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Reagent Control in the Aldol Addition Reaction of Chiral Boron Enolates with Chiral Aldehydes. Total Synthesis of (3*S*,4*S*)-Statine

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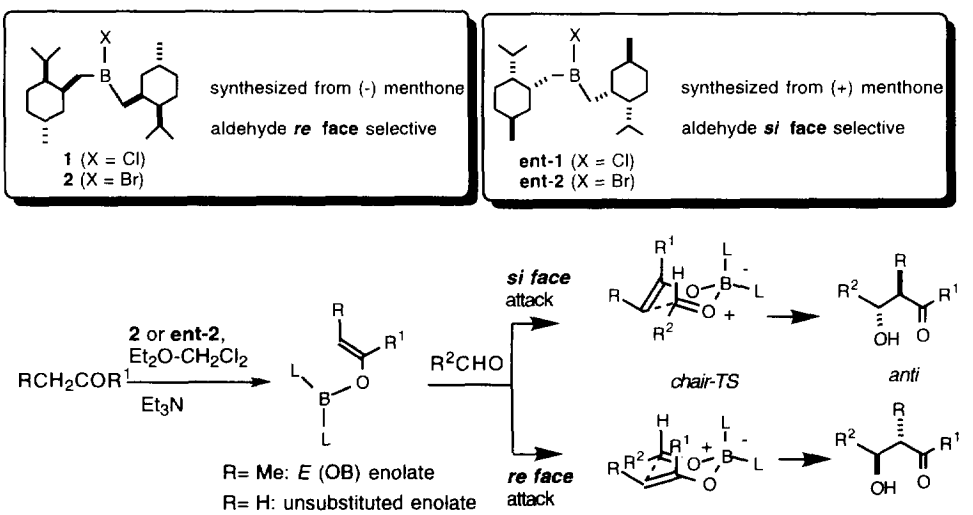
Abstract: Boron enolates bearing menthone-derived chiral ligands are capable of fair to excellent diastereocontrol in their reactions with chiral aldehydes. Thioester-derived (better than ketone derived) enolates are able to control aldol stereochemistry irrespective of the aldehyde preferences. With thioacetate-derived chiral enolates and enantiopure *N,N*-dibenzyl α-amino aldehydes, either the 3,4-*anti* or the 3,4-*syn* aldol adduct can be obtained with very high diastereoselectivity just by changing the chiral boron ligand configuration. The above procedure was used for a stereoselective total synthesis of (3*S*, 4*S*)-statine. © 1997 Elsevier Science Ltd.

The boron aldol reaction has become a powerful method for the control of both relative and absolute stereochemistry in organic synthesis.[1] We have exploited transition state computer modelling to develop two new boron reagents (**1**, X = Cl; **2**, X = Br; **Scheme 1**) which allow the enantioselective synthesis of ketone-derived *anti* (74-88% ee; R = Me; R^1 = alkyl, aryl) and unsubstituted aldols (55-76% ee; R = H; R^1 = alkyl, aryl),[2a] and thioester-derived *anti* (≥98% ee; R = Me, R^1 = SBu^t) and unsubstituted aldols (87-97% ee; R = H, R^1 = SBu^t).[2b]

Scheme 1



In the reaction of chiral enolates with chiral aldehydes the intrinsic diastereofacial selectivities of the two chiral components are either matched or mismatched.[1,3] If the aldehyde (substrate) intrinsic selectivity is moderate and the enolate (reagent) selectivity is very high, reagent control can be obtained.[1,3] Enolates bearing chiral metal ligands are often able to impart a high degree of reagent control, e.g. 2,5-*trans*-dimethylborolanyl enolates,[4a] 2,5-*trans*-diphenylborolanyl enolates,[4b,c] diisopinocampheylboron enolates,[4d] iron acyl enolates,[5] chiral diamine complexed tin(II) enolates.[6] A very efficient "catalyst control" was recently reported in chiral borane-mediated aldol additions to chiral aldehydes.[7]

Here we report that boron enolates derived from **2** or **ent-2** (X = Br) show a high degree of reagent control in reactions with chiral aldehydes, and that the efficiency of double asymmetric synthesis reflects the level of enantiomeric excess of the reactions with achiral aldehydes [thiopropionates (≥98% ee) ≥ thioacetates (87-97% ee) > ethylketones (74-88% ee)].

Protected lactic aldehyde (**3**) shows a very modest inherent preference for the Felkin-type product (3,4-*anti*) in reactions with achiral thioester boron enolates (52:48 with thioacetate; 67:33 with thiopropionate).[8] The chiral boron enolates are able to impart complete reagent control with the propionates and very high selectivity with the acetates (**Scheme 2**, Table 1).

Scheme 2

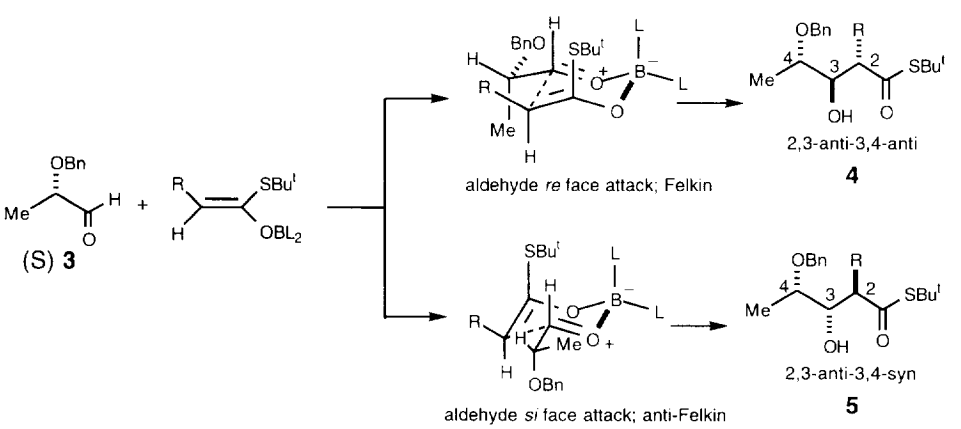


Table 1

Entry	R	Boron reagent	[2,3-Anti: 2,3-Syn]	%E.E. (major diaster.)	2,3-anti 3,4-anti (**4**)	2,3-anti 3,4-syn (**5**)	2,3-syn 3,4-anti	2,3-syn 3,4-syn	Yield %
1	Me	**2**	**>98:2**	100	**≥99**	≤1	Not detected		65
2	Me	ent-**2**	**>98:2**	100	≤1	**≥99**	Not detected		60
3	H	**2**	===	100	**93**	7	===		75
4	H	ent-**2**	===	100	6	**94**	===		65

Protected glyceraldehyde (**6**) shows a more pronounced inherent preference for the Felkin-type product (3,4-*anti*) in reactions with achiral thioester boron enolates (80:20 with thioacetate; 87.5:12.5 with thiopropionate).[8] The chiral boron enolates are again able to impart very high reagent controlled selectivity with both the propionates and the acetates (**Scheme 3**, Table 2).

Scheme 3

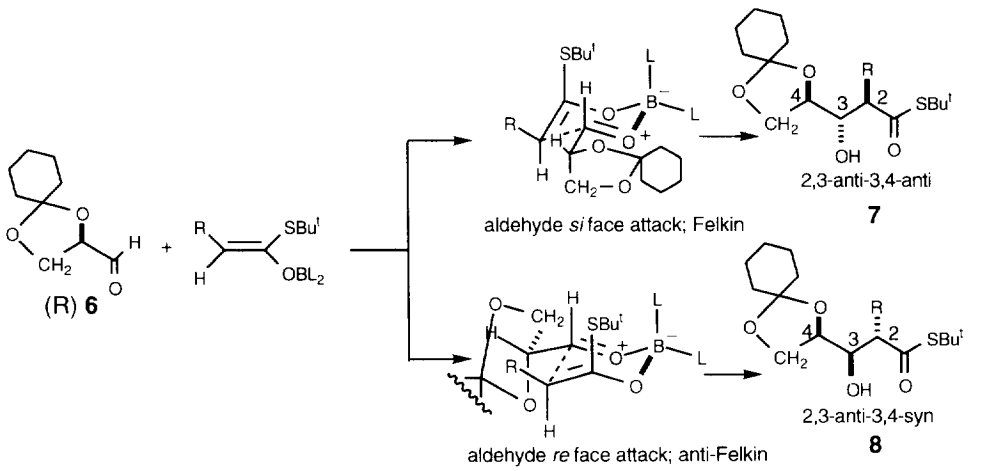


Table 2

Entry	R	Boron reagent	[2,3-Anti: 2,3-Syn]	%E.E. (major diaster.)	2,3-anti 3,4-anti (**7**)	2,3-anti 3,4-syn (**8**)	2,3-syn 3,4-anti	2,3-syn 3,4-syn	Yield %
1	Me	**2**	**>98**:2	100	5	**95**	Not detected		45
2	Me	ent-**2**	**>98**:2	100	**99**	1	Not detected		50
3	H	**2**	===	100	3	**97**	===		72
4	H	ent-**2**	===	100	**96**	4	===		75

The situation is slightly more complicated with α-methyl-β-benzyloxypropionaldehyde (**9**). The aldol addition of the *Z* boron enolate derived from diethyl ketone was recently studied both computationally and experimentally and shown to be moderately 2,3-*syn*-3,4-*anti* (anti-Felkin) selective (65:35).[9a] The "normal" Felkin TS is destabilized by the presence of a (+/-) double gauche pentane interaction between the methyl of the *Z* enolate and that of the aldehyde.[9a,b] The usual Felkin selectivity should be restored with *E* enolates.

