Short Syntheses of Polyhydroxylated α-Alkylated Amino Acids†

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Introduction

Polyhydroxylated amino acids are an important class of natural products (Figure 1). Polyoxamic acid is part of many polyoxines, which are potent antifungal agents.[1] Polyhydroxylated amino acids are also substructures of the sphingofungines, another family of antifungal compounds.[2] Among them, α-alkylated amino acids are important as well. Myriocin,[3] for example, shows very high immunosuppressive activity. In addition, polyhydroxylated amino acids are valuable tools in the design of polyhydroxylated piperidine alkaloids.[2b,4]

For some time, our group has been interested in reactions of metal-chelated enolates of N-protected amino acid esters.[5] Depending on the metal salt used, these chelated enolates show higher stability than the corresponding lithium enolates. In addition, because of the fixed enolate geometry, their reactions are more selective than those of the lithium enolates. Besides chelate enolate Claisen rearrangements, aldol reactions give especially good results.[6] 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.[7] 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 to cleave 2-(trimethylsilyl)ethanesulfonyl (SES) protecting group, developed by Weinreb et al.,[8] can be used.[7]

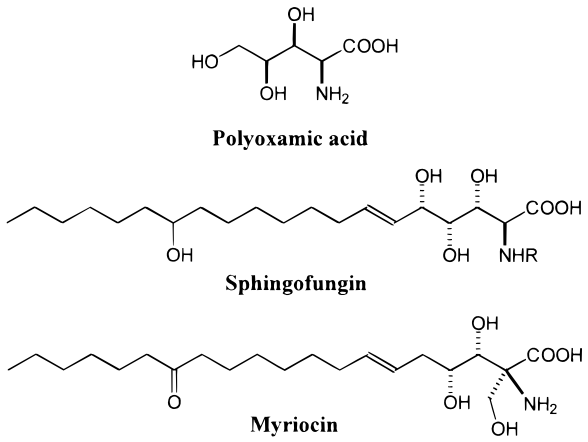

Figure 1. Naturally occurring polyhydroxylated amino acids.

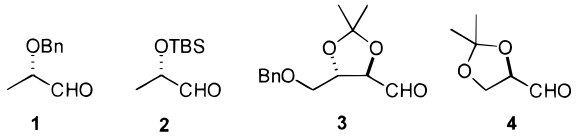

Figure 2. Chiral aldehydes used in asymmetric aldol reactions.

Results and Discussion

Herein, we present the results of an asymmetric version of this reaction.[9] In addition to auxiliary controlled reactions, especially the use of chiral aldehydes is suitable for this purpose.[10] In aldol reactions of chiral α-alkoxy or α-siloxy aldehydes (Figure 2), an induction on the newly formed chiral center in general is observed, and this chirality transfer should be used in the synthesis of optically active polyhydroxylated amino acids.

Deprotonation of N-protected alanine esters (**5** and **6**) with LDA at −78 °C and subsequent addition of metal salts presumably results in the formation of a chelated enolate (Scheme 1), which can be trapped with a chiral aldehyde (**1**−**4**).

Depending on the metal salt used, two aldol products, out of the four possible stereoisomers, were formed preferentially (Table 1). The best results by far were obtained with >2 equiv of tin chloride (Table 1, entries 3, 4, 6, and 7). In comparison to reactions with less than 2 equiv of metal salt (Table 1, entries 2 and 5), the selectivity in the aldol addition is dramatically increased. This is, in general, true for the simple diastereoselectivity (relation **a**/**b**) and the induced diastereoselectivity (ds) of the aldol products **a** and **b** as well. This is in good agreement with observations made earlier.[7] In comparison, other metal salts such as zinc chloride react less selectively, and the four stereoisomers were formed in comparable amounts. Therefore, the zinc enolates were used to obtain a mixture of all possible isomers for analytical purposes.[11] The simple diastereoselectivities observed were nearly independent of the aldehyde employed in the aldol reaction, and the highly oxygenated

† Dedicated to Prof. R. W. Hoffmann on the occasion of his 65th birthday.

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(11) The product mixtures were analyzed by HPLC and NMR.

