Diastereoselective Synthesis of β-Substituted α-Methylserines via Chelated Alanine Ester Enolates☆

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Deprotonation of *N*-protected alanine esters with LDA, and subsequent addition of various metal salts, most likely results in the formation of chelated metal enolates. Aldol reactions of these enolates with aldehydes afford the *anti* isomers of α-methyl α-amino-β-hydroxy acid derivatives in a highly diastereoselectiv fashion. Best results are obtained with tin enolates of *N*-sulfonylated alanine esters, which give excellent results with both aliphatic and aromatic aldehydes. Employing the SES-protected derivatives which show the same good yield and diastereoselectivity as the corresponding Ts-protected esters, allows the preparation of the free α-methylserines.

Introduction

β-Hydroxy-α-amino acids are a widespread and important class of amino acids, among which the α-methylated derivatives have also been of major interest for some years. As enzyme inhibitors these nonproteinogenic amino acids are valuable tools in investigating the mechanism of enzyme reactions.[1] These amino acids also have marked effects on peptide conformation as well as biological activity.[2] α-Alkylated β-hydroxy-α-amino acids can also be found as substructures in biologically active molecules such as the sphingofungines E and F,[3a] the immunosuppressive agent myriocin,[3] or the neurotropic lactacystin.[4]

While various syntheses[5] of α-amino-β-hydroxy acids by reaction of glycine with aldehydes are described in the literature,[6][7] only a few examples are known which provide α-alkylated α-amino-β-hydroxy acids by reaction of other amino acids with aldehydes.[7]

For some time our group has been interested in the reactions of metal chelated enolates of *N*-protected amino acid esters. 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. For example, we found diastereoselectivities of > 95% in the Claisen rearrangement of zinc-chelated enolates of amino acid allyl esters.[8] The aldol reaction is another widely used synthetic method which should proceed with high diastereoselectivities because of the fixed geometry of the chelated amino acid ester enolates.

Recently we presented our results of the aldol reactions of titanium enolates of *N*-(benzyloxycarbonyl)-protected amino acid esters with aliphatic aldehydes.[9] With these substrates, high diastereoselectivities were obtained by adding 2.5 equiv. of $TiCl(OiPr)_3$. Unfortunately aromatic aldehydes did not show any diastereoselectivity in these aldol reactions. We therefore decided to intensify our studies of this reaction.

Results and Discussion

While the reaction of the Z-alanine benzyl ester[10] *rac*-**1** with isobutyraldehyde (eq. 1) proceeded with 92% *anti* diastereoselectivity, using 2.5 equiv. of $TiCl(OiPr)_3$ (Table 1, entries 1 and 2),[9] the Ts-alanine ester *rac*-**2**[11] showed no significant diastereoselectivity (entries 3 and 4).

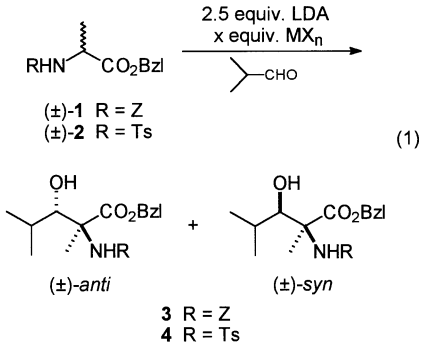

Table 1. Aldol reactions of *N*-protected alanine benzyl esters with isobutyraldehyde

Entry	Ester	x equiv. MX_n	Product	*anti*/*syn*[a]	Yield[b] [%]
1	*rac*-**1**	1.2 equiv. $TiCl(OiPr)_3$	*rac*-**3**	72:28	76
2	*rac*-**1**	2.5 equiv. $TiCl(OiPr)_3$	*rac*-**3**	92:8	87
3	*rac*-**2**	1.2 equiv. $TiCl(OiPr)_3$	*rac*-**4**	65:35	86
4	*rac*-**2**	2.5 equiv. $TiCl(OiPr)_3$	*rac*-**4**	65:35	90
5	*rac*-**2**	1.2 equiv. $SnCl_2$	*rac*-**4**	60:40	70
6	*rac*-**2**	2.5 equiv. $SnCl_2$	*rac*-**4**	98:2	80

[a] Based on HPLC of the crude reaction mixture. – [b] Yield of isolated mixture of diastereomers.

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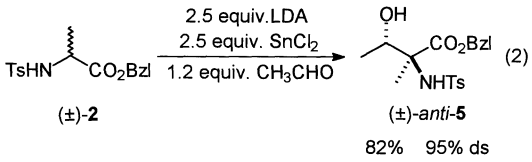
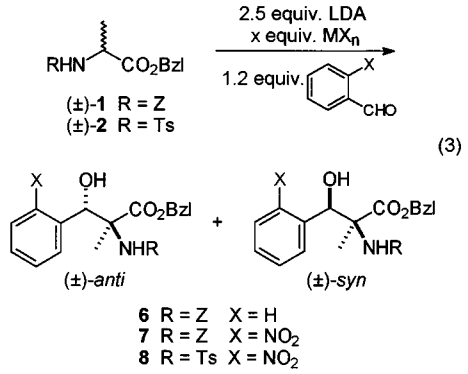
Similar results were obtained with other chelating metals such as $ZnCl_2$, $MgCl_2$, $Al(OiPr)_3$, $NiCl_2$, and $CoCl_2$. On the other hand, the addition of 2.5 equiv. of $SnCl_2$ led to an extremely high diastereoselectivity (98%) in this test reaction (entries 5 and 6). Even with the small acetaldehyde the corresponding α-methylthreonine derivative *rac*-**5** was obtained in high yield and with a high diastereoselectivity (95% ds) by this procedure (eq. 2).



(2)

In contrast to aliphatic aldehydes, no significant diastereoselectivity was observed in the reactions of Z-alanine ester *rac*-**1** with aromatic aldehydes (eq. 3), independent of the nature and the amount of the metal salt used (Table 2, entry 1−4). Employing the Ts-alanine ester *rac*-**2**, again 2.5 equiv. of $SnCl_2$ gave the best result, with 99% diastereoselectivity being obtained (entry 6), while with $TiCl(OiPr)_3$ the selectivity was modest (70% ds, entry 5).



(3)

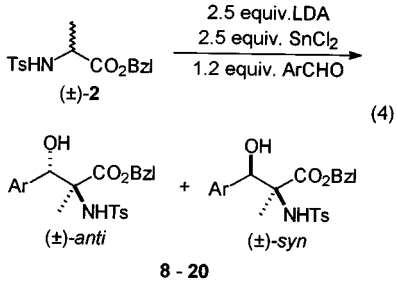
Table 2. Aldol reactions of *N*-protected alanine benzyl esters with benzaldehyde and 2-nitrobenzaldehyde

Entry	Ester	x equiv. MX_n	Product	*anti*/*syn*[a]	Yield[b] [%]
1	*rac*-**1**	2.5 equiv. $TiCl(OiPr)_3$	*rac*-**6**	51:49	54
2	*rac*-**1**	1.2 equiv. $TiCl(OiPr)_3$	*rac*-**7**	48:52	61
3	*rac*-**1**	2.5 equiv. $TiCl(OiPr)_3$	*rac*-**7**	49:51	69
4	*rac*-**1**	2.5 equiv. $SnCl_2$	*rac*-**7**	58:42	74
5	*rac*-**2**	2.5 equiv. $TiCl(OiPr)_3$	*rac*-**8**	70:30	58
6	*rac*-**2**	2.5 equiv. $SnCl_2$	*rac*-**8**	99:1	60

[a] Based on HPLC of the crude reaction mixture. − [b] Yield of isolated mixture of diastereomers.

Encouraged by this result, and in order to test the influence of different substituents in the aromatic side chain (eq. 4, Table 3), we studied the aldol reactions of ester *rac*-**2** with several aromatic aldehydes under these conditions.