The results (**Scheme 4**, Table 3) are less clean than expected. Although it is possible that some aldehyde enolization and racemization is occurring during the aldol reaction [this would also explain some variability (± 3 %) of the product ratios in repeated reactions], there is no rationale at present for the different selectivity of the *E*-(OB) thiopropionate enolate [which is highly 3,4-*syn* (Felkin-type) selective] and of the thioacetate enolate [which is highly 3,4-*anti* (anti-Felkin-type) selective] (Table 3, *cf.* entries 2,3 with 5,6).

Scheme 4

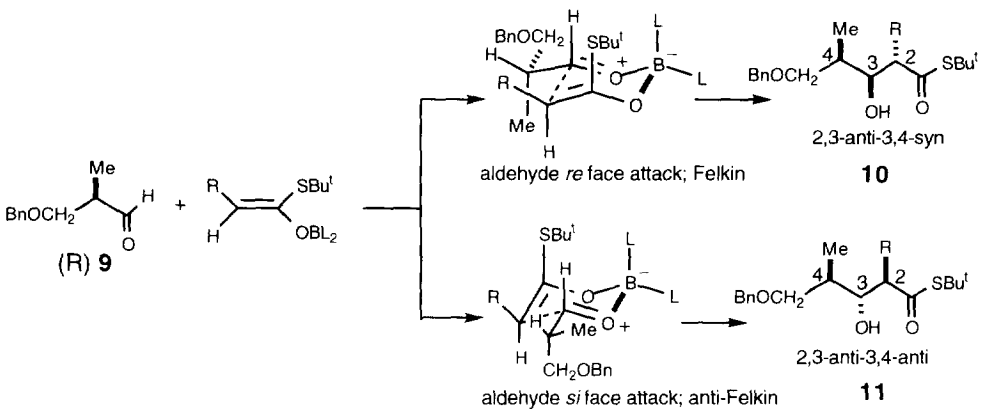
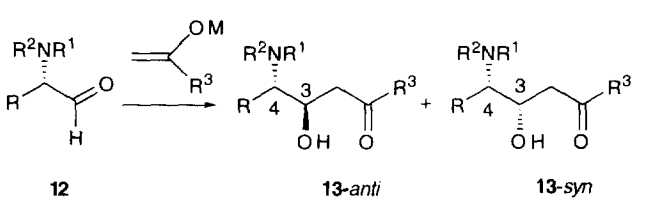


Table 3

Entry	R	Boron reagent	Aldehyde Abs. conf.	[2,3-Anti: 2,3-Syn]	%E.E. (major diaster.)	2,3-anti 3,4-syn (10)	2,3-anti 3,4-anti (11)	2,3-syn 3,4-anti	2,3-syn 3,4-syn	Yield %
1	Me	**2**	R/S	**>98**:2	-	51	49	Not detected		81
2	Me	**2**	R	**>98**:2	100	**95**	5	Not detected		60
3	Me	ent-**2**	R	**>98**:2	100	35	**65**	Not detected		60
4	H	**2**	R/S	===	-	50	50	===		70
5	H	**2**	R	===	100	**68**	32	===		70
6	H	ent-**2**	R	===	100	4	**96**	===		60

Over the past ten years chiral α-amino aldehydes have become very popular as synthetic precursors of biologically active molecules.[10] The aldol reaction between an acetate-derived enolate and a chiral α-amino aldehyde creates a new stereogenic center and two possible diastereoisomers (**Scheme 5**). In recent years two distinct ways of stereochemical control have been used: substrate control, in which the intrinsic stereochemical preference of the α-amino aldehyde determines the stereochemical outcome of the reaction, and reagent control, in which it is the chiral enolate's stereochemical preference that governs the reaction stereochemistry.[1,3] Acetate-derived achiral lithium enolates add stereoselectively to *N,N*-dibenzyl α-amino aldehydes (**12**, $R^1 = R^2 = Bn$) with diastereomeric ratios ≥ 90:10 in favor of the "Felkin-Anh" aldol addition product (**13**-*anti*).[4b,10b,11]

Scheme 5



The same enolates add to monoprotected α-amino aldehydes (NH-Cbz, NH-Boc) with a modest stereochemical preference (1:1 to 4:1) in favor of the "chelation" product (**13**-*syn*).[12,13] In the case of more complex chiral substrates, capable of a more pronounced stereochemical bias, a substantial improvement of the diastereoselectivity in favor of the 3,4-*syn* adduct may be observed, although the levels of stereocontrol are highly dependent on the substrate nature.[14] Attempts to carry out the reaction under complete chelation control (*i.e.* leading to the 3,4-*syn* products exclusively), using enolsilanes, *N,N*-dibenzyl α-amino aldehydes and $TiCl_4$, resulted in poor yields (e.g. 25%).[11] On the contrary, the 3,4-*anti* adducts were obtained with high selectivities (>98%) and in good yields using $EtAlCl_2$ or cat. $LiClO_4$ as promoters.[15,16] Good chelation control (*i.e.* leading to high diastereomeric ratios in favor of the 3,4-*syn* products) and good yields were obtained with monoprotected α-amino aldehydes **12** (R^1 = H, R^2 = Boc, COO*i*Pr), $TiCl_4$ or $SnCl_4$, and acetate derived silyl ketene acetals.[15,17] Using the methods described above, which are based on substrate control, it has not been possible to obtain either of the two diastereoisomers with high stereoselectivity using the same α-amino aldehyde. Using Davies' chiral iron acyl enolates and α-aminoaldehydes **12** (R^1 = R^2 = Bn), a reasonable degree of reagent control was obtained.[5a,b] In a typical matched case the 3,4-*anti* diastereomer was synthesized predominantly (de = 92%, yield = 71%), while in the corresponding mismatched case the 3,4-*syn* isomer was formed with lower selectivity (de = 60%, yield = 48%). Using Reetz's chiral 2,5-diphenylborolane enolates[4b,18] and α-aminoaldehydes **12** (R^1 = R^2 = Bn), the diastereomeric excesses were more substantial, ranging between 87.6 and 92.8% in favor of the 3,4-*anti* isomers (65-85% yields), and between 86.6 and 93% in favor of the 3,4-*syn* isomers (50-80% yields).[4c] Using the Devant-Braun's chiral acetate enolate and α-aminoaldehydes **12** (R^1 = H, R^2 = Boc, Cbz), the 3,4-*syn* isomer was synthesized with a fair diastereoisomeric excess (de = 80-82%, yield = 49-61%).[10k]

Here we report the high efficiency of the menthone-derived boron-reagents (**2** and ent-**2**) in the reaction with *N,N*-dibenzyl α-amino aldehydes **14**[11] and apply this stereoselective transformation to the total synthesis of (3*S*, 4*S*)-statine **21**,[5a,12a,17,19] the main component of pepstatine, which is a specific inhibitor of aspartic proteases.[19c,d] With the chiral boron enolates of *t*-butylthioacetate derived from **ent-2** we are able to overcome the inherent substrate preference for the Felkin-type product (3,4-*anti*) observed with achiral enolates. It is worth noting that in the "matched" cases the 3,4-*anti* : 3,4-*syn* diastereomeric ratios are ≥ 98.2:1.8, while in the "mismatched" cases the 3,4-*syn* : 3,4-*anti* ratios are ≥ 95.4:4.6 (**Scheme 6**, Table 4).