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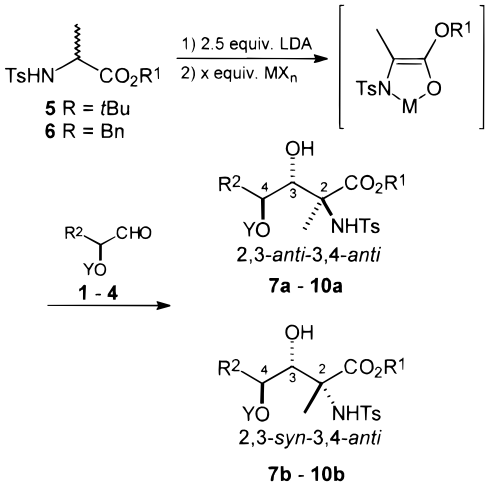
Table 1. Aldol Reactions of Metal Enolates of Ts-alanine Esters 5 and 6 with the Aldehydes 1−4

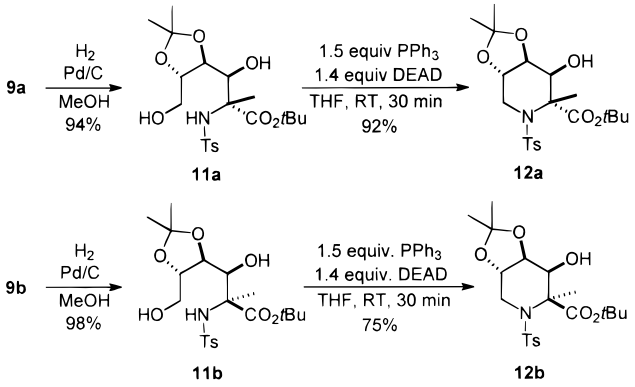
entry	aldehyde	ester	MX_n (equiv)	product	**a**:**b**[a]	**a** (% ds)	**b** (% ds)	yield (%)
1	**1**	**5**	$ZnCl_2$ (2.5)	**7**	55:45	58	15	
2	**1**	**5**	$SnCl_2$ (1.2)	**7**	59:41	66	90	
3	**1**	**5**	$SnCl_2$ (2.5)	**7**	81:19	95	74	88
4	**2**	**6**	$SnCl_2$ (2.5)	**8**	89:11	>99	82	85
5	**3**	**5**	$SnCl_2$ (1.2)	**9**	67:33	76	>99	
6	**3**	**5**	$SnCl_2$ (2.5)	**9**	78:22	95	>99	90
7	**4**	**6**	$SnCl_2$ (2.5)	**10**	80:20	94	>99	87

[a] Based on HPLC of the crude reaction mixture.

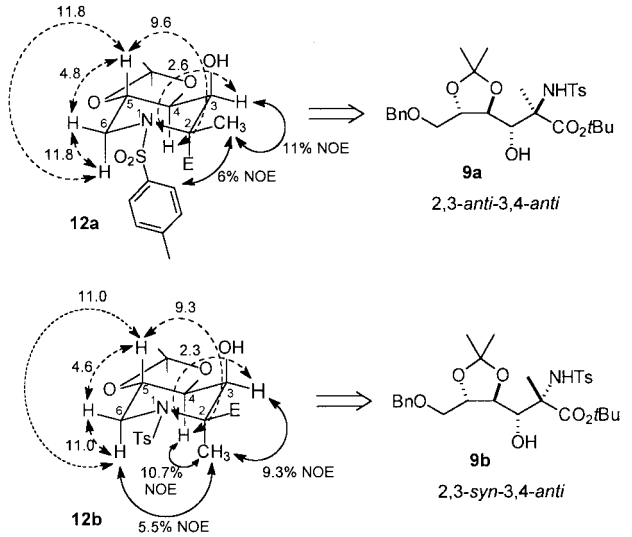
Scheme 1



Scheme 2



Scheme 3



aldehydes **3** and **4** in particular showed excellent induced selectivities.

Therefore, and with respect to the good yields obtained, this procedure allows a straightforward and highly stereoselective synthesis of α-alkylated polyhydroxylated amino acids.[12] These amino acids can also be used for the construction of cyclic oxygenated amino acids such as prolines or pipecolinic acid, interesting classes of potential glycosidase inhibitors.[9] This was one reason we decided to convert the aldol product **10** into the corresponding pipecolinic acid derivative. The other reason was the necessity to confirm the configuration of our products and to determine the selectivities observed. For this purpose, the pipecolinic acid derivatives are especially suitable. Due to the chair conformation, it should be relatively easy to reliably determine the orientation of the substituents by NMR.

