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Enantioselective synthesis of (*S*)- and (*R*)-α-methylserines: application to the synthesis of (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals

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Abstract—This report describes the synthesis of enantiomerically pure (*S*)- and (*R*)-α-methylserines on a multigram scale, starting from the Weinreb amide of 2-methyl-2-propenoic acid and using a stereodivergent synthetic route that involves a Sharpless asymmetric dihydroxylation reaction. As a synthetic application of these quaternary α-amino acids, they were used as starting materials in the synthesis of the well-known valuable homochiral (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal building blocks.

1. Introduction

In recent years, much attention has been focused on the synthesis of α,α-disubstituted α-amino acids with a view to the design and synthesis of short chain peptides having well defined conformation, which can be altered by the nature of the α-substituent.[1] In connection with a research project directed towards the synthesis of new quaternary α-amino acids,[2] we have been interested in the synthesis of conformationally restricted hydroxy-α-amino acids.[3] In this context, especially interesting are (*S*)- and (*R*)-α-methylserines which can be regarded as potential C-terminal α-helix stabilising building blocks.[4] Herein, we present a novel strategy to synthesise on a multigram scale both (*S*)- and (*R*)-α-methylserines and their synthetic application to afford (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals, which are known to be excellent chiral building blocks for the synthesis of different α-methyl-α-amino acids.[5]

2. Results and discussion

The quickest method to obtain (*S*)- and (*R*)-α-methylserines is the Sharpless asymmetric aminohydroxylation (AA)[6] of different 2-methyl-2-propanoic acid derivatives **1a**–**1d**, but all attempts using literature methods (Table 1, entries 2 and 5)[7] and other experiments (Table 1, entries 1, 3 and 4) gave the regioisomer **3a**–**3d** as the major product and poor enantioselectivities (Scheme 1). Considering these results and given that the Sharpless asymmetric dihydroxylation (AD)[8] on benzyl tiglate had already been applied to the synthesis of different α-methyl-α-amino acids,[9] we explored the AD on olefins **1a**–**1c**. The enantiomeric excess (e.e.) obtained with 2-methylpropenoates **1a** and **1b** (Table 1, entries 6 and 7) in the presence of $(DHQ)_2PHAL$ (AD-mix α) was smaller than that obtained with olefin **1c** (Table 1, entry 8), according to the results obtained by Sharpless et al.[10] when AD-mix β was used (Table 1, entry 9). Therefore, we decided to use olefin **1c** as a starting material in the synthesis of enantiomerically pure α-methylserines.

Olefin **1c** was formed from commercially available 2-methyl-2-propenoic acid, which was transformed into the corresponding 2-methyl-2-propionyl chloride by the action of PCl_5. Further in situ addition of methoxymethylamine gave **1c** according to the protocol described in the literature.[11] The AD reaction of **1c** in the presence of AD-mix α proceeded smoothly to yield the diol (*R*)-**4c** with excellent e.e. The amide group of diol (*R*)-**4c** was converted into the corresponding

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Table 1. AA and AD on olefins **1a–1c**

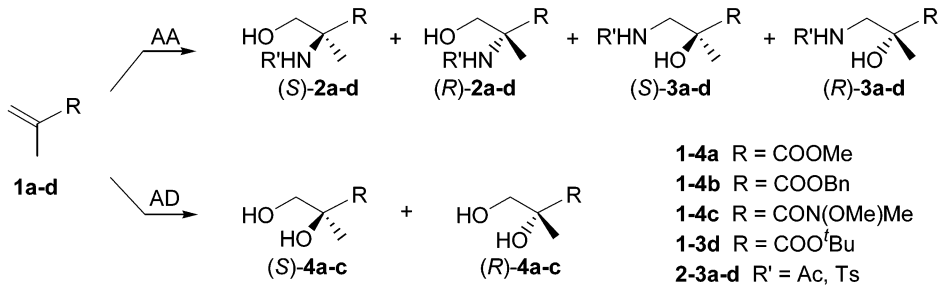
Entry	Olefins	R	R′	Method[a]	% Rto[b]	(**2**/**3**)	(*S*)/(*R*)[c]	Ref.
1	**1a**	COOMe	Ac	A	26	10/90	49/51[d]	–
2	**1a**	COOMe	Ts	B	–	>10/90	45.5/54.5	7
3	**1b**	COOBn	Ac	A	81	10/90	49/51[d]	–
4	**1c**	CON(OMe)Me	Ts	B	64	5/95	50/50[d]	–
5	**1d**	COO^{t}Bu	Ts	B	–	>10/90	41/59	7
6	**1a**	COOMe	–	C	90	–	50/50[d]	–
7	**1b**	COOBn	–	C	90	–	25/75[d]	–
8	**1c**	CON(OMe)Me	–	C	81	–	3.5/96.5[d]	–
9	**1c**	CON(OMe)Me	–	D	81	–	96.5/3.5	9

[a] Method A: $K_2OsO_4{\cdot}2H_2O$, $LiOH{\cdot}H_2O$, $(DHQ)_2PHAL$, MeCONHBr, *tert*-BuOH/H_2O (1:1), 4°C, 12 h. Method B: $K_2OsO_4{\cdot}2H_2O$, $(DHQ)_2PHAL$, $TsNClNa{\cdot}3H_2O$, *tert*-BuOH/H_2O (1:1), 25°C, 12 h. Method C: AD-mix α, $MeSO_2NH_2$, ^{t}BuOH/H_2O (1:1), 0°C, 12 h. Method D: AD-mix β, $MeSO_2NH_2$, ^{t}BuOH/H_2O (1:1), 0°C, 12 h.

[b] Determined after column chromatography.

[c] In the case of AA reactions, the enantioselectivity (*S*)/(*R*) corresponds to the main regioisomer **3a–3d**.

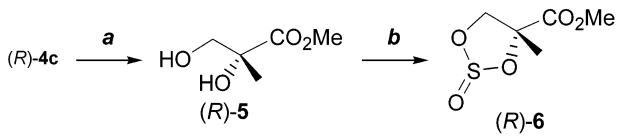
[d] The method to measure the enantioselectivity is described in the Experimental section.