Scheme 6

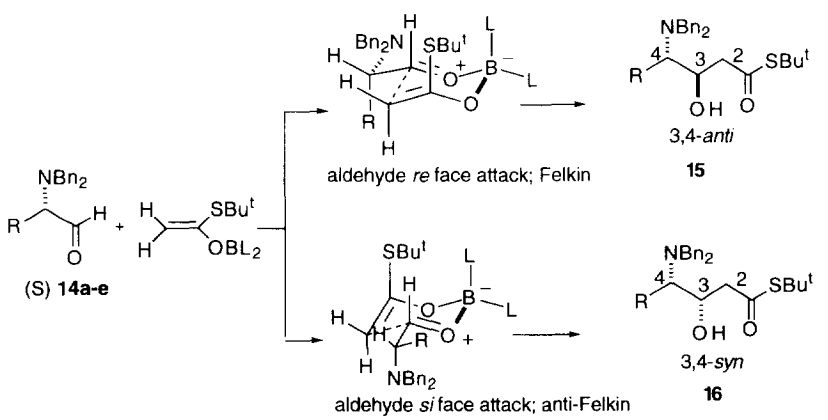


Table 4

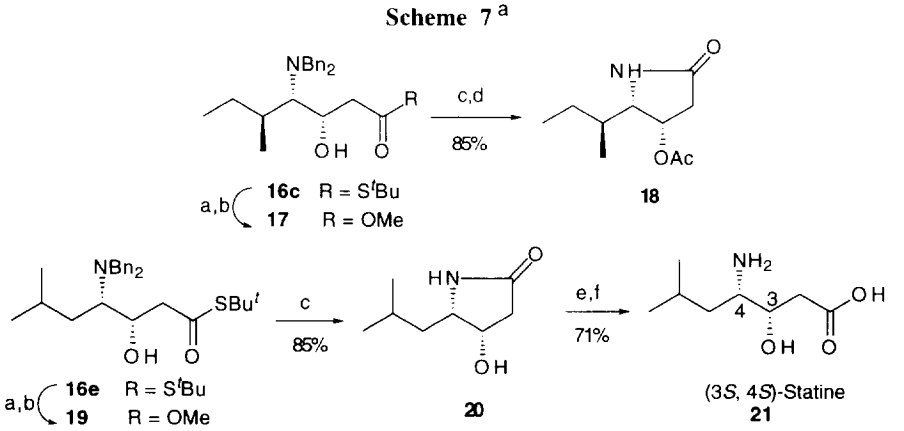
Entry	R	Boron reagent	Substrates	3,4-*anti* **15**	3,4-*syn* **16**	Products	Yield %
1	Bn	**2**	**14a**	**98.6**	1.4	**15a**	75
2	Bn	ent-**2**	**14a**	3.2	**96.8**	**16a**	70
3	Me	**2**	**14b**	**98.5**	1.5	**15b**	80
4	Me	ent-**2**	**14b**	3.7	**96.3**	**16b**	75
5	*s*-Bu	**2**	**14c**	**98.2**	1.8	**15c**	75
6	*s*-Bu	ent-**2**	**14c**	4.6	**95.4**	**16c**	71
7	*i*-Pr	**2**	**14d**	**>100**	<1 [a]	**15d**	80
8	*i*-Pr	ent-**2**	**14d**	3.5	**96.5**	**16d**	72
9	*i*-Bu	**2**	**14e**	**>100**	<1 [a]	**15e**	78
10	*i*-Bu	ent-**2**	**14e**	2.5	**97.5**	**16e**	71

[a] Not detected in the crude reaction mixture

These results prove that it is possible to obtain either the 3,4-*anti* (**15**) or the 3,4-*syn* (**16**) adduct with very high diastereoselectivity just by changing the chiral boron ligand configuration. Although the aldol products are contaminated by small amounts of the unwanted diastereomer (0-4.6%), they can be easily purified by flash chromatography. The ratios of the mixtures **15/16** were determined by ^{13}C-NMR analysis of the crude reaction mixtures after having previously fully characterized each diastereomer. We have determined the relative and absolute configuration of the aldol products by chemical correlation in a couple of cases (see below). We have also determined by these chemical correlations that both **15**- and **16**-type compounds are enantiomerically pure, and therefore that in the aldol reaction the substrates do not suffer any erosion of configurational integrity.

The 3,4-*syn* aldol adducts **16c** and **16e** have been correlated with the known lactams **18**[20] and **20**[19a] respectively, the latter leading in two steps to the natural β-hydroxy-γ-amino acid statine **21** (**Scheme 7**).

Scheme 7 [a]

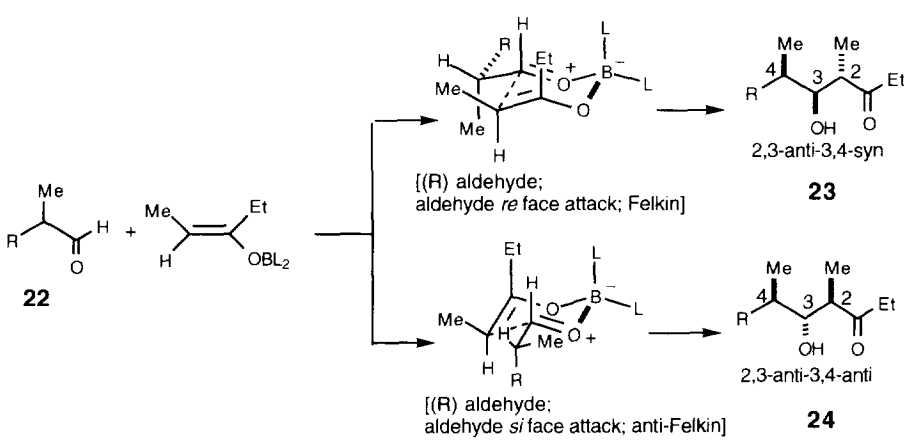


[a]Key: (a)1N NaOH in THF; (b) CH_2N_2 in MeOH; (c) HCO_2NH_4, Pd-C, MeOH, reflux; (d) Ac_2O / Py; (e) conc. HCl, 80°C, 3h; (f) DOWEX 50X8-100 (acid form).

Aldol adducts **16c** and **16e** were saponified and esterified with diazomethane to give methyl esters **17** and **19** in good yield (75% and 80%, respectively). Debenzylation of the -NBn_2 group was achieved using a procedure originally introduced for the deprotection of mono benzylamines (HCO_2NH_4, Pd-C, MeOH, reflux).[21] Under these reaction conditions the hydroxy-amino ester intermediate undergoes cyclization, generating the γ-lactam, which is acetylated to give **18** (in the *iso*-leucine series). Compound **18** is obtained in 85% overall yield from **17**. The $[\alpha]_D$ values of lactams **18** and **20** are in good agreement with those reported in the literature.[19a,20] Although the ring opening of **20** under acidic conditions[19e] has been reported to fail,[19b] we have found that using concentrated hydrochloric acid at 80°C lactam **20** is converted into statine hydrochloride in good yield.[19f] The salt was dissolved in water and loaded onto an ion exchange column to deliver the free amino acid statine **21** as a white solid (**Scheme 7**).

Finally the aldol reactions of the *E* enolate derived from diethyl ketone were studied with α-methyl phenylacetaldehyde and α-methyl-β-benzyloxypropionaldehyde (**Scheme 8**, Table 5). The results reflect the lower enantioinducing power of the ketone enolates compared to the thioester enolates. A computational study of these reactions using transition state computer modelling[2a,9a,22] gave results in qualitative agreement with the experiments (Table 5).

Scheme 8



In summary, we have shown that boron enolates bearing menthone-derived chiral ligands are capable of fair to excellent diastereocontrol in their reactions with chiral aldehydes. Thioester-derived (better than ketone derived) enolates are able to control aldol stereochemistry irrespective of the aldehyde preferences. With thioacetate-derived chiral enolates and enantiopure *N,N*-dibenzyl α-amino aldehydes, either the 3,4-*anti* or the 3,4-*syn* aldol adduct can be obtained with very high diastereoselectivity just by changing the chiral boron ligand configuration.

Table 5

Entry	R	Boron reagent	Aldehyde Abs. conf.	Enolate *E*:*Z* [2,3-Anti: 2,3-Syn]	%E.E. (major diaster.)	2,3-anti 3,4-syn **23**	2,3-anti 3,4-anti **24**	2,3-syn 3,4-syn **25**	2,3-syn 3,4-anti **26**	Yield %
1	Ph	$(c\text{-}C_6H_{11})_2BCl$	R/S	56:44	0	93	7	80	20	65
2	Ph	**2**	R/S	**90**:10	25	**96**	4	≥90	≤10	75
3	CH_2OBn	$(c\text{-}C_6H_{11})_2BCl$	R/S	70:30	0	60	40	40	60	70
4	CH_2OBn	**2**	R/S	**95**:5	-	**65**	35	60	40	68
5	CH_2OBn	**2**	R	**95**:5	100	**75**	25	60	40	72
6	CH_2OBn	ent-**2**	R	**92**:8	100	40	**60**	60	40	64
1	Ph	$(c\text{-}C_6H_{11})_2BCl$	R/S	only *E*		78	22			
2	Ph	**2**	R/S	only *E*		67	33			
3	$CH_2OCH_2Pr^i$	$(c\text{-}C_6H_{11})_2BCl$	R/S	only *E*		86	14			
4	$CH_2OCH_2Pr^i$	**2**	R/S	only *E*		**43**	57			
5	$CH_2OCH_2Pr^i$	**2**	R	only *E*		**62**	38			
6	$CH_2OCH_2Pr^i$	**2**	S	only *E*		26	**74**			

Computational studies

Acknowledgements. We thank the Commission of the European Union (HCM Network Grant: ERB CHR XCT 930141) for a research fellowship (to G.P.) and for financial support.

EXPERIMENTAL SECTION

General. Chromatographic purification of products was carried out by "flash chromatography"[23] using Merck silica gel 60 (230-400 mesh). Thin layer chromatography was carried out on Merck silica gel 60F plates. Organic solutions were dried over sodium sulfate (Na_2SO_4). ^1H NMR spectra were obtained at 200 MHz and ^{13}C NMR at 50.28 MHz at 25 °C (unless otherwise stated). Chemical shifts are reported in parts per million (ppm), δ, from TMS = 0.00 ppm. J vaules are given in Hz.

General Procedure for the *tert*-butyl thioacetate aldol additions (Table 1, entries 3,4; Table 2, entries 3,4; Table 3, entries 4-6). To a cooled (0 °C) solution of *tert*-butyl thioacetate (1.0 mmol) in ethyl ether (3.70 ml) a 0.4 M solution of **2** or ent-**2** (3.75 ml, 1.50 mmol) in dichloromethane was added dropwise, under argon atmosphere, followed by triethylamine (1.8 mmol). The reaction was stirred at 10 °C for 2.5 h before cooling to -78 °C. Then the chiral aldehyde (3.0 mmol) was added dropwise. After being stirred for 18 h at -78 °C, the reaction mixture was quenched with phosphate buffer (1.0 ml) and allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue dissolved in MeOH (10.0 ml) and phosphate buffer (3.0 ml). 30% H_2O_2 (3.0 ml) was then added at 0 °C, and the mixture was stirred at room temperature for 20 min. MeOH was removed *in vacuo*, and the crude mixture was extracted twice with CH_2Cl_2. The combined organic extracts were washed with water and saturated brine, dried over Na_2SO_4, and the solvent was removed *in vacuo*. The crude products were analysed by VPC and ^{13}C-NMR for determining the diastereomeric ratios. The crude products were chromatographed on silica gel to give the pure aldol adducts (see below).