The β-aryl-α-methylserines *rac*-**8**−**20** were synthesized in good to excellent yields. Neither the different substituents on the aromatic ring system, such as methyl (entry 2), methoxy (entry 3), or halogens (entries 4 and 5), nor the substituent position had any significant influence on the high



(4)

diastereoselectivity (98%), obtained in the reaction of the unsubstituted benzaldehyde (entry 1). The selectivities found in the reaction of the *p*-substituted aldehydes were comparable to the results obtained with the corresponding *o*-derivatives, as illustrated with the nitroaldehydes (entries 6 and 7). The dichloro-substituted derivatives *rac*-**15** and *rac*-**16** were also obtained with the same good results (entries 8 and 9). Only the trimethoxy substituted aldol products *rac*-**17** and *rac*-**18** showed lower diastereoselectivities (entries 10 and 11).

Table 3. Aldol reactions of alanine ester **2** with various aromatic aldehydes in the presence of 2.5 equivalents of $SnCl_2$

Entry	RCHO	Product	*anti*/*syn*	Yield[c] [%]
1	benzaldehyde	*rac*-**9**	98:2[a]	91
2	4-methylbenzaldehyde	*rac*-**10**	97:3[a]	66
3	4-methoxybenzaldehyde	*rac*-**11**	98:2[a]	70
4	4-bromobenzaldehyde	*rac*-**12**	98:2[a]	70
5	4-chlorobenzaldehyde	*rac*-**13**	98:2[a]	87
6	4-nitrobenzaldehyde	*rac*-**14**	98:2[a]	60
7	2-nitrobenzaldehyde	*rac*-**8**	99:1[a]	60
8	3,4-dichlorobenzaldehyde	*rac*-**15**	98:2[a]	65
9	2,6-dichlorobenzaldehyde	*rac*-**16**	99:1[a]	70
10	3,4,5-trimethoxybenzaldehyde	*rac*-**17**	90:10[a]	75
11	2,4,6-trimethoxybenzaldehyde	*rac*-**18**	85:15[b]	77
12	9-anthranyl carbaldehyde	*rac*-**19**	99:1[a]	87
13	3-(*N*-Boc-indol)carbaldehyde	*rac*-**20**	96:4[a]	84

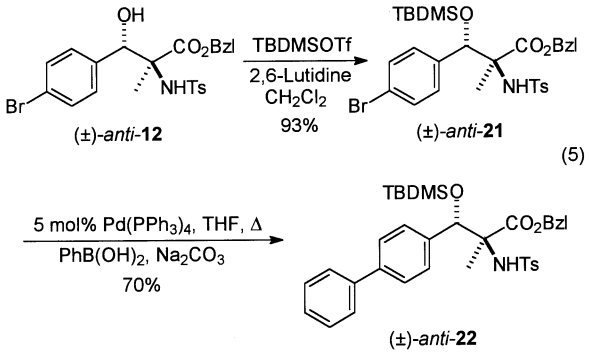
[a] Based on HPLC of the crude reaction mixture. − [b] Based on integration of characteristic signals in the ^{1}H-NMR spectrum of the crude reaction mixture. − [c] Yield of isolated mixture of diastereomers.

The aldol reaction also gave excellent results with the sterically demanding anthranylcarbaldehyde, providing *rac*-**19** in 99% diastereoselectivity and 87% yield (entry 12). The α-methyl-β-hydroxy tryptophan derivative *rac*-**20** was easily obtained in the reaction with the heterocyclic *N*-Boc-indol carbaldehyde (entry 13).

The lower selectivities obtained in the presence of other metal salts like $TiCl(OiPr)_3$, may result from the reversibility of the aldol addition. The ease of the retro aldol reaction can also be seen in reactions of the corresponding aromatic aldol products. The amino acid ester *anti-rac*-**12**, with a bromo substituent in the aromatic side chain, should be well suited for palladium catalyzed coupling reactions, providing more complex β-hydroxy-α-amino acids (eq. 5). In order to test this assumption, the palladium catalysed Suzuki coupling[12] of **12** with phenylboronic acid was investigated. The biphenyl compounds obtained in the Suzuki re-

action are often found as substructures of naturally occurring molecules with various biological activities.[13]

Under the basic conditions of the Suzuki coupling, however, a retro aldol reaction of *anti-rac*-**12** to the ester *rac*-**2** and the corresponding aldehyde took place. In order to prevent this problem, the β-hydroxy function in *anti-rac*-**12** was protected, employing TBDMS-triflate and 2,6-lutidine[14] to furnish *anti-rac*-**21**, which could be converted to the biphenyl derivative *anti-rac*-**22** with phenylboronic acid in 70% yield in the presence of 5 mol% $Pd(PPh_3)_4$ (eq. 5).

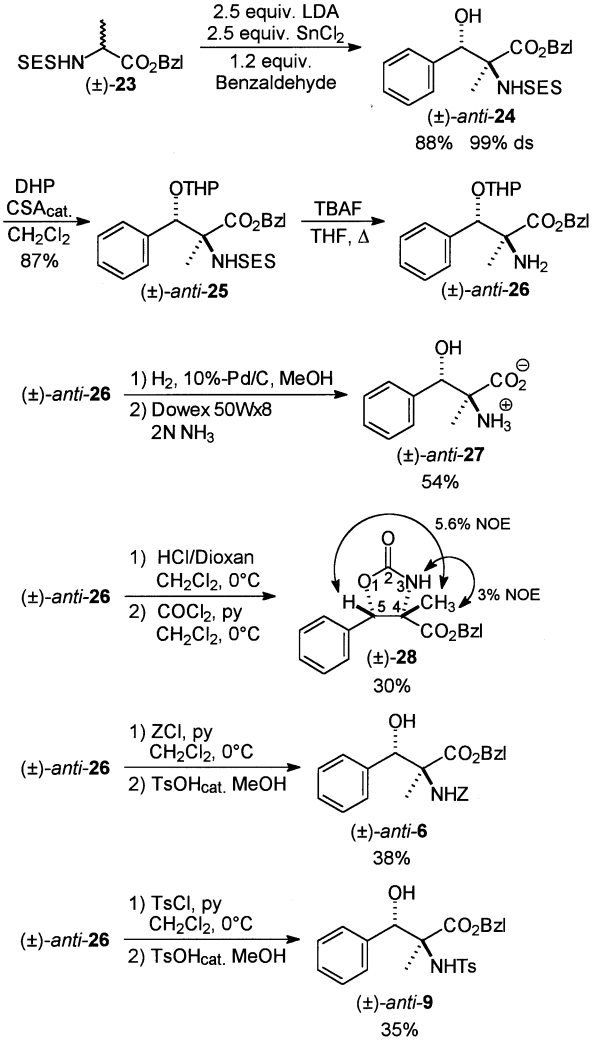


The Ts-protecting group proved to be particularly valuable in our aldol reactions of tin chelated enolates, concerning both yield and diastereoselectivity. From a synthetic point of view, however, it should be possible to use a protecting group which is easier to remove, and still provides the same good yields and selectivities. We therefore tested other sulfonyl protecting groups. Unfortunately, the easily removable 2-nitrobenzenesulfonyl protecting group[15] was not stable under the reaction conditions employed. However, the 2-trimethylsilylethanesulfonyl (SES) protecting group,[16] developed by Weinreb et al., seems to be the protecting group of choice (Scheme 1). The reaction of SES-alanine ester *rac*-**23** with benzaldehyde in the presence of 2.5 equivalents of $SnCl_2$ lead to the aldol product *rac*-**24** in 88% yield and with an excellent diastereoselectivity of 99%. To prevent a retro aldol reaction, under the highly basic conditions needed to cleave the SES group, the β-hydroxy function in *anti-rac*-**24** was protected as the corresponding THP ether *anti-rac*-**25.**[17] Cleavage of the SES group from *anti-rac*-**25,** was finally accomplished by using TBAF in refluxing THF. For the following conversions, the resulting amine *anti-rac*-**26** was employed without further purification.

Hydrogenation of *anti-rac*-**26** in the presence of 10%-Pd/C and ion-exchange chromatography with Dowex 50Wx8 provided *anti* β-phenyl α-methylserine[18] (**27**) in 54% yield.