Starting from the crude aldol product **9**, diastereomerically pure **9a** could be obtained by a single crystallization step. The pure minor diastereomer **9b** could be obtained from the mother liquid by flash chromatography. After cleavage of the benzyl ether, the alcohol **11a** obtained was first converted into the corresponding mesylate.[2b] Unfortunately, this derivative was not a suitable precursor for the required cyclization. Therefore, the alcohols **11a** and **11b** were subjected directly to the Mitsunobu reaction,[13] which gave the tosylated[14] pipecolinic acid derivatives **12a** and **12b**, respectively, in good to excellent yields (Scheme 2).[15]

These cyclic derivatives could also be used to determine the configuration of the two new stereogenic centers formed in the aldol reaction. Scheme 3 shows the coupling constants (in Hz) and the NOEs observed.

The configuration of the *β*-hydroxy group was confirmed from the coupling constant of the hydrogen at C3 to the adjacent proton at C4. Because of the ketal moiety, this proton has to be oriented in an axial position. Coupling constants of 2.3 and 2.6 Hz, respectively, are typical for protons in an axial/equatorial orientation. Therefore, the hydroxy groups in **12a** and **12b** as well are oriented in an axial position. This clearly indicates that the induced diastereoselectivity in the aldol reaction was excellent and that both diastereomers obtained have different configurations at the α-position (C2) (simple diastereomers). This was also confirmed by NOE experiments.

(12) In contrast, reaction of glycin enolates gave a 1:1 diastereomeric mixture at the α center, probably because of epimerization under the reaction conditions used.

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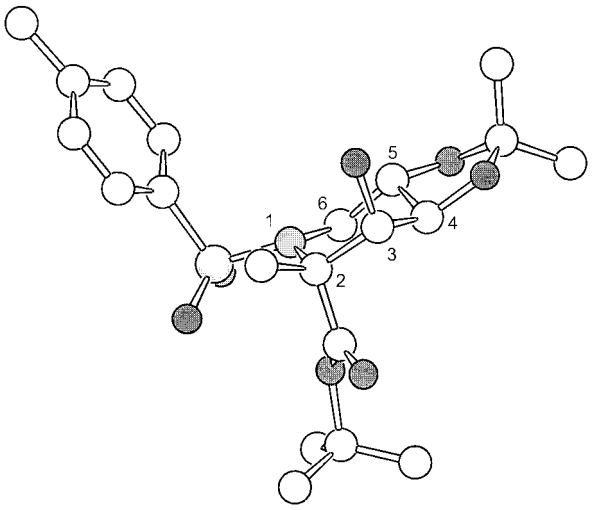

Figure 3. Crystal structure of pipecolic acid derivative **12a**.

Table 2. Bond Angles of Nitrogen and Its NeighborIng Atoms in Pipecolic Acid Derivative 12a

	bond angle (deg)
C6−N−C2	118.9(0.1)
S−N−C2	121.1(0.1)
S−N−C6	113.5(0.1)

Irradiation into the α-methyl group of **12a** gave two NOEs, one to the vicinal equatorial β-H (C3) and the second to an aromatic proton in the ortho position of the tosyl group. In the same experiment, **12b** showed three NOEs. Interactions are observed to the axially oriented protons at C4 and C6 and to the β hydrogen as well. This can be explained by an axial orientation of the methyl group in **12b**, while in **12a** the methyl group is orientated in the equatorial position.

The configuration of this pipecolinic acid derivative (**12a**) could also be confirmed by X-ray structure analysis (Figure 3).[16] The pseudo planar environment of the nitrogen atom (Table 2) leads to a torsion angle between the sulfonyl group and the methyl substituent at C2 of 45°. The expectable interactions between these two groups results in a bond angle at nitrogen 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.

These results allow the determination of the 2,3-anti-3,4-anti configuration for the major aldol product **9a** and the 2,3-syn-3,4-anti configuration for the minor diastereomer **9b**. The 2,3-anti-3,4-anti diastereomer as the major aldol product is in accordance with the Felkin−Anh model.[17] The configuration of the other aldol products was confirmed by comparison of the corresponding NMR spectra. Comparable shifts for the signals of the protons and the substituents at the α- and β-positions were observed in the ^{1}H NMR spectra (Table 3). The same trends were also observed in the ^{13}C NMR spectra.

