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Highly Enantio- and Diastereoselective Boron Aldol Reactions of α-Heterosubstituted Thioacetates with Aldehydes and Silyl Imines

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Abstract: Boron enolates derived from α-heterosubstituted thioacetates and bearing menthone-derived chiral ligands react with aldehydes to give *anti* aldols with excellent diastero- and enantiocontrol. Boron enolates derived from *tert*-butyl α-halothioacetate and bearing menthone-derived chiral ligands react with imines with excellent diastero- and enantiocontrol to give *syn* α-halo-β-aminothioesters, which can be converted to the corresponding aziridines by simple ring closure during LAH reduction. A key precursor of antibiotics (+)-thiamphenicol and (-)-florfenicol was synthesized.

The boron aldol reaction is a powerful method for the control of both relative and absolute stereochemistry in organic synthesis.[1] We wish to report here an efficient diastereo- and enantioselective addition of chiral boron enolates derived from α-heterosubstituted thioacetates to aldehydes and imines. The chiral boron reagent (**1**, **Scheme 1**), derived from (-)-menthone[2a-f] and developed by transition state computer modelling,[2a,3] has previously been shown to allow a highly enantioselective aldol reaction for thioacetates and thiopropionates.[2b]

The new methodology described here involves the enantioselective coupling of chiral boron enolates derived from *t*-butyl (R^1 = Bu^t) and phenyl (R^1 = Ph) α-alkoxy thioacetates (Y = OBn, OTBDMS) and α-halo thioacetates (Y = Cl, Br) with aldehydes [R = Ph, CH_2=C(Me), *i*-Pr, *n*-Pr] and aryl *N*-(trimethylsilyl) imines (Ar = Ph, *p*-MeS-C_6H_4-). **Scheme 1** summarizes the observed stereochemical outcome.

The stereoselective synthesis of β-hydroxy- or β-amino-α-heterosubstitued thioacetates, the aldol products derived from the condensation with aldehydes or imines, is highly desiderable since these aldol motifs appear in the framework of many biologically active natural products.[4a] β-Amino acids, for example, although less abundant than their α-counterparts, are components of natural peptides,[4b] as well as building blocks for the preparation of modified peptides[4c] and β-lactam antibiotics.[4d] Numerous methods for the synthesis of β-amino acids exist, and have been recently reviewed:[4a,4e-h] one of the most useful involves the reaction of imines with enolates.[4g] In order to make this process stereoselective, chiral auxiliaries have been attached either to the enolate[5] or to the imine,[6] or both.[7] In alternative, the use of achiral imines and boron enolates bearing chiral boron ligands was recently described.[8] The aldol condensation between α-alkoxyacetates and aldehydes has been used to synthesize α,β-dihydroxy derivatives with both diastereo-[9] and enantiocontrol.[10-12] Stereoselective synthesis of optically active 1,2-diol motifs is an important process in the preparation of a series of natural products, including macrolides, polyethers and carbohydrates. We have prepared these 1,2-diol units with an excellent diastereo- (*anti-syn* ≥ 97 : 3) and enantiocontrol (e.e. = 94 - 97 %), as shown in **Table 1**.

Scheme 1. Transition state models for the boron aldol addition to aldehydes and imines. L* ligand derived from (-)-menthone.

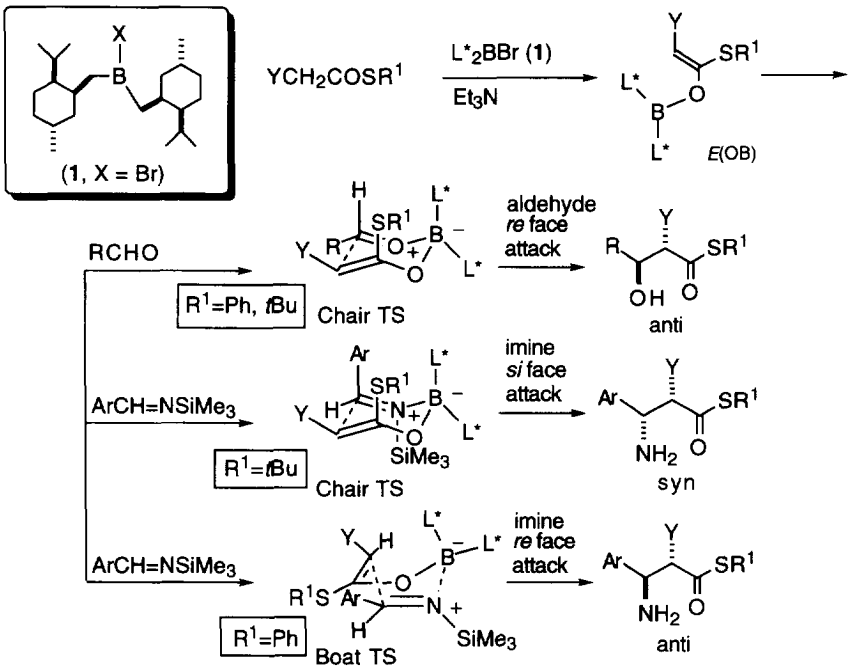
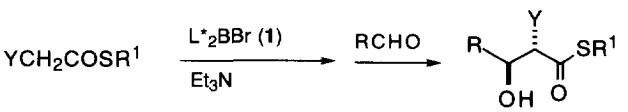


Table 1: Asymmetric synthesis of α-alkoxy-β-hydroxy thioesters via chiral boron enolate - aldehyde condensation

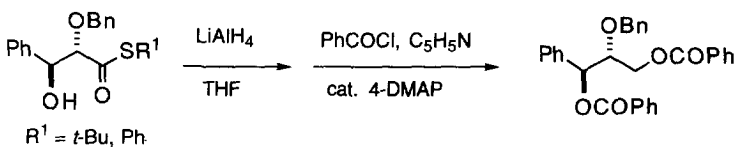


Entry	Y	R^1	R	*re:si*	*anti:syn*	% Yield
1	OBn	*t*-Bu	Ph	97:3	97:3	65
2	OBn	*t*-Bu	CH_2=C(Me)	97.8:2.2	>98:2	78
3	OBn	Ph	Ph	98:2	>99:1	45
4	OTBDMS	Ph	Ph	98.5:1.5	>99:1	79
5	OBn	*t*-Bu	*i*-Pr	97.7:2.3	97:3	55
6	OBn	*t*-Bu	*n*-Pr	97.6:2.4	97.2:2.8	57

The high *anti-syn* ratios observed in the aldol products are the result of a preferential formation of *E* (OB)-enolates, independent of the type of Y and R^1 substituents. *Anti-syn* ratios were determined on the crude products by ^{1}H-NMR analysis in comparison with authentic samples. The enantiomeric ratios of the major *anti*

diastereoisomers were determined by ^{1}H-NMR spectroscopy in presence of Eu(hfc)3, splitting the *t*-Bu singlet (**Table 1**; entries 1, 2, 5, 6), in comparison with racemic samples. In all cases the enantiomeric excesses were confirmed by ^{19}F- and ^{1}H-NMR analysis of the Mosher derivatives. Enantiomeric ratios are independent of the type of Y and R^1 substituents: although the best results were obtained with Y = OTBDMS and R^1 = Ph, the differences with Y = OBn and R^1 = Bu^t are fairly small. The absolute configuration was confirmed in selected cases (**Table 1**; entries 1, 3) by chemical correlation (**Scheme 2**, see the Experimental Section).[10b]

Scheme 2. Assessment of the absolute configuration of α-alkoxy-β-hydroxy thioesters via chemical correlation.



R^1 = *t*-Bu, Ph

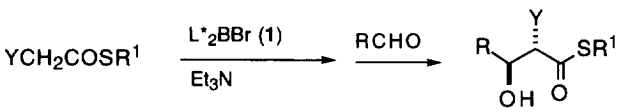
The absolute configuration of the aldol products is consistent with chair transition structures (**Scheme 1**) featuring preferential attack on the aldehyde *re* face, as in the case of the aldol reaction of thiopropionates and unsubstitued thioacetates with aldehydes.[2b] The *E* (OB)-enolates derived from α-alkoxy thioacetates and chiral boron reagent (**1**) have been recently used by our group for the condensation reaction with *N*-(trimethylsilyl) benzaldimine[13,14] (Ar = Ph, **Scheme 1**) in a synthetic approach to the Paclitaxel (Taxol®) C-13 side chain.[15] It is interesting to note that in the addition to imines a strong diastereo- and enantiocontrol is operating as a function of the R^1 substituent (S-Ph *vs* S-Bu^t), while in the addition to aldehydes the role of R^1 has no stereochemical consequences (**Scheme 1**). In the case of imines, a preponderance of the *syn* diastereoisomer is obtained with the *t*-butyl thioester, while a preponderance of the *anti* isomer is obtained with the phenyl thioester. In the addition to both aldehydes and imines the stereochemical role of the oxygen protecting group (e.g. Y = O-Bn *vs* O-TBDMS) is relatively minor. In the case of *t*-butyl thioesters, the stereochemical divergence between aldehydes and imines was reasonably rationalized using chair-like cyclic transition states (cf. the two chair transition states in **Scheme 1**). One can note that in the aldehyde case the R group can adopt an equatorial position (aldehyde *re* face attack, **Scheme 1**) which leads to the *anti* relationship between the hydroxy and the alkoxy groups in the final *anti* β-hydroxy-α-alkoxythioester. The stereochemistry of the imine (*trans*) forces the Ar group in an axial orientation (imine *si* face attack) which determines the *syn* stereochemical relationship in the final *syn* β-amino-α-alkoxythioester. In contrast with the model suggested by Corey,[8a] and in agreement with the models proposed by Cozzi and Cinquini[8b] and Yamamoto,[8c] we believe that the transition state involves an (*E*) configurated imine, that does not isomerize to (*Z*) during the aldol reaction. The stereodivergence caused by the different thioester type (S-Ph *vs* S-Bu^t) in the addition to imines is quite surprising. The stereochemical outcome can be rationalized using a boat *vs* chair transition state structures. *Ab initio* MO calculations (3-21G basis set) featuring the addition of the BH_2 enol borinate derived from acetaldehyde to formaldehyde-imine have recently shown that two competing cyclic transition structures are important: the chair and the boat.[16,17]