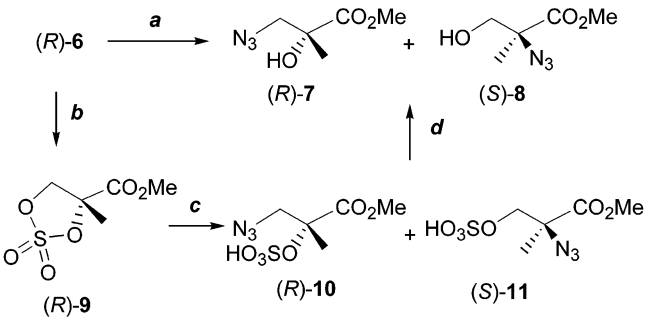
Scheme 1. Asymmetric aminohydroxylations (AA) and dihydroxylations (AD) on olefins **1a–1d**.

methyl ester group to obtain diol (*R*)-**5** in two steps: basic hydrolysis with LiOH in the presence of MeOH (3:1) at room temperature and subsequent esterification with AcCl in refluxing MeOH. Diol (*R*)-**5** was then transformed into its 2,3-cyclic sulfite (*R*)-**6** with thionyl chloride (Scheme 2). Diol (*R*)-**5** has been previously reported by Ziffer et al.[12] using a chromatographic separation of the (–)-menthyl esters of *rac*-2,3-dihydroxy-2-methylpropanoic acid, followed by hydrolysis and methylation.

Reaction of sulfite (*R*)-**6** with NaN_3 at 50°C in DMF gave a mixture of the azido esters (*R*)-**7** and (*S*)-**8** with a regioselectivity[13a,c,g] of 4:1 in favour of the α-azido ester (*S*)-**8**. Nucleophilic substitution by NaN_3 at the α-carbon of cyclic sulfite (*R*)-**6** occurred with clean inversion of configuration (Scheme 3). Alternatively, the mixture of azido esters (*R*)-**7** and (*S*)-**8** could be obtained with a similar regioselectivity from sulfite (*R*)-**6** using three steps: oxidation of sulfite (*R*)-**6** into sulfate (*R*)-**9**, nucleophilic substitution by NaN_3 in the presence of acetone–H_2O as a solvent at room temperature and further acidic hydrolysis. Alternatively, the yield of azido esters (*R*)-**7** and (*S*)-**8** was similar to that obtained by the first method. Indeed, we have demonstrated that the cyclic sulfate and sulfite groups behave as effective leaving groups in highly regioselective reactions, as reported in several articles on the nucleophilic substitution of cyclic sulfites and sulfates.[13] Taking into account the yields of α-azido ester (*S*)-**8** via sulfite or via sulfate, it is clearly unnecessary to carry out the oxidation of sulfite to sulfate to obtain the required α-methylserines (Scheme 3).



Scheme 2. Synthesis of cyclic sulfite (*R*)-**6** from diol (*R*)-**4c**. *Reagents and conditions*: (a) (i) $LiOH{\cdot}H_2O$, H_2O/MeOH (1:3), room temperature, 2 h; (ii) AcCl, MeOH, reflux, 12 h, 85%; (b) $SOCl_2$, CCl_4, reflux, 4 h, 90%.



Scheme 3. Synthesis of α-azido ester (*S*)-**8**. *Reagents and conditions*: (a) NaN_3, DMF, 50°C, 2 days, 93%; (b) $NaIO_4$, $RuCl_3$, $H_2O/CH_3CN/CCl_4$ (1:1:1), 40°C, 7 h, 86%; (c) NaN_3, acetone/H_2O (9:1), room temperature, 2 days; (d) H_2SO_4 20%, room temperature, 2 days, 75% from **9**.

Once separated, α-azido ester (*S*)-**8** was readily hydrogenated in MeOH in the presence of palladium to give the corresponding α-amino ester, which was then hydrolysed in acid to provide the α-methylserine hydrochloride. The free amino acid α-methylserine (*S*)-**12** was obtained in 59% yield by treatment of the hydrochloride with propylene oxide in refluxing EtOH. Alternatively, the yield of α-methylserine (*S*)-**12** was increased to 83% by hydrolysis of the methyl ester group of (*S*)-**8** in aqueous acid and further hydrogenation of the corresponding azido acid (Scheme 4).

In order to improve the yield of α-methylserine (*S*)-**12**, we also explored the conversion of diol (*S*)-**5** into the corresponding amino alcohol using the cyclic iminocarbonate rearrangement process described by Ko et al.[14] The cyclic iminocarbonate intermediate was obtained in a one-pot operation, with net retention of configuration at the α-carbon and was subjected to acid hydrolysis. Liberation of the free amino acid gave α-methylserine (*S*)-**12** in 30% yield. The method that gave the best result involved using the cyclic sulfite and the second transformation (method ***b***) of (*S*)-**8** into (*S*)-**12** (Scheme 4).

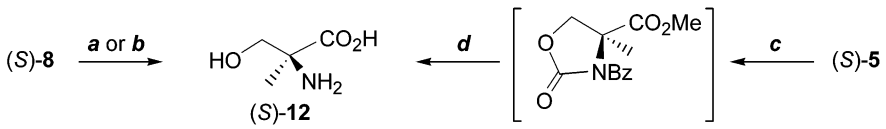
The enantiomer (*R*)-α-methylserine (*R*)-**12** was obtained using the same strategy described above and also starting from olefin **1c**, but changing the Sharpless chiral catalytic ligand to $(DHQD)_2PHAL$ (AD-mix β) in the AD reaction (Scheme 5). The absolute configuration and the enantiomeric purity of these amino acids (*S*)-**12** and (*R*)-**12** were determined by comparing their specific rotations with those reported in the literature.[15] The spectral data of these compounds also proved to be identical to those previously reported.[15,16]

In this way, we have developed a new synthesis of both enantiomers of α-methylserine (*S*)-**12** and (*R*)-**12** starting from the Sharpless AD reaction on olefin **1c** on a multigram scale (6 g of **1c**) in eight steps with 39% overall yield and 93% e.e.