Table 3. Selected ^{1}H NMR and ^{13}C NMR Signals (ppm) of Aldol Products 7−10

	7		8		9		10	
	a	b	a	b	a	b	a	b
C*H*$_3$	1.21	1.40	1.34	1.49	1.32	1.43	1.29	1.48
O*H*	3.46	2.57	3.27	2.67	3.65	3.62	3.53	2.63
N*H*	6.09	6.15	6.02	5.91	6.07	5.92	6.15	5.87
*C*H$_3$	20.45	18.11	20.48	18.99	19.53	17.40	19.56	17.01
α-*C*	64.82	64.62	64.63	63.60	65.57	65.44	64.91	64.27
β-*C*	79.18	77.71	79.82	78.64	79.98	79.00	77.44	75.16
γ-*C*	76.35	76.41	70.90	69.40	77.15	77.09	75.47	172.21
C=O	171.49	172.17	172.52	172.69	170.64	171.40	171.97	172.21

Conclusion

In summary, we have shown that aldol reactions of tosylated amino acid ester enolates with chiral aldehydes give rise to polyhydroxylated amino acid esters in a straightforward and highly stereoselective fashion. α-Alkylated pipecolinic acid esters can be obtained via cyclization under Mitsunobu conditions. In these derivatives, strong interactions between the tosyl protecting group and substituents at the α-position are observed. The question if these sterical interactions can be used as stereocontrolling elements is currently under investigation.

Experimental Section

General Procedure. General procedures and methods for characterization have been described previously.[18] ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (if not noted otherwise) on a Bruker AC-200 or AC-300 spectrometer, respectively. Diastereomeric ratios were determined by analytical HPLC using a Knauer Eurosphere column (250 × 4 mm, Si80, 5 μm, flow; 2 mL/min) or a Daicel Chiralcel OD-H column. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. The aldehydes used in the aldol reactions were prepared according to the literature.

X-ray Crystal and Intensity Data. A colorless crystal of size 0.5 × 0.46 × 0.35 mm of compound **12a** was mounted and aligned on a Siemens CCD diffractometer. Crystal data: orthorhombic; a = 11.1402(2) Å, b = 11.4909(2) Å, c = 18.0835(4) Å; space group $P2_12_12_1$, V = 2314.9(1) Å^3, Z = 4. Intensity data in the 2θ range 4.20−51.02° were collected using the ω scan with Mo Kα radiation (λ = 0.710 73 Å). A total of 3882 reflections were collected, of which 3704 have shown $I > 2\sigma(I)$.

All crystallographic calculations were carried out with the aid of the Siemens SHELXTL program package. The positional and anisotropic thermal parameters were refined for all non-hydrogen atoms. The hydrogens were refined isotropically. For the observed data final R = 2.47%, Rw(F^2) = 6.0%, goodness of fit = 1.05.

(±)-*tert*-Butyl 2-[(4-toluenesulfonyl)amino]propanoate (5). A solution of (±)-*tert*-butyl 2-[(4-benzyloxycarbonyl)amino-]propanoate[19] (5 g, 18 mmol) in THF was hydrogenated in the presence of 70 mg of 10% Pd/C for 24 h. The mixture was filtered, and NEt_3 was added, followed by 4-toluenesulfonyl chloride at 0 °C. After 5 h, the mixture was washed with 1 N HCl and saturated $NaHCO_3$ solution. The combined organic extracts were dried over Na_2SO_4, and the solvent was evaporated. Flash chromatography (hexanes/ethyl acetate 8:2, 7:3) yielded 4.4 g (81%) of a colorless solid, which was crystallized from dichloromethane/hexanes: mp 88−89 °C; ^{1}H NMR δ 1.27 (s, 9H), 1.34 (d, J = 7.1 Hz, 3H), 2.39 (s, 3H), 3.84 (dq, J = 8.6, 7.2 Hz, 1H), 5.22 (d, J = 8.6 Hz, 1H), 7.27 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 20.07, 21.43, 27.65, 51.97, 82.34, 127.27, 129.62, 137.00, 143.48, 171.30. Anal. Calcd for $C_{14}H_{21}NO_4S$ (299.39): C, 56.16; H, 7.07; N, 4.68. Found: C, 56.24; H, 7.06; N, 4.61.

(16) The authors have deposited X-ray structure data at the Cambridge Cystallographic Data Centre. These data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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General Procedure for Aldol Reactions. In a typical experiment, a solution of 1 mmol of LDA in 2 mL of anhydrous THF was added at −78 °C under argon to a solution of 0.4 mmol of N-tosylated amino acid ester and 190 mg (1 mmol) of $SnCl_2$ in 2 mL of THF. In general, a clear orange solution was formed. After 10 min, a solution of 0.48 mmol of the aldehyde in 1 mL of THF was added. After 30 min at −78 °C, the reaction was quenched by adding phosphate buffer pH 7. The mixture was diluted with diethyl ether and was allowed to warm to rt. After filtration of the mixture through a pad of Celite, the aqueous phase was extracted twice with diethyl ether. The combined organic extracts were washed with brine and dried over Na_2SO_4, and the solvent was evaporated. The crude aldol product was purified by flash chromatography.

