Asymmetric aldol reactions of achiral 2-phenylsulfanyl aldehydes with small- and medium-sized carbocyclic rings: the synthesis of homochiral spirocyclic lactones, pyrrolidines and tetrahydrofurans

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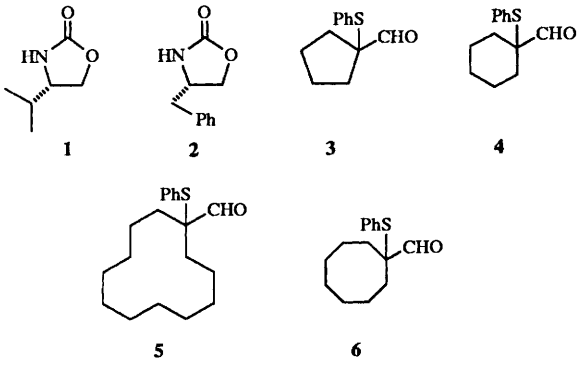
Chiral boron enolates based on the 1,3-oxazolidin-2-one auxiliary react with achiral 1-phenylsulfanylcycloalkanecarbaldehydes in *anti*- and *syn*-selective aldol processes to give the corresponding aldol products with moderate to excellent levels of diastereo- and enantio-control. Stereospecific cyclisation *via* an asymmetric episulfonium (thiiranium) ion leads to optically pure spirocyclic compounds in high chemical yields.

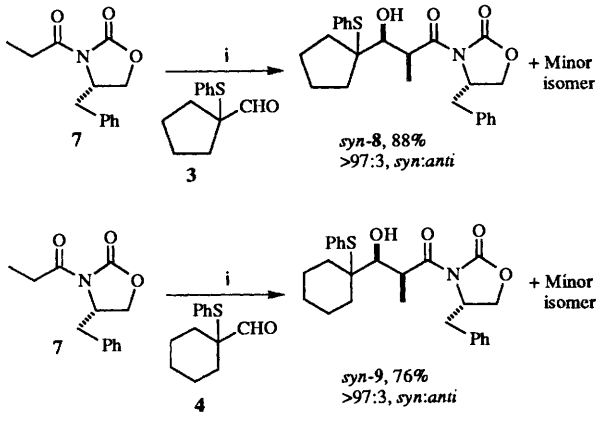
Coupled stereoselective aldol reactions and stereospecific sulfur rearrangements have enabled us to make a variety of unusual racemic oxygen- and nitrogen-containing spirocyclic heterocycles with chiral centres in the heterocyclic ring.[1] However, methods for the synthesis of such important heterocycles in optically active form are almost unknown. We were interested in extending our methodology[1] to optically active compounds by either of two approaches: (*i*) use of a chiral auxiliary on an enolate in asymmetric aldol reactions with achiral 1-phenylsulfanylcycloalkanecarbaldehydes;[2] (*ii*) synthesis of optically pure 2-phenylsulfanyl aldehydes for use in stereoselective aldol reactions with both chiral and achiral enolates.[3] This paper describes asymmetric aldol reactions of chiral boron enolates on achiral 2-phenylsulfanyl aldehydes **3**–**6** and subsequent synthetic manipulations and rearrangements of the resulting homochiral intermediates. The chiral boron enolates are based on the valine- and phenylalanine-derived chiral auxiliaries **1** and **2**.



1 **2** **3** **4** **5** **6**

We have previously studied aldol reactions of various achiral propionate ester enolates on the crowded but reactive 2-phenylsulfanyl aldehydes **3** and **4** and found that the use of boron enolates in *syn*-selective aldol transformations was very efficient with *syn*:*anti* selectivity as high as 95:5.[1b,4] The chiral boron enolates pioneered by Evans and co-workers[5], particularly those using the valine-derived auxiliary **1**, give diastereoisomerically and enantiomerically pure *syn* aldols from many less crowded aldehydes. We selected these enolates for studying *syn*-selective aldol reactions on aldehydes **3** and **4**. We preferred the phenylalanine-derived chiral auxiliary **2** because the aldol products are usually crystalline.

Aldehydes **3**–**6** were prepared by addition of the anion of

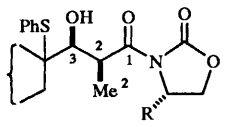


Scheme 1 *Reagents:* i, Bu_2BOTf, Pr^i_2NEt

$PhSCH_2OMe$ to the corresponding cyclic ketones followed by rearrangement.[6] Employing aldehydes **3** and **4** in the Evans[5] *syn*-selective asymmetric aldol reaction we found that the boron enolate of imide **7** indeed combined with these aldehydes in a highly diastereoselective fashion, giving only *syn* aldol products. The aldol reaction on aldehyde **3** was more stereoselective giving exclusively one *syn* product, *syn*-**8** (de >90%), while the corresponding reaction on aldehyde **4** was less stereoselective (de 80%) (Scheme 1). The des were measured from the ^1H NMR (250 MHz) of the crude reaction mixture. The minor isomer, which we believe to be the other *syn* diastereoisomer, could easily be removed by column chromatography.

Although other studies[4] of aldol reactions on aldehydes **3** and **4** revealed excellent *anti* selectivity using the lithium enolate of 2,6-dimethylphenyl propionate, homochiral versions of this reaction are rare. The literature contains, to the best of our knowledge, only one example in which a titanium carbohydrate complex has been used to transmetallate the lithium enolate of the ester 2,6-dimethylphenyl propionate.[7] Using this procedure *syn* aldols are obtained with 91–97% ee (by performing the reaction at −78 °C throughout) and *anti* aldols with 94–98% ee (by warming the enolate to −30 °C). Broadly speaking there is a lack of general routes to asymmetric *anti* aldols. However, we were encouraged by initial studies[8] of *anti*-selective Lewis acid-catalysed asymmetric aldol reactions of boron enolates based on the valine-derived chiral auxiliary **1**. These studies[8] revealed the important role played by certain features such as a sulfur atom and the aromatic ring in the developing stereoselectivities

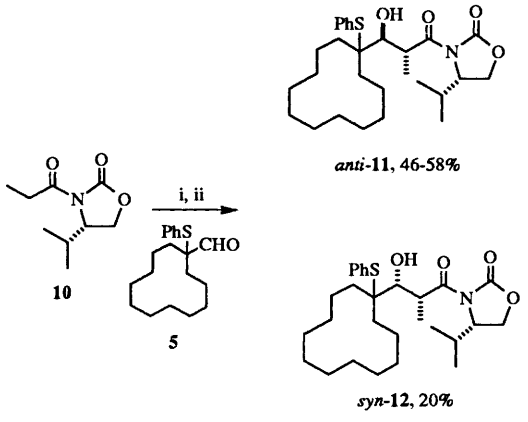
Table 1 Relative stereochemistry of aldols **8–16** (Schemes 1–3)



Aldol	R	$J_{2,3}$ (Hz)	δ_C(C-3)	δ_C(Me)
anti-**11**	Pr^i	8.6	83.3	19.5
anti-**13**	Pr^i	8.6	83.4	18.8
anti-**14**	Pr^i	8.4	83.1	18.5
syn-**8**	$PhCH_2$	5.0	74.5	14.0
syn-**9**	$PhCH_2$	5.1	74.2	14.6
syn-**12**	Pr^i	5.6	—	—
syn-**15**	Pr^i	5.5	74.0	14.5
syn-**16**	Pr^i	4.9	73.9	14.6

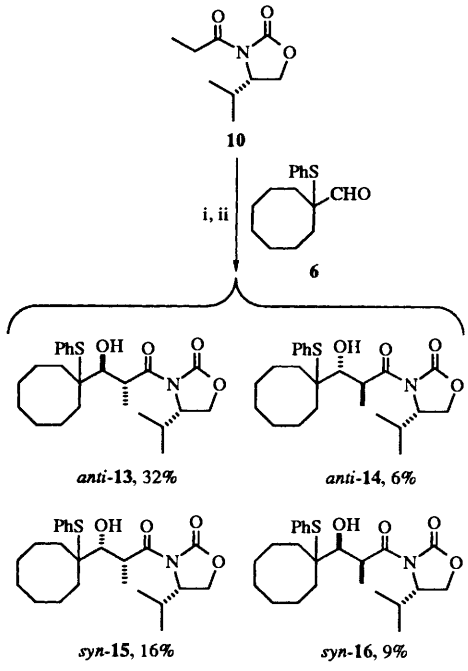
and indeed the successful development and optimisation of this reaction [9] was timely for us.[2]

We decided to study this reaction on our aldehydes in order to test the generality of the methodology as well as to explore the aldol route to spirocyclic compounds from aldehydes **5** and **6** with medium-sized carbocyclic rings.[2b] In the event application of Heathcock and co-workers' procedure[8,9] resulted in some useful levels of stereocontrol. Reaction with aldehyde **5** proceeded (Scheme 2) with a synthetically useful level of diastereoselection at higher Lewis acid concentration (6.0 eq Et_2AlCl, *anti*:*syn*, **11**:**12**, 84:16). The corresponding aldol reaction on aldehyde **6** was poorly diastereoselective even at higher Lewis acid concentration (6.0 eq Et_2AlCl). All four possible aldol products **13–16** were isolated by column chromatography.