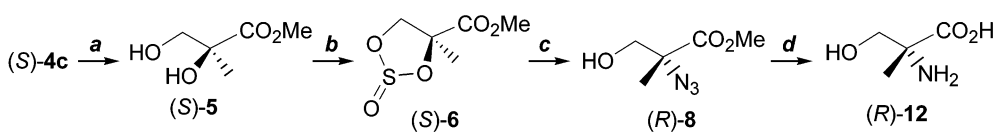
As part of our research project directed towards the synthesis of restricted α-amino acids, we have recently reported two syntheses of (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals, which are known to be excellent building blocks in new approaches to the synthesis of different quaternary α-methylamino acids.[5a]

The best procedure for the achievement of both (*S*)- and (*R*)- forms of *N*-Boc-*N*,*O*-isopropylidene-α-methylserinal is described by a stereodivergent synthesis, on a multigram scale, from (*R*)-2-methylglycidol, which is no longer commercially available. Because of this and taking into account that in the original synthesis of (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal, carried out in a milligram scale, (*S*)-α-methylserine was used as starting material,[15] our goal was to obtain (*S*)- and (*R*)-α-methylserines in large quantities to be used as starting materials in the synthesis of (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals on a multigram scale. Thus, we actually used the protected *N*-Boc-α-methylserine methyl esters (*S*)-**13** and (*R*)-**13** as starting materials, which were obtained starting from azido esters (*S*)-**8** and (*R*)-**8** instead of starting from the α-methylserines (*S*)-**12** and (*R*)-**12**. In this way, (*S*)-**8** and (*R*)-**8** were, respectively, hydrogenated in the presence of palladium catalyst and subsequently treated with $(Boc)_2O$ in basic medium. We also attempted these transformations in one single step using $(Boc)_2O$, hydrogen, palladium–carbon and MeOH as a solvent or PMe_3, Boc-ON in toluene at −20°C, as described in the literature,[17] but the yield of **13** decreased dramatically (Scheme 6).

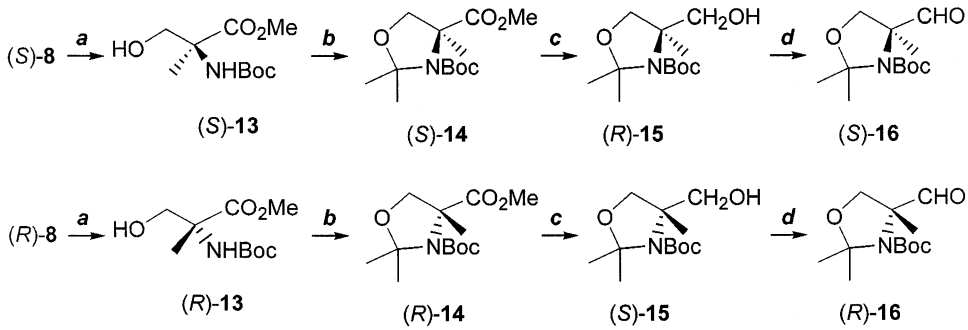
Compounds (*S*)-**13** and (*R*)-**13** were converted into oxazolidines (*S*)-**14** and (*R*)-**14** by the use of 2,2-dimethoxypropane (DMP) in acetone at room temperature with boron trifluoride etherate as a catalyst. When DMP and *p*-TsOH were used in toluene at reflux, a decrease in yield was observed. Reduction of the methyl



Scheme 4. Synthesis of α-methylserine (*S*)-**12**. *Reagents and conditions*: (a) (i) H_2/Pd–C, MeOH, room temperature, 24 h, (ii) HCl 6N, reflux, 12 h, (iii) EtOH/propylene oxide (3:1), reflux, 2 h, 59%; (b) (i) HCl 6N, reflux, 12 h, (ii) H_2/Pd–C, MeOH, room temperature, 24 h, 83%; (c) (i) Bu_2SnO, BzNCS, Et_3N, Bu_4NBr, dichloroethane, reflux, 21 h, 45%; (d) (i) HCl 6N, reflux, 12 h, (ii) EtOH/propylene oxide (3:1), 60%.



Scheme 5. Synthesis of α-methylserine (*R*)-**12**. *Reagents and conditions*: (a) (i) $LiOH{\cdot}H_2O$, H_2O/MeOH (1:3), room temperature, 2 h; (ii) AcCl, MeOH, reflux, 12 h, 85%; (b) $SOCl_2$, CCl_4, reflux, 4 h, 85%; (c) NaN_3, DMF, 50°C, 2 days, 75%; (d) (i) HCl 6N, reflux, 12 h, (ii) H_2/Pd–C, MeOH, room temperature, 24 h, 83%.



Scheme 6. Synthesis of chiral building blocks *N*-Boc-α-methylserinal acetonides (*S*)-**16** and (*R*)-**16**. *Reagents and conditions*: (a) (i) H_2/Pd–C, MeOH, room temperature, 24 h, (ii) Boc_2O, $Na_2CO_3{\cdot}10H_2O$, H_2O/THF (1:5), room temperature, 19 h, 70%; (b) DMP, $BF_3{\cdot}OEt_2$, acetone, room temperature, 1 h, 93%; (c) $LiAlH_4$, THF, room temperature, 6 h, 91%; (d) DMSO, oxalyl chloride, Et_3N, dichloromethane, room temperature, 12 h, 96%.

ester groups of (*S*)-**14** and (*R*)-**14** into the corresponding required aldehydes (*S*)-**16** and (*R*)-**16** was carried out more conveniently in two steps involving a reduction–oxidation sequence, since the treatment of (*S*)-**14** with DIBAL-H, in toluene at −78°C, gave only a 35% yield of aldehyde (*S*)-**16**. Since the attempts of reduction with $LiBH_4$ or $NaBH_4$ were unsuccessful, the reduction was carried out with $LiAlH_4$ in THF at room temperature and the alcohols (*R*)-**15** and (*S*)-**15** were oxidised under Swern conditions to give the desired aldehydes (*S*)-**16** and (*R*)-**16** (Scheme 6).

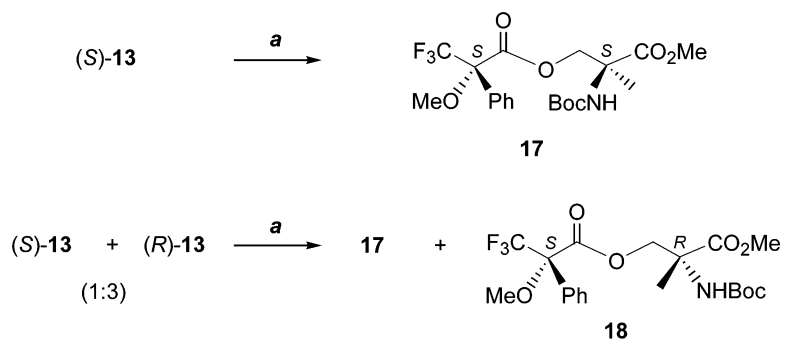
The enantiomeric purity of the two quaternary amino acids α-methylserines and the two quaternary α-methylaldehydes was examined by preparation of the Mosher esters of alcohols (*S*)-**13** and (*R*)-**13** (Scheme 7).[18] Alcohol (*S*)-**13** was coupled with (*S*)-(−)-methoxytrifluorophenylacetic acid [(*S*)-MTPA] in the presence of DCC and DMAP to give Mosher ester **17**. For comparison the mixture of alcohols (*S*)-**13** and (*R*)-**13** (in a ratio of 1:3) was transformed into Mosher esters **17** and **18**, respectively. Analysis of the NMR spectra of ester **17** showed that the enantiomeric purity of compound (*S*)-**13** was at least 96% (only one isomer was observed in the ^1H and ^{19}F NMR spectra) (Scheme 7).