The aldol condensation between α-haloacetates and aldehydes has been used to synthesize α-halo-β-hydroxy derivatives (and glycidic derivatives) with both diastereo- and enantiocontrol.[18] Our chiral haloacetate

enolates are able to impart excellent diastereo- (*anti* 91 - >99 %) and enantiocontrol (e.e. = 94 - >98 %), as shown in **Table 2.**

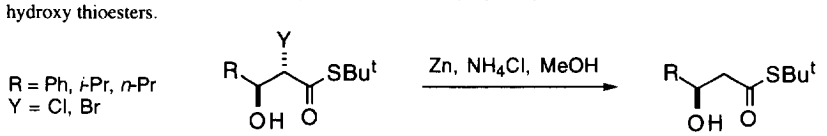
Anti-syn ratios were determined by ^{1}H-NMR analysis in comparison with authentic samples. The enantiomeric ratios of the major *anti* products were determined by Eu(hfc)3 ^{1}H-NMR analysis in comparison with the racemic samples. The absolute configuration was determined by correlation with the corresponding β-hydroxy thioacetates of known configuration[2b] (**Scheme 3**), which were obtained by reductive elimination of the halogen atom of the α-halo-β-hydroxy thioesters (Zn/NH_4Cl/MeOH).

Table 2: Asymmetric synthesis of α-halo-β-hydroxy thioesters via chiral boron enolate - aldehyde condensation



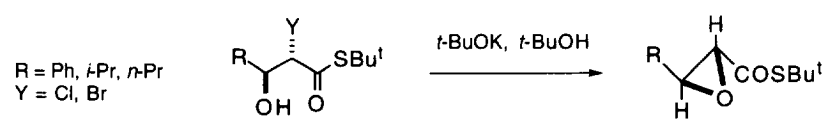
Entry	Y	R^1	R	*re:si*	*anti:syn*	% Yield
1	Cl	*t*-Bu	Ph	>99:1	91:9	65
2	Br	*t*-Bu	Ph	>99:1	97.5:2.5	45
3	Cl	*t*-Bu	*i*-Pr	97:3	96:4	70
4	Br	*t*-Bu	*i*-Pr	>99:1	97.8:2.2	55
5	Cl	*t*-Bu	*n*-Pr	97.3:2.7	96:4	73
6	Br	*t*-Bu	*n*-Pr	>99:1	>99:1	45
7	Cl	Ph	CH_2=C(Me)-	96.3:3.7	52:48	55
8	Br	Ph	CH_2=C(Me)-	96:4	80:20	55

Scheme 3. Assessment of the absolute configuration of α-halo-β-hydroxy thioesters via chemical correlation. Synthesis of β-hydroxy thioesters.



The *anti* relative configuration of the aldols was unequivocally established by measuring the ^{1}H-NMR coupling constants (typical J_{trans} = 1.5-2.0 Hz, J_{cis} = 4.0-5.0 Hz) of the *trans* glycidic thioesters obtained by treatment with *t*-BuOK/*t*-BuOH (**Scheme 4**).[19]

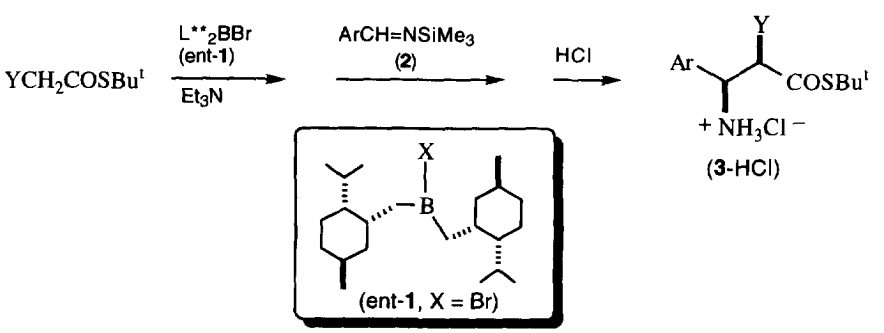
Scheme 4. Transformation of α-halo-β-hydroxy thioesters into glycidic thioesters.



The *anti-syn* ratios observed in the aldol products depend on the type of Y and R^1 substituents, and are particularly high for bulky substituents at sulfur (R^1 = Bu^t *vs* Ph) and Y = Br *vs* Cl. The enantiomeric ratios are independent of the type of Y and R^1 substituents. Although the best results were obtained with Y = Br and R^1 = Bu^t, the differences for example with Y = Cl are fairly small (see **Table 2**). The absolute configuration of the aldol products is consistent with chair transition structures featuring preferential attack on the aldehyde *re* face, as suggested by the computer model (see **Scheme 1** and the discussion above).[2a] The use of thioesters is necessary: in spite of the presence of an electron-withdrawing substituent (Y = Cl, Br) esters are not enolized and do not react.

We also investigated the addition of boron enolates derived from *tert*-butyl α-halothioacetates (Y = Cl, Br) and the chiral boron reagent ent-**1** [derived from (+)-menthone],[2a-e,3] to achiral *N*-trimethylsilylimines **2**[13,14] (**Table 3**). α-Halo-β-amino thioesters were isolated in 77-89% yield as hydrochloride salts (**3**-HCl). The diastereoselectivity of the reaction was checked on the *N*-benzoyl derivatives (**6**, Scheme 6, *vide infra*) and on the Mosher derivatives, and shown to be high (*syn: anti* 92:8 - ≥99:1). The enantiomeric ratios of the major *syn* products were determined by ^{1}H-NMR analysis of the Mosher derivatives,[20] and shown to be 97:3 - >99:1 (**Table 3**).

Table 3: Addition of the chiral boron enolates derived from α-halothioacetates to silylimines. Asymmetric synthesis of α-halo-β-amino thioacetates (**3**).

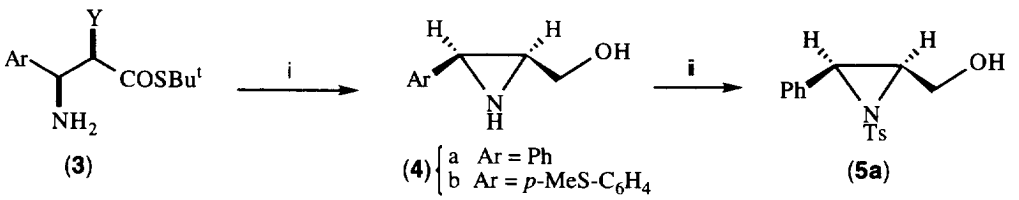


Entry	Y	Ar	*re:si*	*syn:anti*	% Yield
1	Br	Ph-	98.5 : 1.5	≥ 99: 1	80
2	Br	*p*-MeS-C_6H_4-	>99 : 1	≥ 99: 1	77
3	Cl	Ph-	97 : 3	92: 8	89
4	Cl	*p*-MeS-C_6H_4-	97.9: 2.1	94: 6	85

Non protected chiral aziridine alcohols (**4**) were easily obtained (86-91%) by simple reduction with $LiAlH_4$ of the α-halo-β-amino thioesters **3**. The *syn* relationship of the aldol adducts **3** was thus proved by the formation of *cis* aziridine alcohols **4** (**Scheme 5**). The *cis* aziridine stereochemistry was demonstrated by the ^{1}H-NMR coupling constants (*J cis* = 6.4-6.6 Hz; average literature values for *J trans* = 2.5-3.0 Hz)[21a,b] and by correlation with the known compound **4b**.[22] (1H)-(2*S*,3*S*)-(+)-3-[(4-methylthio)phenyl] aziridine-2-methanol (**4b**) is a key intermediate for the synthesis of the broad spectrum, antibacterial, synthetic antibiotics (+)-thiamphenicol and (-)-florfenicol.[22b,d]

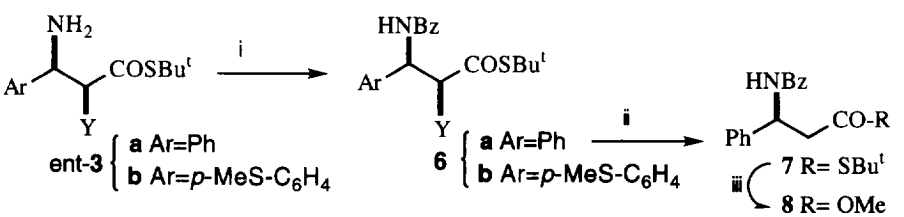
The synthesis of chiral non-racemic aziridines continues to be a major area of interest in organic chemistry: aziridines are useful building blocks for the preparation of amino alcohols and amino acids, and many ring-opening reactions have been described using a range of nucleophiles.[21] Aziridine **4a** was transformed into the corresponding *cis* *N*-tosyl-3-phenyl-2-aziridinemethanol **5a** (89%).[21c,d] Chiral *N*-tosylaziridinemethanols are key intermediates for the synthesis of various classes of compounds, as they easily undergo nucleophilic S_N2-type ring-opening and aza-Payne rearrangement due to the presence of the activating *p*-toluensulfonyl group.[21c,d]

Scheme 5. Synthesis of chiral *cis* aziridine alcohols. i) $LiAlH_4$, THF, 0°C (86-91%); ii) from **4a**: TsCl, $CHCl_3$, Et_3N, -40°C to 0°C (89%).