Scheme 2 *Reagents:* i, Pr^i_2NEt, Bu_2BOTf, CH_2Cl_2, 0 °C; ii, Et_2AlCl, −16 °C

The ratios of aldol products **11–16** were determined by HPLC analysis of the crude reaction mixtures. Presumably due to the size of aldehydes **5** and **6** the reactions proceeded very slowly at −16 °C and took 17–20 h to go to completion. At −78 °C no reaction had taken place even after 4–5 h. Reactions at room temperature may not be possible as this is likely to lead to poor *anti* stereoselectivity. The (2,3)-*anti* or -*syn* stereochemistry[10] of aldol products **8–16** was determined by examination of the coupling constants (^1H NMR) and chemical shift values (^{13}C NMR, Table 1) and confirmed in the subsequent cyclisations. The absolute stereochemistry at the hydroxy position (C-3) of the major *anti*, **11** and **13** and *syn*, **8**, **9**, **12** and **15**, aldols is assumed from previous work under identical conditions.[5,9]

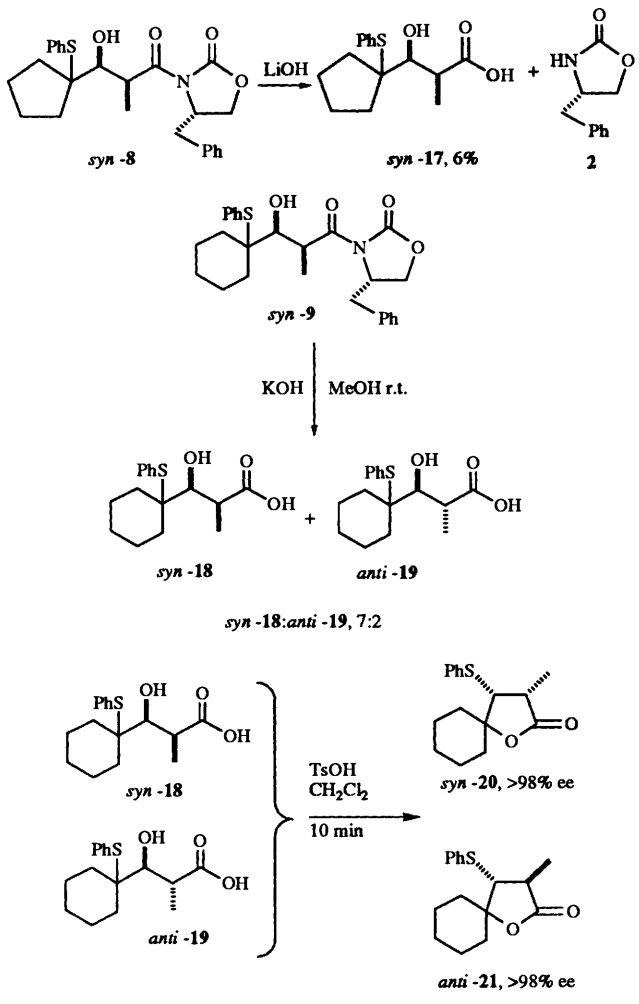


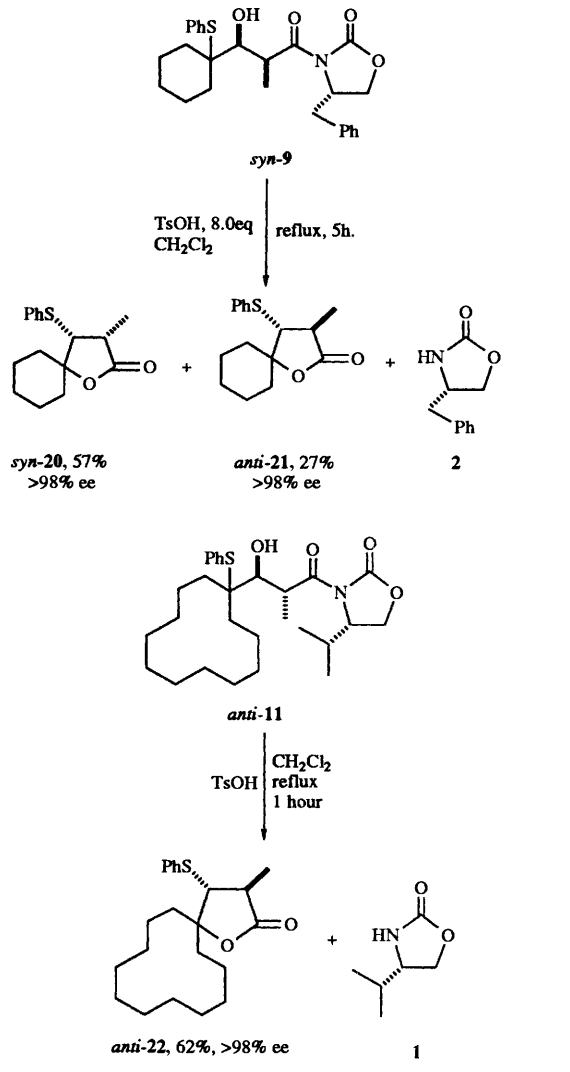
Scheme 3 *Reagents:* i, Pr^i_2NEt, Bu_2BOTf, CH_2Cl_2, 0 °C; ii, Et_2AlCl, −16 °C

From the results obtained in the *anti* aldol series the superior conformational flexibility of the 12-membered ring in aldehyde **5** compared to the 8-membered ring in aldehyde **6** is evident and perhaps taking into account the reaction temperature (−16 °C) the aldol reaction on aldehyde **5** could be even more stereoselective at lower temperatures (−78 °C). We have also observed some curious behaviour of the 8-membered ring in simple rearrangements involving phenylsulfanyl migration.[11]

Next we considered methods (hydrolysis, reduction and transamination) for the racemisation-free non-destructive removal of the chiral auxiliaries to furnish homochiral intermediates which were required for the rearrangements. Repeated attempts to hydrolyse aldol products **8** and **9** with the often successful and widely used LiOOH [5] proved fruitless. We obtained complex mixtures of unidentified products but none of the desired acids. Hydrolysis with LiOH resulted in poor yields of the desired acid **17** (6%) while hydrolysis of *syn*-**9** using KOH (2 mol dm^{-3}; 4.0 equiv.) at room temperature gave a mixture of the desired acid *syn*-**18** and its epimer *anti*-**19** in a 7:2 ratio. Nevertheless, the inseparable mixture of acids *syn*-**18** and *anti*-**19** was cyclised stereospecifically with a catalytic amount of TsOH under our usual conditions[1–4] *via* an asymmetric episulfonium ion with inversion of configuration at the chiral centre adjacent to the C–SPh bond, C-3, to give the respective spirocyclic lactones *syn*-**20** and *anti*-**21**. These were obtained in a 2.3:1 ratio and in enantiomerically pure form as determined by ^1H NMR in the presence of 1-(9-anthryl)-2,2,2-trifluoroethanol, Pirkle's chiral solvating alcohol[12] and by comparison with the corresponding racemic compounds. The stereochemistry of the homochiral lactones was confirmed by their characteristic $J_{2,3}$ values in the ^1H NMR spectrum: for *syn*-**20** 8.9 Hz and for *anti*-**21** 12.3 Hz.