3. Conclusion

In conclusion, we have developed a straightforward synthetic route on a multigram scale for the achievement of the valuable chiral building blocks *N*-Boc-*N*,*O*-isopropylidene-α-methylserinals (*S*)-**16** and (*R*)-**16** in three steps with an overall yield of 81% from *N*-Boc protected α-methylserine methyl esters (*S*)-**13** and (*R*)-**13** (or in 10 steps with a 23% yield from commercially available 2-methyl-2-propenoic acid).

4. Experimental

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). The assignment of all separate signals in the ^1H NMR spectra was made on the basis of coupling constants, selective proton–proton homonuclear decoupling experiments, proton–proton COSY experiments and proton–carbon HETCOR experiments. Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter in a 1 dm cell of 1 mL capacity. Microanalyses were carried out on a CE Instruments EA-1110 analyser and were in good agreement with the calculated values. IR spectra were recorded on a Perkin Elmer FT-IR Spectrum 1000 spectrometer. Mass spectra were obtained by one of the



Scheme 7. Determination of enantiomeric purity of (*S*)-**13**. *Reagents and conditions*: (a) (*S*)-MTPA, DCC, DMAP, dichloromethane, room temperature, 6 h, 48%.

following ionization techniques: electron impact (EI) or electrospray ionization (ESI) on a Hewlett Packard 5989B mass spectrometer.

4.1. Determination of enantioselectivity in AA and AD reactions

The enantioselectivity of the major regioisomer obtained in the AA reaction with olefins **1a** and **1b** was determined by the acid hydrolysis of compounds **3a** and **3b** to α-methylisoserines and further comparison of the optical activities with the values reported.[19]

The enantioselectivity of the main regioisomer obtained in the AA reaction with olefin **1c** was determined by transformation of compounds **3c** into methyl 2-hydroxy-2-methyl-3-(tosylamino)-propanoates and further comparison with the data reported in the literature.[7] In this way, compounds **3c** were hydrolysed into the corresponding carboxylic acids by the action of $LiOH{\cdot}H_2O$. These acids were esterified using AcCl and MeOH.

The enantioselectivity obtained in the AD reaction with olefins **1a** and **1b** was determined by their transformation into cyclic sulfites **6** and further comparison of their optical rotation with enantiomerically pure (*R*)-**6**. In this way, compounds **4a** were transformed into cyclic sulfites **6** using the method described in the experimental section for the synthesis of compound (*R*)-**6** from (*R*)-**5**. Compounds **4b** were treated with hydrogen/palladium on carbon to remove the benzyl group, obtaining the corresponding carboxylic acids, which were transformed into cyclic sulfites **6** following the method described in the experimental section. The enantioselectivity of AD reactions with olefin **1** was determined by comparing our results with those reported in the literature.[9]

4.2. Methyl 2,3-dihydroxy-2-methylpropenoates (*R*)-5 and (*S*)-5

To a solution of (*R*)-**4c** (8.60 g, 52.7 mmol) in H_2O/MeOH (1:3, 120 mL) was added $LiOH{\cdot}H_2O$ (11.1 g, 264 mmol) and the mixture was stirred at room temperature for 2 h. The *N*,*O*-dimethylhydroxylamine formed in the reaction and MeOH were removed and the mixture was acidified with conc. HCl to pH 1–2. After removing the solvent, the white solid was dissolved in HCl in MeOH, previously prepared by dropwise addition of AcCl (30 mL) to a pre-cooled MeOH (120 mL) at 0°C, and the mixture was heated under reflux for 12 h. The mixture was concentrated and the residue partitioned between H_2O (50 mL) and $CHCl_3$/propan-2-ol (3:1, 100 mL). The aqueous layer was successively washed with $CHCl_3$/propan-2-ol (4×100 mL), dried (Na_2SO_4), concentrated and the crude product was purified by column chromatography (hexane:ethyl acetate, 3:7) to give (*R*)-**5** as a colourless oil (5.98 g, 44.6 mmol); yield: 85%. $[\alpha]_D^{25}=-1.0$ (*c* 2.66, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 3H, CH_3), 3.57 (d, 1H, $J=11.2$ Hz, CH_2), 3.80 (d, 1H, $J=11.2$ Hz, CH_2), 3.81 (s, 3H, CO_2CH_3). Anal. calcd for $C_5H_{10}O_4$: C, 44.77; H, 7.51. Found: C, 44.61; H, 7.45%. Spectral data were identical to those reported in the literature.[12]

As described for its enantiomer (*R*)-**5**, compound (*S*)-**5** (5.95 g, 85%) was obtained from compound (*S*)-**4c** (8.62 g, 52.7 mmol). $[\alpha]_D^{25}=+0.8$ (*c* 2.66, MeOH). Anal. calcd for $C_5H_{10}O_4$: C, 44.77; H, 7.51. Found: C, 44.58; H, 7.48%.

4.3. Methyl 4-methyl-2-oxo-2λ^4-[1,3,2]dioxathiolane-4-carboxylates (*R*)-6 and (*S*)-6

Diol (*R*)-**5** (5.70 g, 42.5 mmol) was dissolved in CCl_4 (75 mL) and $SOCl_2$ (7.74 g, 65.0 mmol) was then added. The resulting solution was heated under reflux for 4 h. The solvent and excess $SOCl_2$ were evaporated and the crude product was purified by column chromatography (hexane:ethyl acetate, 4:1) to give (*R*)-**6** as a colourless liquid (6.90 g, 38.3 mmol); yield: 90%. $[\alpha]_D^{25}=-49.8$ (*c* 1.16, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.63, 1.81 (2s, 3H, CH_3), 3.79, 3.82 (2s, 3H, CO_2CH_3), 4.26, 4.48 (2d, 1H, $J=9.0$ Hz, CH_2), 4.83, 5.04 (2d, 1H, $J=9.0$ Hz, CH_2); ^{13}C NMR ($CDCl_3$): δ 21.5, 23.1 (CH_3), 53.4 (CO_2CH_3), 73.7, 73.8 (CH_2), 86.0, 87.6 ($C(CH_3)O$), 170.1, 170.5 (CO_2CH_3); IR (CH_2Cl_2) 1759, 1743 (C=O); MS (EI) (m/z) = 57, 121, 181; ESI$^+$ (m/z) = 180+Na. Anal. calcd for $C_5H_8O_5S$: C, 33.33; H, 4.48; S, 17.80. Found: C, 33.28; H, 4.50; S, 17.84%.