***tert*-Butyl 4-(Benzyloxy)-3-hydroxy-2-methyl-2-[(4-toluenesulfonyl)amino]pentanoate (7).** According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine *tert*-butyl ester (**5**) (268 mg, 0.80 mmol) with aldehyde **1**[20] (158 mg, 0.96 mmol) yielded after flash chromatography (hexanes/ethyl acetate 8:2) a mixture of the two major diastereomers (**7a** and **7b**) (328 mg, 88%), which could be separated by flash chromatography (hexanes/ethyl acetate, 85:15).

7a: colorless solid, which was crystallized from dichloromethane/hexanes; mp 83−84 °C; [α] +51.1 (*c* = 0.4, $CHCl_3$); ^{1}H NMR *δ* 1.21 (s, 3H), 1.23 (s, 9H), 1.34 (d, *J* = 5.4 Hz, 3H), 2.42 (s, 3H), 3.46 (d, *J* = 12.4 Hz, 1H), 3.64−3.80 (m, 2H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), 6.09 (s, 1H), 7.27−7.36 (m, 7H), 7.76 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR *δ* 17.22, 20.45, 21.50, 27.59, 64.82, 71.57, 76.35, 79.18, 82.95, 126.73, 127.77, 128.23, 128.93, 129.67, 137.91, 139.95, 143.31, 171.49; HRMS (FAB) calcd for $C_{24}H_{33}NO_6SNa$ [M^+ + Na] 486.1926, found 486.1900. Anal. Calcd for $C_{24}H_{33}NO_6S$ (463.59): C, 62.17; H, 7.18; N, 3.02. Found: C, 62.38; H, 7.12; N, 2.90.

7b: colorless oil; [α] +24.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR *δ* 1.28 (d, *J* = 5.8 Hz, 3H), 1.40 (s, 3H), 1.41 (s, 9H), 2.37 (s, 3H), 2.57 (bs, 1H), 3.60−3.70 (m, 2H), 4.43 (d, *J* = 11.2 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 6.15 (s, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.24−7.37 (m, 5H), 7.71 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR *δ* 16.07, 18.11, 21.45, 27.79, 64.62, 70.78, 76.41, 77.71, 83.04, 127.03, 127.88, 128.00, 128.50, 129.37, 137.57, 140.04, 142.93, 172.17; HRMS (FAB) calcd for $C_{24}H_{34}NO_6S$ [M^+ + H] 464.2106, found 464.2137.

Benzyl 4-*O*-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-2-methyl-2-[(4-toluenesulfonyl)amino]pentanoate (8). According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (**6**) (134 mg, 0.40 mmol) with aldehyde **2**[21] (106 mg, 0.48 mmol) yielded **8** (167 mg, 85%). The diastereomers were separated by flash chromatography (hexanes/ethyl acetate 85:15).

8a: colorless oil; [α] +69.6 (*c* = 1.9, $CHCl_3$); ^{1}H NMR *δ* 0.12, 014 (2s, 6H), 0.89 (s, 9H), 1.31 (d, *J* = 6.1 Hz, 3H), 1.34 (s, 3H), 2.41 (s, 3H), 3.27 (d, *J* = 11.6 Hz, 1H), 3.71 (dd, *J* = 11.6, 8.0 Hz, 1H), 3.98 (dq, *J* = 8.0, 6.1 Hz, 1H), 5.07 (d, *J* = 12.3 Hz, 1H), 5.17 (d, *J* = 12.3 Hz, 1H), 6.02 (s, 1H), 7.20−7.38 (m, 7H), 7.77 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* −4.44, −3.77, 18.11, 20.48, 21.50, 21.62, 26.11, 64.63, 67.76, 70.90, 79.82, 126.91, 127.97, 128.49, 128.60, 129.62, 135.07, 139.73, 143.37, 172.52; HRMS (FAB) calcd for $C_{26}H_{40}NO_6SSi$ [M^+ + H] 522.2346, found 522.2301.