At this point we wondered whether we could successfully cyclise aldol product *syn*-**9** directly to the homochiral spirocyclic lactone *syn*-**20** with simultaneous removal of the chiral auxiliary without the risk of allyl sulfide formation.[4] In the event, treatment of product *syn*-**9** with an excess of TsOH in dichloromethane under reflux for 5 h gave the expected spirocyclic lactone *syn*-**20** in optically pure form and in



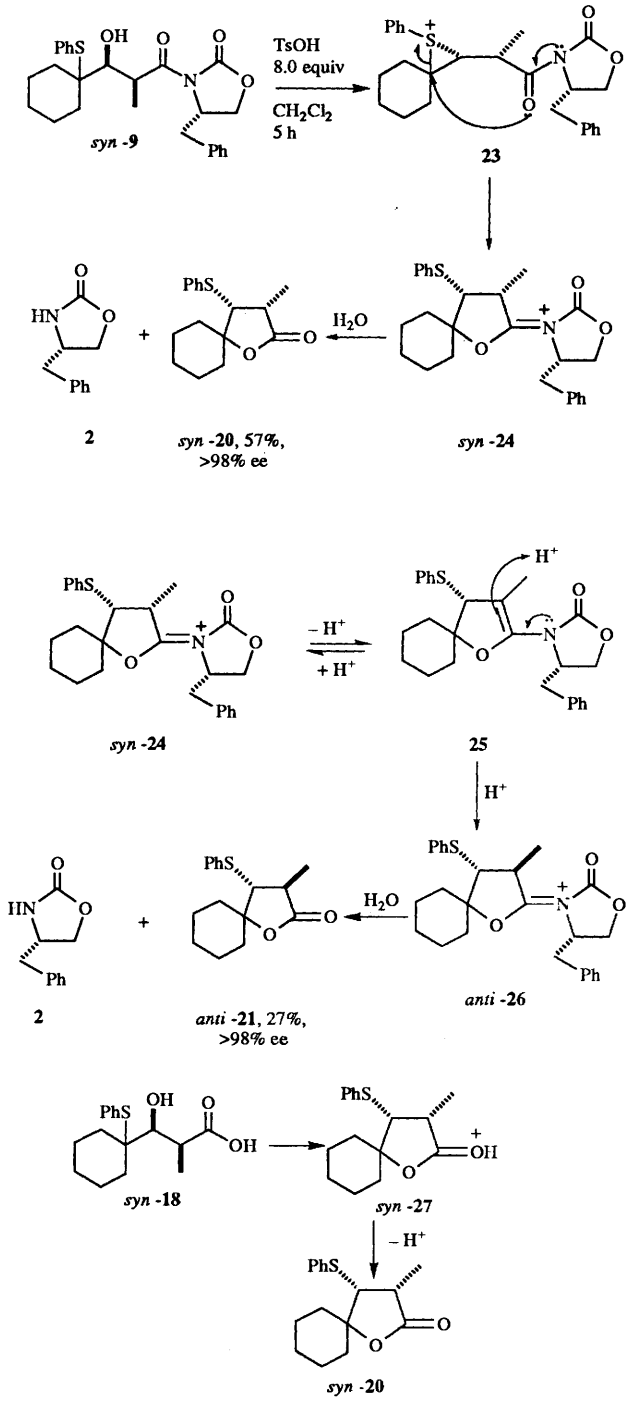


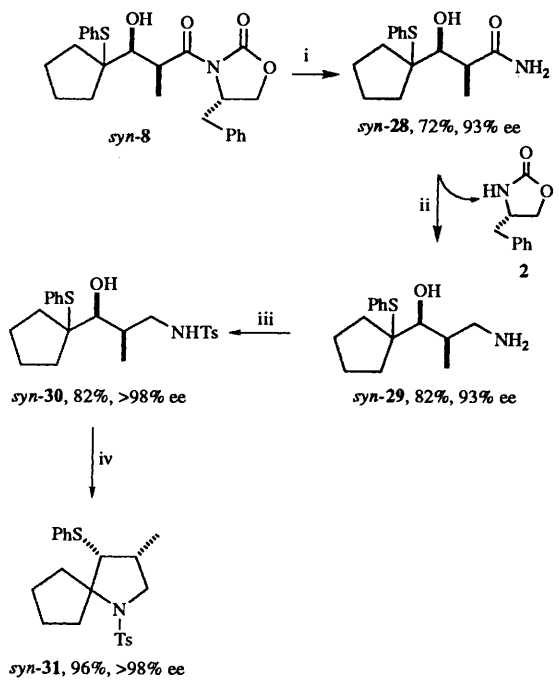
moderate yield. Disappointingly, some *anti* spirocyclic lactone **21** was also obtained (though in optically pure form). The chiral auxiliary **2** was nevertheless recovered non-destructively under the reaction conditions and no allyl sulfide formation had occurred. The corresponding *anti* aldol product **11** rearranged successfully to the homochiral spirocyclic lactone *anti*-**22** under identical conditions and in moderate yield without epimerisation or allyl sulfide formation. Some starting material, *anti*-**11** (21%), was also isolated along with the non-destructively removed chiral auxiliary **1**. The ees of the lactones *syn*-**20**, *anti*-**21** and *anti*-**22** were determined by ^{1}H NMR in the presence of Pirkle's chiral solvating alcohol[12] and by comparison with the corresponding racemic compounds.

The rearrangement of *syn*-**9** (and *anti*-**11**) presumably involves participation of the *exo* amide oxygen atom on the oxazolidinone in the opening of the asymmetric episulfonium ion **23** at the more highly substituted end to give the iminium-like species *syn*-**24** which is in turn hydrolysed by the water produced earlier in the formation of **23**. No allyl sulfide formation occurs apparently because the oxazolidinone in both aldols *syn*-**9** and *anti*-**11** participates more effectively than the aryl or methyl ester of other aldols we have previously used.[4,13]

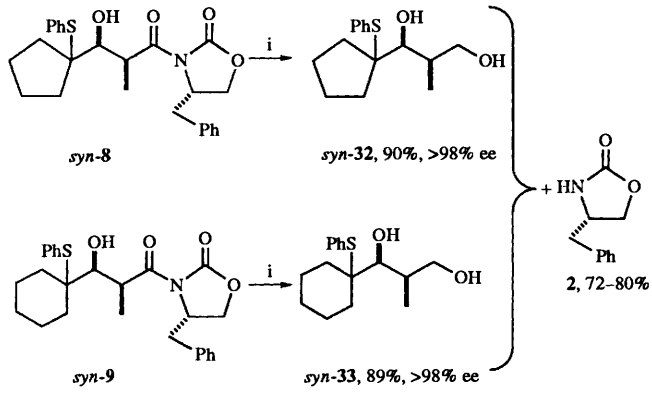
We[1b,2b,4,13] have generally observed that rearrangement of *anti* aldols is more favourable than rearrangement of the corresponding *syn* aldols. Presumably during cyclisation of *syn* aldols epimerisation to give some of the *anti* product occurs due to the unfavourable *syn* relationship that develops as the PhS group migrates towards the methyl group in the transition state. The apparent epimerisation in the rearrangement of *syn*-**9** resulting in the formation of *anti*-**21** may be occurring by proton loss from species *syn*-**24** to form **25** followed by reprotonation giving the iminium-like intermediate *anti*-**26** which is subsequently hydrolysed. The driving force for the proton loss may be the unfavourable *syn* relationship between the PhS, Me, and the benzyl group on the auxiliary. By contrast, rearrangement of the acid *syn*-**18** is rapid and not accompanied by epimerisation[14] in spite of the developing *syn* relationship between the Me and PhS groups in the transition state because it simply involves rapid loss of a proton from oxygen in the intermediate *syn*-**27** and hydrolysis is not needed. Other factors are of course involved in the outcome of the cyclisation.[15]