General Procedure for the *tert*-butyl thiopropionate aldol additions (Table 1, entries 1,2; Table 2, entries 1,2; Table 3, entries 1-3). To a cooled (0 °C) solution of *tert*-butyl thiopropionate (1.0 mmol) in ethyl ether (3.70 ml) a 0.4 M solution of **2** or ent-**2** (4.50 ml, 1.8 mmol) in dichloromethane was added dropwise, under argon atmosphere, followed by triethylamine (2.8 mmol). The reaction was stirred at 10 °C for 5 h before cooling to -78 °C. Then the chiral aldehyde (3.0 mmol) was added dropwise. After being stirred for 18 h at -78 °C, the reaction mixture was allowed to warm to -10 °C and quenched with phosphate buffer (1.0 ml). The solvent was removed *in vacuo* and the residue dissolved in MeOH (10.0 ml) and phosphate buffer (3.0 ml). 30% H_2O_2 (3.0 ml) was then added at 0 °C, and the mixture was stirred at room temperature for 20 min. MeOH was removed *in vacuo*, and the crude mixture was extracted twice with CH_2Cl_2. The combined organic extracts were washed with water and saturated brine, dried over Na_2SO_4, and the solvent was removed *in vacuo*. The crude products were analysed by VPC and ^{13}C-NMR for determining the diastereomeric ratios. The crude products were chromatographed on silica gel to give the pure aldol adducts (see below).

2,3-anti-3,4-anti (**4**, Table 1, entry 1). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, CH_3, d, J =7.3 Hz), 1.28 (3H, CH_3, d, J = 6.2 Hz), 1.48 (9H, ^{t}Bu, s), 2.90-3.03 (2H, OH and CHCO, m), 3.51 (1H, C<u>H</u>OBn, dq, J = 6.2 Hz), 3.62-3.67 (1H, C<u>H</u>OH, m), 4.48 (A part of AB system, J = 11.3 Hz), 4.64 (B part of AB system, J = 11.3 Hz), 7.32-7.40 (5H, Ar-H, m). ^{13}C-NMR ($CDCl_3$) δ: 15.67, 16.28, 30.45, 48.95, 49.50, 71.66, 77.47, 77.90, 128.20, 128.36, 128.58, 129.09, 139.17, 206.28. $[\alpha]_D^{25}$ = +46.6 ($CHCl_3$, c = 1.76); $[\alpha]_{365(Hg)}^{25}$ = +158.0 ($CHCl_3$, c = 1.76). VPC (SE-30, 30m, 0.25 mm; 100-220°C): 23.75 min. Calcd for $C_{17}H_{26}O_3S$: C 65.77, H 8.44. Found: C 65.70; H 8.51.

2,3-anti-3,4-syn (**5**, Table 1, entry 2). ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, CH_3, d, J =7.2 Hz), 1.29 (3H, CH_3, d, J = 6.2 Hz), 1.46 (9H, ^{t}Bu, s), 2.66 (1H, OH, d, J = 8.4 Hz), 2.83 (1H, CHCO, dq, J = 7.2 and 7.1 Hz), 3.55-3.65 (2H, C<u>H</u>OH and C<u>H</u>OBn, m), 4.33 (A part of AB system, J = 11.7 Hz), 4.69 (B part of AB system, J = 11.7 Hz), 7.30-7.42 (5H, Ar-H, m). ^{13}C-NMR ($CDCl_3$) δ: 15.62, 16.48, 30.45, 48.76, 52.00, 71.38, 74.75, 77.85, 128.42, 128.56, 129.10, 139.03, 204.56. $[\alpha]_D^{25}$ = -39.1 ($CHCl_3$, c = 0.78); $[\alpha]_{365(Hg)}^{25}$ = -155.4 ($CHCl_3$, c = 0.78). VPC (SE-30, 30m, 0.25 mm; 100-220°C): 24.94 min. Calcd for $C_{17}H_{26}O_3S$: C 65.77, H 8.44. Found: C 65.67; H 8.53.

3,4-anti (**4**, Table 1, entry 3). ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, CH_3, d, J = 6.4 Hz), 1.48 (9H, ^{t}Bu, s), 2.61-2.73 (2H, CH_2CO, m), 2.82 (1H, OH, d, J = 4.5 Hz), 3.52 (1H, C<u>H</u>OBn, dq, J = 6.4 and 6.0 Hz), 4.00-4.25 (1H, C<u>H</u>OH, m), 4.47 (A part of AB system, J = 11.7 Hz), 4.67 (B part of AB system, J = 11.7 Hz), 7.25-7.40 (5H, Ar-H, m). ^{13}C-NMR ($CDCl_3$) δ: 15.70, 30.46, 47.37, 49.09, 71.73, 71.98, 128.18, 128.42, 129.12, 139.14, 200.75. $[\alpha]_D^{25}$ = +31.6 ($CHCl_3$, c = 1.16); $[\alpha]_{365(Hg)}^{25}$ = +95.1 ($CHCl_3$, c = 1.16). VPC (SE-30, 30m, 0.25 mm; 100-220°C): 24.22 min. Calcd for $C_{16}H_{24}O_3S$: C 64.83, H 8.16. Found: C 64.81; H 8.20.

3,4-syn (**5**, Table 1, entry 4). ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, CH_3, d, J = 6.4 Hz), 1.49 (9H, ^{t}Bu, s), 2.70 (2H, CH_2CO, d, J = 6.4 Hz), 2.78 (1H, OH, d, J = 4.5 Hz), 3.52 (1H, C<u>H</u>OBn, dq, J = 6.4 and 6.0 Hz), 4.03 (1H, C<u>H</u>OH, ddt, J = 5.4, 6.0 and 6.4 Hz), 4.40 (A part of AB system, J = 11.7 Hz), 4.79 (B part of AB system, J = 11.7 Hz), 7.25-7.40 (5H, Ar-H, m). ^{13}C-NMR ($CDCl_3$) δ: 15.86, 30.49, 48.22, 49.03, 71.80, 72.21, 77.29, 128.50, 129.16, 139.06, 200.00. $[\alpha]_D^{25}$ = +6.33 ($CHCl_3$, c = 0.49); $[\alpha]_{365(Hg)}^{25}$ = +24.9 ($CHCl_3$, c = 0.49). VPC (SE-30, 30m, 0.25 mm; 100-220°C): 24.53 min. Calcd for $C_{16}H_{24}O_3S$: C 64.83, H 8.16. Found: C 64.79; H 8.19.

2,3-anti-3,4-syn (**8**, Table 2, entry 1). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, CH_3, d, J = 7.2 Hz); 1.48 (9H, tBu, s); 1.30-1.75 (10H, CH_2, m); 2.65-2.82 (1H, C<u>H</u>Me, m); 3.56-3.70 (1H, C<u>H</u>OH, m); 3.80-4.27 (3H, CH_2O + CHO, m). ^{13}C-NMR ($CDCl_3$) δ: 15.50, 24.56, 24.69, 25.93, 30.54, 35.76, 36.76, 48.96, 53.00, 66.64, 73.74, 76.64, 110.86, 203.89. $[\alpha]_D^{25}$ = +30.0° ($CHCl_3$, c = 0.41); $[\alpha]_{365(Hg)}^{25}$ = +109.5° ($CHCl_3$, c = 0.41). VPC (SE-30, 30m, 0.25 mm; 100-220°C): 46.69 min. Calcd for $C_{16}H_{28}O_4S$: C 60.73, H 8.92. Found: C 60.69; H 8.99.

2,3-anti-3,4-anti (**7**, Table 2, entry 2). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, CH_3, d, J = 7.2 Hz); 1.49 (9H, tBu, s); 1.30-1.70 (10H, CH_2, m); 2.89 (1H, C<u>H</u>Me, dq, J = 3.6, 7.2 Hz); 3.08 (1H, OH, br.s), 3.60 (1H, C<u>H</u>OH, m); 3.90-4.10 (3H, CH_2O + CHO, m). ^{13}C-NMR ($CDCl_3$) δ: 16.18, 24.62, 24.82, 26.06, 30.58, 35.77, 37.35, 49.20, 50.55, 50.65, 67.43, 76.32, 110.74, 206.10. $[\alpha]_D^{25}$ = - 62.4° ($CHCl_3$, c = 0.83); $[\alpha]_{365(Hg)}^{25}$ = - 222.4° ($CHCl_3$, c = 0.83). VPC (SE-30, 30m, 0.25 mm; 100-220°C): 44.18 min. Calcd for $C_{16}H_{28}O_4S$: C 60.73, H 8.92. Found: C 60.70; H 8.97.