8b: colorless oil; [α] +14.5 (*c* = 0.8, $CHCl_3$); ^{1}H NMR *δ* 0.03, 0.05 (2s, 6H), 0.86 (s, 9H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.49 (s, 3H), 2.40 (s, 3H), 2.67 (d, *J* = 3.9 Hz, 1H), 3.66 (dd, *J* = 4.3, 3.9 Hz, 1H), 3.92 (dq, *J* = 6.3, 4.3 Hz, 1H), 5.03 (d, *J* = 12.4 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 5.91 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.25−7.39 (m, 5H), 7.72 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR *δ* −4.76, −4.40, 17.84, 17.98, 18.99, 21.50, 25.80, 63.60, 67.61, 69.40, 78.64, 127.22, 128.04, 128.53, 129.40, 129.68, 135.32, 139.56, 143.05, 172.69; HRMS (FAB) calcd for $C_{26}H_{40}NO_6SSi$ [M^+ + H] 522.2346, found 522.2324.

***tert*-Butyl 6-*O*-(Benzyloxy)-4,5-(isopropylidenedioxy)-3-hydroxy-2-methyl-2-[(4-toluenesulfonyl)amino]hexanoate (9).** According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine *tert*-butyl ester (**5**) (240 mg, 0.80 mmol) with aldehyde **3**[22] (240 mg, 0.96 mmol) afforded 292 mg (66%) of **9a** and 82 mg (19%) of **9b** after flash chromatography (hexanes/ethyl acetate (1) 9:1, (2) 8:2, (3) 7:3).

9a: crystallization from dichloromethane/hexanes; mp 115−117 °C; [α] −32.7 (*c* = 0.2, $CHCl_3$); ^{1}H NMR *δ* 1.32, 1.36, 1.38 (3s, 9H), 1.43 (s, 9H), 2.41 (s, 3H), 3.65 (d, *J* = 10.2 Hz, 1H), 3.66 (dd, *J* = 10.1, 6.0 Hz, 1H), 3.75 (dd, *J* = 10.1, 3.5 Hz, 1H), 3.85 (dd, *J* = 10.2, 9.1 Hz, 1H), 3.97 (dd, *J* = 9.1, 7.7 Hz, 1H), 4.20 (ddd, *J* = 7.7, 6.0, 3.6 Hz, 1H), 4.62 (s, 2H), 6.07 (s, 1H), 7.27 (d, *J* = 7.1 Hz, 2H), 7.31−7.36 (m, 5H), 7.76 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR *δ* 19.53, 21.49, 26.81, 26.91, 27.79, 65.57, 71.03, 73.59, 77.05, 77.10, 79.98, 83.26, 109.78, 126.78, 127.66, 127.81, 128.39, 129.60, 137.83, 139.73, 143.36, 170.64; HRMS (FAB) calcd for $C_{28}H_{40}NO_8S$ [M^+ + H] 550.2475, found 550.2493. Anal. Calcd for $C_{28}H_{39}NO_8S$ (549.68): C, 61.18; H, 7.15; N, 2.55. Found: C, 60.90; H, 7.02; N, 2.44.

9b: colorless oil; [α] −11.6 (*c* = 0.2, $CHCl_3$); ^{1}H NMR *δ* 1.34, 1.38 (2s, 6H), 1.41 (s, 9H), 1.42 (s, 3H), 2.38 (s, 3H), 3.53 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.62−3.68 (m, 2H), 3.71 (dd, *J* = 9.4, 4.4 Hz, 1H), 3.95 (dd, *J* = 8.1, 7.7 Hz, 1H), 4.11 (ddd, *J* = 7.4, 6.6, 4.4 Hz, 1H), 4.55 (d, *J* = 12.1 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 5.92 (s, 1H), 7.22−7.34 (m, 7H), 7.76 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR *δ* 17.40, 21.44, 26.70, 27.78, 65.44, 70.38, 73.82, 77.09, 78.59, 79.00, 82.75, 109.91, 127.18, 127.97, 128.08, 128.57, 129.35, 136.94, 140.01, 142.93, 171.40; HRMS (FAB) calcd for $C_{28}H_{39}NO_8SNa$ [M^+ + Na] 572.2294, found 572.2320.

Benzyl 4,5-(sopropylidenedioxy)-3-hydroxy-2-methyl-2-[(4-toluenesulfonyl)amino]pentanoate (10). According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (**6**) (134 mg, 0.40 mmol) with aldehyde **4**[23] (104 mg, 0.80 mmol) provided 135 mg (73%) of **10a** and 27 mg (14%) of **10b** after flash chromatography (hexanes/ethyl acetate (1) 8:2, (2) 7:3).