As described for its enantiomer (*R*)-**6**, cyclic sulfite (*S*)-**6** (6.92 g, 90%) was obtained from compound (*S*)-**5** (5.73 g, 42.7 mmol). $[\alpha]_D^{25}=+49.1$ (*c* 1.15, MeOH). Anal. calcd for $C_5H_8O_5S$: C, 33.33; H, 4.48; S, 17.80. Found: C, 33.25; H, 4.53; S, 17.87%.

4.4. Methyl 2-azido-3-hydroxy-2-methylpropanoates (*S*)-8 and (*R*)-8

4.4.1. Method A. To a solution of cyclic sulfite (*R*)-**6** (5.70 g, 31.6 mmol) in DMF (30 mL) was added NaN_3 (2.72 g, 41.8 mmol). The mixture was stirred at 50°C for 2 days to give a mixture of azido alcohols (*R*)-**7** and (*S*)-**8** in a ratio of 1:4. The solvent was then removed and the residue partitioned between H_2O (30 mL) and ethyl acetate (70 mL). The aqueous layer was successively washed with ethyl acetate (4×40 mL), dried (Na_2SO_4), concentrated and the crude product was chromatographed (hexane:ethyl acetate, 4:1) to give (*R*)-**7** (0.90 g, 18%) and the required α-azido ester (*S*)-**8** as a colourless liquid (3.77 g, 23.7 mmol); yield: 75%. Overall yield: 93%. Compound (*R*)-**7**: $[\alpha]_D^{25}=+59.4$ (*c* 1.51, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 3H, CH_3), 3.37–3.47 (m, 2H, CH_2), 3.62–3.67 (br s, 1H, OH), 3.79 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$): δ 23.3 (CH_3), 53.2 (CO_2CH_3), 58.3 (CH_2), 75.2 ($C(CH_3)OH$), 175.1 (CO_2CH_3); MS (EI) (m/z) = 15, 43, 103, 160; ESI$^-$ (m/z) = 158. Anal. calcd for $C_5H_9N_3O_3$: C, 37.74; H, 5.70; N, 26.40. Found: C, 37.68; H, 5.66; N, 26.31%. Compound (*S*)-**8**: $[\alpha]_D^{25}=-2.2$ (*c* 0.98, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 3H, CH_3), 2.08 (br s, 1H, OH), 3.63 (d, 1H, $J=11.6$ Hz, CH_2), 3.80 (d, 1H, $J=11.6$ Hz, CH_2), 3.83 (CO_2CH_3); ^{13}C NMR ($CDCl_3$): δ 19.1 (CH_3), 52.9 (CO_2CH_3), 67.4 (CH_2), 67.5 ($C(CH_3)N_3$), 172.0 (CO_2CH_3); IR (CH_2Cl_2) 3593 (OH),

1743 (C=O); MS (EI) (m/z) = 59, 85, 160; ESI$^+$ (m/z) = 159+Na. Anal. calcd for $C_5H_9N_3O_3$: C, 37.74; H, 5.70; N, 26.40. Found: C, 37.70; H, 5.72; N, 26.35%.

As described for its enantiomer (*S*)-**8**, α-azido ester (*R*)-**8** (3.85 g, 75%) was obtained from compound (*S*)-**6** (5.72 g, 31.7 mmol). $[\alpha]_D^{25} = +1.9$ (*c* 1.49, MeOH). Anal. calcd for $C_5H_9N_3O_3$: C, 37.74; H, 5.70; N, 26.40. Found: C, 37.67; H, 5.69; N, 26.31%.

4.4.2. Method B. To a stirred solution of cyclic sulfate (*R*)-**9** (0.42 g, 2.14 mmol) in acetone (20 mL) and water (2 mL) was added NaN_3 (0.35 g, 5.38 mmol). The mixture was stirred at room temperature for 2 days to give a mixture of (*R*)-**10** and (*S*)-**11** in a ratio of 1:9. The reaction was concentrated under reduced pressure, ethyl ether (30 mL) and water (1 mL) were added and the solution was chilled to 0°C followed by addition of 20% aqueous H_2SO_4 (3 mL). The solution was vigorously stirred at room temperature for 2 days. The organic layer was collected and concentrated and the crude product was chromatographed (hexane:ethyl acetate, 4:1) to give the compound (*R*)-**7** (26 mg, 8%) and the required α-azido ester (*S*)-**8** as a colourless liquid (0.23 g, 1.44 mmol); yield: 67%. Overall yield: 75%.

4.5. Methyl 4-methyl-2-dioxo-2λ^6-[1,3,2]dioxathiolane-4-carboxylates (*R*)-9 and (*S*)-9

Compound (*R*)-**6** (0.50 g, 2.78 mmol) was dissolved in a mixture of water (15 mL), CH_3CN (10 mL) and CCl_4 (10 mL). $NaIO_4$ (1.16 g, 5.42 mmol) and $RuCl_3$ hydrate (10 mg, 0.05 mmol) were added and the solution was vigorously stirred for 7 h at 40°C. Ethyl ether (75 mL) was added to the cooled mixture. The organic layer was removed, dried (Na_2SO_4) and concentrated. The crude product was chromatographed (hexane:ethyl acetate, 4:1) to give compound (*R*)-**9** as a colourless liquid (0.38 g, 2.36 mmol); yield: 86%. $[\alpha]_D^{25} = -20.4$ (*c* 1.42, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.78 (s, 3H, CH_3), 3.85 (s, 3H, CO_2CH_3), 4.47 (d, 1H, J = 9.3 Hz, CH_2), 4.98 (d, 1H, J = 9.0 Hz, CH_2); ^{13}C NMR ($CDCl_3$): δ 22.2 (CH_3), 54.0 (CO_2CH_3), 74.8 (CH_2), 86.2 ($C(CH_3)O$), 168.3 (CO_2CH_3); IR (CH_2Cl_2) 1748 (C=O), 1400 (sulfate), 1217 (sulfate); MS (EI) (m/z) = 57, 137, 197; ESI$^+$ (m/z) = 197. Anal. calcd for $C_5H_8O_6S$: C, 30.61; H, 4.11; S, 16.35. Found: C, 31.21; H, 4.23; S, 16.21%.