In order to confirm the relative configuration of the major isomer of aldol product *rac*-**24**, oxazolidinone *rac*-**28** was prepared from *rac*-**26** by reaction with phosgene, after cleavage of the THP ether with HCl/dioxane. The ^{1}H-NMR spectrum of *rac*-**28** showed a significant NOE (5.6%) between the methyl group at C-4 and the proton at C-5 (Scheme 1), which is a clear indication for the *anti* configuration of the major isomer of aldol product *rac*-**24**.

Scheme 1



Reaction of amine *anti-rac*-**26** with benzyl chloroformate (ZCl) and tosyl chloride, gave rise to the main isomers of the aldol products *rac*-**6** and *rac*-**9**, respectively, after removal of the THP-group. Therefore, these diastereomers also have the *anti* configuration.

Due to the fact that the major isomers of *rac*-**6**, *rac*-**9**, and *rac*-**24**, as well as all major isomers of the Ts-protected aldol products discussed here, had a shorter retention time in the HPLC than the minor isomers, we assigned the *anti* configuration to all major isomers. This assignment is confirmed by the shifts of characteristic signals in the ^{1}H-NMR spectra of the diastereomeric aldol products (Table 4). The ^{1}H-NMR spectra show an upfield shift of the signals of the protons at C-3 and a downfield shift of the OH-signals of the major isomers relative to those of the minor isomers. The ^{1}H-NMR spectra of the tosylated aldol products also show a downfield shift of the signals of the aromatic protons − *ortho* to the sulfonyl group − of the major isomers compared with those of the minor isomers.

Table 4. Characteristic ^{1}H-NMR signals of aldol products (in $CDCl_3$)

Product	*anti* Isomer			*syn* Isomer		
	3-H	OH	*o*-Ts-H	3-H	OH	*o*-Ts-H
rac-**8**	5.79	3.68	7.65	5.83	3.29	7.61
rac-**9**	4.80	3.58	7.72	4.85	2.95	7.61
rac-**10**	4.75	3.66	7.71	4.81	3.25	7.62
rac-**11**	4.73	3.41	7.71	4.80	2.78	7.63
rac-**12**	4.80	3.88	7.69	4.83	3.42	7.59
rac-**13**	4.82	3.71	7.72	4.83	2.80	7.61
rac-**14**	5.02	4.05	7.72	5.07	-	7.62
rac-**15**	4.86	3.83	7.71	4.86	3.23	7.58
rac-**16**	5.61	3.92	7.75	5.75	3.72	7.65
rac-**17**	4.85	3.76	7.72	4.85	3.00	7.65
rac-**18**	5.18	4.52	7.71	5.34	4.67	7.62
rac-**19**	6.75	3.43	7.78	6.95	3.35	7.69
rac-**20**	5.12	3.35	7.72	5.15	3.29	7.62
rac-**24**	4.86	3.57	-	4.92	-	-

Conclusion

In conclusion, we have shown that aldol reactions of the tin enolates of *N*-sulfonylated alanine esters with both aliphatic and aromatic aldehydes, proceed with extremely high *anti* selectivity. Starting from the SES-protected alanine ester, which showed the same good yield and diastereoselectivity as the corresponding Ts-protected ester, the free β-phenyl-α-methylserine could easily be obtained. An application of this procedure to the synthesis of chiral β-hydroxy α-amino acids by using chiral aldehydes is currently under investigation.

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Experimental Section

All reactions were carried out in oven-dried glassware (100°C), under argon. All solvents were dried before use. THF and toluene were distilled from sodium benzophenone, dichloromethane and diisopropylamine from calcium hydride. Dowex 50Wx8 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. The starting materials and the products were purified by flash chromatography on silica gel (32−63 μm). Mixtures of ethyl acetate and hexanes (b.p. 30−75°C) were used as eluents. − TLC: Commercially precoated Polygram© SIL-G/UV 254 plates (Macherey-Nagel). Visualisation was accomplished with UV light, iodine, and potassium permanganate solution. − ^{1}H and ^{13}C NMR: Bruker AC-200 or AC-300 spectrometer, respectively. − Diastereomeric ratios were determined by analytical HPLC using a Knauer Eurosphere column (250 × 4 mm, Si80, 5μm, flow: 2 ml/min), and a Knauer UV detector.

General Procedure for the Aldol Reactions of Tin Enolates of N-protected Alanine Esters: 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*-protected alanine benzyl ester and 190 mg (1 mmol) of $SnCl_2$ in 2 ml of THF. In general, a clear orange colored solution was formed. After 10 min, a solution of 0.48 mmol of the aldehyde in 1 ml of THF was added. The reaction was quenched after 30 min at −78°C by adding phosphate buffer (pH = 7). The mixture was diluted with diethyl ether and 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. The combined organic extracts were washed with brine, dried with Na_2SO_4, and the solvent was evaporated. The crude aldol product was purified by flash chromatography. In order to obtain sufficient portions of the minor *syn* isomer for analytical data, the less selective reactions of the magnesium enolates were performed in a similar manner, employing 1 mmol of $MgBr_2{\cdot}OEt_2$ instead of $SnCl_2$.

Benzyl (±)-anti-3-Hydroxy-2,4-dimethyl-2-[(4-toluenesulfonyl)-amino]pentanoate (*anti-rac*-**4**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with isobutyraldehyde (42 μl, 0.48 mmol) yielded *rac*-**4** (130 mg, 80%) after flash chromatography (hexanes/ethyl acetate, 7:3) as a colorless solid, which was crystallized from dichloromethane/hexanes, m.p. 120−121°C. − HPLC (hexanes/ethyl acetate, 91:9): retention time: 23.35 min (major diastereomer), 26.37 min (minor diastereomer). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 7.7 Hz, 3 H), 0.86 (d, *J* = 6.9 Hz, 3 H), 1.37 (s, 3 H), 1.85 (m_c, 1 H), 2.41 (s, 3 H), 2.83 (d, *J* = 11.6 Hz, 1 H), 3.45 (dd, *J* = 11.6, 4.8 Hz, 1 H), 5.07 (s, 2 H), 6.00 (s, 1 H), 7.27 (d, *J* = 7.0 Hz, 2 H), 7.30−7.37 (m, 5 H), 7.75 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1, 19.8, 21.4, 21.5, 29.9, 65.2, 68.2, 80.9, 127.0, 128.5, 128.70, 128.73, 129.6, 134.5, 139.4, 143.5, 173.1. − HRMS: calcd. for $C_{21}H_{28}NO_5S$ [M^+ + H] 406.1688; found 406.1652.

syn-rac-**4** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 7.1 Hz, 3 H), 0.92 (d, *J* = 7.2 Hz, 3 H), 1.37 (s, 3 H), 3.54 (m_c, 1 H), 5.66 (s, 1 H), 7.73 (d, *J* = 8.2 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.8, 67.8, 79.2, 135.0, 143.2, 173.3.

Benzyl (±)-anti-3-Hydroxy-2-methyl-2-[(4-toluenesulfonyl)-amino]butanoate (*anti-rac*-**5**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with acetaldehyde (60 μl, 0.5 mmol) yielded *rac*-**5** (124 mg, 82%) after flash chromatography (hexanes/ethyl acetate, 7:3) as a colorless oil. − HPLC (hexanes/ethyl acetate, 91:9): retention time: 12.39 min. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.4 Hz, 3 H), 1.38 (s, 3 H), 2.40 (s, 3 H), 2.69 (d, *J* = 8.2 Hz, 1 H), 3.80 (m_c, 1 H), 5.07 (s, 2 H), 5.93 (s, 1 H), 7.26 (d, *J* = 8.1 Hz, 2 H), 7.30−7.39 (m, 5 H), 7.75 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 18.4, 21.4, 65.5, 67.8, 72.4, 127.1, 127.2, 128.2, 128.3, 128.6, 128.7, 129.5, 129.6, 134.9, 139.2, 143.4, 172.3. − HRMS: calcd. for $C_{19}H_{24}NO_5S$ [M^+ + H] 378.1375; found 378.1306.

syn-rac-**5** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.3 Hz, 3 H), 1.36 (s, 3 H), 2.48 (bs, 1 H), 3.95 (m_c, 1 H), 5.03 (d, J_{AB} = 12.4 Hz, 1 H), 5.08 (d, J_{AB} = 12.3 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.5, 67.7, 135.1, 143.3, 172.9.