The imine π-face selectivity was further proved by determining the absolute configuration at the C-N stereocenter by chemical correlation with the known compound **8** (**Scheme 6**). α-Halo-β-amino thioesters ent-**3** [obtained using **1** derived from (-)-menthone][2,3] were benzoylated using benzoic acid and DCC to give **6** (85%). The *syn:anti* ratios were checked on *N*-benzoyl derivatives **6** via ^{1}H-NMR spectroscopy. Reductive elimination of the halogen atom of **6a** using Zn/NH_4Cl in methanol gave **7** (60-75%), which was transformed into methyl ester **8** by reaction with $Hg(NO_3)_2$ in methanol (82%). The $[\alpha]_D$ value of **8** was in good agreement with that reported in the literature.[6a] The optical purity of methylester **8** [O.P. = 97.8% for **8** derived from ent-**3a** (Y = Br); 90% for **8** derived from ent-**3a** (Y = Cl)] reflects the higher stereoselectivity of the reaction using the α-bromoacetate compared to the α-chloroacetate. It is also worthnoting that, in the case of **8** derived from ent-**3a** (Y = Cl), this value was obtained starting from a *syn:anti* mixture (*syn:anti* 92:8) without removing the minor *anti* diasteroisomer. The NMR analysis of the Mosher derivatives of ent-**3a** (Y = Cl) shows that while the major *syn* isomer is 94% enantiomerically pure, the minor *anti* isomer is more or less racemic.

Scheme 6. Chemical correlation of α-halo-β-amino thioesters ent-3 [obtained using L*$_2$BBr (**1**) derived from (-)-menthone]: i) $PhCO_2H$, DCC, CH_2Cl_2 (85%); ii) Zn, NH_4Cl, MeOH (60% X=Cl; 75% X=Br); iii) $Hg(NO_3)_2$, MeOH (82%).



In summary, we have shown that the chiral boron enolates derived from *t*-butyl and phenyl α-alkoxy thioacetates and α-halothioacetates react with aldehydes and aryl *N*-(trimethylsilyl) imines with excellent

stereoselectivities. The stereochemical outcome is well rationalized by the use of cyclic chair- and boat-like transition structures, as shown in **Scheme 1**.

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 (unless otherwise stated). *J* vaules are given in Hz.

Di{[(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl]-methyl} boron bromide (1) (see ref. 2a,b): A solution of (-)-(2*S*,5*R*)-2-isopropyl-5-methyl-1-methylenecyclohexane (98%, 7.2 g, 47.37 mmol) in freshly distilled dichloromethane (21.95 ml) was treated with $BrBH_2$-SMe_2 (95%, Aldrich)(2.55 ml, 23.93 mmol) at 0 °C, under argon, with stirring. The reaction mixture was stirred at room temperature overnight. The solvent dichloromethane and dimethylsulfide liberated during hydroboration were removed under vacuum (0.1 mmHg) and the residue (a thick liquid or a low melting solid) was dissolved in dry diethyl ether (11.4 ml) under argon at room temperature. The solution was cannulated off of a small amount of insoluble residue (white powder) into another flask. The solution was cooled to -50 °C and left to crystallise for 1.0 h. The solvent was removed via double-tipped needle (cannula) under argon at -50 °C. The remaining white crystals were then dissolved in dry diethyl ether (7.3 ml) at room temperature and the resulting solution was cooled (SLOWLY) to -40 °C and after 1.0 h the mother liquor was removed via cannula from the crystals formed. The crystals were redissolved in dry ether (7.6 ml) at room temperature. The solution was cooled (SLOWLY) to -30 °C and after 1.0 h the mother liquor was removed via cannula from the crystals formed. The crystals (containing 1 eq. of diethyl ether per eq. of boron atom) were weighed under argon (3.23 g, 30%). The ratio between the distereoisomers was determined by decomposition with hydrogen peroxide and VPC analysis (OV-1 column, 70-150°C) of alcohols (1*S*,2*S*,5*R*)-1-(hydroxymethyl)-2-isopropyl-5-methylcyclohexane and (1*R*,2*S*,5*R*)-1-(hydroxymethyl)-2-isopropyl-5-methylcyclohexane (≥ 100:1). Boron reagent **1**: ^{11}B NMR [$CDCl_3$, 25 °C, ppm relative to BF_3-Et_2O (0.0)]: δ = 78.83. Methanolysis gave X = OMe: ^{11}B NMR [$CDCl_3$, 25 °C, ppm relative to BF_3-Et_2O (0.0)]: δ = 55.05; ^{13}C NMR ($CDCl_3$): δ = 53.30 (OCH_3), 48.39, 42.26, 35.85, 31.38, 29.57, 26.17, 24.54, 22.74, 21.41, 20.69, 16.3 (broad, C-B). Treatment of X = OMe with $HOCH_2CH_2NH_2$ in Et_2O gave X = $OCH_2CH_2NH_2$ (see ref 2a): ^{13}C NMR ($CDCl_3$): δ = 65.52 (OCH_2), 48.86, 42.62 (CH_2NH_2), 41.93, 35.98, 31.82, 29.41, 26.24, 24.51, 22.76, 21.45, 20.71, 16 (broad, C-B); $C_{24}H_{48}BNO$ (377.5): calcd C 76.37, H 12.82, N 3.71; found C 76.32, H 12.91, N 3.67.

A 0.4 M stock solution was prepared dissolving reagent **1** (3.23 g) in dichloromethane (13.82 ml). This solution may be kept for weeks in the refrigerator at 0 °C without any appreciable decomposition. Boron reagent ent-**1** was prepared analogously, starting from (+)-(2*R*,5*S*)-2-isopropyl-5-methyl-1-methylenecyclohexane derived from (+)-menthone (see ref. 2a,b).

Preparation of thioesters (YCH_2COSR^1; Table 1, 2, 3). General procedure: To a cooled (0 °C) 0.5 M solution of thiol (1.0 mol. eq.) and Et_3N (1.1 mol. eq.) in dry dichloromethane, the acid chloride in dichloromethane (1.0 mol. eq., 0.5 M) was added dropwise. After 30-60 min stirring at 0 °C the reaction was poured into cold water. The organic phase was separated and washed with a cold 5% aqueous solution of sodium hydroxide, water, dried and concentrated under reduced pressure. Pyridine was used instead of triethylamine for the synthesis of phenyl α-halothioesters.

t-Butyl α-benzyloxythioacetate (R^1 = *t*-Bu; Y = OBn): The crude product was purified by fractional distillation: 150-160 °C (ca. 0.1 mmHg). ^1H NMR ($CDCl_3$): δ = 1.52 (s, 9H, t-Bu); 4.07 (s, 2H, CH_2CO); 4.65 (s, CH_2O, 2H); 7.3-7.4 (5H, ArH). $C_{13}H_{18}O_2S$ (238.35): calcd C 65.51, H 7.61; found C 65.49, H 7.70.

Phenyl α-benzyloxythioacetate (R^1 = Ph; Y = OBn): ^1H NMR ($CDCl_3$): δ = 4.29 (s, 2H, CH_2CO); 4.76 (s, CH_2O, 2H); 7.3-7.4 (10H, ArH). $C_{15}H_{14}O_2S$ (258.34): calcd C 69.74, H 5.46; found C 69.70, H 5.51.

t-Butyl α-chlorothioacetate (R^1 = *t*-Bu; Y = Cl): The crude product was purified by fractional distillation: 110-115 °C (ca. 15 mmHg). ^1H NMR ($CDCl_3$): δ = 1.52 (s, 9H, t-Bu); 4.12 (s, 2H, CH_2CO). $C_6H_{11}OSCl$ (166.67): calcd C 43.24, H 6.65; found C 43.19, H 6.70.

t-Butyl α-bromothioacetate (R^1 = *t*-Bu; Y = Br): The crude product was purified by fractional distillation: 78-80 °C (ca. 15 mmHg). ^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 9H, t-Bu); 3.95 (s, 2H, CH_2CO). $C_6H_{11}OSBr$ (211.13): calcd C 34.13, H 5.25; found C 34.08, H 5.31.

Phenyl α-chlorothioacetate (R^1 = Ph; Y = Cl): ^{1}H NMR ($CDCl_3$): δ = 4.3 (s, 2H, CH_2); 7.4 (5H, Ar). C_8H_7OSCl (186.66): calcd C 51.48, H 3.78; found C 51.25, H 3.74.

Phenyl α-bromothioacetate (R^1 = Ph; Y = Br): ^{1}H NMR ($CDCl_3$): δ = 4.14 (s, 2H, CH_2); 7.4 (5H, Ar). C_8H_7OSBr (231.12): calcd C 41.58, H 3.05; found C 41.81, H 3.35.