3,4-syn (**8**, Table 2, entry 3). ^{1}H-NMR ($CDCl_3$) δ: 1.3-1.7 (10H, CH_2, m), 1.48 (9H, ^{t}Bu, s), 2.59-2.99 (2H, CH_2CO, AB part of an ABX system, J_{AB} = 15.5 Hz; J_{AX} = 4.5 Hz; J_{BX} = 5.1 Hz; ν_A = 2.63, ν_B = 2.78 ppm), 3.78-3.86 (1H, C<u>H</u>OH, m), 3.90-4.13 (3H, CHO, CH_2O, m). ^{13}C-NMR ($CDCl_3$) δ: 24.29, 24.51, 25.72, 30.33, 35.31, 36.68, 48.57, 48.94, 65.86, 69.36, 78.06, 110.70, 198.94. $[\alpha]_D^{25}$ = +11.8 ($CHCl_3$, c = 1.76); $[\alpha]_{365(Hg)}^{25}$ = +36.7 ($CHCl_3$, c = 1.76). VPC (SE-30, 30m, 0.25 mm; 100-220°C; 2.5°C/min): 45.68 min. Calcd for $C_{15}H_{26}O_4S$: C 59.57, H 8.67. Found: C 59.49; H 8.76.

3,4-anti (**7**, Table 2, entry 4). ^{1}H-NMR ($CDCl_3$) δ: 1.3-1.7 (10H, CH_2, m), 1.48 (9H, ^{t}Bu, s), 2.56-2.92 (2H, CH_2CO, AB part of an ABX system, J_{AB} = 16.0 Hz; J_{AX} = 2.9 Hz; J_{BX} = 8.2 Hz; ν_A = 2.62, ν_B = 2.86 ppm), 3.00 (1H, OH, d, J = 3.2 Hz), 3.90-4.10 (4H, C<u>H</u>O, C<u>H</u>$_2$O, C<u>H</u>OH, m). ^{13}C-NMR ($CDCl_3$) δ: 24.34, 24.56, 25.76, 30.38, 35.39, 37.03, 48.22, 49.06, 66.78, 70.55, 77.99, 110.65, 200.40. $[\alpha]_D^{25}$ = - 11.2 ($CHCl_3$, c = 1.88); $[\alpha]_{365(Hg)}^{25}$ = -27.2 ($CHCl_3$, c = 1.88). VPC (SE-30, 30m, 0.25 mm; 100-220°C; 2.5°C/min): 43.79 min. Calcd for $C_{15}H_{26}O_4S$: C 59.57, H 8.67. Found: C 59.51; H 8.72.

2,3-anti-3,4-syn (**10**, Table 3, entry 2). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, CH_3, d, J =7.2 Hz), 1.13 (3H, CH_3, d, J = 7.2 Hz), 1.49 (9H, ^{t}Bu, s), 1.7-2.0 (1H, C<u>H</u>Me, m), 2.7 (1H, C<u>H</u>Me, dq, J = 7.2 and 7.1 Hz), 2.95 (1H, OH, br. s), 3.56 (2H, CHMeC<u>H</u>$_2$O, d, J = 5.0 Hz), 4.0 (1H, C<u>H</u>OH, dd, J = 8.4 and 2.7 Hz), 4.45 (A part of AB system, J = 5.2 Hz), 4.58 (B part of AB system, J = 5.2 Hz), 7.20-7.45 (5H, Ar-H, m). ^{13}C-NMR ($CDCl_3$) δ: 10.65, 15.83, 30.44, 36.12, 48.75, 52.60, 74.09, 75.26, 75.64, 128.29, 129.07, 138.88, 205.42. $[\alpha]_D^{25}$ = +24.7 ($CHCl_3$, c = 1.35); $[\alpha]_{365(Hg)}^{25}$ = +82.7 ($CHCl_3$, c = 1.35). Calcd for $C_{18}H_{28}O_3S$: C 66.63, H 8.70. Found: C 66.59; H 8.75.

2,3-anti-3,4-anti (**11**, Table 3, entry 3). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, CH_3, d, J = 7.0 Hz); 1.24 (3H, CH_3, d, J = 7.5 Hz); 2.84 (1H, CH, dq). ^{13}C-NMR ($CDCl_3$) δ (selected values): 16.26, 30.42, 37.41, 48.90, 51.94, 73.46, 74.09. Calcd for $C_{18}H_{28}O_3S$: C 66.63, H 8.70. Found: C 66.53; H 8.77.

3,4-syn (**10**, Table 3, entry 5). ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, CH_3, d, J = 6.9 Hz), 1.48 (9H, ^{t}Bu, s), 1.80-1.98 (1H, C<u>H</u>Me, m), 2.56-2.73 (2H, C<u>H</u>$_2$CO, m), 3.09 (1H, OH, J = 3.8 Hz), 3.46-3.60 (2H, CHMeC<u>H</u>$_2$O, m), 4.20-4.32 (1H, C<u>H</u>OH, m), 4.52 (2H, PhC<u>H</u>$_2$, s), 7.25-7.40 (5H, Ar-H, m). ^{13}C-NMR ($CDCl_3$) δ: 11.83, 30.48, 38.80, 49.54, 71.02, 74.09, 128.17, 128.32, 129.10, 138.93, 200.64. VPC (SE-30, 30m, 0.25 mm; 100-220°C): 26.58 min. Calcd for $C_{17}H_{26}O_3S$: C 65.77, H 8.44. Found: C 65.70; H 8.49.

3,4-anti (**11**, Table 3, entry 6). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, CH_3, d, J =7.0 Hz), 1.48 (9H, ^{t}Bu, s), 1.80-1.95 (1H, C<u>H</u>Me, m), 2.56-2.73 (2H, C<u>H</u>$_2$CO, m), 3.46-3.60 (3H, O<u>H</u> + CHMeC<u>H</u>$_2$O, m), 3.98-4.10

(1H, C<u>H</u>OH, m), 4.52 (2H, PhC<u>H</u>$_2$, s), 7.25-7.40 (5H, Ar-H, m). ^{13}C-NMR ($CDCl_3$) δ: 14.42, 30.48, 39.14, 48.96, 49.93, 72.75, 74.34, 128.17, 128.32, 129.10, 138.82, 200.64. VPC (SE-30, 30m, 0.25 mm; 100-220°C): 26.58 min. Calcd for $C_{17}H_{26}O_3S$: C 65.77, H 8.44. Found: C 65.72; H 8.51.

General Procedure for the *tert*-butyl thioacetate aldol additions to *N,N*-dibenzylamino aldehydes (Table 4, entries 1-10). To a cooled (0 °C) solution of *tert*-butyl thioacetate (1.0 mmol) in ethyl ether (4.16 ml) a 0.4 M solution of **2** or ent-**2** (3.7 ml, 1.48 mmol) in dichloromethane was added dropwise, under argon atmosphere, followed by triethylamine (1.6 mmol). The reaction was stirred at 10 °C for 2.5 h before cooling to -78 °C. Then *N,N*-dibenzylamino aldehyde **14** (1.3 mmol) was added dropwise. After being stirred for 18 h at -78 °C, the reaction mixture was quenched with phosphate buffer (1.0 ml) and allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue dissolved in MeOH (10.0 ml) and phosphate buffer (3.0 ml). 30% H_2O_2 (3.0 ml) was then added at 0 °C, and the mixture was stirred at room temperature for 45 min. MeOH was removed *in vacuo*, and the crude mixture was extracted twice with CH_2Cl_2. The combined organic extracts were washed with water and saturated brine, dried over Na_2SO_4, and the solvent was removed *in vacuo*. The crude products were analysed by ^{13}C-NMR for determining the diastereomeric ratios. The crude products were chromatographed on silica gel (hexanes : ethyl ether 6 : 1) to give the pure aldol adducts (**15** and **16**, see below) as colourless oils.

(3*R*, 4*S*)-4-[*N,N*]-dibenzylamino-3-hydroxy-5-phenylpentanoic acid *tert*-butyl thioester (**15a**, Table 4, entry 1). Yield: 75%. ^{1}H NMR ($CDCl_3$) δ: 1.48 (9H, tBu, s), 2.30-2.45 (1H, C<u>H</u>HCO, m), 2.70-3.20 (5H, CH<u>H</u>CO, C<u>H</u>N, C<u>H</u>$_2$Ph, O<u>H</u>, m), 3.58-3.78 (4H, 2 x PhC<u>H</u>$_2$N, AB system, ν_A= 3.63, ν_B= 3.74, J_{AB}= 13.8 Hz), 4.25-4.40 (1H, C<u>H</u>OH, m), 7.10-7.40 (15H, ArH, m); ^{13}C-NMR ($CDCl_3$) δ: 29.74, 32.21, 48.41, 49.45, 54.58, 63.01, 69.24, 125.88, 126.90, 128.20, 128.27, 128.80, 129.51, 139.57, 140.94, 200.74. $[\alpha]_D^{25}$ = -16.3° ($CHCl_3$, *c* = 1.42); $[\alpha]_{365(Hg)}^{25}$ = -84.6° ($CHCl_3$, *c* = 1.42). Calcd for $C_{29}H_{35}NO_2S$: C 75.45, H 7.64, N 3.03. Found: C 75.40; H 7.70, N 3.00.