Benzyl (±)-anti/syn-2-(Benzyloxycarbonyl)amino-3-hydroxy-2-methyl-3-phenylpropanoate (*rac*-**6**): A solution of 1 mmol of LDA in 2 ml of THF was added at −78°C under argon to a solution of *N*-(benzyloxycarbonyl)alanine benzyl ester (*rac*-**1**) (125 mg, 0.4 mmol) in 1 ml of THF. A clear yellow solution was formed. Subsequently, a solution of $TiCl(OiPr)_3$ (261 mg, 1 mmol) in 1 ml of THF was added, whereby the solution turned dark red immediately. A solution of benzaldehyde (51 mg, 0.48 mmol) in 1 ml of THF was finally added. After 30 min at −78°C the reaction was quenched by adding aq. 1 N HCl. The mixture was diluted with diethyl ether and allowed to warm to room temp. The aqueous phase was extracted twice with diethyl ether. The combined organic extracts were washed with brine, dried with Na_2SO_4, and the sol-

vent was evaporated. The crude aldol product was purified by flash chromatography (hexanes/ethyl acetate, 7:3), yielding *rac*-**6** (90 mg, 54%) as a colorless oil (diastereomeric ratio: *anti*/*syn* 51:49). − HPLC (hexanes/ethyl acetate, 9:1): retention time: 11.08 min (major diastereomer), 21.05 min (minor diastereomer). *anti-rac*-**6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63 (s, 3 H), 5.04−5.27 (m, 6 H), 5.52 (s, 1 H), 7.14−7.36 (m, 15 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 63.8, 67.2, 67.9, 76.7, 127.8, 127.9, 128.2, 128.3, 128.6, 128.66, 128.68, 134.9, 136.1, 139.2, 156.3, 173.4. − HRMS: calcd. for $C_{25}H_{26}NO_5$ [M^+ + H] 420.1811; found 420.1823. *syn-rac*-**6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H), 5.00−5.25 (m, 6 H), 5.48 (s, 1 H), 7.20−7.40 (m, 15 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 64.4, 67.1, 67.6, 78.0, 127.4, 127.6, 127.9, 128.1, 128.16, 128.20, 128.25, 128.32, 128.53, 135.3, 136.2, 138.6, 156.4, 172.3. − HRMS: calcd. for $C_{25}H_{26}NO_5$ [M^+ + H] 420.1811; found 420.1834.

Benzyl (±)-anti/syn-2-(Benzyloxycarbonyl)amino-3-hydroxy-2-methyl-3-(2-nitrophenyl)propanoate (*rac*-**7**): According to the general procedure, the aldol reaction of *N*-(benzyloxycarbonyl)alanine benzyl ester (*rac*-**1**) (125 mg, 0.4 mmol) with 2-nitrobenzaldehyde (73 mg, 0.48 mmol) yielded *rac*-**7** (137 mg, 74%) after flash chromatography (hexanes/ethyl acetate, 8:2, 7:3) as a colorless oil (diastereomeric ratio: 58:42). − HPLC (hexanes/ethyl acetate, 9:1): retention time: 22.79 min (major diastereomer), 28.38 min (minor diastereomer). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 1.5 H), 1.52 (s, 1.5 H), 1.75 (bs, 0.5 H), 4.99−5.17 (m, 2 H), 5.25 (bs, 0.5 H), 5.46 (bs, 0.5 H), 5.64 (s, 0.5 H), 5.98 (s, 0.5 H), 6.05 (bs, 0.5 H), 7.20−7.80 (m, 14 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 20.2, 63.5, 64.9, 67.4, 67.6, 68.0, 68.2, 70.8, 71.9, 124.1, 128.18, 128.24, 128.29, 128.34, 128.37, 128.46, 128.55, 128.57, 128.7, 128.8, 129.4, 129.8, 132.1, 132.7, 133.1, 134.0, 134.8, 135.0, 135.8, 135.9, 148.1, 149.3, 156.2, 156.9, 171.7, 172.6. − HRMS: calcd. for $C_{25}H_{25}N_2O_7$ [M^+ + H] 465.1661; found 465.1674.

Benzyl (±)-anti-3-Hydroxy-2-methyl-3-(2-nitrophenyl)-2-[(4-toluenesulfonyl)amino]propanoate (*anti-rac*-**8**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with 2-nitrobenzaldehyde (73 mg, 0.48 mmol) yielded *rac*-**8** (114 mg, 59%) after flash chromatography (hexanes/ethyl acetate, 75:25) as a yellow oil. − HPLC (hexanes/ethyl acetate, 8:2): retention time: 10.54 min (major diastereomer), 12.32 min (minor diastereomer). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 2.37 (s, 3 H), 3.68 (bs, 1 H), 4.89 (d, J_{AB} = 12.3 Hz, 1 H), 5.04 (d, J_{AB} = 12.3 Hz, 1 H), 5.79 (s, 1 H), 5.86 (s, 1 H), 7.20−7.55 (m, 9 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 7.60−7.90 (m, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1, 21.5, 66.1, 68.1, 71.8, 124.5, 126.5, 127.2, 128.1, 128.4, 128.5, 128.6, 129.2, 129.6, 129.7, 132.8, 133.0, 134.7, 138.7, 143.7, 149.0, 171.3; HRMS: calcd. for $C_{24}H_{25}N_2O_7S$ [M^+ + H] 485.1383, found 485.1417.

syn-rac-**8** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.29 (bs, 1 H), 5.07 (s, 2 H), 5.83 (s, 1 H), 5.97 (s, 1 H), 7.61 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4, 21.0, 71.7, 143.5, 149.2, 172.1.

Benzyl (±)-anti-3-Hydroxy-2-methyl-3-phenyl 2-[(4-toluenesulfonyl)aminopropanoate (*anti-rac*-**9**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with benzaldehyde (51 mg, 0.48 mmol) yielded *anti-rac*-**9** (166 mg, 91%) after flash chromatography (hexanes/ethyl acetate, 8:2) as a colorless solid, which was crystallized from dichloromethane/hexanes,m.p. 117−118°C. − HPLC (hexanes/ethyl acetate, 85:15): retention time: 9.53 min (major diastereomer), 9.78 min (minor diastereomer). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 3 H), 2.40 (s, 3 H), 3.58 (d, *J* = 8.3 Hz, 1 H), 4.80 (d, *J* = 8.3 Hz, 1 H), 4.98 (s, 2 H), 5.78 (s, 1 H), 7.12−7.36 (m, 12 H), 7.72 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 21.5, 66.1, 67.9, 78.9, 127.10, 127.14, 128.2, 128.45, 128.48, 128.58, 128.61, 129.6, 134.6, 138.0, 139.1, 143.5, 171.6. − $C_{24}H_{25}NO_5S$ (439.5): calcd. C 65.58, H 5.73, N 3.19; found: C 65.31, H 5.66, N 3.09.

syn-rac-**9** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 2.95 (bs, 1 H), 4.85 (bs, 1 H), 5.03 (d, J_{AB} = 12.4 Hz, 1 H), 5.11 (d, J_{AB} = 12.3 Hz, 1 H), 5.83 (s, 1 H), 7.61 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1, 65.9, 68.0, 135.1, 137.5, 139.2, 143.1, 172.6.

Benzyl (±)-anti-3-Hydroxy-2-methyl-3-(4-methylphenyl)-2-[(4-toluenesulfonyl)amino]propanoate (*anti-rac*-**10**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with 4-methylbenzaldehyde (58 mg, 0.48 mmol) yielded *anti-rac*-**10** (120 mg, 66%) after flash chromatography (hexanes/ethyl acetate, 8:2) as a colorless solid, which was crystallized from dichloromethane/hexanes, m.p. 122−123°C. − HPLC (hexanes/ethyl acetate, 85:15): retention time: 10.34 min (major diastereomer), 12.05 min (minor diastereomer). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H), 2.29 (s, 3 H), 2.39 (s, 3 H), 3.66 (d, *J* = 8.0 Hz, 1 H), 4.75 (d, *J* = 8.0 Hz, 1 H), 4.96 (s, 2 H), 5.82 (s, 1 H), 7.02 (s, 4 H), 7.16−7.34 (m, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 7.32−7.34 (m, 3 H), 7.71 (d, *J* = 8.2 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 21.1, 21.5, 66.1, 67.7, 78.8, 127.0, 127.1, 128.4, 128.46, 128.53, 128.9, 129.5, 134.8, 135.0, 138.2, 139.2, 143.4, 171.6. − $C_{25}H_{27}NO_5S$ (453.6): calcd. C 66.20, H 6.00, N 3.09; found C 66.05, H 5.99, N, 3.01.

syn-rac-**10** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 2.35 (s, 3 H), 3.25 (bs, 1 H), 4.81 (bs, 1 H), 5.85 (s, 1 H), 7.62 (d, *J* = 8.2 Hz, 2 H).