As described for its enantiomer (*R*)-**9**, compound (*S*)-**9** (0.52 g, 86%) was obtained from compound (*S*)-**6** (0.68 g, 3.78 mmol). $[\alpha]_D^{25} = +19.8$ (*c* 1.43, MeOH). Anal. calcd for $C_5H_8O_6S$: C, 30.61; H, 4.11; S, 16.35. Found: C, 31.00; H, 4.15; S, 16.62%.

4.6. α-Methylserines (*S*)-12 and (*R*)-12

4.6.1. Method A. A solution of α-azido ester (*S*)-**8** (1.20 g, 7.54 mmol) in MeOH (40 mL) was hydrogenated using palladium on carbon as catalyst (1:5 catalyst/substrate by weight) and the resulting suspension was stirred at room temperature for 24 h. The catalyst was removed by filtration and the solvent was evaporated to give the corresponding amino alcohol as a pale yellow oil. To this compound was added an aqueous HCl solution (6N, 20 mL) and the mixture was heated under reflux for 12 h. The solvent was removed to give α-methylserine hydrochloride as a white solid. This compound was dissolved in EtOH/propylene oxide (3:1, 4 mL) and the mixture was heated under reflux for 2 h. After this time, the α-methylserine (*S*)-**12** partially precipitated as a white solid (312 mg). The filtrate was concentrated and the residue was dissolved in water and eluted through a C_{18} reverse-phase Sep-pak cartridge to give, after removal of the water, 218 mg of (*S*)-**12** as a white solid; total amount (530 mg, 4.45 mmol); yield: 59%. $[\alpha]_D^{25} = +5.3$ (*c* 1.02, H_2O). ^{1}H NMR (D_2O): δ 1.28 (s, 3H, CH_3), 3.52 (d, 1H, J = 12.0 Hz, CH_2), 3.77 (d, 1H, J = 12.0 Hz, CH_2). ESI$^-$ (m/z) = 118. Anal. calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.25; H, 7.66; N, 11.68%. Spectral data were identical to those reported in the literature.[15]

4.6.2. Method B. A suspension of α-azido ester (*S*)-**8** (1.50 mg, 9.42 mmol) in aqueous HCl solution (6N, 15 mL) was heated under reflux for 12 h to give, after complete evaporation, the crude acid. This compound was dissolved in MeOH (50 mL) and was hydrogenated using palladium on carbon as catalyst (1:5 catalyst/substrate by weight). The resulting suspension was stirred at room temperature for 24 h. The catalyst was then removed by filtration and the solvent was evaporated to give (*S*)-**12** as a white solid (0.93 g, 7.82 mmol); yield: 83%.

4.6.3. Method C. Diol (*S*)-**5** (300 mg, 2.24 mmol) was dissolved in dichloroethane (30 mL). Dibutyltin oxide (0.62 g, 2.46 mmol) was added and the mixture heated to reflux for 7 h using a Dean–Stark trap to remove the water formed in the reaction. Benzoyl isothiocyanate (0.53 mL, 3.8 mmol) and triethylamine (0.38 mL, 2.7 mmol) were added and the mixture was heated to reflux. After stirring for 7 h, tetrabutylammonium bromide (0.8 g, 2.46 mmol) was added and heating was continued for a further 7 h to give a mixture of two cyclic iminocarbonates in a ratio of 1:4 in favour of the desired regioisomer. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed with brine and dried (Na_2SO_4). The concentrated crude product was chromatographed on a silica column (hexane:ethyl acetate, 8:2) to give the desired iminocarbonate (0.26 g, 1.01 mmol) as a colourless oil. A suspension of this compound in aqueous HCl solution (6N, 7 mL) was heated under reflux for 12 h to give, after removing the solvent, the α-methylserine hydrochloride as a white solid. Compound (*S*)-**12** (70 mg, 0.59 mmol) was obtained using the same procedure described in Method A; yield: 26% from (*S*)-**5**.

As described for α-methylserine (*S*)-**12** (Method B), its enantiomer (*R*)-**12** (195 mg, 83%) was obtained from (*R*)-**8** (313 mg, 1.97 mmol). $[\alpha]_D^{25} = -5.4$ (*c* 1.01, H_2O). Anal. calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.29; H, 7.65; N, 11.70%.

4.7. *N*-(*tert*-Butoxycarbonyl)-α-methylserine methyl esters (*S*)-13 and (*R*)-13

A solution of α-azido ester (*S*)-**8** (5.50 g, 34.6 mmol) in MeOH (50 mL) was hydrogenated using palladium on carbon as catalyst (1:5 catalyst/substrate by weight) and the resulting suspension was stirred at room temperature for 24 h. The catalyst was removed by filtration and the solvent was evaporated to give the corresponding amino alcohol as a pale yellow oil. This compound was dissolved in H_2O/THF (1:5, 60 mL) and $Na_2CO_3 \cdot 10H_2O$ (12.9 g, 45.0 mmol) and Boc_2O (9.82 g, 45.0 mmol) were then added. The mixture was stirred at room temperature for 19 h and the reaction was quenched with saturated NH_4Cl (20 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (hexane:ethyl acetate, 7:3) to give (*S*)-**13** as a colourless oil (5.64 g, 24.2 mmol); yield: 70%. $[\alpha]_D^{25} = -10.8$ (*c* 2.26, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.41 (s, 9H, $(CH_3)_3C$), 1.44 (s, 3H, CH_3), 3.25 (br s, 1H, OH), 3.75 (s, 3H, CO_2CH_3), 3.73–3.78 (m, 1H, CH_2), 3.92 (br d, 1H, $J = 11.4$ Hz, CH_2), 5.26 (br s, 1H, NH). Anal. calcd for $C_{10}H_{19}NO_5$: C, 51.49; H, 8.21; N, 6.00. Found: C, 51.38; H, 8.16; N, 6.10%. Spectral data were identical to those reported in the literature.[16]

As described for *N*-Boc protected α-methylserine methyl ester (*S*)-**13**, its enantiomer (*R*)-**13** (5.63 g, 70%) was obtained from (*R*)-**8** (5.52 g, 34.7 mmol). $[\alpha]_D^{25} = +11.8$ (*c* 2.84, MeOH). Anal. calcd for $C_{10}H_{19}NO_5$: C, 51.49; H, 8.21; N, 6.00. Found: C, 51.40; H, 8.13; N, 6.12%.