(3*S*, 4*S*)-4-[*N,N*]-dibenzylamino-3-hydroxy-5-phenylpentanoic acid *tert*-butyl thioester (**16a**, Table 4, entry 2). Yield: 70%. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (9H, tBu, s), 2.20-2.66 (2H, C<u>H</u>H<u>C</u>O, AB part of an ABX system, ν_A= 2.27, ν_B= 2.57, J_{AB}= 15.5, J_{AX}= 2.2, J_{BX}= 9.3 Hz), 2.76-2.89 (2H, C<u>H</u>$_2$Ph), 3.06-3.20 (1H, C<u>H</u>N, m), 3.39-4.09 (4H, 2 x PhC<u>H</u>$_2$N, AB system, ν_A= 3.42, ν_B= 4.05, J_{AB}= 13.3 Hz), 3.97-4.09 (1H, C<u>H</u>OH, m), 7.19-7.40 (15H, ArH, m); ^{13}C-NMR ($CDCl_3$) δ: 29.71, 31.01, 48.18, 49.37, 54.35, 62.99, 68.20, 126.21, 127.15, 128.40, 128.60, 128.97, 129.19, 139.10, 140.01, 200.00. $[\alpha]_D^{25}$ = -2.6° ($CHCl_3$, *c* = 1.38); $[\alpha]_{436(Hg)}^{25}$ = -2.8° ($CHCl_3$, *c* = 1.38). Calcd for $C_{29}H_{35}NO_2S$: C 75.45, H 7.64, N 3.03. Found: C 75.38; H 7.69, N 3.05.

(3*R*, 4*S*)-4-[*N,N*]-dibenzylamino-3-hydroxypentanoic acid *tert*-butyl thioester (**15b**, Table 4, entry 3). Yield: 80%. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, <u>Me</u>CHN, *J* = 6.6 Hz); 1.47 (9H, tBu, s); 2.28 (1H, CHCO, dd, *J* = 16.0, 9.7 Hz); 2.62 (1H, CHN, dq, *J* = 7.15, 6.6 Hz); 2.84 (1H, OH, m); 3.21 (1H, CHCO, dd, *J* = 16.0, 2.15 Hz); 3.37-3.78 (4H, 2 x PhC<u>H</u>$_2$N, AB system, ν_A= 3.41, ν_B= 3.74, J_{AB}= 13.6 Hz); 4.03 (1H, C<u>H</u>OH, m); 7.28-7.34 (10H, ArH, m); ^{13}C-NMR ($CDCl_3$) δ: 8.29, 29.77, 48.38, 48.91, 54.41, 56.90, 70.73, 126.97, 128.31, 128.86, 139.72, 202.08. $[\alpha]_D^{25}$ = - 17.5° ($CHCl_3$, *c* = 0.93); $[\alpha]_{436(Hg)}^{25}$ = - 46.4° ($CHCl_3$, *c* = 0.93); $[\alpha]_{365(Hg)}^{25}$ = - 98.0° ($CHCl_3$, *c* = 0.93). Calcd for $C_{23}H_{31}NO_2S$: C 71.65, H 8.10, N 3.63. Found: C 71.59; H 8.19, N 3.60.

(3*S*, 4*S*)-4-[*N,N*]-dibenzylamino-3-hydroxypentanoic acid *tert*-butyl thioester (**16b**, Table 4, entry 4). Yield: 75%. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, <u>Me</u>CHN, *J* = 6.6 Hz); 1.47 (9H, tBu, s); 2.45 (1H, CHCO, dd, *J* = 15.7, 8.0 Hz); 2.55 (1H, CHCO, dd, *J* = 15.7, 3.6 Hz); 2.63 (1H, CHN, dq, *J* = 9.6,

6.6 Hz); 3.30-3.91 (4H, 2 x PhC$\underline{H}_2$N, AB system, ν_A= 3.33, ν_B= 3.88, J_{AB}= 13.3 Hz); 4.01 (1H, C$\underline{H}$OH, ddd, J = 3.6, 8.0, 9.6 Hz); 4.46 (1H, OH, br.s); 7.18-7.40 (10H, ArH, m); ^{13}C-NMR ($CDCl_3$) δ: 7.96, 29.44, 47.91, 48.94, 53.31, 57.79, 68.53, 127.12, 128.35, 128.87, 138.66, 198.8. $[\alpha]_D^{25}$ = + 2.32° ($CHCl_3$, c = 1.35). Calcd for $C_{23}H_{31}NO_2S$: C 71.65, H 8.10, N 3.63. Found: C 71.61; H 8.15, N 3.58.

(3*R*, 4*S*, 5*S*)-4-[*N,N*]-dibenzylamino-3-hydroxy-5-methylheptanoic acid *tert*-butyl thioester (**15c**, Table 4, entry 5). Yield: 75%. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, C$\underline{H}_3$CH$_2$, t, J = 7.4 Hz); 1.05 (3H, C$\underline{H}_3$CH, d, J = 6.7 Hz); 1.22-1.42 (1H, CH$_3$C$\underline{H}$, m); 1.47 (9H, tBu, s); 1.47-1.75 (1H, CH$_3$C$\underline{H}$, m); 1.80-2.0 (1H, CH$_3$C$\underline{H}$, m); 2.44 (1H, CHCO, dd, J = 15.5, 11.4 Hz); 2.45 (1H, CHN, dd, J = 6.1, 6.05 Hz); 2.82 (1H, OH, d, J = 5.13 Hz); 3.04 (1H, CHCO, dd, J = 15.5, 1.87 Hz); 3.55-3.78 (4H, 2 x PhC$\underline{H}_2$N, AB system, ν_A= 3.59, ν_B= 3.74, J_{AB}= 13.5 Hz); 4.35 (1H, C$\underline{H}$OH, m); 7.16-7.36 (10H, ArH, m); ^{13}C-NMR ($CDCl_3$) δ: 12.00, 16.03, 29.32, 29.80, 32.91, 48.40, 49.66, 55.11, 64.37, 67.60, 127.09, 128.36, 129.09, 139.66, 201.03. $[\alpha]_D^{25}$ = - 23.3° ($CHCl_3$, c = 0.725); $[\alpha]_{436(Hg)}^{25}$ = - 57.5° ($CHCl_3$, c = 0.725). Calcd for $C_{26}H_{37}NO_2S$: C 73.02, H 8.72, N 3.28. Found: C 72.98; H 8.80, N 3.21.

(3*S*, 4*S*, 5*S*)-4-[*N,N*]-dibenzylamino-3-hydroxy-5-methylheptanoic acid *tert*-butyl thioester (**16c**, Table 4, entry 6). Yield: 71%. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, C$\underline{H}_3$CH$_2$, t, J = 7.3 Hz); 1.07 (3H, C$\underline{H}_3$CH, d, J = 7.1 Hz); 1.22-1.40 (2H, CH$_3$C$\underline{H}_2$, m); 1.48 (9H, tBu, s); 1.88-2.08 (1H, CH$_3$C$\underline{H}$, m); 2.32-2.51 (3H, CH$_2$CO + CHN, m); 3.41-4.00 (4H, 2 x PhC$\underline{H}_2$N, AB system, ν_A= 3.44, ν_B= 3.97, J_{AB}= 13.2 Hz); 4.29 (1H, C$\underline{H}$OH, dt, J = 3.3, 8.4 Hz); 4.35 (1H, OH, m); 7.20-7.34 (10H, ArH, m); ^{13}C-NMR ($CDCl_3$) δ: 12.58, 16.21, 29.77, 30.51, 31.83, 48.22, 50.24, 53.96, 64.71, 65.22, 127.21, 128.36, 128.41, 129.11, 129.22, 138.94, 199.08. $[\alpha]_D^{25}$ = -41.5° ($CHCl_3$, c = 1.72); $[\alpha]_{436(Hg)}^{25}$ = -88.4° ($CHCl_3$, c = 1.72); $[\alpha]_{365(Hg)}^{25}$ = -147.5° ($CHCl_3$, c = 1.72). Calcd for $C_{26}H_{37}NO_2S$: C 73.02, H 8.72, N 3.28. Found: C 73.09; H 8.75, N 3.25.

(3*R*, 4*S*)-4-[*N,N*]-dibenzylamino-3-hydroxy-5-methylhexanoic acid *tert*-butyl thioester (**15d**, Table 4, entry 7). Yield: 80%. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, C$\underline{H}_3$CH, d, J = 6.7 Hz); 1.17 (3H, C$\underline{H}_3$CH, d, J = 6.7 Hz); 1.49 (9H, tBu, s); 2.20 (1H, Me$_2$C$\underline{H}$, m); 2.44 (1H, C$\underline{H}$N, m); 2.51 (1H, C$\underline{H}$COS-tBu, dd, J = 15.2, 10.5 Hz); 2.87 (1H, C$\underline{H}$COS-tBu, dd, J = 15.2, 1.54 Hz); 3.04 (1H, OH, d, J = 6.0 Hz); 3.65-3.81 (4H, 2 x PhC$\underline{H}_2$N, AB system, ν_A= 3.70, ν_B= 3.76, J_{AB} = 13.6 Hz); 4.31(1H, C$\underline{H}$OH, m); 7.18-7.40 (10H, ArH, m); ^{13}C-NMR ($CDCl_3$) δ: 20.20, 23.23, 26.81, 29.79 (CH$_3$ *t*-Bu), 48.40, 49.54, 55.49, 66.08, 67.50, 127.24, 128.46, 129.22, 139.53, 200.47 (CO). $[\alpha]_D^{25}$ = -27.8° ($CHCl_3$, c = 3.91); $[\alpha]_{436(Hg)}^{25}$ = -65.5° ($CHCl_3$, c = 3.91); $[\alpha]_{365(Hg)}^{25}$ = -123.3° ($CHCl_3$, c = 3.91). Calcd for $C_{25}H_{35}NO_2S$: C 72.60, H 8.53, N 3.39. Found: C 72.51; H 8.59, N 3.30.