Removal of the chiral auxiliary by transamination with the reagent derived from trimethylaluminium and ammonium chloride under Weinreb's conditions[16] furnished the primary amide *syn*-**28** in high optical purity and in reasonable yield. Borane reduction to the amine *syn*-**29** followed by tosylation gave the sulfonamide *syn*-**30** which was recrystallised before stereospecific cyclisation *via* an asymmetric episulfonium ion generated by treatment with Me_3SiOTf.[17] The optically pure spirocyclic pyrrolidine *syn*-**31** was thus obtained with inversion of configuration at the migration terminus. The ee of *syn*-**28** and *syn*-**29** was determined by ^{1}H and ^{19}F NMR analysis of the corresponding Mosher amides[18] while that of the sulfonamide *syn*-**30** was determined by ^{1}H NMR using the chiral shift

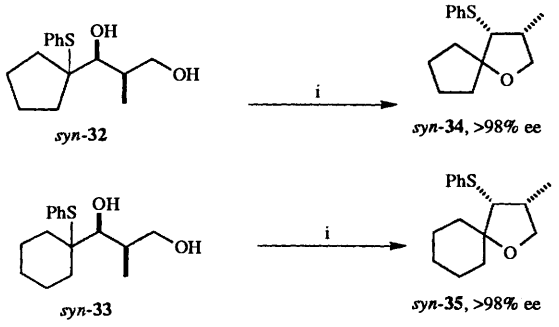




Scheme 4 *Reagents and conditions:* i, Me_3Al, NH_4Cl, 51–53 °C, 3 days; ii, BH_3; iii, TsCl, DMAP; iv, TMSOTf, CH_2Cl_2, −78 °C to r.t.



Reagents and conditions: i, $LiBH_4$, H_2O, Et_2O, 0 °C–r.t., 1 h



Reagents and conditions: i, TsOH (0.2 equiv.), benzene, reflux 5 min, 98%

reagent, $Eu(hfc)_3$, and by comparison with racemic compounds.

Clean reduction of the aldol products *syn*-**8** and *syn*-**9** using the $LiBH_4$–H_2O system [19] gave the homochiral diols *syn*-**32** and *syn*-**33** in high yields along with the recovered chiral auxiliary. Stereospecific cyclisation in acid gave excellent yields of the optically pure spirocyclic tetrahydrofurans *syn*-**34** and *syn*-**35** with inversion of configuration at the migration terminus. The ees of the diols *syn*-**32** and *syn*-**33** were determined by ^1H and ^{19}F NMR analysis of the corresponding Mosher esters [18] while those of the tetrahydrofurans were determined by ^1H NMR in the presence of Pirkle's chiral solvating alcohols [12] and by comparison with the racemic compounds.

As in our other studies,[2b] the steric hindrance caused by the small- and medium-sized carbocyclic rings in aldehydes **3**–**6** is less of a problem partly because of the conformational flexibility of these carbocyclic rings and partly because of the reactivity imparted by the PhS at C-2 of the aldehydes which adopts a Felkin conformation with the C–SPh bond parallel to the p orbitals of the carbonyl group. However, it is worth noting

that the higher levels of asymmetric induction and chemical reactivity achieved in the *syn* aldol reactions of small-size 2-phenylsulfanyl aldehydes **3** and **4** and to some extent in the *anti* aldol reaction involving the medium-sized aldehyde **6** does not automatically follow from the Evans or Heathcock aldol technology. Other similar crowded aldehydes may not be as successful under identical conditions.

Experimental

Thin layer chromatography (TLC) was carried out on commercially available pre-coated plates (Merck Kieselgel $60F_{254}$ silica). Gravity and normal column chromatography was carried out on Merck Kieselgel 60 (70–230 mesh) silica, or at slightly greater than atmospheric pressure using Merck Kieselgel 60 (230–400 mesh) unless otherwise stated. High performance liquid chromatography (HPLC) was performed using a Dynamax prepacked silica column with a Gilson model 303 pump and a Cecil Instruments CE 212A UV detection system measuring the absorbance between 247–254 nm.

Melting points were measured on a Reichart hot stage microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer 297 grating spectrophotometer, calibrated against polystyrene. ^{1}H NMR spectra were recorded on Bruker WM 250 (250 MHz), Bruker AM-400 (400 MHz) and Bruker WP 80 SY (80 MHz) instruments while the ^{13}C NMR spectra were recorded on a Bruker WM 250 (250 MHz) spectrophotometer. δ Values are quoted relative to tetramethylsilane (δ_H 0.00 ppm) or chloroform (δ_H 7.25 ppm) for ^{1}H NMR spectra, and relative to chloroform (δ_C 77.0 ppm) for ^{13}C NMR spectra. Coupling constants J are in Hz. Mass spectra were recorded on an AEI Kratos MS 30, a VG Trio 2, or a VG 7070E mass spectrometer. The DS503 data system was used for high resolution analysis. Microanalyses were carried out using a Carlo Erba 1106 or Perkin-Elmer 240 automatic analyser. Optical rotation measurements were performed on a Perkin-Elmer 241 Na 589 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}.

All solvents were distilled before use. Diethyl ether (referred to as 'ether') was distilled from lithium aluminium hydride and dichloromethane from calcium hydride. Benzene was distilled over sodium wire. Brine refers to saturated aqueous sodium chloride. Most reagents were either used as received from commercial suppliers or purified by standard methods.

(4*S*)-3-[(2*S*,3*S*)-3-Hydroxy-2-methyl-1-oxo-3-(1-phenylsulfanylcyclopentyl)propyl]-4-phenylmethyl-1,3-oxazolidin-2-one, *syn*-8

Dibutylboron trifluoromethanesulfonate (Bu_2BOTf; 7.72 cm^3 of a 1.0 mol dm^{-3} solution in dichloromethane) was added to a solution of the imide **7**[5] (1.64 g, 7.04 mmol) in dichloromethane (17 cm^3) at 0 °C under argon, followed by a dropwise addition of diisopropylethylamine (1.5 cm^3, 8.7 mmol). The mixture was stirred at 0 °C for 1 h, cooled to −78 °C and the aldehyde **3** (1.45 g, 7.04 mmol) in dichloromethane (7 cm^3) was slowly added to the mixture at −78 °C. After the mixture had been stirred for 1 h at −78 °C and 5 h at room temperature, pH 7 buffer (21 cm^3) and ether (30 cm^3) were added. After separation, the aqueous layer was extracted with ether (30 cm^3) and the combined extracts were washed with brine (17 cm^3) and evaporated under reduced pressure. The residue was dissolved in methanol (28 cm^3), the solution cooled (0 °C) and 30% hydrogen peroxide (7 cm^3) added slowly. After the mixture had been stirred at 0 °C for 1 h, water (28 cm^3) was added and the methanol evaporated under reduced pressure. The aqueous layer was extracted with Et_2O (3 × 30 cm^3) and the combined extracts were washed with cold hydrochloric acid (3.9 cm^3 of a 3.0 mol dm^{-3} solution) and aq. $NaHCO_3$ (17 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography of the residue on silica gel with EtOAc–hexane, (3:17) as the eluent yielded *aldol syn*-**8** (3.16 g, 88%) as plates, mp 69–71 °C; R_f(EtOAc–hexane, 3:17) 0.20 (Found: C, 68.1; H, 6.4; N, 3.4; S, 7.4. $C_{25}H_{29}NO_4S$ requires C, 68.34; H, 6.61; N, 3.19; S, 7.29%); ν_{max}(Nujol)/cm^{-1} 3520 (OH), 1780 and 1695 (C=O) and 1580 (SPh); δ_H(250 MHz; $CDCl_3$) 7.56–7.17 (10 H, m, PhS and Ph), 4.70–4.66 (1 H, m, NCH), 4.46–4.21 (3 H, m, MeC*H*CO and OCH_2), 4.1 (1 H, d, *J* 5.0, C*H*OH), 3.24 (1 H, dd, *J* 3.2 and 13.3, CH_AH_BPh), 2.93 (1 H, br s, OH), 2.76 (1 H, dd, *J* 9.5 and 13.4, CH$_A$*H*$_B$Ph), 2.04–1.56 (8 H, m, C_4H_8) and 1.34 (3 H, d, *J* 7.0, Me); δ_C($CDCl_3$) 177.4, 152.8, 136.2, 135.1, 132.4, 129.4, 128.9, 128.8, 128.7, 127.4, 74.5, 66.5, 66.1, 55.3, 39.9, 37.8, 35.0, 34.1, 24.3, 23.9 and 14.0; *m*/*z* 439 (0.2%, M$^+$), 330 (2.2, M − SPh), 262 (2, M − $C_{10}H_{11}NO_2$), 233 (8.3, M − $C_{12}H_{15}OS$), 206 (8.6, $C_{11}H_{10}NO_3$), 86 (15, $C_4H_6O_2$) and 57 (100, CNO_2).