4.8. *N*-(*tert*-Butoxycarbonyl)-4-methoxycarbonyl-2,2,4-trimethyl-3-oxazolidines (*S*)-14 and (*R*)-14

Compound (*S*)-**13** (6.25 g, 26.8 mmol) was dissolved in a mixture of acetone (70 mL) and DMP (35.7 g, 343 mmol) before adding $BF_3 \cdot OEt_2$ (0.2 mL, 1.58 mmol). The resulting solution was stirred at room temperature for 1 h and the solvent was then removed. The residual oil was taken up in CH_2Cl_2 (100 mL) and the resulting solution was washed with a mixture of saturated $NaHCO_3/H_2O$ (1:1, 40 mL) and brine (40 mL), and then dried (Na_2SO_4). The solvent was evaporated and the crude product was purified by chromatography (hexane:ethyl acetate, 9.5:0.5) to give (*S*)-**14** as a liquid (6.80 g, 24.9 mmol); yield: 93%. $[\alpha]_D^{25} = -18.6$ (*c* 1.04, MeOH). ^{1}H NMR ($CDCl_3$, 333 K): δ 1.40 (s, 3H, CH_3), 1.43 (s, 9H, $(CH_3)_3C$), 1.56 (s, 6H, $(CH_3)_2C$), 3.72 (s, 3H, CO_2CH_3), 3.76 (d, 1H, $J = 8.7$ Hz, CH_2), 4.07 (d, 1H, $J = 8.7$ Hz, CH_2). Anal. calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.00; H, 8.40; N, 5.10%. Spectral data were identical to those reported in the literature.[16]

As described for compound (*S*)-**14**, its enantiomer (*R*)-**14** (6.86 g, 93%) was obtained from (*R*)-**13** (6.28 g, 26.9 mmol). $[\alpha]_D^{25} = +18.1$ (*c* 1.12, MeOH). Anal. calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.08; H, 8.41; N, 5.06%.

4.9. *N*-(*tert*-Butoxycarbonyl)-4-hydroxymethyl-2,2,4-trimethyl-3-oxazolidines (*S*)-15 and (*R*)-15

To a suspension of $LiAlH_4$ (301 mg, 7.92 mmol) in THF (20 mL) was added dropwise a solution of (*S*)-**14** (1.03 g, 3.77 mmol) in THF (30 mL). The mixture was vigorously stirred for 6 h at room temperature and was then carefully quenched by addition of water (0.4 mL), NaOH solution (1N, 1.5 mL) and water (1.5 mL). After stirring at room temperature for 3 h, the white precipitate was filtered off and washed with ethyl ether. The filtrate was concentrated and the residue purified by column chromatography (hexane:ethyl acetate, 8:2) to give (*S*)-**15** as a white solid (0.84 g, 3.42 mmol); yield: 91%. Mp 59–60°C. $[\alpha]_D^{25} = -1.7$ (*c* 1.99, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.43, 1.49, 1.56 (3s, 18H, $(CH_3)_3C$, CH_3, $(CH_3)_2C$), 3.52–3.75 (m, 4H, CH_2, CH_2OH), 4.55, 4.57 (2br s, 1H, OH). Anal. calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.72; H, 9.38; N, 5.60%. Spectral data were identical to those reported in the literature.[5a]

As described for compound (*S*)-**15**, its enantiomer (*R*)-**15** (0.86 g, 91%) was obtained from (*R*)-**14** (1.05 g, 3.84 mmol). $[\alpha]_D^{25} = +1.3$ (*c* 1.99, $CHCl_3$). Anal. calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.70; H, 9.41; N, 5.65%.

4.10. *N*-(*tert*-Butoxycarbonyl)-4-formyl-2,2,4-trimethyl-3-oxazolidines (*S*)-16 and (*R*)-16

DMSO (2.23 g, 28.6 mmol) was added, at −78°C, to a solution of oxalyl chloride (2.18 g, 17.2 mmol) in CH_2Cl_2 (30 mL). The resulting solution was stirred for 5 min at −78°C, then a solution of (*S*)-**15** (3.52 g, 14.3 mmol) in CH_2Cl_2 (30 mL) was added. The resulting mixture was stirred for 15 min at −78°C and Et_3N (5.79 g, 57.2 mmol) was then added. The solution was allowed to warm to room temperature and quenched by the addition of saturated $NaHCO_3$ (70 mL) and then diluted with ethyl ether (70 mL). The phases were separated and the organic phase was washed with 1 M $KHSO_4$ (30 mL), saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography (hexane:ethyl acetate, 9:1) to give (*S*)-**16** as a white solid (3.34 g, 96%). Mp 54–55°C; $[\alpha]_D^{25} = -21.8$ (*c* 2.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.30–1.70 (m, 18H, $(CH_3)_3C$, CH_3, $(CH_3)_2C$), 3.65, 3.68 (2d, 1H, $J = 6.9$ Hz, CH_2), 3.92 (d, 1H, $J = 9.3$ Hz, CH_2), 9.39, 9.46 (2s, 1H, CHO). Anal. calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.20; H, 8.65; N, 5.78%. Spectral data were identical to those reported in the literature.[5a]

As described for aldehyde (*S*)-**16**, its enantiomer (*R*)-**16** (3.35 g, 96%) was obtained from (*R*)-**15** (3.53 g, 14.3 mmol). $[\alpha]_D^{25} = +22.0$ (*c* 2.05, $CHCl_3$). Anal. calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.22; H, 8.75; N, 5.76%.

4.11. (2*S*,2′*S*)-3′,3′,3′-Trifluoro-2′-methoxy-2′-phenylpropionic acid 2-*tert*-butoxycarbonylamino-2-methoxycarbonylpropyl ester 17