(3S, 4*S*)-[*N,N*]-4-dibenzylamino-3-hydroxy-5-methylhexanoic acid *tert*-butyl thioester (**16d**, Table 4, entry 8). Yield: 72%. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, C$\underline{H}_3$CH, d, J = 6.6 Hz); 1.09 (3H, C$\underline{H}_3$CH, d, J = 6.8 Hz); 1.48 (9H, tBu, s); 2.22-2.35 (2H, C$\underline{H}$N, Me$_2$C$\underline{H}$, m); 2.37 (1H, C$\underline{H}$COS-tBu, dd, J = 15.0, 2.7 Hz); 2.51 (1H, C$\underline{H}$COS-tBu, dd, J = 15.0, 8.8 Hz); 3.51-4.03 (4H, 2 x PhC$\underline{H}_2$N, AB system, ν_A= 3.55, ν_B= 4.00, J_{AB}= 13.0 Hz); 4.14 (1H, OH, s); 4.24 (1H, C$\underline{H}$OH, ddd, J = 2.7, 8.8, 6.8 Hz); 7.22-7.40 (10H, ArH, m); ^{13}C-NMR ($CDCl_3$) δ: 20.00, 23.56, 25.92, 29.77 (CH$_3$ *t*-Bu), 48.23, 50.34, 54.53, 65.38, 66.34, 127.15, 128.36, 129.33, 139.22, 199.66. $[\alpha]_D^{25}$ = -58.2° ($CHCl_3$, c = 2.47); $[\alpha]_{436(Hg)}^{25}$ = -123.0° ($CHCl_3$, c = 2.47); $[\alpha]_{365(Hg)}^{25}$ = -204.2° ($CHCl_3$, c = 2.47). Calcd for $C_{25}H_{35}NO_2S$: C 72.60, H 8.53, N 3.39. Found: C 72.55; H 8.61, N 3.33.

(3*R*, 4*S*)-4-[*N,N*]-dibenzylamino-3-hydroxy-6-methylheptanoic acid *tert*-butyl thioester (**15e**, Table 4, entry 9). Yield: 78%. ^{1}H-NMR ($CDCl_3$) δ: 0.74 (3H, C$\underline{H}_3$CH, d, J = 6.5 Hz); 0.92 (3H,

$C\underline{H}_3CH$, d, J = 6.5 Hz); 1.25 (1H, C<u>H</u>HCHN, m); 1.49 (9H, tBu, s); 1.67 (1H, CH<u>H</u>CHN, dd, J = 14.0, 6.9 Hz); 1.85 (1H, $Me_2C\underline{H}$, m); 2.47 (1H, CHCO, dd, J = 15.3, 9.8 Hz); 2.60 (1H, CHN, q, J = 6.2 Hz); 2.76 (1H, CHCO, dd, J = 15.3, 2.7 Hz); 2.85 (1H, OH, m); 3.59-3.75 (4H, 2 x $PhC\underline{H}_2N$, AB system, ν_A= 3.64, ν_B= 3.70, J_{AB}= 13.6 Hz); 4.10 (1H, C<u>H</u>OH, m); 7.19-7.38 (10H, ArH, m); ^{13}C-NMR ($CDCl_3$) δ: 22.64, 23.20, 25.04, 29.78, 35.17, 48.46, 49.38, 54.70, 58.44, 68.41, 126.97, 128.27, 129.00, 140.00, 200.64. $[\alpha]_D^{25}$ = -35.5° ($CHCl_3$, c = 6.94); $[\alpha]_{436(Hg)}^{25}$ = -82.4° ($CHCl_3$, c = 6.94); $[\alpha]_{365(Hg)}^{25}$ = -157.7° ($CHCl_3$, c = 6.94). Calcd for $C_{26}H_{37}NO_2S$: C 73.02, H 8.72, N 3.28. Found: C 72.98; H 8.79, N 3.21.

(3S, 4*S*)-4-[*N,N*]-dibenzylamino-3-hydroxy-6-methylheptanoic acid *tert*-butyl thioester (16e, Table 4, entry 10). Yield: 71%. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (6H, $C\underline{H}_3CH$, d, J = 6.5 Hz); 1.27-1.44 (1H, C<u>H</u>HCHN, m); 1.49 (9H, tBu, s); 1.53-1.80 (2H, CH<u>H</u>CHN, $Me_2C\underline{H}$, m); 2.43-2.67 (3H, $C\underline{H}_2CO$, CHN, m); 3.41-3.97 (4H, 2 x $PhC\underline{H}_2N$, AB system, ν_A= 3.45, ν_B= 3.93, J_{AB}= 13.4 Hz); 4.04 (1H, C<u>H</u>OH, dd, J = 8.2, 3.0 Hz); 4.18 (1H, OH, m); 7.20-7.40 (10H, ArH, m); ^{13}C-NMR ($CDCl_3$) δ: 22.79, 23.33, 26.24, 29.74, 34.84, 48.22, 49.36, 54.08, 59.62, 68.91, 127.09, 128.36, 129.01, 139.28, 199.52. $[\alpha]_D^{25}$ = -28.3° ($CHCl_3$, c = 3.03); $[\alpha]_{436(Hg)}^{25}$ = -60.3° ($CHCl_3$, c = 3.03); $[\alpha]_{365(Hg)}^{25}$ = -102.3° ($CHCl_3$, c = 3.03). Calcd for $C_{26}H_{37}NO_2S$: C 73.02, H 8.72, N 3.28. Found: C 73.05; H 8.77, N 3.19.

Preparation of (3*S*, 4*S*, 5*S*)-4-[*N,N*]-dibenzylamino-3-hydroxy-5-methylheptanoic acid methyl ester 17. The aldol adduct **16c** (56 mg, 0.13mmol) was dissolved in THF (8 ml) at 0°C, and 1N sodium hydroxyde (0.6 ml, 0.6 mmol) was then added. The solution was stirred for 18 h at room temperature. The solvent was removed under reduced pressure, and 5 ml of water were added. At 0 °C the aqueous layer was acidified with 1N aqueous HCl until pH 2. The water was evaporated to give the acid as a pale-yellow solid, which was esterified after being dissolved in MeOH (5 ml) under standard conditions using an ethereal diazomethane solution. Methyl ester **17** was obtained in 75% yield after extraction with methylene chloride. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, $C\underline{H}_3CH_2$, t, J = 7.1 Hz); 1.08 (3H, $C\underline{H}_3CH$, d, J = 7.0 Hz); 1.17-1.7 (2H, $CH_3C\underline{H}_2$, m); 1.89-2.06 (1H, $CH_3C\underline{H}$, m); 2.15-2.43 (3H, CH_2CO + CHN, m); 3.42-4.01 (4H, 2 x $PhC\underline{H}_2N$, AB system, ν_A= 3.46, ν_B= 3.97, J_{AB}= 13.2 Hz); 3.69 (3H, $C\underline{H}_3OH$, s); 4.26 (1H, C<u>H</u>OH, m); 7.12-7.43 (10H, ArH, m); ^{13}C-NMR ($CDCl_3$) δ: 12.49, 16.13, 30.33, 31.73, 40.31, 51.62, 53.95, 55.24, 64.76, 126.99, 128.28, 128.91, 172.32. $[\alpha]_D^{25}$ = -7.4° ($CHCl_3$, c = 5.35); $[\alpha]_{436(Hg)}^{25}$ = -13.6° ($CHCl_3$, c = 5.35); $[\alpha]_{365(Hg)}^{25}$ = -19.8° ($CHCl_3$, c = 5.35). Calcd for $C_{23}H_{31}NO_3$: C 74.76, H 8.46, N 3.79. Found: C 74.70; H 8.52, N 3.70.

Preparation of Isostatin Lactam 18. The methyl ester **17** (46 mg, 0.12 mmol) was dissolved in MeOH (1.5 ml) and HCO_2NH_4 (82 mg, 1.2 mmol) was added. After 5 min 10% Pd/C was added (77 mg). and the reaction was heated at 65 °C and stirred for 30 min. The reaction mixture was concentrated under reduced presure and filtered through Celite. The residue was washed three times with $CHCl_3$ and the combined extracts were concentrated *in vacuo* to give the crude lactam. Without further purification, the crude lactam was dissolved in pyridine (1 ml) and Ac_2O (0.6 ml) was added dropwise. The reaction was stirred 5 h and the solvent was removed *in vacuo*. Ethyl acetate was added and the solution was washed twice with water. After drying over Na_2SO_4, the organic layer was concentrated to give lactam **18** in 85% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, $C\underline{H}_3CH$, d, J = 6.7 Hz); 0.95 (3H, $C\underline{H}_3CH_2$, d, J = 7.3 Hz); 1.12-1.83 (3H, $C\underline{H}CH_3$, $C\underline{H}_2CH_3$, m); 2.09 (3H, CH_3CO, s); 2.36 (1H, C<u>H</u>HCO, dd, J = 17.8, 1 Hz); 2.71 (1H, CH<u>H</u>CO, dd, J = 17.8, 5.7 Hz); 3.50 (1H, CHN, dd, J = 9.5, 4.5); 5.41 (1H, CHOAc, ddd, J = 5.7, 4.5, 1 Hz); 6.55 (1H, NH, s broad). $[\alpha]_D^{25}$ = +38° ($CHCl_3$, c = 0.1); $[\alpha]_{436(Hg)}^{25}$ = +75° ($CHCl_3$, c = 0.1); $[\alpha]_{365(Hg)}^{25}$ = +121° ($CHCl_3$, c = 0.1); $[\alpha]_D^{25}$

= +30° (MeOH, *c* = 0.1); Lit. (ref. 20) = +31° (MeOH, *c* = 0.1). Calcd for $C_{10}H_{17}NO_3$: C 60.28, H 8.60, N 7.03. Found: C 60.21; H 8.69, N 7.00.

