hz, 1 H), 5.05 (d, *J* = 12.2 Hz, 1 H), 5.08 (d, *J* = 1.9 Hz, 1 H), 5.17 (d, *J* = 12.2 Hz, 1 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 7.26−7.34 (m, 5 H), 7.72 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 21.53, 26.49, 26.60, 46.54, 61.52, 67.64, 67.67, 68.54, 78.90, 110.87, 127.47, 127.60, 128.28, 128.70, 129.53, 134.85, 136.75, 143.60, 168.40. − HRMS (FAB) $C_{23}H_{28}NO_7S$ [M^+ + H]: calcd. 462.1586, found 462.1589. − MS (FAB); *m/z* (%): 484 [M^+ + Na] (6), 462 [M^+ + H] (6), 404 (12), 391 (10), 329 (14), 289 (20).

12: Yield 41 mg (30%), colorless oil. − $[\alpha]_D^{20}$ = +3.9 (*c* = 0.7, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.30 (s, 3 H), 1.36 (s, 3 H), 2.42 (s, 3 H), 3.35−3.60 (m, 3 H), 3.71 (m_c, 1 H), 5.26 (s, 2 H), 6.57 (d, *J* = 1.8 Hz, 1 H), 7.23−7.33 (m, 5H), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.77 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 21.60, 26.48, 26.63, 45.77, 67.67, 75.38, 77.09, 113.98, 125.00, 127.92, 128.40, 128.53, 128.58, 129.75, 130.81, 134.44, 135.38, 144.51, 163.88. − HRMS (FAB) $C_{23}H_{25}NO_6SNa$ [M^+ + Na]: calcd. 466.1301, found

466.1318. – MS (FAB); *m/z* (%): 466 [M^+ + Na] (1), 444 [M^+ + H] (8), 438 (13), 135 (6), 415 (26).

☆ Dedicated to Prof. *W. Steglich* on the occasion of his 65th birthday.

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[26] Introduction of the THP protecting group results in the generation of a new stereogenic center (1:1) and therefore a second set of diastereomers (second set of signals in the NMR spectra). In the experimental section these diastereomers are reported as **4a**, **4a′**; **4b**, **4b′** and so on. Because this chiral center has no influence on the stereochemical outcome of the reactions described, and because the protecting group is removed at the end of the synthesis, the THP protecting group is treated as an achiral protecting group in the context.

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