(4*S*)-3-[(2*S*,3*S*)-3-Hydroxy-2-methyl-1-oxo-3-(1-phenylsulfanylcyclohexyl)propyl]-4-phenylmethyl-1,3-oxazolidin-2-one, *syn*-9

In the same way the imide **7** (1.32 g, 5.7 mmol) and the aldehyde **4** (1.4 g, 6.2 mmol) after 20 h at room temperature gave the *aldol syn*-**9** (1.95 g, 76%) as needles, mp 85–87 °C; R_f(EtOAc–hexane, 6:14) 0.30 (Found: C, 69.0; H, 6.9; N, 2.9; S, 7.2. $C_{26}H_{31}NO_4S$ requires C, 68.87; H, 6.84; N, 3.09; S, 7.06%); ν_{max}(Nujol)/cm^{-1} 3520 (OH), 1780 and 1695 (C=O) and 1455 (SPh); δ_H(250 MHz; $CDCl_3$) 7.5–7.2 (10 H, m, SPh and Ph), 4.65–4.25 (4 H, m, MeC*H*CO and OCH_2C*H*N), 3.90 (1 H, d, *J* 5.1, C*H*OH), 3.23 (1 H, dd, *J* 3.3 and 13.4, CH_AH_BPh), 3.00 (1 H, br s, OH), 2.71 (1 H, dd, *J* 9.7 and 13.3, CH$_A$*H*$_B$Ph), 1.95–1.42 (10 H, m, C_5H_{10}) and 1.35 (3 H, d, *J* 7.0, MeCHCO); δ_C($CDCl_3$) 177.0, 152.8, 136.8, 135.1, 130.7, 129.4, 128.9, 128.8, 128.7, 127.4, 74.2, 66.0, 61.2, 55.3, 38.3, 37.7, 31.2, 30.8, 29.2, 26.9, 22.6, 21.9 and 14.6; *m*/*z* 137 (95%, $C_9H_{13}O$) and 91 (100, $PhCH_2$).

(4*S*)-3-[(2*R*,3*S*)- and (4*S*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-1-oxo-3-(1-phenylsulfanylcyclododecyl)propyl]-4-(1-methylethyl)-1,3-oxazolidin-2-one, *anti*-11 and *syn*-12

Diisopropylethylamine (0.08 cm^3, 0.43 mmol) was added to the imide **10**[5] (0.07 g, 0.37 mmol) in dichloromethane (0.7 cm^3) at 0 °C under argon followed by dibutylboron trifluoromethanesulfonate (1.0 mol dm^{-3} solution in dichloromethane; 0.45 cm^3). After 45 min, the enolate was cooled to −78 °C and added to a pre-complexed and stirred mixture of diethylaluminium chloride (1.0 mol dm^{-3} solution in hexane; 1.5 cm^3) and the aldehyde **5** (0.134 g, 0.75 mmol) at −78 °C. After 1 h at −78 °C the reaction was quenched with methanol (2.5 cm^3) and 30% hydrogen peroxide (0.50 cm^3). The reaction mixture was then allowed to warm to 0 °C and held at this temperature for 1 h before it was diluted with water and the layers were separated. The aqueous layer was extracted with diethyl ether and the combined extracts were washed with aq. $NaHCO_3$ (1.0 mol dm^{-3}) and brine, dried ($MgSO_4$) and evaporated under reduced pressure. Gravity column chromatography of the residue on silica gel with EtOAc–hexane, (1:3) as eluent yielded the *aldol anti*-**11** (71 mg, 58%) as an oil; R_f(EtOAc–hexane, 1:3) 0.20; ν_{max}(film)/cm^{-1} 3510 (OH), 1780 and 1690 (C=O) and 1580 (SPh); δ_H(250 MHz; $CDCl_3$) 7.6–7.2 (5 H, m, SPh), 5.04 (1 H, d, *J* 8.6, C*H*OH), 4.62–4.22 (4 H, m, MeC*H*CO and OCH_2C*H*N), 3.61 (1 H, br s, OH), 2.31 (1 H, dqq, *J* 3.0, 6.8 and 7.0, C*H*Me$_2$), 1.73–1.19 (25 H, m, *Me*CH and $C_{11}H_{22}$), 0.86 (3 H, d, *J* 6.8, *Me*CHMe) and 0.83 (3 H, d, *J* 7.2, MeCH*Me*); δ_C($CDCl_3$) 179.3, 153.4, 139.5, 136.9, 135.6, 132.5, 128.7, 127.8, 83.3, 63.4, 62.6, 58.6, 34.4, 32.4, 30.6, 27.7, 26.9, 26.2, 25.2, 24.7, 24.2, 23.0, 20.3, 19.5, 18.7, 18.5 and 14.6; *m*/*z* 489 (20%, M$^+$), 380 (30, M − SPh), 360 (15, M − $C_6H_{11}NO_2$), 275 (100, $C_{12}H_{22}SPh$), 251 (30, $C_{16}H_{27}O_2$), 214 (46, M − $C_{12}H_{22}SPh$) and 110 (45, PhSH) (Found: M$^+$, 489.2947. $C_{28}H_{43}NO_4S$ requires *M*,

489.2600), and *aldol syn*-**12** as an oil (24 mg, 20%); δ_H(250 MHz; $CDCl_3$) 7.6–7.2 (5 H, m, SPh), 4.49–4.19 (4 H, m, MeC*H*CO and OCH_2C*H*N), 4.11 (1 H, d, *J* 5.6, C*H*OH), 2.67 (1 H, br s, OH), 2.27 (1 H, dqq, *J* 3.6, 7.0 and 7.0, C*H*Me$_2$), 1.75–1.37 (22 H, m, $C_{11}H_{22}$), 1.26 (3 H, d, *J* 6.7, *Me*CH), 0.89 (3 H, d, *J* 7.0, *Me*CHMe) and 0.86 (3 H, d, *J* 6.9, MeCH*Me*).

(4*S*)-3-[(2*R*,3*S*)-, (4*S*)-3-[(2*S*,3*R*)-, (4*S*)-3-[(2*R*,3*R*)- and (4*S*)-3-[(2*S*,3*S*)-3-Hydroxy-2-methyl-1-oxo-3-(1-phenylsulfanylcyclooctyl)propyl]-4-(1-methylethyl)-1,3-oxazolidin-2-one, *anti*-13, *anti*-14, *syn*-15 and *syn*-16