Benzyl (±)-anti-3-Hydroxy-3-(4-methoxyphenyl)-2-methyl-2-[(4-toluenesulfonyl)amino]propanoate (*anti-rac*-**11**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)-alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with 4-methoxybenzaldehyde (65 mg, 0.48 mmol) yielded *anti-rac*-**11** (131 mg, 70%) after flash chromatography (hexanes/ethyl acetate, 7:3) as a colorless foam, which was crystallized from dichloromethane/hexanes, m.p. 100−101°C. − HPLC (hexanes/ethyl acetate, 75:25): retention time: 5.59 min (major diastereomer), 6.32 min (minor diastereomer). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 2.39 (s, 3 H), 3.41 (d, *J* = 8.4 Hz, 1 H), 3.75 (s, 3 H), 4.73 (d, *J* = 8.3 Hz, 1 H), 4.97 (s, 2 H), 5.73 (s, 1 H), 6.73 (d, *J* = 8.7 Hz, 2 H), 7.02 (d, *J* = 8.7 Hz, 2 H), 7.17−7.34 (m, 7 H), 7.71 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 21.5, 55.2, 66.1, 67.8, 78.6, 113.6, 127.1, 128.3, 128.55, 128.59, 129.6, 130.0, 134.7, 139.1, 143.4, 159.7, 171.6. − $C_{25}H_{27}NO_6S$ (469.6): calcd. C 63.95, H 5.80, N 2.98; found C 63.72, H 5.84, N 2.87.

syn-rac-**11** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.78 (s, 1 H), 3.78 (s, 3 H), 4.80 (s, 1 H), 5.02 (d, J_{AB} = 12.3 Hz, 1 H), 5.10 (d, J_{AB} = 12.3 Hz, 1 H), 5.78 (s, 1 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 7.63 (d, *J* = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.2, 21.0, 65.9, 67.7, 113.6, 172.3.

Benzyl (±)-anti-3-(4-Bromophenyl)-3-hydroxy-2-methyl-2-[(4-toluenesulfonyl)amino]propanoate (*anti-rac*-**12**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with 4-bromobenzaldehyde (89 mg, 0.48 mmol) yielded *anti-rac*-**12** (145 mg, 70%) after flash chromatography (hexanes/ethyl acetate, 8:2) as a colorless solid, which was crystallized from dichloromethane/hexanes, m.p.

117−118°C. − HPLC (hexanes/ethyl acetate, 85:15): retention time: 11.05 min (major diastereomer), 13.60 min (minor diastereomer). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 2.39 (s, 3 H), 3.88 (d, J = 6.6 Hz, 1 H), 4.80 (d, J = 5.3 Hz, 1 H), 4.94 (d, J_{AB} = 12.2 Hz, 1 H), 5.00 (d, J_{AB} = 12.2 Hz, 1 H), 5.92 (s, 1 H), 7.01 (d, J = 8.5 Hz, 2 H), 7.17−7.36 (m, 9 H), 7.69 (d, J = 8.3 Hz, 2 H). − ^{13}C NMR (75 M Hz, $CDCl_3$): δ = 18.4, 21.5, 66.0, 68.0, 78.1, 122.4, 127.1, 128.3, 128.5, 128.7, 129.0, 129.6, 131.2, 134.6, 137.2, 139.0, 143.6, 171.5. − $C_{24}H_{24}BrNO_5S$ (518.4): calcd. C 55.60, H 4.67, N 2.70; found C 55.64, H 4.68, N 2.66.

syn-rac-**12** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 3.42 (bs, 1 H), 4.83 (s, 1 H), 5.95 (s, 1 H), 7.59 (d, J = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.0, 21.0, 172.4.

Benzyl (±)-anti-3-(4-Chlorophenyl)-3-hydroxy-2-methyl-2-[(4-toluenesulfonyl)amino]propanoate (*anti-rac*-**13**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with 4-chlorobenzaldehyde (68 mg, 0.48 mmol) yielded *anti-rac*-**13** (164 mg, 87%) after flash chromatography (hexanes/ethyl acetate, 75:25) as a colorless solid, which was crystallized from dichloromethane/hexanes, m.p. 123−124°C. − HPLC (hexanes/ethyl acetate, 85:15): retention time: 11.52 min (major diastereomer), 13.65 min (minor diastereomer). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 3 H), 2.41 (s, 3 H), 3.71 (d, J = 8.0 Hz, 1 H), 4.82 (d, J = 7.2 Hz, 1 H), 4.98 (d, J_{AB} = 12.0 Hz, 1 H), 5.04 (d, J_{AB} = 12.0 Hz, 1 H), 5.73 (s, 1 H), 7.04 (d, J = 8.5 Hz, 2 H), 7.17 (d, J = 8.5 Hz, 2 H), 7.18−7.37 (m, 7 H), 7.72 (d, J = 8.4 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 21.5, 66.2, 68.1, 78.2, 127.1, 128.3, 128.56, 128.62, 128.7, 128.8, 129.7, 134.3, 134.4, 136.6, 139.0, 143.7, 171.4. − $C_{24}H_{24}ClNO_5S$ (474.0): calcd. C 60.82, H 5.10, N 2.96; found C 60.55, H 5.15, N 2.84.

syn-rac-**13** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 2.80 (bs, 1 H), 4.83 (bs, 1 H), 5.07 (s, 2 H), 5.73 (s, 1 H), 7.61 (d, J = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.0, 65.8, 67.9, 78.3, 135.9, 143.4, 172.8.

Benzyl (±)-anti-3-Hydroxy-2-methyl-3-(4-nitrophenyl)-2-[(4-toluenesulfonyl)amino]propanoate (*anti-rac*-**14**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with 4-nitrobenzaldehyde (73 mg, 0.48 mmol) yielded *anti-rac*-**14** (116 mg, 60%) after flash chromatography (hexanes/ethyl acetate, 8:2) as a colorless solid, which was crystallized from dichloromethane/hexanes, m.p. 144−145°C. HPLC (hexanes/ethyl acetate, 85:15): retention time: 18.64 min (major diastereomer), 21.64 min (minor diastereomer). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 3 H), 2.41 (s, 3 H), 4.05 (bs, 1 H), 4.97 (d, J_{AB} = 12.0 Hz, 1 H), 5.02 (s, 1 H), 5.12 (d, J_{AB} = 12.0 Hz, 1 H), 5.77 (s, 1 H), 7.21−7.42 (m, 9 H), 7.72 (d, J = 8.3 Hz, 2 H), 7.99 (d, J = 8.7 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 21.5, 66.4, 68.4, 77.8, 123.1, 127.0, 128.3, 128.8, 129.1, 129.5, 129.8, 134.2, 138.8, 143.9, 145.5, 147.7, 171.1. − $C_{24}H_{24}N_2O_7S$ (484.5): calcd. C 59.49, H 4.99, N 5.78; found C 59.40, H 5.01, N 5.74.

syn-rac-**14** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.07 (s, 1 H), 5.82 (s, 1 H), 7.62 (d, J = 8.3 Hz, 2 H).