10a: crystallization from dichloromethane/hexanes; mp 90−91 °C; [α] −67.7 (*c* = 0.5, $CHCl_3$); ^{1}H NMR *δ* 1.28, 1.29, 1.33 (3s, 9H), 2.40 (s, 3H), 3.53 (d, *J* = 11.7 Hz, 1H), 3.79 (dd, *J* = 11.7, 8.7 Hz, 1H), 4.00 (dd, *J* = 8.5, 5.2 Hz, 1H), 4.17 (dd, *J* = 8.5, 6.5 Hz, 1H), 4.24 (ddd, *J* = 8.6, 6.5, 5.1 Hz, 1H), 4.97 (d, *J* = 12.3 Hz, 1H), 5.2 (d, *J* = 12.3 Hz, 1H), 6.15 (s, 1H), 7.24−7.34 (m, 7H), 7.73 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR *δ* 19.56, 21.53, 24.87, 26.24, 64.91, 67.78, 68.13, 75.47, 77.44, 109.73, 126.79, 127.96, 128.60, 128.69, 129.74, 134.66, 139.33, 143.61, 171.97. Anal. Calcd for $C_{23}H_{29}NO_7S$ (463.55): C, 59.60; H, 6.31; N, 3.02. Found: C, 59.55; H, 6.29; N, 2.96.

10b: crystallization from dichloromethane/hexanes; mp 115−116 °C; [α] −16.4 (*c* = 0.2, $CHCl_3$); ^{1}H NMR *δ* 1.27, 1.36, 1.48 (3s, 9H), 2.38 (s, 3H), 2.63 (d, *J* = 4.9 Hz, 1H), 3.81 (dd, *J* = 5.1, 4.4 Hz, 1H), 3.91−4.35 (m, 3H), 5.00 (d, *J* = 12.3 Hz, 1H), 5.08 (d, *J* = 12.3 Hz, 1H), 5.87 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.24−7.35 (m, 5H), 7.71 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR *δ* 17.01, 21.53, 25.34, 26.36, 64.27, 66.19, 67.80, 75.16, 76.29, 108.19, 127.21, 128.05, 128.45, 128.58, 129.52, 135.01, 139.01, 143.40, 172.21. Anal. Calcd for $C_{23}H_{29}NO_7S$ (463.55): C, 59.60; H, 6.31; N, 3.02. Found: C, 59.71; H, 6.39; N, 2.97.

(2*R*,3*S*,4*S*,5*S*)-*tert*-Butyl 4,5-(sopropylidendioxy)-3,6-dihydroxy-2-methyl-2-[(4-toluenesulfonyl)amino]hexanoate (11a). A solution of **9a** (1.00 g, 1.82 mmol) in methanol was hydrogenated in the presence of 50 mg of 10% Pd/C. After being stirred for 24 h, the mixture was filtered and the solvent was evaporated, giving rise to a colorless solid (784 mg, 94%), which was crystallized from dichloromethane/hexanes: mp 171−172 °C; [α] −36.4 (*c* = 0.6, $CHCl_3$); ^{1}H NMR *δ* 1.30 (s, 3H), 1.33, 1.36 (2s, 6H), 1.42 (s, 9H), 2.39 (s, 3H), 2.68 (m_c, 1H), 3.79 (dd, *J* = 11.8, 4.8 Hz, 1H), 3.84 (*J* = 11.8, 5.2 Hz, 1H), 3.90−4.00 (m, 3H), 4.05 (m_c, 1H), 6.08 (s, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR *δ* 19.80, 21.53, 26.76, 26.90, 27.79, 63.12, 65.39, 76.49, 78.06, 81.35, 83.61, 109.34, 126.70, 129.72, 139.45, 143.59, 170.50. Anal. Calcd for $C_{21}H_{33}NO_8S$ (459.56): C, 54.88; H, 7.24; N, 3.05. Found: C, 54.88; H, 7.27; N, 2.87.