In the same way the imide **10** (0.108 g, 0.59 mmol) and the aldehyde **6** gave after gravity column chromatography eluting with EtOAc–hexane (1:3) the *aldol anti*-**13** (80 mg, 32%) as an oil; R_f(EtOAc–hexane, 1:3) 0.34; ν_{max}(film)/cm^{-1} 3454 (OH), 1782 and 1667 (C=O) and 1582 (SPh); δ_H(250 MHz; $CDCl_3$) 7.7–7.2 (5 H, m, SPh), 4.88 (1 H, d, *J* 8.6, C*H*OH), 4.70–4.21 (4 H, m, MeC*H*CO and OCH_2C*H*N), 3.65 (1 H, dd, *J* 1.6 and 8.6, OH), 2.44 (1 H, dqq, *J* 3.1, 7.0 and 7.0, C*H*Me$_2$), 1.94–1.57 (14 H, m, C_7H_{14}), 1.38 (3 H, d, *J* 7.1, *Me*CH), 0.93 (3 H, d, *J* 7.0, *Me*CHMe) and 0.91 (3 H, d, *J* 7.0, MeCH*Me*); δ_C($CDCl_3$) 179.4, 153.4, 137.2, 132.0, 128.5, 83.4, 62.6, 62.1, 58.6, 34.6, 33.0, 30.6, 28.8, 28.0, 27.8, 25.6, 23.6, 23.4, 18.8, 18.2 and 14.5; *m*/*z* 324 (48%, M – SPh), 195 (100, $C_{12}H_{19}O_2$), 130 (90, $C_6H_{12}NO_2$), 111 (48, C_8H_{15}) and 55 (35, C_4H_7) (Found: M – SPh, 324.2182. $C_{18}H_{30}NO_4$ requires *M* – SPh, 324.2112); *aldol anti*-**14** (16 mg, 6%) as an oil; R_f(EtOAc–hexane, 1:3) 0.23; ν_{max}(film)/cm^{-1} 3500 (OH), 1778 and 1693 (C=O) and 1582 (SPh); δ_H(250 MHz; $CDCl_3$) 7.7–7.3 (5 H, m, SPh), 4.74 (1 H, d, *J* 8.4, C*H*OH), 4.51–4.43 (2 H, m, MeC*H*CO and C*H*N), 4.32 (2 H, m, OCH$_2$), 3.68 (1 H, dd, *J* 1.5 and 8.4, OH), 2.40 (1 H, dqq, *J* 3.1, 7.0 and 7.0, C*H*Me$_2$), 1.87–1.50 (14 H, m, C_7H_{14}), 1.44 (3 H, d, *J* 7.1, *Me*CH), 0.93 (3 H, d, *J* 7.0, *Me*CHMe) and 0.92 (3 H, d, *J* 6.9, MeCH*Me*); δ_C($CDCl_3$) 180.0, 153.9, 137.5, 132.0, 130.1, 128.7, 83.1, 64.7, 61.6, 58.9, 34.6, 33.2, 30.5, 29.6, 28.8, 28.4, 25.7, 25.3, 22.7, 18.5, 18.0 and 15.1; *aldol syn*-**15** (40 mg, 16%) as an oil; R_f(EtOAc–hexane, 1:3) 0.12; ν_{max}(film)/cm^{-1} 3500 (OH), 1770 and 1694 (C=O) and 1582 (SPh); δ_H(250 MHz; $CDCl_3$) 7.7–7.3 (5 H, m, SPh), 4.47–4.12 (4 H, m, MeC*H*CO and OCH_2C*H*N), 3.99 (1 H, t, *J* 5.5, C*H*OH), 2.97 (1 H, d, *J* 6.5, OH), 2.26 (1 H, dqq, *J* 3.6, 6.9 and 7.0, C*H*Me$_2$), 1.90–1.51 (14 H, m, C_7H_{14}), 1.26 (3 H, d, *J* 6.9, *Me*CH), 0.91 (3 H, d, *J* 7.0, *Me*CHMe) and 0.82 (3 H, d, *J* 6.9, MeCH*Me*); δ_C($CDCl_3$) 176.5, 153.4, 137.3, 130.8, 129.0, 128.7, 74.0, 65.5, 62.9, 58.4, 39.1, 31.0, 30.9, 28.8, 28.3, 27.8, 25.0, 23.6, 23.0, 18.0, 14.5 and 13.9; and *aldol syn*-**16** (23 mg, 9%) as an oil; R_f(EtOAc–hexane, 1:3) 0.16; ν_{max}(film)/cm^{-1} 3450 (OH), 1730 and 1700 (C=O) and 1582 (SPh); δ_H(250 MHz; $CDCl_3$) 7.6–7.3 (5 H, m, SPh), 4.44–4.16 (4 H, m, MeC*H*CO and OCH_2C*H*N), 3.95 (1 H, d, *J* 4.9, C*H*OH), 2.35 (1 H, dqq, *J* 3.0, 6.8 and 7.0, C*H*Me$_2$), 1.84–1.41 (14 H, m, C_7H_{14}), 1.36 (3 H, d, *J* 7.0, *Me*CH), 0.90 (3 H, d, *J* 6.8, *Me*CHMe) and 0.88 (3 H, d, *J* 7.2, MeCH*Me*); δ_C($CDCl_3$) 177.0, 153.3, 137.5, 130.9, 128.9, 73.9, 64.8, 63.4, 58.4, 38.8, 31.0, 30.6, 29.1, 28.7, 28.3, 27.8, 24.9, 23.5, 23.0, 17.9 and 14.6.

(2*S*,3*S*)-3-Hydroxy-2-methyl-3-(1-phenylsulfanylcyclopentyl)-propanoic acid, *syn*-17

Lithium hydroxide monohydrate (38.3 mg) in water (2.0 cm^3) was added to a stirred solution of the aldol *syn*-**8** (0.2 g, 0.46 mmol) in THF–H_2O (3:1; 10 cm^3) under argon at 0 °C. After 12 h at room temperature, the mixture was extracted with dichloromethane. The aqueous layer was cooled in ice and acidified with hydrochloric acid to pH 1 and extracted with EtOAc. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the acid *syn*-**17** (7 mg, 6%) as a colourless oil; δ_H(250 MHz; $CDCl_3$) 7.66–7.40 (5 H, m, SPh), 5.7 (2 H, br s, 2 OH), 4.1 (1 H, d, *J* 4.2, C*H*OH), 3.42–3.28 (1 H, m, C*H*Me), 1.98–1.46 (8 H, m, C_4H_8) and 1.30 (3 H, d, *J* 7.1, Me).

(2*S*,3*S*)- and (2*R*,3*S*)-3-Hydroxy-2-methyl-3-(1-phenylsulfanylcyclohexyl)propanoic acid, *syn*-18 and *anti*-19

Potassium hydroxide (2.0 mol dm^{-3} solution; 4.4 cm^3) was added dropwise to a solution of aldol *syn*-**9** (1.0 g, 2.2 mmol) in methanol (10 cm^3) under argon at 0 °C. After the mixture had been stirred for 24 h at room temperature, it was treated with aq. Na_2CO_3 (12 cm^3) and water (40 cm^3) and extracted with dichloromethane. After acidification to pH 1 with hydrochloric acid, the aqueous layer was extracted with EtOAc and the extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a 7:2 (*syn*:*anti*) inseparable mixture of acids: *syn*-**18**; δ_H(250 MHz; $CDCl_3$) 7.6–7.3 (5 H, m, SPh), 3.80 (1 H, d, *J* 4.6, C*H*OH), 3.03 (1 H, dq, *J* 4.8 and 7.2, C*H*Me), 1.92–1.51 (10 H, m, C_5H_{10}) and 1.31 (3 H, d, *J* 7.1, Me) and *anti*-**19**; δ_H(250 MHz; $CDCl_3$) 7.6–7.3 (5 H, m, SPh), 3.10 (1 H, d, *J* 4.8, C*H*OH), 2.8 (1 H, m, C*H*Me), 1.92–1.51 (10 H, m, C_6H_{10}) and 1.31 (3 H, d, *J* 7.1, Me).

(3*R*,4*R*)- and (3*S*,4*R*)-3-Methyl-4-phenylsulfanyl-1-oxaspiro-[4.5]decan-2-one, *syn*-20 and *anti*-21

Method A (from *syn*-9). The aldol *syn*-**9** (0.35 g, 0.8 mmol) and toluene-*p*-sulfonic acid (TsOH·H_2O; 1.2 g) under argon were heated in dichloromethane (7 cm^3) under reflux for 5 h. After cooling to room temperature the residue was chromatographed on silica gel with diethyl ether–hexane (1:2) as eluent to give *syn*-**20** (0.12 g, 57%) as an oil; δ_H(250 MHz; $CDCl_3$) 7.4–7.2 (5 H, m, SPh), 3.80 (1 H, d, *J* 8.9, C*H*SPh), 3.10 (1 H, dq, *J* 7.6 and 8.9, C*H*Me), 2.0–1.5 (10 H, m, C_6H_{10}) and 1.3 (3 H, d, *J* 7.6, Me) along with *anti*-**21** (57 mg, 27%), as needles, mp 100–103 °C (from diethyl ether–hexane); δ_H(250 MHz; $CDCl_3$) 7.5–7.2 (5 H, m, SPh), 3.10 (1 H, d, *J* 12.3, C*H*SPh), 2.7 (1 H, dq, *J* 12.3 and 7.0, C*H*Me), 2.0–1.4 (10 H, m, C_5H_{10}) and 1.3 (3 H, d, *J* 7.0, Me).