Preparation of (3S, 4*S*)-4-[*N,N*]-dibenzylamino-3-hydroxy-6-methylheptanoic acid methyl ester 19. It was prepared from the aldol adduct **16e** according to the procedure described for methyl ester **17**, yielding 80% of **19**. Methyl ester **19**: ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, C<u>H</u>$_3$CH, d, *J* = 6.2 Hz); 0.95 (3H, C<u>H</u>$_3$CH, d, *J* = 6.2 Hz); 1.31 (1H, C<u>H</u>HCHN, m); 1.51-1.76 (2H, CH<u>H</u>CHN, Me$_2$C<u>H</u>, m); 2.31-2.60 (3H, C<u>H</u>$_2$CO, CHN, m); 3.41-3.97 (4H, 2 x PhC<u>H</u>$_2$N, AB system, ν_A= 3.44, ν_B= 3.93, J_{AB}= 13.4 Hz); 3.69 (3H, CH$_3$O, s); 3.99 (1H, C<u>H</u>OH, m); 7.22-7.37 (10H, ArH, m). $[\alpha]_D^{25}$ = -3.2° ($CHCl_3$, *c* = 2.77); $[\alpha]_{436(Hg)}^{25}$ = -6.1° ($CHCl_3$, *c* = 2.77); $[\alpha]_{365(Hg)}^{25}$ = -7.2° ($CHCl_3$, *c* = 2.77). Calcd for $C_{23}H_{31}NO_3$: C 74.76, H 8.46, N 3.79. Found: C 74.68; H 8.50, N 3.72.

Preparation of Statin Lactam 20. The procedure described above for lactam **18** yielded 85% of lactam **20** from methyl ester **19**. Lactam **20**: ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, C<u>H</u>$_3$CH, d, *J* = 6.3 Hz); 0.99 (3H, C<u>H</u>$_3$CH, d, *J* = 6.3 Hz); 1.55 (2H, C<u>H</u>$_2$CHN, m); 1.68 (1H, Me$_2$C<u>H</u>, m); 2.35 (1H, C<u>H</u>HCO, dd, *J* = 17.2, 2.0 Hz); 2.67 (1H, C<u>H</u>HCO, dd, *J* = 17.2, 5.8 Hz); 3.73 (1H, CHN, ddd, *J* = 7.6, 6.2, 4.7 Hz); 4.43 (1H, C<u>H</u>OH, ddd, *J* = 5.8, 4.7, 2.0 Hz); 5.79 (1H, NH, br. s); ^{13}C-NMR ($CDCl_3$) δ: 22.37, 23.18, 25.30, 37.58, 41.13, 57.74, 69.32, 176.25; MS *m/z*: 157 (M^+, 80), 114 (100%), 100 (80), 86 (45); IR: 3300, 2960, 2840, 1700, 1460, 1370, 1250 cm^{-1}; $[\alpha]_{436(Hg)}^{25}$ = - 41.1° ($CHCl_3$, *c* = 0.22); $[\alpha]_{365(Hg)}^{25}$ = - 50.3° ($CHCl_3$, *c* = 0.22); $[\alpha]_D^{25}$ = -22.2° ($CHCl_3$, *c* = 0.22); Lit. (ref. 19a) = - 21° ($CHCl_3$, *c* = 0.71). Calcd for $C_8H_{15}NO_2$: C 61.12, H 9.62, N 8.91. Found: C 61.09; H 9.70, N 8.89.

Preparation of (3*S*, 4*S*)-Statine 21. Lactam **20** (70 mg, 0.45 mmol) was dissolved in concentrated HCl (30 ml) and the reaction mixture was warmed to 80 °C for 3 h. Then the water was removed *in vacuo* to give the crude hydrochloride salt. The crude salt was applied to an ion exchange Dowex column [50X8-100(acidic form)] eluting first with water and then with a 2N NH_4OH solution. This procedure led to statine **21** as a white solid (56 mg, 71%). Compound **21:** ^{1}H-NMR (D_2O) δ: 0.75 (3H, C<u>H</u>$_3$CH, d, *J* = 6.3 Hz); 0.77 (3H, C<u>H</u>$_3$CH, d, *J* = 6.3 Hz); 1.34 (2H, C<u>H</u>$_2$CHN, t, *J* = 7.0 Hz); 1.52 (1H, C<u>H</u>Me$_2$, m); 2.26-2.54 (2H, C<u>H</u>$_2$CHOH, AB part of an ABX system, ν_A= 2.32, ν_B= 2.48, J_{AB}= 15.9, J_{AX}= 10.0, J_{BX}= 4.0 Hz); 3.13 (1H, C<u>H</u>NH$_2$, dt, *J* = 6.6, 5.8 Hz); 3.90 (1H, C<u>H</u>OH, ddd, *J* = 10.0, 5.8, 4.0 Hz); ^{13}C-NMR (D_2O) δ: 23.23, 24.47, 26.24, 40.66, 42.38, 56.12, 70.15, 179.26; MS *m/z*: 157 (65), 114 (100%), 100 (92), 86 (40). Calcd for $C_8H_{17}NO_3$: C 54.84, H 9.78, N 7.99. Found: C 54.79; H 9.82, N 7.90.

Table 5: NMR and analytical data.

23-26 (Table 5, entries 1,2). Calcd for $C_{14}H_{20}O_2$: C 76.33, H 9.15. Found: C 76.29; H 9.21.

2,3-anti-3,4-syn (**23**, Table 5, entries 1,2). ^{1}H-NMR ($CDCl_3$) δ (selected values): 3.63 (1H, C<u>H</u>OH, ddd, J_{CHCH} = 4.9, 7.5 Hz; J_{CHOH} = 7.5 Hz). ^{13}C-NMR ($CDCl_3$) δ (selected values): 7.31, 15.28, 16.88, 36.02, 44.20, 46.83, 79.32, 144.68, 217.92.

2,3-anti-3,4-anti (**24**, Table 5, entries 1,2). ^{1}H-NMR ($CDCl_3$) δ (selected values): 3.85 (1H, C<u>H</u>OH, m, J_{CHOH} = 6.0 Hz). ^{13}C-NMR ($CDCl_3$) δ (selected values): 7.22, 14.61, 19.20, 35.62, 42.57, 48.72, 78.50, 142.70.

2,3-syn-3,4-syn (**25**, Table 5, entries 1,2). ^{1}H-NMR ($CDCl_3$) δ (selected values): 4.05 (1H, C<u>H</u>OH, ddd, J_{CHCH} = 2.2, 9.4 Hz; J_{CHOH} = 3.0 Hz). ^{13}C-NMR ($CDCl_3$) δ (selected values): 7.47, 9.19, 18.93, 34.42, 42.90, 46.83, 75.08, 144.11, 217.10.

2,3-syn-3,4-anti (**26**, Table 5, entries 1,2). ^{1}H-NMR ($CDCl_3$) δ (selected values): 4.22 (1H, C<u>H</u>OH, ddd, J_{CHCH} = 3.3, 8.9 Hz; J_{CHOH} = 3.0 Hz). ^{13}C-NMR ($CDCl_3$) δ (selected values): 9.70, 18.30, 42.90, 47.90, 75.42, 143.70.

23-26 (Table 5, entries 3-6). Calcd for $C_{16}H_{24}O_3$: C 72.69, H 9.15. Found: C 72.59; H 9.19.

2,3-anti-3,4-syn (**23**, Table 5, entries 3-6). ^{1}H-NMR ($CDCl_3$) δ (selected values): 3.90 (1H, C<u>H</u>OH, m); 4.52 (2H, OC<u>H</u>$_2$Ph, s). ^{13}C-NMR ($CDCl_3$) δ (selected values): 7.54, 11.80, 12.47, 34.99, 35.86, 48.70, 73.19, 73.83, 74.27.

2,3-anti-3,4-anti (**24**, Table 5, entries 3-6). ^{1}H-NMR ($CDCl_3$) δ (selected values): 4.50 (2H, OC<u>H</u>$_2$Ph, s). ^{13}C-NMR ($CDCl_3$) δ (selected values): 7.36, 14.37, 15.21, 35.70, 35.86, 48.81, 72.53, 73.35, 77.50.

2,3-syn-3,4-syn (**25**, Table 5, entries 3-6). ^{1}H-NMR ($CDCl_3$) δ (selected values): 2.76 (1H, CHCO, dq, J = 6.6, 7.0 Hz); 3.91 (1H, C<u>H</u>OH, dd, J_{CHCH} = 6.6, 4.6 Hz); 4.48 (2H, OC<u>H</u>$_2$Ph, s). ^{13}C-NMR ($CDCl_3$) δ (selected values): 7.35, 9.92, 13.84, 34.98, 35.89, 48.41, 73.34, 74.73, 75.43.

2,3-syn-3,4-anti (**26**, Table 5, entries 3-6). ^{1}H-NMR ($CDCl_3$) δ (selected values): 3.84 (1H, C<u>H</u>OH, ddd, J_{CHCH} = 3.25, 8.4 Hz; J_{CHOH} = 3.1 Hz); 4.52 (2H, OC<u>H</u>$_2$Ph, s). ^{13}C-NMR ($CDCl_3$) δ (selected values): 7.60, 9.24, 13.84, 34.15, 35.89, 48.22, 73.34, 74.26, 74.90.

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