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(2*S*,3*S*,4*S*,5*S*)-*tert*-Butyl 4,5-(Isopropylidendioxy)-3,6-dihydroxy-2-methyl-2-[(4-toluenesulfonyl)amino]hexanoate (11b). According to the synthesis of **11a**, 317 mg (0.58 mmol) of **9b** was hydrogenated to yield 260 mg (98%) of a colorless oil: [α] −13.3 (*c* = 0.3, $CHCl_3$); ^{1}H NMR *δ* 1.23 (s, 3H), 1.37, 1.40 (2s, 6H), 1.43 (s, 9H), 1.50−1.80 (m, 2H), 2.39 (s, 3H), 3.70 (d, *J* = 8.5 Hz, 1H), 3.77 (d, *J* = 4.4 Hz, 2H), 3.88 (dd, *J* = 8.5, 7.7 Hz, 1H), 4.07 (td, *J* = 7.7, 4.4 Hz, 1H), 5.94 (s, 1H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR *δ* 17.46, 21.49, 26.74, 26.85, 27.76, 62.80, 65.13, 77.00, 78.67, 80.51, 83.44, 109.74, 127.42, 129.48, 139.68, 143.22, 171.73; HRMS (FAB) calcd for $C_{21}H_{34}NO_8S$ [M^+ + H] 460.2005, found 460.2038.

(2*R*,3*S*,4*R*,5*S*)-2-(*tert*-Butyloxycarbonyl)-4,5-(isopropylidendioxy)-3-hydroxy-2-methyl-1-(4-toluenesulfonyl)piperidine (12a). To a solution of **11a** (167 mg, 0.36 mmol) in 15 mL of THF was added PPh_3 (143 mg, 0.55 mmol) at rt before DEAD (80 μL, 0.51 mmol) was added dropwise as slowly as possible. After complete addition, the mixture was stirred for 30 min and the solvent was evaporated. The residue obtained was stirred with hexanes/ethyl acetate 9:1 and filtered. After flash chromatography (hexanes/ethyl acetate 8:2, 7:3), 146 mg (92%) of a colorless solid was obtained. Crystallization from dichloromethane/hexanes afforded colorless rhombes: mp 126−128 °C; [α] +42.6 (*c* = 1.8, $CHCl_3$); ^{1}H NMR *δ* 1.41, 1.45 (2s, 6H), 1.46 (s, 9H), 1.61 (s, 3H), 2.40 (m_c, 1H), 2.39 (s, 3H), 3.29 (dd, *J* = 11.8, 11.0 Hz, 1H), 3.36 (dd, *J* = 9.6, 2.6 Hz, 1H), 3.90 (ddd, *J* = 11.0, 9.6, 4.8 Hz, 1H), 4.39 (d, *J* = 2.6 Hz, 1H), 4.49 (dd, *J* = 12.1, 4.8 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 21.45, 22.10, 26.52, 26.72, 27.74, 49.14, 69.16, 69.34, 71.92, 79.39, 83.19, 110.98, 126.81, 129.44, 139.89, 143.14, 170.72; HRMS (FAB) calcd for $C_{21}H_{32}NO_7S$ [M^+ + H] 442.1900, found 442.1890. Anal. Calcd for $C_{21}H_{31}NO_7S$ (441.54): C, 57.13; H, 7.08; N, 3.17. Found: C, 57.18; H, 7.04; N, 3.10.

(2*S*,3*S*,4*R*,5*S*)-2-(*tert*-Butyloxycarbonyl)-4,5-(isopropylidendioxy)-3-hydroxy-2-methyl-1-(4-toluenesulfonyl)piperidine (12b). According to the synthesis of **12a**, 260 mg (0.56 mmol) of **11b** was reacted with PPh_3 (224 mg, 0.86 mmol) and DEAD (124 μL, 0.79 mmol). After flash chromatography (hexanes/ethyl acetate 8:2, 7:3), a colorless oil (186 mg, 75%) was obtained: [α] +32.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR *δ* 1.39, 1.42 (2s, 6H), 1.52 (s, 9H), 1.70 (s, 3H), 2.41 (s, 3H), 3.12 (dd, *J* = 11.3, 11.0 Hz, 1H), 3.32 (d, *J* = 2.1 Hz, 1H), 3.51 (dd, *J* = 10.8, 4.6 Hz, 1H), 3.64 (dd, *J* = 9.3, 2.3 Hz, 1H), 3.96 (ddd, *J* = 11.3, 9.3, 4.6 Hz, 1H), 4.06 (dd, *J* = 2.3, 2.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.92 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR *δ* 20.15, 21.30, 26.30, 26.58, 27.56, 46.64, 67.40, 68.75, 72.02, 78.05, 83.29, 111.49, 128.16, 129.25, 135.98, 143.69, 169.67; HRMS (FAB) calcd for $C_{21}H_{31}NO_7SNa$ [M^+ + Na] 464.1719, found 464.1718.

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Supporting Information Available: Crystallographic data for **12a** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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