Method B (from acid mixture *syn*-9 and *syn*-19). The mixture of acids *syn*-**18** and *syn*-**19** was heated under reflux under argon with catalytic amounts of TsOH·H_2O in dichloromethane for 5 min to give the lactones *syn*-**20** and *anti*-**21** as a 2.3:1 mixture.

(3*S*,4*R*)-3-Methyl-4-phenylsulfanyl-1-oxaspiro[4.11]hexadecan-2-one, *anti*-22

In the same way the aldol *anti*-**11** (53 mg, 0.11 mmol) gave the *lactone anti*-**22** (24 mg, 62%) as needles, mp 135–137 °C (from Et_2O–hexane), along with recovered starting material *anti*-**11** (11 mg, 21%); R_f(dichloromethane) 0.53 (Found: C, 73.6; H, 9.0; S, 8.65. $C_{22}H_{32}O_2S$ requires C, 73.33; H, 8.89; S, 8.89%); $[\alpha]_D^{25}$ –38.5 (*c* 0.2 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1764 (C=O) and 1582 (SPh); δ_H(250 MHz; $CDCl_3$) 7.7–7.2 (5 H, m, SPh), 3.29 (1 H, d, *J* 11.4, C*H*SPh), 2.78 (1 H, dq, *J* 7.1 and 11.4, C*H*Me), 2.20–1.22 (22 H, m, $C_{11}H_{22}$) and 1.18 (3 H, d, *J* 7.1, Me); δ_C($CDCl_3$) 176.4, 132.5, 129.3, 128.0, 89.3, 61.1, 44.0, 35.5, 29.6, 26.4, 26.3, 25.8, 22.6, 22.5, 22.3, 22.0, 20.1, 19.4 and 14.2; *m*/*z* 360 (64%, M$^+$), 250 (10, M – PhSH), 150 (100, C_3H_5SPh) and 109 (10, SPh).

(2*S*,3*S*)-3-Hydroxy-2-methyl-3-(1-phenylsulfanylcyclopentyl)-propanamide, *syn*-28

The aluminium amide reagent prepared from ammonium chloride (0.114 g, 2.1 mmol) and trimethylaluminium (2.1 mmol) in dichloromethane (2 cm^3) at 0 °C for 1 h was added to the aldol *syn*-**8** (0.31 g, 0.7 mmol) in dichloromethane (5 cm^3). The resulting solution was heated at 51–53 °C for 65 h. After cooling to room temperature, the reaction mixture was treated with hydrochloric acid (3.0 mol dm^{-3} solution; 0.73 cm^3), slowly and carefully added, after which it was stirred for a further 1 h. After separation of the organic layer, the aqueous

layer was extracted with ethyl acetate and the combined organic layer and extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography of the residue on silica gel with dichloromethane–methanol (20:1) as eluent yielded *amide syn*-**22** (0.14 g, 72%) as needles, mp 95–97 °C (from dichloromethane–methanol); R_f(CH_2Cl_2–MeOH, 20:1) 0.25 (Found: C, 64.6; H, 7.6; N, 4.95; S, 11.4. $C_{15}H_{21}NO_2S$ requires C, 64.49; H, 7.52; N, 5.02; S, 11.46%); ν_{max}(film)/cm^{-1} 3350 and 3068 (NH_2 and OH) and 1625 (C=O); δ_H(250 MHz; $CDCl_3$) 7.6–7.2 (5 H, m, SPh), 5.74 (2 H, br s, NH_2), 3.95 (1 H, d, *J* 3.6, C*H*OH), 3.14 (1 H, dq, *J* 3.6 and 7.1, C*H*Me), 2.02–1.42 (8 H, m, C_4H_8) and 1.26 (3 H, d, *J* 7.1, Me); δ_C($CDCl_3$) 179.6, 136.5, 132.3, 128.9, 74.7, 66.6, 42.3, 34.8, 34.4, 24.3, 23.8 and 13.3; *m/z* 279 (79%, M^+), 178 (100, M − $C_{10}H_{11}NO_2$), 110 (100, PhSH) and 91 (94, $PhSC_5H_9$).

(2*S*,3*S*)-3-Hydroxy-2-methyl-3-(1-phenylsulfanylcyclopentyl)propylamine, *syn*-29

The amide *syn*-**28** (0.26 g, 0.92 mmol) in THF (5 cm^3) was added to a BH_3–THF mixture (1.0 mol dm^{-3} solution in THF; 2.8 cm^3) under argon at 0 °C. After the mixture had been refluxed for 1 h 20 min it was diluted with water (46 cm^3) and dichloromethane (185 cm^3) and basified with sodium hydroxide. The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 185 cm^3). The combined organic layer and extracts were dried (Na_2SO_4) and evaporated under reduced pressure. Chromatography of the residue on silica gel with dichloromethane–methanol–triethylamine (87:12:1) as eluent yielded *amine syn*-**29** (0.2 g, 82%) as an oil; R_f(CH_2Cl_2–MeOH–Et_3N 87:12:1) 0.10; ν_{max}(film)/cm^{-1} 3420 and 3100 (OH, NH_2) and 1580 (SPh); δ_H(250 MHz; $CDCl_3$) 7.5–7.3 (5 H, m, SPh), 3.87 (1 H, d, *J* 1.7, C*H*OH), 3.02 (1 H, dd, *J* 4.2 and 12.3, C$H_A$$H_B$N), 2.82 (1 H, dd, *J* 3.9 and 12.3, CH$_A$$H_B$N), 2.74 (3 H, br s, OH and NH_2), 2.54–2.50 (1 H, m, C*H*Me), 2.04–1.52 (8 H, m, C_4H_8) and 1.04 (3 H, d, *J* 7.1, Me); δ_C($CDCl_3$) 136.3, 132.9, 128.6, 128.5, 65.9, 48.8, 35.1, 34.6, 32.9, 24.9, 23.7 and 11.3; *m/z* 265 (3%, M^+), 197 (2, M − C_5H_8), 156 (10, M − SPh), 110 (84, PhSH), 109 (64, SPh), 88 (100, $C_4H_{10}NO$) and 68 (50, C_5H_8) (Found: M^+, 265.1499. $C_{15}H_{23}NOS$ requires *M*, 265.1500).

(2*S*,3*S*)-3-Hydroxy-2-methyl-3-(1-phenylsulfanylcyclopentyl)-propyl-*N*-tosylamide, *syn*-30

A solution of the amine *syn*-**29** (99 mg, 0.4 mmol), tosyl chloride (75 mg, 0.4 mmol) and 4-dimethylaminopyridine (DMAP; 48 mg, 0.4 mmol) in dichloromethane (3 cm^3) under argon was stirred at room temperature for 5 h. The solvent was evaporated under reduced pressure. Chromatography of the residue on silica gel with ether–hexane (1:1) as eluent yielded the *sulfonamide syn*-**30** (0.14 g, 89%) as a semisolid; R_f(CH_2Cl_2) 0.20; ν_{max}(Nujol)/cm^{-1} 3600 (OH), 3291 (NH), 1598 (SPh), 1323 and 1159 (SO_2); δ_H(250 MHz; $CDCl_3$) 7.70 (2 H, d, *J* 8.2, C_6H_2Me), 7.5–7.2 (7 H, m, SPh and C_6H_2Me), 5.06 (1 H, dd, *J* 4.9 and 7.4, CNH), 3.68 (1 H, d, *J* 1.6, C*H*OH), 2.99 (1 H, dt, *J* 7.6 and 12.8, C$H_A$$H_B$N), 2.81 (1 H, dt, *J* 4.8 and 12.7, CH$_A$$H_B$N), 2.40 (3 H, s, ArMe), 2.33–2.21 (1 H, m, C*H*Me), 1.96–1.54 (8 H, m, C_4H_8) and 0.91 (3 H, d, *J* 6.9, Me); δ_C($CDCl_3$) 143.3, 137.0, 136.4, 132.2, 129.7, 128.9, 127.0, 74.0, 66.8, 49.0, 34.9, 34.3, 33.7, 24.5, 24.0, 21.5 and 11.8; *m/z* 419 (30%, M^+), 248 (20, M − $C_7H_9NSO_2$) and 235 (10, M − CH_2NHSO_2Tol) (Found: M^+, 419.1628. $C_{22}H_{29}NO_3S_2$ requires *M*, 419.1616).