Phenyl α-*t*-butyldimethylsilyloxythioacetate (R^1 = Ph; Y = OTBDMS): Methyl glycolate (1.90 ml, 2.20 g, 24.5 mmol) was added to a suspension of TBDMS-Cl (4.43 g, 29.4 mmol) and imidazole (4.17 g, 61.25 mmol) in dry dimethylformamide (DMF) (4.9 ml) at 0 °C, under stirring. After 90 min stirring at room temperature, water (60 ml) was added, and the resulting mixture was extracted with ethyl ether (3 x 35 ml). The organic extracts were combined, washed with water (3 x 35 ml), dried and evaporated to give TBDMS-OCH_2CO_2Me (5.0 g, 100%): ^{1}H NMR ($CDCl_3$): δ = 0.12 (6H, s, Me), 0.93 (9H, s, ^{t}Bu), 3.75 (3H, s, OMe), 4.26 (2H, s, CH_2). $C_9H_{20}O_3Si$ (204.34): calcd C 52.90, H 9.87; found C 52.81, H 9.93.
A solution of $AlMe_3$ (2.0 M in hexanes, 12.25 ml, 24.5 mmol) in dichloromethane (49 ml) was treated at 0 °C with PhSH (2.5 ml, 24.5 mmol). After 20 min at 0 °C, a solution of TBDMS-OCH_2CO_2Me (2.5 g, 12.25 mmol) in dichloromethane (6.125 ml) was added at 0 °C. The mixture was stirred at room temperature for 0.5 h, then quenched with a NH_4Cl saturated aqueous solution (12 ml), filtered through celite, washing the celite cake with dichloromethane. The organic phase was washed with 5% aqueous NaOH, saturated brine, dried and evaporated to give a crude mixture which was purified by flash chromatography (hexanes-ethyl ether 95:5) to afford pure phenyl α-*t*-butyldimethylsilyloxythioacetate (2.74 g, 79%): ^{1}H NMR ($CDCl_3$): δ = 0.20 (6H, s, Me), 1.01 (9H, s, ^{t}Bu), 4.38 (2H, s, CH_2), 7.43 (5H, m, Ar-H). $C_{14}H_{22}O_2SSi$ (282.48): calcd C 59.53, H 7.85; found C 59.65, H 7.83.

Aldol condensation of α-heterosubstitued thioacetates with aldehydes (Table 1, 2). General procedure: To a stirred solution of the thioester (0.40 mmol) in ethyl ether (1.80 ml) at 0 °C (ice cooling), under argon atmosphere, a solution of **1** in dichloromethane (0.4 M; 1.80 ml, 0.72 mmol) , and then Et_3N (0.156 ml, 1.12 mmol) were added dropwise. Enolborinate was generated with concurrent formation and precipitation of Et_3N-HBr. After 5 min at 0 °C and 5.0 h at +15 °C, the mixture was cooled to -78 °C and the aldehyde (1.2 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 15 h, and then quenched with Et_2O (2 ml) and pH 7 phosphate buffer (2 ml). The aqueous phase was extracted with Et_2O (3 x 5 ml), and the combined organic extracts were dried and evaporated. The residue was dissolved in MeOH (3.5 ml) and phosphate buffer (1 ml) at 0 °C, and treated with 30% H_2O_2 (1 ml). After 20 min stirring at RT, the mixture was diluted with water and extracted with CH_2Cl_2 (3 x 5 ml). The organic phase was dried and evaporated. The crude product was flash chromatographed to give the desired aldol compound.

The *anti-syn* ratio of the aldol products was determined by ^{1}H NMR analysis, by integration of the relevant peaks of the *anti* and *syn* diastereoisomers. Characterization of the aldol derivatives (Table 1, 2) is reported below:

Table 1, Entry 1. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = 1.46 (s, 9H, tBu); 3.14 (d, 1H, OH, J_{CHOH} = 3.8 Hz); 3.96 (d, 1H, CHOBn, J_{CHCH} = 7.1 Hz); 4.22 (d, 1H, OCH_2Ph, J = 11.1 Hz); 4.65 (d, 1H, OCH_2Ph, J = 11.1 Hz); 4.92 (dd, 1H, CHOH, J_{CHCH} = 7.1, J_{CHOH} = 3.8 Hz); 7.3 (ArH). $[\alpha]_D$ = - 89.92 (c = 1.24, $CHCl_3$). $C_{20}H_{24}O_3S$ (344.48): calcd C 69.74, H 7.02; found C 69.71, H 7.11.

2,3-Syn ^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 9H, tBu); 2.97 (d, 1H, OH, J_{CHOH} = 5.2 Hz); 3.95 (d, 1H, CHOBn, J_{CHCH} = 5.0 Hz); 4.37 (d, 1H, OCH_2Ph, J = 11.2 Hz); 4.74 (d, 1H, OCH_2Ph, J = 11.2 Hz); 4.98 (dd, 1H, CHOH, J_{CHCH} = 5.0, J_{CHOH} = 5.2 Hz); 7.3 (ArH).

Table 1, Entry 2. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = 1.49 (s, 9H, *t*-Bu); 1.72 (s, 3H, CH_3); 2.61 (d, 1H, OH, J_{CHOH} = 4.92 Hz); 3.92 (d, 1H, CHOBn, J_{CHCH} = 5.85 Hz); 4.33 (m, 1H, CHOH); 4.48 (d, 1H, OCH_2Ph, J = 11.3 Hz); 4.82 (d, 1H, OCH_2Ph, J = 11.3 Hz); 4.97 (1H, =CH); 5.04 (1H, =CH); 7.3-7.4 (5H, ArH). $[\alpha]_D$ = - 84.4 (c = 1.93, $CHCl_3$). $C_{17}H_{24}O_3S$ (308.44): calcd C 66.20, H 7.84; found C 66.11, H 7.87.

Table 1, Entry 3. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = 3.09 (d, 1H, OH, J_{CHOH} = 3.68 Hz); 4.22 (d, 1H, CHOBn, J_{CHCH} = 6.8 Hz); 4.42 (d, 1H, OCH_2Ph, J = 11.0 Hz); 4.73 (d, 1H, OCH_2Ph, J = 11.0 Hz); 4.99 (dd, 1H, CHOH, J_{CHCH} = 6.8, J_{CHOH} = 3.68 Hz); 7.48 (15H, ArH). $[\alpha]_D$ = - 125.53 (c = 0.76, $CHCl_3$). $C_{22}H_{20}O_3S$ (364.47): calcd C 72.50, H 5.53; found C 72.41, H 5.59.

2,3-Syn ^{1}H NMR ($CDCl_3$): δ = 4.23 (d, 1H, CHOBn, J_{CHCH} = 3.2 Hz); 5.11 (dd, 1H, CHOH, J_{CHCH} = 3.2, J_{CHOH} = 6.0 Hz).

Table 1, Entry 4. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = - 0.24 (s, 3H, CH_3); 0.12 (s, 3H, CH_3); 0.95 (s, 9H, *t*-Bu); 2.89 (d, 1H, OH, J_{CHOH} = 3.18 Hz); 4.36 (d, 1H, CHOSi, J_{CHCH} = 6.24 Hz); 4.88 (dd, 1H, CHOH, J_{CHCH} = 6.24, J_{CHOH} = 3.18 Hz); 7.4 (10H, ArH). $[\alpha]_D$ = -163.0 (*c* = 1.48, $CHCl_3$). $C_{21}H_{28}O_3SSi$ (388.61): calcd C 64.91, H 7.26; found C 64.86, H 7.31.

2,3-Syn ^{1}H NMR ($CDCl_3$): δ = 3.06 (d, 1H, CHOH, J_{CHOH} = 8.5 Hz); 4.42 (d, 1H, CHOSi, J_{CHCH} = 2.7 Hz).

Table 1, Entry 5. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = 0.83 (d, 3H, CH_3, *J* = 6.7 Hz); 0.98 (d, 3H, CH_3, *J* = 6.7 Hz); 1.52 (s, 9H, *t*-Bu); 1.97 (m, 1H, $Me_2C\underline{H}$); 2.25 (d, 1H, OH, J_{CHOH} = 4.9 Hz); 3.63 (m, 1H, $C\underline{H}OH$); 3.83 (d, 1H, CHOBn, *J* = 6.6 Hz); 4.47 (d, 1H, OCH_2Ph, *J* = 11.3 Hz); 4.84 (d, 1H, OCH_2Ph, *J* = 11.3 Hz); 7.4 (5H, ArH). $[\alpha]_D$ = - 89.6 (*c* = 1.07, $CHCl_3$). $C_{17}H_{26}O_3S$ (310.46): calcd C 65.77, H 8.44; found C 65.70, H 8.50.

2,3-Syn ^{1}H NMR ($CDCl_3$): δ = 3.90 (d, 1H, CHOBn, J_{CHCH} = 4.2 Hz).

Table 1, Entry 6. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = 0.91 (t, 3H, CH_3, *J* = 6.9 Hz); 1.51 (s, 9H, *t*-Bu); 1.3-1.6 (m, 4H, CH_2CH_2); 2.14 (d, 1H, OH, J_{CHOH} = 4.58 Hz); 3.86 (m, 2H, $C\underline{H}OH$ + $C\underline{H}OBn$); 4.48 (d, 1H, OCH_2Ph, *J* = 11.3 Hz); 4.86 (d, 1H, OCH_2Ph, *J* = 11.3 Hz); 7.4 (5H, ArH). $[\alpha]_D$ = - 79.7 (*c* = 0.96, $CHCl_3$). $C_{17}H_{26}O_3S$ (310.46): calcd C 65.77, H 8.44; found C 65.67, H 8.52.

2,3-Syn ^{1}H NMR ($CDCl_3$): δ = 4.46 (d, 1H, OCH_2Ph, *J* = 11.06 Hz).

Table 2, Entry 1. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = 1.49 (s, 9H, *t*-Bu); 4.39 (d, 1H, CHCl, J_{CHCH} = 7.3 Hz); 5.10 (d, 1H, CHOH, J_{CHCH} = 7.3 Hz); 7.3-7.4 (5H, ArH). $[\alpha]_D$ = + 70.93 (*c* = 1.07, $CHCl_3$). $C_{13}H_{17}O_2SCl$ (272.80): calcd C 57.24, H 6.28; found C 57.21, H 6.33.

2,3-Syn ^{1}H NMR ($CDCl_3$): δ = 1.40 (s, 9H, tBu); 4.41 (d, 1H, CHCl, J_{CHCH} = 6.0 Hz); 5.18 (d, 1H, CHOH, J_{CHCH} = 6.0 Hz); 7.3-7.4 (5H, ArH).