To a solution of alcohol (*S*)-**13** (47 mg, 0.19 mmol), DCC (42 mg, 0.20 mmol) and DMAP (3 mg, 0.02 mmol) in CH_2Cl_2 (3 mL) was added a solution of (*S*)-(−)-MTPA (53 mg, 0.22 mmol) in CH_2Cl_2 (3 mL). After stirring the mixture at room temperature for 6 h, the resulting white suspension was filtered to remove *N*,*N*′-dicyclohexylurea. The filtrate was concentrated to give a white slurry, to which Et_2O was added. The resulting suspension was filtered to remove the dicyclohexylurea and the solvent was evaporated. The residue was purified by column chromatography (hexane/ethyl acetate, 9:1) to give **17** (42 mg, 0.09 mmol) as a colourless oil; yield: 48%. $[\alpha]_D^{25} = -41.7$ (*c* 0.88, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.41 (s, 9H, $(CH_3)_3C$), 1.49 (s, 3H, CH_3), 3.52 (s, 3H, OCH_3), 3.68 (s, 3H, CO_2CH_3), 4.65–4.90 (m, 2H, CH_2O), 5.28 (br s, 1H, NHCO), 7.35–7.42 (m, 3H, Ph), 7.45–7.55 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 20.5 (CH_3), 28.2 ($(CH_3)_3C$), 52.9 (CO_2CH_3), 55.4 (OCH_3), 58.6 ($C(CH_3)NH$), 66.7 (CH_2), 80.0 ($(CH_3)_3C$), 121.3 ($C(CF_3)$), 125.1 (CF_3), 127.3, 128.4, 129.6, 132.0 (Ph), 153.8 (OCON), 165.8 (CO_2CH_2), 172.3 (CO_2CH_3); ^{19}F NMR ($CDCl_3$): δ −72.0; MS (EI) (m/z) = 57, 102, 189, 290; ESI$^+$ (m/z) = 449+Na. Anal. calcd for $C_{20}H_{26}F_3NO_7$: C, 53.45; H, 5.83; N, 3.12. Found: C, 53.92; H, 5.62; N, 3.13%.

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References

1. (a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517 and references cited therein; (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732 and references cited therein.
2. (a) Avenoza, A.; Cativiela, C.; Díaz-de-Villegas, M. D.; Mayoral, J. A.; Peregrina, J. M. *Tetrahedron* **1993**, *49*, 677; (b) Avenoza, A.; Cativiela, C.; Díaz-de-Villegas, M. D.; Peregrina, J. M. *Tetrahedron* **1993**, *49*, 10987; (c) Avenoza, A.; Cativiela, C.; París, M.; Peregrina, J. M. *J. Org. Chem.* **1994**, *59*, 7774; (d) Avenoza, A.; Busto, J. H.; Cativiela, C.; Peregrina, J. M. *Tetrahedron Lett.* **1995**, *36*, 7123; (e) Aubry, A.; Avenoza, A.; Cativiela, C.; Jiménez, A. I.; Marraud, M.; París, M.; Peregrina, J. M. *Tetrahedron Lett.* **1998**, *39*, 7841; (f) Avenoza, A.; Busto, J. H.; Cativiela, C.; Peregrina, J. M.; Rodríguez, F. *Tetrahedron* **1998**, *54*, 11659.
3. (a) Avenoza, A.; Cativiela, C.; Peregrina, J. M. *Tetrahedron* **1994**, *50*, 10021; (b) Avenoza, A.; Cativiela, C.; Fernández-Recio, M. A.; Peregrina, J. M. *Synlett* **1995**, 891; (c) Avenoza, A.; Cativiela, C.; Fernández-Recio, M. A.; Peregrina, J. M. *Tetrahedron: Asymmetry* **1996**, *7*, 721; (d) Avenoza, A.; Cativiela, C.; París, M.; Peregrina, J. M.; Sáenz-Torre, B. *Tetrahedron: Asymmetry* **1997**, *8*, 1123; (e) Avenoza, A.; Busto, J. H.; Cativiela, C.; Peregrina, J. M. *An. Quím. Int. Ed.* **1998**, *94*, 50; (f) Avenoza, A.; Cativiela, C.; Fernández-Recio, M. A.; Peregrina, J. M. *Tetrahedron: Asymmetry* **1999**, *10*, 3999; (g) Avenoza, A.; Cativiela, C.; Fernández-Recio, M. A.; Peregrina, J. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3375; (h) Avenoza, A.; Busto, J. H.; Cativiela, C.; Peregrina, J. M. *Amino Acids* **2000**, *18*, 117; (i) Avenoza, A.; Barriobero, J. I.; Cativiela, C.; Fernández-Recio, M. A.; Peregrina, J. M.; Rodríguez, F. *Tetrahedron* **2001**, *57*, 2745–2755.
4. Obrecht, D.; Altorfer, M.; Lehmann, C.; Schönholzer, P.; Müller, K. *J. Org. Chem.* **1996**, *61*, 4080.
5. (a) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **1999**, *64*, 8220; (b) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 4653; (c) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2195.
6. (a) Sharpless, K. B.; Bruncko, M.; Schlingloff, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483; (b) Sharpless, K. B.; Tao, B.; Schlingloff, G. *Tetrahedron Lett.* **1998**, *39*, 2507; (c) Song, C. E.; Oh, C. R.; Roh, E. J.; Lee, S.; Choi, J. H. *Tetrahedron: Asymmetry* **1999**, *10*, 671; (d) O'Briean, P. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 326.
7. Sharpless, K. B.; Li, G.; Chang, H.-T. *Catalytic asymmetric aminohydroxylation of olefins with sulfonamides*. PCT Int. Appl. (1997), 77 pp. CODEN: PIXXD2 WO 9744316 A1 19971127 CAN 128:48387 AN 1997:776148 CAPLUS.
8. For reviews on AD reactions, see: (a) Kolb, H. C.; VanNiewenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483; (b) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059; (c) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; pp. 227–272.
9. Shao, H.; Rueter, J. K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 5240.
10. Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2079.
11. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
12. Rodriguez, J. B.; Markey, S. P.; Ziffer, H. *Tetrahedron: Asymmetry* **1993**, *4*, 101.
13. (a) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 4317; (b) Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2623; (c) Lohray, B. B. *Synthesis* **1992**, 1035; (d) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538; (e) Berridge, M. S.; Franceschini, M. P.; Rosenfeld, E.; Twson, T. J. *J. Org. Chem.* **1990**, *55*, 1211; (f) Yokumatsu, T.; Yoshida, Y.; Shibuya, S. *J. Org. Chem.* **1994**, *59*, 7930; (g) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051.

14. (a) Park, J. N.; Ko, S. Y.; Koh, H. Y. *Tetrahedron Lett*. **2000**, *41*, 5553; (b) Cho, G. Y.; Ko, S. Y. *J. Org. Chem*. **1999**, *64*, 8745.
15. Colson, P.-J.; Hegedus, L. S. *J. Org. Chem*. **1993**, *58*, 5918.
16. Alías, M.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; Lapeña, Y. *Tetrahedron* **1998**, *54*, 14963.
17. Ariza, X.; Urpí, F.; Viladomat, C.; Vilarrasa, J. *Tetrahedron Lett*. **1998**, *39*, 9101.
18. (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem*. **1969**, *34*, 2543; (b) Garner, P.; Park, J. M. *J. Org. Chem*. **1987**, *52*, 2361.
19. Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1996**, *52*, 687.