(3*R*,4*R*)-3-Methyl-4-phenylsulfanyl-1-tosyl-1-azaspiro[4.4]-nonane, *syn*-31

Trimethylsilyl trifluoromethanesulfonate (TMSOTf; 0.06 cm^3, 0.3 mmol) was added to the solution of the sulfonamide *syn*-**30** (0.12 g, 0.3 mmol) in dichloromethane (4 cm^3) under argon at −78 °C. The solution was allowed to warm to room temperature slowly and kept at that temperature for 4 h. After evaporation of the mixture under reduced pressure, the residue was chromatographed on silica gel with ether–hexane (1:2) as eluent to give the *pyrrolidine syn*-**31** as a colourless oil; R_f(Et_2O–hexane, 1:2) 0.27; $[\alpha]_D^{25}$ +2.3 (*c* 2.2 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1582 (SPh), 1323 and 1142 (SO_2); δ_H(250 MHz; $CDCl_3$) 7.73 (2 H, d, *J* 8.3, $C_6H_2SO_2$), 7.5–7.2 (7 H, m, SPh and $C_6H_2SO_2$), 3.61 (1 H, dd, *J* 7.2 and 9.1, C$H_A$$H_B$N), 3.37 (1 H, d, *J* 5.2, C*H*SPh), 3.09 (1 H, t, *J* 8.7, CH$_A$$H_B$N), 2.88–2.56 (1 H, sym m, C*H*Me), 2.42 (3 H, s, ArMe), 2.39–2.11 (2 H, m, C_5H_2), 1.99–1.34 (6 H, m, C_5H_6) and 1.11 (3 H, d, *J* 6.7, CH*Me*); δ_C($CDCl_3$) 143.1, 142.8, 138.9, 137.4, 136.3, 131.0, 129.5, 129.1, 128.9, 128.7, 127.5, 126.9, 126.7, 78.1, 65.8, 54.0, 40.5, 35.1, 34.3, 24.8, 24.0, 18.8 and 14.4; *m/z* 401 (0.2%, M^+), 246 (30, M − SO_2Tol) and 110 (100, PhSH) (Found: M^+, 401.1742. $C_{22}H_{27}NO_2S_2$ requires *M*, 401.1782).

(1*S*,2*S*)-2-Methyl-1-(1-phenylsulfanylcyclopentyl)propane-1,3-diol, *syn*-32

Lithium borohydride (2.0 mol dm^{-3} solution in THF; 0.93 cm^3) was added to a stirred solution of the aldol *syn*-**31** (0.742 g, 1.7 mmol) in ether (35 cm^3) and water (0.0334 cm^3, 1.854 mmol) under argon at 0 °C. After 3 h at room temperature, aq. sodium hydroxide (2.5 mol dm^{-3} solution; 0.6 cm^3) was added to the mixture which was then stirred until both layers were clear. The mixture was poured into ether (75 cm^3) and distilled water (75 cm^3) and after separation of the layers, the aqueous layer was extracted with ether (3 × 75 cm^3). The combined extracts were washed with brine (75 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Chromatography of the residue on silica eluting with ethyl acetate–hexane (3:17) yielded the *diol syn*-**32** (0.433 g, 96%) as a colourless oil; R_f(CH_2Cl_2–MeOH, 19:1) 0.46; $[\alpha]_D^{24}$ −17.2 (*c* 2.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3500 (2 OH, broad hump) and 1590 (SPh); δ_H(250 MHz; $CDCl_3$) 7.6–7.2 (5 H, m, SPh), 3.83 (1 H, d, *J* 2.0, C*H*OH), 3.69 (1 H, dd, *J* 4.2 and 10.4, C$H_A$$H_B$O), 3.61 (1 H, dd, *J* 5.4 and 10.4, CH$_A$$H_B$O), 2.43–2.20 (1 H, m, C*H*Me), 2.02–1.55 (8 H, m, C_4H_8) and 1.04 (3 H, d, *J* 7.0, Me); δ_C($CDCl_3$) 136.6, 132.3, 128.8, 75.4, 69.2, 67.3, 36.1, 34.5, 33.7, 24.5, 24.0 and 11.0; *m/z* 266 (2.3%, M^+), 177 (44, M − $C_4H_9O_2$), 157 (30, M − SPh), 139 (18, M − $C_6H_7O_6$) and 69 (99, C_5H_9) (Found: M^+, 266.1321. $C_{15}H_{22}O_2S$ requires *M*, 266.1340).

(1*S*,2*S*)-2-Methyl-1-(1-phenylsulfanylcyclohexyl)propane-1,3-diol, *syn*-33

In the same way the aldol *syn*-**9** (0.47 g, 1.16 mmol) gave the diol *syn*-**33** as an oil; $[\alpha]_D^{25}$ −35.9 (*c* 1.8 in $CHCl_3$); δ_H(250 MHz; $CDCl_3$) 7.52–7.27 (5 H, m, SPh), 3.60 (1 H, dd, *J* 4.6 and 10.4, C$H_A$$H_B$OH), 3.55 (1 H, d, *J* 5.4, C*H*OH), 3.53 (1 H, dd, *J* 5.4 and 10.4, CH$_A$$H_B$OH), 2.10–1.20 (11 H, m, C_5H_{10} and C*H*Me) and 1.10 (3 H, d, *J* 7.0, Me).

(3*R*,4*R*)-3-Methyl-4-phenylsulfanyl-1-oxaspiro[4.4]nonane, *syn*-34

A solution of the diol *syn*-**32** (86.5 mg) and toluene-*p*-sulfonic acid (TsOH; 15.73 mg) in benzene (4.0 cm^3) was heated under reflux for 5 min, allowed to cool to room temperature and filtered through silica gel with dichloromethane as the eluent. The filtrate was evaporated under reduced pressure to give the *tetrahydrofuran syn*-**34** (80 mg, 98%) as an oil; R_f(hexane–ether, 2:1) 0.46; $[\alpha]_D^{24}$ −130 (*c* 1.1 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1580 (SPh); δ_H(250 MHz; $CDCl_3$) 7.39–7.20 (5 H, m, SPh), 4.0 (1 H, dd, *J* 7.1 and 8.7, C$H_A$$H_B$O), 3.70 (1 H, d, *J* 7.6, C*H*SPh), 3.48 (1 H, dd, *J* 5.8 and 8.7, CH$_A$$H_B$O), 2.71–2.60 (1 H, m, C*H*Me), 1.88–1.60 (8 H, m, C_4H_8) and 1.10 (3 H, d, *J* 7.0, Me); δ_C($CDCl_3$) 137.1, 129.7, 129.0, 126.1, 93.0, 72.1, 58.2, 38.9, 36.9,

34.7, 25.1, 23.6 and 15.5; *m/z* 248 (14%, M^+), 164 (100, M − C_5H_8O), 109 (10, SPh) and 55 (60, C_4H_7) (Found: M^+, 248.1242. $C_{15}H_{20}OS$ requires *M*, 248.1234).

(3*R*,4*R*)-3-Methyl-4-phenylsulfanyl-1-oxaspiro[4.5]decane, *syn*-35

In the same way the diol *syn*-**33** (46.4 mg) gave the tetrahydrofuran *syn*-**35** (41 mg, 98%) as an oil; $[\alpha]_D^{25}$ −16.8 (*c* 2.0 in $CHCl_3$); δ_H(250 MHz; $CDCl_3$) 7.4–7.1 (5 H, m, SPh), 4.0 (1 H, dd, *J* 7.1 and 8.7, CH_AH_BO), 3.51 (1 H, dd, *J* 6.2 and 8.8, CH_AH_BO), 3.44 (1 H, d, *J* 8.2, C*H*SPh), 2.70–2.62 (1 H, m, C*H*Me), 1.76–1.15 (10 H, m, C_5H_{10}) and 1.10 (3 H, d, *J* 7.0, Me).

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