Table 2, Entry 2. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = 1.49 (s, 9H, *t*-Bu); 3.17 (d, 1H, OH, J_{CHOH} = 5.5 Hz); 4.42 (d, 1H, CHBr, J_{CHCH} = 7.6 Hz); 5.11 (dd, 1H, CHOH, J_{CHCH} = 7.6, J_{CHOH} = 5.5 Hz); 7.3-7.4 (5H, ArH). $[\alpha]_D$ = + 54.55 (*c* = 1.45, $CHCl_3$). $C_{13}H_{17}O_2SBr$ (317.25): calcd C 49.22, H 5.40; found C 49.13, H 5.47.

2,3-Syn ^{1}H NMR ($CDCl_3$): δ = 1.40 (s, 9H, tBu); 3.05 (d, 1H, OH, J_{CHOH} = 2.9 Hz); 4.44 (d, 1H, CHBr, J_{CHCH} = 6.65 Hz); 5.106 (dd, 1H, CHOH, J_{CHCH} = 6.65, J_{CHOH} = 2.9 Hz); 7.3-7.4 (5H, ArH).

Table 2, Entry 3. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = 0.95 (d, 3H, CH_3, *J* = 6.7 Hz); 1.04 (d, 3H, CH_3, *J* = 6.7 Hz); 1.52 (s, 9H, *t*-Bu); 2.10 (dq, 1H, $Me_2C\underline{H}$, *J* = 4.3 and 6.7 Hz); 2.43 (d, 1H, OH, J_{CHOH} = 6.0 Hz); 3.82 (ddd, 1H, $C\underline{H}OH$, *J* = 6.0, 7.7, 4.3 Hz); 4.22 (d, 1H, CHCl, *J* = 7.7 Hz). $[\alpha]_D$ = - 5.50 (*c* = 1.09, $CHCl_3$). $C_{10}H_{19}O_2SCl$ (238.78): calcd C 50.30, H 8.02; found C 50.21, H 8.10.

2,3-Syn ^{1}H NMR ($CDCl_3$): δ = 0.95 (d, 3H, CH_3, *J* = 6.7 Hz); 1.05 (d, 3H, CH_3, *J* = 6.7 Hz); 1.50 (s, 9H, *t*-Bu); 1.86 (m, 1H, $Me_2C\underline{H}$); 2.31 (m, 1H, OH); 3.77 (m, 1H, $C\underline{H}OH$); 4.45 (d, 1H, CHCl, *J* = 3.66 Hz).

Table 2, Entry 4. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = 0.94 (d, 3H, CH_3, *J* = 6.7 Hz); 1.03 (d, 3H, CH_3, *J* = 6.7 Hz); 1.52 (s, 9H, *t*-Bu); 2.13 (m, 1H, $Me_2C\underline{H}$); 2.50 (d, 1H, OH, J_{CHOH} = 6.6 Hz); 3.85 (m, 1H, $C\underline{H}OH$); 4.27 (d, 1H, CHBr, $J_{CH\text{-}CH}$ = 7.5 Hz). $[\alpha]_D$ = - 31.9 (*c* = 0.97, $CHCl_3$). $C_{10}H_{19}O_2SBr$ (283.23): calcd C 42.41, H 6.76; found C 42.30, H 6.84.

2,3-Syn ^{1}H NMR ($CDCl_3$): δ = 4.47 (d, 1H, CHBr, $J_{CH\text{-}CH}$ = 4.1 Hz).

Table 2, Entry 5. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = 0.96 (t, 3H, CH_3, *J* = 6.8 Hz); 1.51 (s, 9H, *t*-Bu); 1.3-1.7 (m, 4H, CH_2CH_2); 2.34 (d, 1H, OH, J_{CHOH} = 6.74 Hz); 4.07 (m, 1H, $C\underline{H}OH$); 4.27 (d, 1H, CHCl, $J_{CH\text{-}CH}$ = 6.1 Hz). ^{13}C NMR ($CDCl_3$): δ = 13.72, 18.39, 29.41, 34.83, 49.23, 66.86, 72.63, 196.42.
$[\alpha]_D$ = -16.06 (*c* = 0.94, $CHCl_3$). $C_{10}H_{19}O_2SCl$ (238.78): calcd C 50.30, H 8.02; found C 50.26, H 8.09.

2,3-Syn ^{1}H NMR ($CDCl_3$): δ = 4.27 (d, 1H, CHCl, $J_{CH\text{-}CH}$ = 4.0 Hz). ^{13}C NMR ($CDCl_3$): δ (selected peaks) = 18.60, 35.64, 68.59, 71.97.

Table 2, Entry 6. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = 0.96 (t, 3H, CH_3, J = 6.9 Hz); 1.51 (s, 9H, *t*-Bu); 1.2-1.8 (m, 4H, CH_2CH_2); 2.47 (d, 1H, OH, J_{CHOH} = 6.7 Hz); 4.03 (m, 1H, C<u>H</u>OH); 4.26 (d, 1H, CHBr, J_{CH-CH} = 6.66 Hz). $[\alpha]_D$ = - 28.65 (c = 1.86, $CHCl_3$). $C_{10}H_{19}O_2SBr$ (283.23): calcd C 42.41, H 6.76; found C 42.35, H 6.80.

2,3-Syn ^{1}H NMR ($CDCl_3$): δ = 1.48 (s, 9H, *t*-Bu); 2.66 (d, 1H, OH, J_{CHOH} = 4.3 Hz); 4.29 (d, 1H, CHBr, J_{CH-CH} = 4.6 Hz).

Table 2, Entry 7. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = 1.8 (s, 3H, CH_3); 2.74 (d, 1H, OH, J_{CHOH} = 4.2 Hz); 4.48 (d, 1H, CHCl, J_{CHCH} = 7.8 Hz); 4.56 (dd, 1H, C<u>H</u>OH, J_{CHCH} = 7.8 Hz, J_{CHOH} = 4.2 Hz); 5.11 (1H, =CH), 5.15 (1H, =CH); 7.4-7.5 (ArH). $C_{12}H_{13}O_2SCl$ (256.75): calcd C 56.14, H 5.10; found C 56.08, H 5.21.

2,3-Syn ^{1}H NMR ($CDCl_3$): δ = 1.8 (s, 3H, CH_3); 2.51 (d, 1H, OH, J_{CHOH} = 5.5 Hz); 4.68 (m, 2H, CHCl + C<u>H</u>OH); 5.11 (1H, =CH), 5.19 (1H, =CH); 7.4-7.5 (ArH).

Table 2, Entry 8. *2,3-Anti* ^{1}H NMR ($CDCl_3$): δ = 1.82 (s, 3H, CH_3); 2.77 (d, 1H, OH, J_{CHOH} = 5.16 Hz); 4.48 (d, 1H, CHBr, J_{CH-CH} = 7.94 Hz); 4.58 (m, 1H, C<u>H</u>OH); 5.10 (1H, =CH), 5.11 (1H, =CH); 7.4-7.5 (ArH). $C_{12}H_{13}O_2SBr$ (301.21): calcd C 47.85, H 4.35; found C 47.76, H 4.38.

2,3-Syn ^{1}H NMR ($CDCl_3$): δ = 1.83 (s, 3H, CH_3); 2.69 (d, 1H, OH, J_{CHOH} = 4.75 Hz); 4.62 (m, 1H, C<u>H</u>OH); 4.68 (d, 1H, CHBr, J_{CH-CH} = 5.36 Hz); 5.10 (1H, =CH), 5.18 (1H, =CH); 7.4-7.5 (ArH).

Determination of the enantiomeric excess of the aldol products (Table 1, 2) via Mosher ester derivatives. General procedure: The % enantiomeric excess of the aldols products was determined by ^{1}H NMR analysis of the Mosher ester derivatives. The aldol products (1.0 mol. eq.) were treated with excess (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (2.0 mol. eq.) in pyridine (0.2 M) in the presence of catalytic (0.1 mol. eq.) 4-dimethylaminopyridine (DMAP). The reaction was followed by t.l.c. while stirring at 0 °C (typically 4-6 h), then quenched by dilution with ethyl ether and treatment with cold 1N aqueous HCl. The organic phase was washed with 1N aqueous HCl, saturated $NaHCO_3$ aqueous solution, saturated brine, dried and evaporated. The crude reaction products were flash chromatographed to give the pure Mosher ester derivatives. Selected examples:

Table 1, Entry 1. Mosher ester derivative of the aldol product derived from *re* face attack: ^{1}H NMR ($CDCl_3$): δ = 1.42 (s, 9H, *t*-Bu); 3.52 (m, 3H, OCH_3); 4.20 (d, 1H, CHOBn, J = 5.6 Hz); 4.44 (d, 1H, OCH_2Ph, J = 11.42 Hz); 4.70 (d, 1H, OCH_2Ph, J = 11.42 Hz); 6.23 (d, 1H, CHOCO, J = 5.6 Hz); 7.4 (15H, Ar).

^{19}F NMR (188.15 MHz, $CDCl_3$, 25 °C, $CFCl_3$): δ = - 71.39.

Mosher ester derivative of the aldol product derived from *si* face attack: ^{1}H NMR ($CDCl_3$): δ = 1.38 (s, 9H, *t*-Bu); 3.48 (m, 3H, OCH_3); 4.18 (d, 1H, CHOBn, J = 5.0 Hz); 4.35 (d, 1H, OCH_2Ph, J = 11.24 Hz); 4.61 (d, 1H, OCH_2Ph, J = 11.24 Hz); 6.34 (d, 1H, CHOCO, J = 5.0 Hz); 7.4 (15H, Ar).

^{19}F NMR (188.15 MHz, $CDCl_3$, 25 °C, $CFCl_3$): δ = - 71.19.