Benzyl (±)-anti-3-(3,4-Dichlorophenyl)-3-hydroxy-2-methyl-2-[(4-toluenesulfonyl)amino]propanoate (*anti-rac*-**15**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)-alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with 3,4-dichlorobenzaldehyde (84 mg, 0.48 mmol) yielded *anti-rac*-**15** (132 mg, 65%) after flash chromatography (hexanes/ethyl acetate, 8:2) as a colorless solid, which was crystallized from dichloromethane/hexanes, m.p. 53−54°C. − HPLC (hexanes/ethyl acetate, 85:15): retention time: 12.21 min (major diastereomer), 15.01 min (minor diastereomer). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H), 2.41 (s, 3 H), 3.83 (d, J = 7.8 Hz, 1 H), 4.86 (d, J = 7.7 Hz, 1 H), 4.99 (d, J_{AB} = 12.1 Hz, 1 H), 5.05 (d, J_{AB} = 12.1 Hz, 1 H), 5.77 (s, 1 H), 6.99 (dd, J = 8.3, 2.0 Hz, 1 H), 7.20−7.36 (m, 9 H), 7.71 (d, J = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 21.5, 66.3, 68.3, 77.5, 126.7, 127.0, 127.2, 128.5, 128.8, 129.3, 129.7, 130.1, 132.3, 132.4, 134.3, 138.6, 138.9, 143.8, 171.3. − $C_{24}H_{23}Cl_2NO_5S$ (508.4): calcd. C 56.70, H 4.56, N 2.76; found C 56.57, H 4.59, N 2.74.

syn-rac-**15** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.23 (bs, 1 H), 4.86 (bs, 1 H), 5.81 (s, 1 H), 7.58 (d, J = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9, 19.8, 65.5, 68.0, 77.5, 172.3.

Benzyl (±)-anti-3-(2,6-Dichlorophenyl)-3-hydroxy-2-methyl-2-[(4-toluenesulfonyl)amino]propanoate (*anti-rac*-**16**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)-alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with 2,6-dichlorobenzaldehyde (84 mg, 0.48 mmol) yielded *anti-rac*-**16** (142 mg, 70%) after flash chromatography (hexanes/ethyl acetate, 8:2) as a colorless oil. − HPLC (hexanes/ethyl acetate, 85:15): retention time: 8.76 min (major diastereomer), 10.22 min (minor diastereomer). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 3 H), 2.40 (s, 3 H), 3.92 (d, J = 11.5 Hz, 1 H), 5.00 (d, J_{AB} = 12.5 Hz, 1 H), 5.10 (d, J_{AB} = 12. 5 Hz, 1 H), 5.61 (d, J = 11.4 Hz, 1 H), 6.09 (s, 1 H), 7.15 (t, J = 7.9 Hz, 1 H), 7.22−7.35 (m, 9 H), 7.75 (d, J = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 21.5, 66.0, 68.3, 77.3, 127.0, 127.2, 128.1, 128.4, 128.6, 129.6, 129.7, 130.0, 131.8, 134.7, 139.2, 143.5, 171.2. − $C_{24}H_{23}Cl_2NO_5S$ (508.4): calcd. C 56.70, H 4.56, N 2.76; found C 56.96, H 4.75, N 2.53.

syn-rac-**16** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.72 (d, J = 8.3 Hz, 1 H), 5.75 (d, J = 8.0 Hz, 1 H), 6.03 (s, 1 H), 7.65 (d, J = 8.4 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4, 19.9, 67.0, 68.2, 76.8, 139.5, 143.0, 172.5.

Benzyl (±)-3-Hydroxy-2-methyl-2-[(4-toluenesulfonyl)amino]-3-(3,4,5-trimethoxyphenyl)propanoate (*rac*-**17**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with 3,4,5 trimethoxybenzaldehyde (94 mg, 0.48 mmol) yielded *rac*-**17** (159 mg, 75%) after flash chromatography (hexanes/ethyl acetate, 65:35) as a colorless solid, which was crystallized from dichloromethane/hexanes, m.p. 124−125°C. Diastereomeric ratio *anti*/*syn* 9:1. Major diastereomer: HPLC (hexanes/ethyl acetate, 7:3): retention time: 8.85 min. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3 H), 2.39 (s, 3 H), 3.76 (d, J = 7.6 Hz, 1 H), 3.76 (s, 6 H), 3.82 (s, 3 H), 4.85 (d, J = 7.8 Hz, 1 H), 5.00 (s, 2 H), 5.68 (s, 1 H), 6.49 (s, 2 H), 7.16−7.34 (m, 7 H), 7.72 (d, J = 8.30, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 21.5, 56.2, 60.8, 66.4, 67.8, 78.7, 104.7, 127.0, 127.8, 127.9, 128.58, 128.62, 128.7, 129.4, 129.6, 133.7, 134.6, 138.2, 139.1, 143.5, 153.0, 171.6. Minor diastereomer: HPLC (hexanes/ethyl acetate, 7:3): retention time: 10.24 min. − Selected signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 3.00 (bs, 1 H), 4.85 (bs, 1 H), 5.03 (d, J_{AB} = 12.4 Hz, 1 H), 5.11 (d, J_{AB} = 12.4 Hz, 1 H), 5.77 (s, 1 H), 6.57 (s, 2 H), 7.65 (d, J = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5, 21.0, 65.9, 79.2, 105.3, 152.9, 172.1. − $C_{27}H_{31}NO_8S$ (530.6): calcd. C 61.23, H 5.90, N 2.65; found C 61.04, H 5.98, N 2.52.

Benzyl (±)-3-Hydroxy-2-methyl-2-[(4-toluenesulfonyl)amino]-3-(2,4,6-trimethoxyphenyl)propanoate (*rac*-**18**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with 2,4,6-trimethoxybenz-

aldehyde (94 mg, 0.48 mmol) yielded *rac*-**18** (164 mg, 77%) after flash chromatography (hexanes/ethyl acetate, 65:35) as a colorless solid, which was crystallized from dichloromethane/hexanes, m.p. 137−138°C. Diastereomeric ratio *anti*/*syn* 85:15. − Major diastereomer: HPLC (hexanes/ethyl acetate, 75:25): retention time: 12.22 min. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 2.39 (s, 3 H), 3.72 (s, 6 H), 3.79 (s, 3 H), 4.52 (d, J = 11.9 Hz, 1 H), 4.91 (d, J_{AB} = 12.9 Hz, 1 H), 5.07 (d, J_{AB} = 12.9 Hz, 1 H), 5.18 (d, J = 12.0 Hz, 1 H), 6.08 (s, 2 H), 6.20 (s, 1 H), 7.21 (d, J = 8.2 Hz, 2 H), 7.26−7.37 (m, 5 H), 7.71 (d, J = 8.2, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 21.5, 55.4, 55.6, 55.8, 66.3, 67.0, 73.5, 91.1, 105.4, 126.8, 127.1, 127.4, 127.6, 128.0, 128.4, 128.5, 129.2, 129.4, 135.6, 139.7, 142.9, 159.0, 161.4, 171.9. − Minor diastereomer: HPLC (hexanes/ethyl acetate, 75/25): retention time: 13.38 min. − Selected signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 3 H), 2.35 (s, 3 H), 4.67 (d, J = 10.8 Hz, 1 H), 5.34 (d, J = 10.8 Hz, 1 H), 5.82 (s, 1 H), 6.13 (s, 2 H), 7.11 (d, J = 8.3 Hz, 2 H), 7.62 (d, J = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1, 67.2, 67.7, 73.9, 91.3, 105.6, 159.2, 172.8. − $C_{27}H_{31}NO_8S$ (530.6): calcd. C 61.23, H 5.90, N 2.65; found C 61.33, H 5.89, N 2.56.