Table 1, Entry 4. Mosher ester derivative of the aldol product derived from *re* face attack: ^{1}H NMR ($CDCl_3$): δ = - 0.10 (s, 3H, CH_3); 0.12 (s, 3H, CH_3); 0.90 (s, 9H, *t*-Bu); 3.58 (m, 3H, OCH_3); 4.60 (d, 1H, CHOSi); 6.12 (d, 1H, CHOCO); 7.4 (15H, Ar).

Mosher ester derivative of the aldol product derived from *si* face attack: ^{1}H NMR ($CDCl_3$): δ = -0.20 (s, 3H, CH_3); 0.00 (s, 3H, CH_3); 0.92 (s, 9H, *t*-Bu); 3.47 (m, 3H, OCH_3); 4.51 (d, 1H, CHOSi); 6.20 (d, 1H, CHOCO); 7.4 (15H, Ar).

Assessment of the absolute configuration of α-benzyloxy-β-hydroxythioesters (Table 1, entry 1, 3) via chemical correlation. Procedure for entry 1 of Table 1. Synthesis of (1*S*,2*R*) 2-benzyloxy-1-phenyl-1,3-propanediol (Scheme 2): A solution of thioester (51.67 mg, 0.15 mmol) in THF was treated with $LiAlH_4$ (17.08 mg, 0.45 mmol) at 0 °C and stirred for 4 h at 0 °C. The reaction mixture was then quenched with H_2O (18 μl), 15% aq. NaOH (18 μl), H_2O (37 μl), stirred at room temperature for 1 h and then treated with Na_2SO_4. After filtration, the solution was evaporated and the crude product was purified by flash chromatography (hexanes-ethyl ether 20:80) to afford pure (1*S*,2*R*) 2-benzyloxy-1-phenyl-1,3-propanediol (26.7 mg, 69%). ^{1}H NMR ($CDCl_3$): δ = 2.2 (br, 1H, CH_2O<u>H</u>); 2.78 (br, 1H, PhCHO<u>H</u>); 3.63 (m, 1H, C<u>H</u>OBn); 3.76 (br, 2H, CH_2OH); 4.49 (d, 1H, OCH_2Ph, J = 11.40 Hz); 4.57 (d, 1H, OCH_2Ph, J = 11.40 Hz); 4.97 (d, 1H, PhC<u>H</u>OH, J = 5.3 Hz). $C_{16}H_{18}O_3$ (258.32): calcd C 74.40, H 7.02; found C 74.38, H 7.07.

Synthesis of (1*S*,2*R*) 1,3-dibenzoyl-2-benzyloxy-1-phenylpropane (Scheme 2): (1*S*,2*R*) 2-benzyloxy-1-phenyl-1,3-propanediol (26.7 mg, 0.10 mmol) was dissolved in pyridine (517 µl) and treated at 0 °C with catalytic 4-dimethylaminopyridine (DMAP) and benzoyl chloride (48.03 µl, 0.41 mmol). The mixture was stirred at room temperature for 15 h, then diluted with ethyl ether. The organic phase was washed with 1N aq. HCl, saturated $NaHCO_3$ aq. solution, saturated brine, dried and evaporated. The crude reaction product was flash chromatographed (pentanes-ethyl ether 86:14) to give pure (1*S*,2*R*) 1,3-dibenzoyl-2-benzyloxy-1-phenylpropane (41.0 mg, 90.4%). ^{1}H NMR ($CDCl_3$): δ = 4.22 (ddd, 1H, CHOBn, J = 4.0, 5.6, 6.3 Hz); 4.49 (dd, 1H, CH_2, J = 6.3, 11.5 Hz); 4.59 (d, 1H, OCH_2Ph, J = 11.7 Hz); 4.61 (dd, 1H, CH_2, J = 4.0 Hz, 11.5 Hz); 4.66 (d, 1H, OCH_2Ph, J = 11.7 Hz); 6.29 (d, 1H, PhCHOBz, J = 5.6 Hz); 7.16-7.60 (m, 16H); 7.95-8.00 (m, 2H); 8.08-8.12 (m, 2H). ^{13}C NMR ($CDCl_3$): δ (selected peaks) = 63.6, 72.8, 74.9, 78.7. $[\alpha]_D^{25}$ = - 31.6 (*c* 0.95, benzene) [literature (ref.10b and personal communication from S. Kobayashi): $[\alpha]_D^{25}$ = - 33.6 (*c* 0.91, benzene)]. $C_{30}H_{26}O_5$ (466.54): calcd C 77.24, H 5.62; found C 77.16, H 5.69.

Assessment of the absolute configuration of α-halo-β-hydroxythioesters via chemical correlation (Scheme 3). Synthesis of β-hydroxythioesters. General procedure: A solution of thioester (1.0 mol. eq.) in MeOH (0.06 M) was treated with Zn (4.0 mol. eq.) and NH_4Cl (4.0 mol. eq.) at room temperature. The mixture was stirred at room temperature for 1-2 h and then filtered through celite. The organic phase was evaporated to give a crude mixture which was purified by flash chromatography to afford pure β-hydroxythioesters. R = Ph, $[\alpha]_D^{25}$ = +30.9 (*c* 5.06, $CHCl_3$); R = *i*-Pr, $[\alpha]_D^{25}$ = +34.1 (*c* 1.79, $CHCl_3$); R = *n*-Pr, $[\alpha]_D^{25}$ = + 24.6 (*c* 1.89, $CHCl_3$); for literature $[\alpha]_D^{25}$ values, see ref. 2b and references therein.

Assessment of the relative configuration of α-halo-β-hydroxythioesters via chemical correlation (Scheme 4). Transformation of α-halo-β-hydroxythioesters into glycidic thioesters. General procedure: A solution of thioester (1.0 mol. eq.) in *t*-BuOH (0.06 M) was treated with *t*-BuOK (1.0 mol. eq.) at room temperature. The mixture was stirred at room temperature for 2-3 h and then diluted with ethyl acetate. The organic phase was washed with pH 7 phosphate buffer, saturated brine, dried and evaporated. The crude reaction products were flash chromatographed to give pure glycidic thioesters.

R = Ph. ^{1}H NMR ($CDCl_3$): δ = 1.52 (s, 9H, *t*-Bu); 3.54 (d, 1H, CH, J = 1.65 Hz); 4.07 (d, 1H, CH, J = 1.65 Hz); 7.3 (5H, ArH). $C_{13}H_{16}O_2S$ (236.34): calcd C 66.07, H 6.82; found C 65.99, H 6.90.

R = *i*-Pr. ^{1}H NMR ($CDCl_3$): δ = 1.0 (dd, 3H, CH_3); 1.45 (s, 9H, *t*-Bu); 1.6 (m, 1H, Me_2CH); 2.94 (dd, 1H, CH, J = 6.7, 1.52 Hz); 3.29 (d, 1H, CH, J = 1.52 Hz). $C_{10}H_{18}O_2S$ (202.32): calcd C 59.37, H 8.97; found C 59.31, H 9.02.

R = *n*-Pr. ^{1}H NMR ($CDCl_3$): δ = 1.0 (m, 3H, CH_3); 1.51 (s, 9H, *t*-Bu); 1.2-1.8 (m, 4H, CH_2CH_2); 3.12 (dt, 1H, CH, J = 1.97 Hz); 3.23 (d, 1H, CH, J = 1.97 Hz). $C_{10}H_{18}O_2S$ (202.32): calcd C 59.37, H 8.97; found C 59.27, H 9.05.

Preparation of *N*-trimethylsilylimines (2) : *N*-trimethylsilylimines (**2**) were prepared according to the procedure reported in ref. 13. Imine **2b** (Ar = *p*-MeS-C_6H_4-) : to a cooled (0 °C) solution of hexamethyldisilazane (6.95 ml, 32.9 mmol) in THF (30 ml), *n*-BuLi (1.6 M in *n*-hexane, 18.8 ml, 30 mmol) was added in 5 min. The reaction was stirred at this temperature for 30 min before adding *p*-thiomethylbenzaldehyde (4.38 ml, 32.9 mmol). The reaction was strirred for 4 h at 0 °C, then the solvent was removed under reduced presure and the imine sublimated at 200 °C / 0.1 mmHg to give imine **2b** (Ar = *p*-MeS-C_6H_4-) in 90% yield. ^{1}H NMR ($CDCl_3$): δ = 0.26 (9H, Me_3Si, s); 2.53 (3H, CH_3S, s); 7.26-7.74 (4H, ArH, AB system, ν_A = 7.28, ν_B = 7.72, J_{AB} = 8.3 Hz); 8.92 (1H, CH, s). $C_{11}H_{17}NSSi$ (223.41): calcd C 59.14, H 7.67, N 6.27; found C 59.07, H 7.72, N 6.21.

Aldol condensation of *tert*-butyl α-halothioacetates with imines (Table 3). General procedure: To a stirred solution of *tert*-butyl α-halothioacetate (0.88 mmol) in ethyl ether (3.3 ml) at 0 °C (ice cooling), under argon atmosphere, a 0.4 M solution of **ent-1** [derived from (+)-menthone] in dichloromethane (3.3 ml, 1.28 mmol), and then Et_3N (0.196 ml, 1.4 mmol) were added dropwise. Enolborinate was generated with concurrent formation and precipitation of Et_3N-HBr. After 1.5 h at 0 °C, the mixture was cooled to -78 °C and a solution of *N*-trimethylsilylimine (**2**) (1.75 mmol) in a minimum volume of CH_2Cl_2, cooled to -78 °C, was added dropwise via cannula. The resulting mixture was stirred at -78 °C for 2 h and then slowly warmed to 0 °C during 16 h. The mixture was then quenched with pH 7 phosphate buffer (1 ml), and allowed to warm to room temperature. The solvent was removed *in vacuo* and the crude mixture was extracted twice with CH_2Cl_2. The combined organic extracts were concentrated and dissolved in Et_2O. After removing the Et_3N-HCl salt which had precipated, the ether layer was acidified with 1N HCl. After one hour the solvent was removed *in vacuo* and the salt was purified by washing it with diethyl ether. The amine hydrochloride salt was obtained as a white

solid in 77-89% yield. The *syn:anti* ratios of the reaction products were checked on *N*-benzoyl derivatives **6** (*vide infra*).

Spectroscopic data of *syn* α-halo-β-aminothioester hydrochloride salts (**3**-HCl, Table 3) are reported below:

Table 3, Entry 1. ^{1}H NMR ($CDCl_3$): δ= 1.34 (9H, *t*-Bu, s); 1.87 (2H, NH_2, br. s); 4.40-4.51 (2H, CHN and CHBr, AB system, ν_A = 4.43, ν_B = 4.48, J_{AB}= 7.9 Hz); 7.32-7.36 (5H, ArH, m). $C_{13}H_{19}NOSBrCl$ (352.73): calcd C 44.27, H 5.43, N 3.97; found C 44.07, H 5.53, N 3.88.

Table 3, Entry 2. ^{1}H NMR ($CDCl_3$): δ= 1.35 (9H, *t*-Bu, s); 2.05 (2H, NH_2, br. s); 2.48 (3H, CH_3S, s); 4.35-4.47 (2H, C<u>H</u>Br, C<u>H</u>NH_2, AB system, ν_A= 4.38, ν_B= 4.44, J_{AB} = 7.9 Hz); 7.19-7.32 (4H, ArH, AB_q, J = 8.4 Hz). $C_{14}H_{21}NOS_2BrCl$ (398.82): calcd C 42.16, H 5.31, N 3.51; found C 41.98, H 5.42, N 3.40.

Table 3, Entry 3. ^{1}H NMR ($CDCl_3$): δ= 1.37 (9H, *t*-Bu, s); 2.18 (2H, NH_2, br. s); 4.39 (1H, CHCl, d, J = 6.7 Hz); 4.53 (1H, C<u>H</u>NH_2, d, J = 6.7 Hz); 7.36 (5H, ArH, m); ^{13}C NMR ($CDCl_3$): δ = 29.40, 49.05, 58.60, 70.58, 127.43, 128.19, 128.55, 195.46. $C_{13}H_{19}NOSCl_2$ (308.27): calcd C 50.65, H 6.21, N 4.54; found C 50.54, H 6.26, N 4.50.

Table 3, Entry 4. ^{1}H NMR ($CDCl_3$): δ= 1.39 (9H, *t*-Bu, s); 1.78 (2H, NH_2, br. s); 2.49 (3H, CH_3S, s); 4.36 (1H, CHCl, A part of an AB system, J = 6.5 Hz); 4.51 (1H, C<u>H</u>NH_2, B part of an AB system, J = 6.5 Hz); 7.21-7.32 (4H, ArH, AB_q, J = 8.5 Hz). $C_{14}H_{21}NOS_2Cl_2$ (354.36): calcd C 47.45, H 5.97, N 3.95; found C 47.36, H 6.01, N 3.90.

Determination of the enantiomeric excess of *syn* α-halo-β-aminothioesters (3, Table 3) via derivatization with *R*-(+)-Mosher acid. General procedure. The % enantiomeric excess of *syn* α-halo-β-aminothioesters (**3**) was determined by ^{1}H NMR analysis of the Mosher ester derivatives. *Syn* α-halo-β-aminothioesters (**3**) (1.0 mol. eq.) in dichloromethane were treated with excess (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid in the presence of 1,3-dicyclohexylcarbodiimide (DCC).

Table 3, Entry 1. ^{1}H NMR ($CDCl_3$): δ= 3.40 [OMe, br. q, *syn* (2*R*, 3*S*), 98.5%], 3.64 [OMe, q, J = 1.5 Hz, *syn* (2*S*, 3*R*), 1.5%].

Table 3, Entry 2. ^{1}H NMR ($CDCl_3$): δ= 3.39 [OMe, q, J = 1.1 Hz, *syn* (2*R*, 3*S*), ≥ 99.5%], 3.63 [OMe, q, J = 1.6 Hz, *syn* (2*S*, 3*R*), ≤ 0.5%].

Table 3, Entry 3. ^{1}H NMR ($CDCl_3$): δ= 3.38 [OMe, br. q, *syn* (2*R*, 3*S*), 97%], 3.60 [OMe, q, J = 1.5 Hz, *syn* (2*S*, 3*R*), 3%].

Table 3, Entry 4. ^{1}H NMR ($CDCl_3$): δ= 3.39 [OMe, q, J = 1.4 Hz, *syn* (2*R*, 3*S*), 97.85%], 3.61 [OMe, q, J = 1.4 Hz, *syn* (2*S*, 3*R*), 2.15%].

Synthesis of *cis* aziridines (4a,b; Scheme 5). General procedure: To a cooled (0 °C) suspension of $LiAlH_4$ (0.77 mmol) in dry THF (1.3 ml), a solution of α-halo-β-aminothioester (0.13 mmol) in THF (1.0 ml) was added dropwise. After two hours the reaction was quenched by the addition of water (0.5 ml). The crude reaction mixture was filtered through a short Celite pad and purified by flash cromatography on silica gel to give the pure aziridine in 86-91% yield.

(1H)-(2*S*,3*S*)-(+)-3-(phenyl)aziridine-2-methanol (4a, Scheme 5) (from entry 1, 3 of Table 3): (86% yield), ^{1}H NMR ($CDCl_3$): δ= 1.97 (2H, NH and OH, br.s); 2.69 (1H, CHN, AB_q, J = ca. 6.5 Hz); 3.29 (1H, C<u>H</u>HOH, dd, J = 12.0, 7.3 Hz); 3.44 (1H, C<u>H</u>Ph, d, J = 6.6 Hz); 3.47 (1H, CH<u>H</u>OH, dd, J = 12.0, 5.6 Hz); 7.13-7.48 (5H, ArH, m); ^{13}C NMR ($CDCl_3$): δ = 36.93, 37.69, 61.34, 127,10, 127.44, 128.20. $[\alpha]_D^{25}$(*c* 0.75, $CHCl_3$) of **4a** (derived from entry 1 of Table 3) = + 97.7°; $[\alpha]_{436(Hg)}^{25}$ (*c* 0.75, $CHCl_3$) = + 215.8°; $[\alpha]_{365(Hg)}^{25}$ (*c* 0.75, $CHCl_3$) = + 378.2°. $C_9H_{11}NO$ (149.19): calcd C 72.46, H 7.43, N 9.39; found C 72.50, H 7.47, N 9.35.

(1H)-(2*S*,3*S*)-(+)-3-[(4-methylthio)phenyl]aziridine-2-methanol (4b, Scheme 5) (from entry 2, 4 of Table 3): (91% yield), ^{1}H NMR ($CDCl_3$): δ= 1.84 (2H, NH and OH, br.s); 2.48 (3H, s, SCH_3); 2.64 (1H, C<u>H</u>CH_2OH, AB_q, J = ca. 6.4 Hz); 3.25 (1H, C<u>H</u>HOH, dd, J = 11.8, 6.9 Hz); 3.39 (1H, C<u>H</u>Ar, d, J = 6.4 Hz); 3.44 (1H, CH<u>H</u>OH, dd, J = 5.8, 11.8 Hz); 7.19-7.32 (4H, ArH, AB_q, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ = 15.85, 36.42, 37.79, 61.28, 126.37, 127.94, 136.99. $[\alpha]_D^{25}$(*c* 0.71, $CHCl_3$) of **4b** (derived from entry 2 of Table 3) = + 95.7°; $[\alpha]_{436(Hg)}^{25}$ (*c* 0.71, $CHCl_3$) = + 114.8°; $[\alpha]_{365(Hg)}^{25}$ (*c* 0.71, $CHCl_3$) = + 217.9°. Lit. (ref. 22b) $[\alpha]_D^{25}$ (*c* 0.70, $CHCl_3$) = + 96.8°. $C_{10}H_{13}NOS$ (195.29): calcd C 61.51, H 6.71, N 7.17; found C 61.48, H 6.77, N 7.14.

Preparation of (2*S*,3*S*)-(+)-1-(4-methylphenyl)sulfonyl-3-(phenyl)aziridine-2-methanol (5a, Scheme 5): A solution of (1H)-(2*S*,3*S*)-(+)-3-(phenyl)aziridine-2-methanol (23 mg, 0.15 mmol) in chloroform (0.24 ml) was treated with triethylamine (0.065 ml, 0.45 mmol) and tosyl chloride (30 mg, 0.15 mmol) at - 40 °C, under nitrogen, with stirring. The mixture was stirred overnight at - 40 °C and for 3 h at 0 °C, then quenched with $NaHCO_3$ saturated aqueous solution (0.25 ml) and extracted with ethyl acetate. The organic extracts were washed with 5% aqueous HCl, dried and evaporated. The crude product was purified by flash-chromatography (*n*-hexane : EtOAc 4:1) to give (2*S*,3*S*)-(+)-1-(4-methylphenyl)sulfonyl-3-(phenyl)aziridine-2-methanol (44.5 mg, 89%). $[\alpha]_D^{25}$ (*c* 0.90, $CHCl_3$) of **5a** (derived from entry 1 of Table 3) = + 123.1°; $[\alpha]_{436(Hg)}^{25}$ (*c* 0.9, $CHCl_3$) = + 264.6°; $[\alpha]_{365(Hg)}^{25}$ (*c* 0.9, $CHCl_3$) = + 446.6°. Lit. (ref. 21d) for ent-**5a**: $[\alpha]_D^{25}$ (*c* 1.32, $CHCl_3$) = - 126.9°. $C_{16}H_{17}NO_3S$ (303.38): calcd C 63.35, H 5.65, N 4.62; found C 63.31, H 5.71, N 4.58.