Benzyl (±)-anti-3-(9-Anthranyl)-3-hydroxy-2-methyl-2-[(4-toluenesulfonyl)amino]propanoate (*anti-rac*-**19**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with 9-anthranyl carbaldehyde (99 mg, 0.48 mmol) yielded *anti-rac*-**19** (187 mg, 87%) after flash chromatography (hexanes/ethyl acetate, 8:2) as a yellow solid, which was crystallized from dichloromethane/ hexanes, m.p. 118−120°C. − HPLC (hexanes/ethyl acetate, 85:15): retention time: 11.16 min (major diastereomer), 12.90 min (minor diastereomer). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 2.39 (s, 3 H), 3.43 (d, J = 4.3 Hz, 1 H), 4.23 (d, J_{AB} = 12.4 Hz, 1 H), 4.78 (d, J_{AB} = 12.4 Hz, 1 H), 6.26 (s, 1 H), 6.56 (d, J = 7.1 Hz, 2 H), 6.75 (d, J = 4.0 Hz, 1 H), 7.07−7.18 (m, 2 H), 7.24 (d, J = 8.2 Hz, 2 H), 7.35−7.50 (m, 5 H), 7.78 (d, J = 8.2 Hz, 2 H), 7.93−7.99 (m, 2 H), 8.29 (d, J = 9.0 Hz, 1 H); 8.42 (s, 1 H), 8.98 (d, J = 8.4 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 21.5, 67.6, 68.1, 76.6, 123.9, 124.6, 124.8, 125.4, 126.5, 127.1, 127.6, 128.0, 128.2, 129.2, 129.6, 129.8, 131.1, 131.3, 131.9, 134.4, 139.4, 143.4, 171.4. − $C_{32}H_{29}NO_5S$ (539.7): calcd C 71.22, H 5.42, N 2.60; found C 70.98, H 5.51, N 2.45.

syn-rac-**19** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.35 (bs, 1 H), 6.11 (s, 1 H), 6.95 (d, J = 8.1 Hz, 1 H), 7.69 (d, J = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 67.39, 67.41, 76.3, 143.6, 172.0.

Benzyl (±)-anti-3-Hydroxy-3-[3-(N-tert-butyloxycarbonyl)-indolyl]-2-methyl-2-[(4-toluenesulfonyl)amino]propanoate (*anti-rac*-**20**): According to the general procedure, the aldol reaction of *N*-(4-toluenesulfonyl)alanine benzyl ester (*rac*-**2**) (134 mg, 0.4 mmol) with *N*-(*tert*-butyloxycarbonyl)indol-3-carbaldehyde (118 mg, 0.48 mmol) yielded *anti-rac*-**20** (189 mg, 84%) after flash chromatography (hexanes/ethyl acetate, 8:2) as a colorless solid, which was crystallized from dichloromethane/hexanes, m.p. 95−98°C. − HPLC (hexanes/ethyl acetate, 85:15): retention time: 12.93 min (major diastereomer), 15.35 (minor diastereomer). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 3 H), 1.62 (s, 9 H), 2.37 (s, 3 H), 3.35 (m_c, 1 H), 4.81 (d, J_{AB} = 12.4 Hz, 1 H), 4.92 (d, J_{AB} = 12.3 Hz, 1 H), 5.12 (m_c, 1 H), 5.99 (s, 1 H), 7.00−7.05 (m, 2 H), 7.15−7.34 (m, 7 H), 7.50−7.60 (m, 2 H), 7.72 (d, J = 8.3 Hz, 2 H), 8.10 (d, J = 8.1 Hz, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 21.5, 28.1, 65.9, 67.9, 73.0, 84.1, 115.3, 118.2, 119.7, 122.8, 124.3, 124.7, 127.1, 127.9, 128.0, 128.4, 128.5, 129.1, 129.5, 134.5, 135.1, 139.0, 143.5, 149.3, 171.7. − $C_{31}H_{34}N_2O_6S$ (562.7): calcd C 64.34, H 5.92, N 4.84; found C 64.24, H 5.87, N 4.81.

syn-rac-**20** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.29 (bs, 1 H), 5.15 (bs, 1 H), 5.90 (s, 1 H), 7.62 (d J = 8.3 Hz, 2 H).

Benzyl (±)-anti-3-(4-Bromophenyl)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-[(4-toluenesulfonyl)amino]propanoate (*anti-rac*-**21**): TBDMS triflate[14] (139 mg, 0.6 mmol) was added dropwise under an atmosphere of argon to an ice-cold solution of aldol product *anti-rac*-**12** (207 mg, 0.4 mmol) and 2,6-lutidine (93 µl, 0.8 mmol) in dry dichloromethane (0.5 ml). The mixture was warmed to room temp., stirred for 1 h and diluted with ethyl acetate. The solution was washed with aq. 1 N HCl and brine. The organic extracts were combined, dried with Na_2SO_4 and evaporated. After flash chromatography (hexanes/ethyl acetate, 8:2) *anti-rac*-**21** (234 mg, 93%) was obtained as a colorless foam, which was crystallized from dichloromethane/hexanes, m.p. 136−137°C. − HPLC (hexanes/ethyl acetate, 9:1): retention time: 4.57 min. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.31 (s, 3 H), 0.05 (s, 3 H), 0.85 (s, 9 H), 1.35 (s, 3 H), 2.38 (s, 3 H), 4.72 (s, 1 H), 4.89 (d, J_{AB} = 12.2 Hz, 1 H), 4.96 (d, J_{AB} = 12.2 Hz, 1 H), 5.53 (s, 1 H), 7.01 (d, J = 8.4 Hz, 2 H), 7.18−7.20 (m, 4 H), 7.31−7.35 (m, 5 H), 7.66 (d, J = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.4, −4.6, 17.7, 18.0, 21.5, 25.7, 66.0, 67.6, 79.9, 122.5, 127.1, 128.4, 128.5, 128.6, 129.4, 129.5, 131.0, 134.8, 137.5, 139.3, 143.2, 171.0. − $C_{30}H_{38}BrNO_5SSi$ (632.7): calcd C 56.95, H 6.05, N 2.22; found C 57.07, H 6.14, N 2.16.

Benzyl (±)-anti-3-(4-Biphenyl)-3-[(tert-butyldimethylsilyl)oxy]-2-methyl-2-[(4-toluenesulfonyl)amino]propanoate (*anti-rac*-**22**): Phenylboronic acid (30 mg, 0.25 mmol) and 2 ml of aq. 2 M Na_2CO_3 were added to a solution of *anti-rac*-**21** (136 mg, 0.22 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) in dry THF (1 ml). The mixture was refluxed for 10 h. The end of the reaction was determined by HPLC. The mixture was diluted with diethyl ether, washed with aq. 1 N NaOH and brine. The organic extracts were combined, dried with Na_2SO_4 and evaporated. After flash chromatography (hexanes/ethyl acetate, 8:2) *anti-rac*-**22** (97 mg, 70%) was obtained as a colorless foam which was crystallized from dichloromethane/hexanes m.p.. 124−126°C. − HPLC (hexanes/ethyl acetate, 9:1): retention time: 5.44 min. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.29 (s, 3 H); 0.04 (s, 3 H), 0.85 (s, 9 H), 1.40 (s, 3 H), 2.34 (s, 3 H), 4.77 (s, 1 H), 4.88 (d, J_{AB} = 12.3 Hz, 1 H), 4.95 (d, J_{AB} = 12.3 Hz, 1 H), 5.51 (s, 1 H), 7.11−7.40 (m, 12 H), 7.44 (d, J = 8.3 Hz, 2 H), 7.54 (d, J = 7.1 Hz, 2 H), 7.65 (d, J = 8.3 Hz, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.4, −4.6, 17.9, 18.1, 21.5, 25.7, 66.2, 67.5, 80.2, 126.5, 127.0, 127.2, 127.5, 128.2, 128.41, 128.43, 128.8, 129.4, 135.0, 137.3, 139.3, 140.5, 141.2, 143.1, 171.2. − $C_{36}H_{43}NO_5SSi$ (629.9): calcd. C 68.65, H 6.88, N 2.22; found C 68.78, H 7.06, N 2.19.

Benzyl (±)-2-[(2-Trimethylsilylethanesulfonyl)amino]propanoate (*rac*-**23**): A solution of 2-trimethylsilylethanesulfonyl chloride (1.33 g, 6.64 mmol)[16] in dry dichloromethane (7 ml) was added at 0°C to a solution of alanine benzyl ester toluenesulfonate (2.00 g, 5.69 mmol) and triethylamine (5.55 ml, 39.85 mmol) in dry dichloromethane (7 ml). After warming to room temp. and stirring for 2 h the solution was washed with aq. 1 N $KHSO_4$, saturated aq. $NaHCO_3$ and brine, dried with Na_2SO_4 and evaporated. After flash chromatography (hexanes/ethyl acetate, 75:25) *rac*-**23** (1.12 g, 57%) was obtained as a colorless oil. − HPLC (hexanes/ethyl acetate, 83:17): retention time: 4.26 min. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.22 (s, 9 H), 0.99−1.12 (m, 2 H), 1.47 (d, J = 7.2 Hz, 3 H), 2.86−2.97 (m, 2 H), 4.22 (m_c, 1 H), 4.96 (d, J = 8.5 Hz, 1 H), 5.19 (s, 2 H), 7.33−7.41 (m, 5 H). − ^{13}C NMR (75 MHz,

$CDCl_3$): δ = −2.0, 10.5, 20.1, 50.1, 51.8, 67.5, 128.2, 128.6, 128.7, 135.1, 172.7. − $C_{15}H_{25}NO_4SSi$ (343.5): calcd. C 52.45, H 7.34, N 4.07; found C 52.63, H 7.18, N 3.99.

Benzyl (±)-anti-3-Hydroxy-2-methyl-2-[(2-trimethylsilylethanesulfonyl)amino]propanoate (*anti-rac*-**24**): According to the general procedure, the aldol reaction of *N*-(2-trimethylsilylethanesulfonyl)-alanine benzyl ester (*rac*-**23**) (550 mg, 1.6 mmol) with benzaldehyde (204 mg, 1.92 mmol) yielded *anti-rac*-**24** (484 mg, 88%) after flash chromatography (hexanes/ethyl acetate, 8:2) as a colorless solid, which was crystallized from dichloromethane/hexanes, m.p. 112−114°C. − HPLC (hexanes/ethyl acetate, 83:17): retention time: 6.20 min (major diastereomer), 6.64 min (minor diastereomer). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.00 (s, 9 H), 0.96−1.01 (m, 2 H), 1.66 (s, 3 H), 2.92−2.98 (m, 2 H), 3.57 (bs, 1 H), 4.86 (bs, 1 H), 5.11 (d, J_{AB} = 12.4 Hz, 1 H), 5.15 (d, J_{AB} = 12.3 Hz, 1 H), 5.21 (s, 1 H), 7.18−7.36 (m, 10 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −2.1, 10.7, 19.8, 52.3, 66.2, 68.0, 78.7, 127.3, 127.9, 128.2, 128.55, 128.60, 128.63, 134.7, 138.0, 172.0. − $C_{22}H_{31}NO_5SSi$ (449.7): calcd C 58.77, H 6.94, N 3.12; found C 58.53, H 6.85, N 3.02.

syn-rac-**24** (selected signals): ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.06 (s, 9 H), 0.81−0.92 (m, 2 H), 2.72−2.88 (m, 2 H), 4.92 (s, 1 H), 5.18 (d, J_{AB} = 12.3 Hz, 1 H), 5.25 (d, J_{AB} = 12.4 Hz, 1 H), 5.32 (s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 52.3, 65.9, 67.9, 78.7, 135.2, 137.6, 172.9.

Benzyl (±)-anti-2-Methyl-3-phenyl-3-[(tetrahydropyranyl)oxy]-2-[(2-trimethylsilylethanesulfonyl)amino]propanoate (*anti-rac*-**25**): DL-10-Camphorsulfonic acid (3 mg) was added to an ice-cold solution of *anti-rac*-**24** (433 mg, 1.26 mmol) and 2,3-dihydro-2*H*-pyrane (228 µl, 2.52 mmol) in dry dichloromethane (10 ml). The solution was stirred at 0°C for 30 min and 1 h at room temp. Sodium bicarbonate powder (3 mg, 0.04 mmol) was added to the reaction mixture, which was concentrated after filtration. After flash chromatography (hexanes/ethyl acetate/NEt_3, 85:13:2) *anti-rac*-**25** (585 mg, 87%) was obtained as a colorless oil. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = −0.15 (s, 3 H), 0.00 (s, 6 H), 0.83−1.12 (m, 2 H), 1.38−2.00 (m, 9 H), 2.77−3.20 (m, 2 H), 3.45−3.62 (m, 1 H), 3.82−4.00 (m, 1 H), 4.35−4.45 (m, 1 H), 4.76−4.82 (m, 1 H), 4.84 (s, 1 H), 5.07−5.16 (m, 2 H), 7.16−7.44 (m, 10 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −2.06, −2.03, 10.6, 18.7, 19.3, 19.6, 20.6, 25.1, 25.3, 30.0, 30.4, 51.8, 52.0, 52.2, 62.0, 62.7, 65.9, 66.3, 67.5, 67.6, 81.6, 83.9, 95.6, 100.7, 127.9, 128.0, 128.2, 128.3, 128.5, 128.6, 128.8, 135.1, 135.3, 135.4, 137.5, 171.1, 171.4. − HRMS: calcd for $C_{27}H_{40}NO_6SSi$ [M^+ + H] 534.2346; found 534.2346.

(±)-anti-2-Amino-3-hydroxy-2-methyl-3-phenylpropanoic Acid (*anti-rac*-**27**): A solution of *anti-rac*-**25** (243 mg, 0.46 mmol) and TBAF (1.37 mmol, 1 M solution in THF) in THF (12 ml) was refluxed for 48 h. The mixture was diluted with diethyl ether and washed with saturated aq. $NaHCO_3$ and brine. The organic extracts were combined, dried with Na_2SO_4 and evaporated. A solution of the resulting amine *anti-rac* **26** in MeOH was hydrogenated in the presence of 10%-Pd/C for 2 h. After filtration of the catalyst the mixture was concentrated to a volume of 5 ml, and Dowex 50Wx8 (100 mg) was added. After stirring at room temp. for 1 h the mixture was filtered, and subsequently washed with MeOH and water. The remaining residue was eluted with 2 M NH_4OH. The solution was evaporated with toluene to give *anti-rac*-**27** (48 mg, 54%), which was crystallized from water/acetone, m.p. 204−206°C (dec.). − ^{1}H NMR (300 MHz, D_2O): δ = 1.49 (s, 3 H), 4.72 (bs, 4 H), 4.94 (s, 1 H), 7.29−7.34 (m, 5 H). − ^{13}C NMR (75 MHz, D_2O): δ = 21.1, 66.6, 75.9, 127.7, 129.5, 129.6, 138.7, 161.3. − $C_{10}H_{13}NO_3$ (195.2): calcd C 61.53, H 6.71, N 7.18; found C 61.38, H 6.77, N 7.03.

(±)-4-Benzyloxycarbonyl-4-methyl-5-phenyloxazolidin-2-one (*rac*-**28**): A solution of *anti-rac*-**25** (117 mg, 0.22 mmol) and TBAF (0.66 mmol, 1 M solution in THF) in THF (6 ml) was refluxed for 48 h. The mixture was diluted with diethyl ether and washed with saturated aq. $NaHCO_3$ and brine. The organic extracts were combined, dried with Na_2SO_4 and evaporated. The residue was dissolved in dichloromethane (2 ml) and HCl/dioxane was added at 0°C. After 1 h the solvent was evaporated and the residue was dissolved in dichloromethane (2 ml). Pyridine (0.1 ml) and phosgene (0.5 ml, 1.93 M solution in toluene) was added dropwise at 0°C. After stirring for 1 h the mixture was diluted with ethyl acetate and washed with brine. The organic extracts were combined, dried with Na_2SO_4 and evaporated. Flash chromatography (hexanes/ethyl acetate, 7:3) yielded *rac*-**28** (21 mg, 30%) as a colorless solid, which was crystallized from dichloromethane/hexanes, m.p. 90−91°C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (s, 3 H), 4.45 (d, J_{AB} = 12.2 Hz, 1 H), 4.76 (d, J_{AB} = 12.2 Hz, 1 H), 5.32 (s, 1 H), 6.18 (s, 1 H), 7.26−7.33 (m, 10 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7, 66.8, 67.7, 86.5, 126.2, 128.3, 128.45, 128.50, 128.52, 129.4, 134.1, 134.5, 158.2, 170.3. − $C_{18}H_{17}NO_4$ (311.3): calcd C 69.44, H 5.50, N 4.50; found C 69.70, H 5.60, N 4.54.

☆ Dedicated to Prof. Dr. *D. Seebach* on the occasion of his 60th birthday.

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