Determination of the *syn* : *anti* diastereoisomeric ratios (see Table 3) of α-halo-β-aminothioesters (*ent*-3; Scheme 6) on the *N*-benzoyl derivatives (6a,b; Scheme 6). General procedure: The *syn* : *anti* diastereomeric ratios of α-halo-β-aminothioesters [obtained using **1** derived from (-)-menthone] were determined by ^{1}H-NMR analysis of the *N*-benzoyl derivatives. To a solution of DCC (45 mg, 0.22 mmol) in dry dichloromethane (1.0 ml) was added benzoic acid (27 mg, 0.22 mmol) and a solution of α-halo-β-aminothioester (0.088 mmol) in dichloromethane (200 µl). The reaction was stirred for 5 hours, quenched, and the crude mixture was purified by flash cromatography on silica gel to give the *N*-benzoyl derivative **6** (mixture of diastereomers) in 85% yield as a white solid.

3-(*R*)-benzoylamino-2-(*S*)-bromo-3-phenylpropanoic acid *tert*-butyl thioester, 6a (Y=Br). *Syn* :*anti* ratio ≥ 99:1. ^{1}H NMR ($CDCl_3$): δ = 1.44 (9H, *t*-Bu, s); 4.81 (1H, CHBr, d, *J* = 4.4 Hz); 5.87 (1H, CHNH, dd, *J* = 8.4, 4.4 Hz); 6.98 (1H, NH, d, *J* = 8.4 Hz); 7.35-7.88 (10H, ArH, m). $[\alpha]_D^{25}$ = + 48.2° (*c* 1.70, $CHCl_3$); $[\alpha]_{436(Hg)}^{25}$ = + 120.1° (*c* 1.70, $CHCl_3$). $C_{20}H_{22}NO_2SBr$ (420.38): calcd C 57.14, H 5.28, N 3.33; found C 57.07, H 5.32, N 3.30.

3-(*R*)-benzoylamino-2-(*S*)-bromo-3-[(4-methylthio)phenyl]propanoic acid *tert*-butyl thioester, 6b (Y=Br). *Syn* :*anti* ratio ≥ 99:1. ^{1}H NMR ($CDCl_3$): δ = 1.43 (9H, *t*-Bu, s); 2.48 (3H, CH_3S, s); 4.78 (1H, CHBr, d, *J* = 4.6 Hz); 5.80 (1H, CHNH, dd, *J* = 8.2, 4.6 Hz); 7.05 (1H, NH, d, *J* = 8.2 Hz); 7.21-7.33 (4H, C_6H_4, AB_q, *J* = 8.6 Hz); 7.43-7.55 (3H, ArH, m); 7.84 (2H, ArH, m). $[\alpha]_D^{25}$ = + 52.8° (*c* 1.53, $CHCl_3$); $[\alpha]_{436(Hg)}^{25}$ = + 138.0° (*c* 1.53, $CHCl_3$). $C_{21}H_{24}NO_2S_2Br$ (466.47): calcd C 54.07, H 5.19, N 3.00; found C 53.98, H 5.25, N 2.97.

3-(*R*)-benzoylamino-2-(*S*)-chloro-3-phenylpropanoic acid *tert*-butyl thioester, 6a (Y=Cl). *Syn* :*anti* ratio = 92 : 8. ^{1}H NMR ($CDCl_3$): δ = 1.45 (9H, *t*-Bu, s); 4.70 (1H, $CHCl_{anti}$, d, *J* = 4.5 Hz); 4.79 (1H, $CHCl_{syn}$, d, *J* = 3.3 Hz); 5.78 (1H, $CHNH_{anti}$, dd, *J* = 8.3, 4.5 Hz); 6.02 (1H, $CHNH_{syn}$, dd, *J* = 8.7, 3.3 Hz); 7.29-7.66 (10H, ArH, m); 8.12 (1H, NH, d, *J* = 4.5 Hz). $C_{20}H_{22}NO_2SCl$ (375.92): calcd C 63.90, H 5.90, N 3.73; found C 63.81, H 5.95, N 3.70.

3-(*R*)-benzoylamino-2-(*S*)-chloro-3-[(4-methylthio)phenyl]propanoic acid *tert*-butyl thioester, 6b (Y=Cl). *Syn* :*anti* ratio = 94:6. ^{1}H NMR ($CDCl_3$): δ = 1.45 (9H, *t*-Bu, s); 2.48 (3H, CH_3S, s); 4.67 (1H, $CHCl_{anti}$, d, *J* = 4.5 Hz); 4.75 (1H, $CHCl_{syn}$, d, *J* = 3.5 Hz); 5.71 (1H, $CHNH_{anti}$, dd, *J* = 8.2, 4.5 Hz); 5.94 (1H, $CHNH_{syn}$, dd, *J* = 8.7, 3.5 Hz); 7.08 (1H, NH, d, *J* = 8.7 Hz); 7.24-7.88 (9H, ArH, m). $C_{21}H_{24}NO_2S_2Cl$ (422.01): calcd C 59.77, H 5.73, N 3.32; found C 59.69, H 5.80, N 3.29.

Preparation of 3(*S*)-benzoylamino-3-phenylpropanoic acid *tert*-butyl thioester (7, Scheme 6). To a solution of **6a** (Y=Cl) (13 mg, 0.034 mmol) in MeOH (0.2 ml) was added NH_4Cl (7.5 mg, 0.14 mmol) and a suspension of Zn (9 mg, 0.14 mmol) in MeOH (0.38 ml). Zn was previously activated with a 0.5 N solution of HCl and washed with acetone and methanol. After one hour the solvent was removed *in vacuo* and the crude product was dissolved in CH_2Cl_2 and treated with a saturated solution of $NaHCO_3$. After purification by flash cromatography, compound **7** was obtained. This compound was prepared from compound **6a** (Y = Cl) (60% yield) or compound **6a** (Y = Br) (75% yield) as a white solid. **7**: ^{1}H NMR ($CDCl_3$): δ = 1.41 (9H, *t*-Bu, s); 2.96-3.18 (2H, CH_2CO, AA'X System, ν_A = 3.04, $\nu_{A'}$ = 3.13, $J_{AA'}$ = 15.0, J_{AX} = 5.8 Hz); 5.54-5.65 (1H, CHN, dt, *J* = 8.0, 5.8 Hz); 7.22-7.88 (11H, ArH, NH, m); ^{13}C NMR ($CDCl_3$): δ = 29.50, 49.00, 51.23, 126.29, 127.03, 127.53, 128.56, 131.53, 166.39, 199.14. **7** derived from **6a** (Y = Cl): $[\alpha]_D^{25}$ = + 13.6° (*c* 1.57, $CHCl_3$); $[\alpha]_{436(Hg)}^{25}$ = + 37.5° (*c* 1.57, $CHCl_3$); $[\alpha]_{365(Hg)}^{25}$ = + 82.5° (*c* 1.57, $CHCl_3$); **7** derived from **6a** (Y = Br) : $[\alpha]_D^{25}$ = + 15.2° (*c* 0.94, $CHCl_3$); $[\alpha]_{436(Hg)}^{25}$ = + 38.3° (*c* 0.94, $CHCl_3$);

$[\alpha]_{365(Hg)}^{25}$ = + 85.1° (*c* 0.94, $CHCl_3$). $C_{20}H_{23}NO_2S$ (341.48): calcd C 70.35, H 6.79, N 4.10; found C 70.30, H 6.83, N 4.06.

Preparation of 3-(*S*)-benzoylamino-3-phenylpropanoic acid methyl ester (8, Scheme 6). To a solution of **7** (34 mg, 0.1 mmol) in MeOH (5 ml) was added $Hg(NO_3)_2$ (65 mg, 0.2 mmol). The reaction was stirred under nitrogen for one hour and then filtered through Celite. After purification by flash cromatography, compound **8** was obtained as a colorless oil (23 mg, 82%). ^{1}H NMR ($CDCl_3$): δ= 2.91-3.13 (2H, $C\underline{H}_2CO_2Me$, AA'X System, ν_A = 2.98, $\nu_{A'}$ = 3.06, $J_{AA'}$ = 15.7, J_{AX} = 5.6 Hz); 3.66 (3H, CH_3O, s); 5.61-5.70 (1H, C<u>H</u>N, dt, *J* = 8.4, 5.6 Hz); 7.24-7.88 (11H, ArH, NH, m); ^{13}C NMR ($CDCl_3$): δ= 39.50, 49.70, 51.82, 126.11, 126.97, 127.57, 128.53, 128.68, 131.56, 134.10, 140.41, 166.44, 172.00; **8** derived from **6a** (Y = Cl): $[\alpha]_D^{25}$ = + 18.40° (*c* 1.5, $CHCl_3$); $[\alpha]_{436(Hg)}^{25}$ = + 40.81° (*c* 1.5, $CHCl_3$); $[\alpha]_{365(Hg)}^{25}$ = + 77.00° (*c* 1.5, $CHCl_3$); **8** derived from **6a** (Y = Br) : $[\alpha]_D^{25}$ = + 20.0° (*c* 0.63, $CHCl_3$); $[\alpha]_{436(Hg)}^{25}$ = + 45.2° (*c* 0.63, $CHCl_3$); $[\alpha]_{365(Hg)}^{25}$ = + 86.6° (*c* 0.63, $CHCl_3$); Lit. (ref. 6a) for *ent*-**8**: $[\alpha]_D^{25}$ = - 20.45° (*c* 1.12, $CHCl_3$). $C_{17}H_{17}NO_3$ (283.33): calcd C 72.07, H 6.05, N 4.94; found C 72.01, H 6.12, N 4.89.

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