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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 3979–3988

Asymmetric synthesis of 2-substituted butane-1,4-diols by hydrogenation of homochiral fumaramide derivatives

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Received 1 November 2004; accepted 15 November 2004

Abstract—Diastereoselective hydrogenation of homochiral fumaramides **1** derived from (2*R*)-Oppolzer's sultam was observed by analysis of the ^{1}H NMR spectra of the succinamide mixtures with de's of 77–88%. Reduction of these succinamides using $LiAlH_4$ gave the corresponding (2*S*)-butane-1,4-diols and established that addition of hydrogen takes place selectively on the *re*-face of fumaramides **1**. The stereoselectivity was confirmed by estimating the ee's from the ^{19}F NMR spectra of the Mosher's diesters of the diols. This methodology was applied to the synthesis of selected pyrrolidine natural products in homochiral form.

1. Introduction

Butane-1,4-diols are important four-carbon building blocks in organic chemistry and they are precursors for the synthesis of a number of pyrrolidine natural products.[1] Oppolzer's camphorsultam[2] was introduced in 1984 and ranks today among the most useful chiral auxiliaries available for asymmetric synthesis. In the synthesis of chiral compounds, the reduction of prochiral unsaturated reactants has great importance. The diastereoselective hydrogenation of *N*-enoylsultams has previously been reported by Oppolzer et al.[3]

The diastereoselective conjugate addition of a series of Grignard reagents has recently been carried out using *N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-fumaramide.[4] This occurred with moderate to high levels of diastereoselectivity.

We report the diastereoselective hydrogenation of a number of novel fumaramide derivatives **1a**–**i** containing *N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-fumaramide. Some of the products were reduced using $LiAlH_4$ to produce 2-substituted butane-1,4-diols **4a**–**e**. The enantiomer of the methyl derivative **4a** was used in the synthesis of a series of pyrrolidine natural products.[5]

2. Results and discussion

Synthesis of the novel fumaramide derivatives **1a**–**j** required the corresponding 2-substituted fumaric acids as starting materials. These were synthesised according to known literature procedures.[6,7] Modification of a literature procedure[6] improved yields by 10–20%. Coupling of the acids to commercially available (2*R*)-(−)-2,10-camphorsultam was carried out either by treating the acid chloride with the camphorsultam in the presence of sodium hydride or by using DCC and DMAP as coupling reagents with the diacid and camphorsultam. Optimisation of the conditions for the catalytic hydrogenation using **1a** involved the investigation of solvent, catalyst, temperature and pressure effects. The use of dry toluene and 10% Pd/C catalyst under 7 bar pressure at 25 °C was found to be the best set of conditions. More polar solvents gave lower de's. Under the best conditions catalytic hydrogenation produced diastereomerically enriched mixtures of succinamides **2** and **3** (**a**–**g**) (Scheme 1) in near quantitative yields (Table 1). ^{1}H NMR spectra were used to determine de's. The ABX system of the succinamide protons resonated at different chemical shifts for each pair of diastereomers. The ABX system of the minor diastereomer was consistently at a lower δ value than the major diastereomer. Integration of the signals gave an estimate of the diastereomeric excess.

The length of time to reach completion for the hydrogenation varied with the R group. The hexyl and octyl derivatives **1d** and **1e** took 2 and 7 days, respectively,

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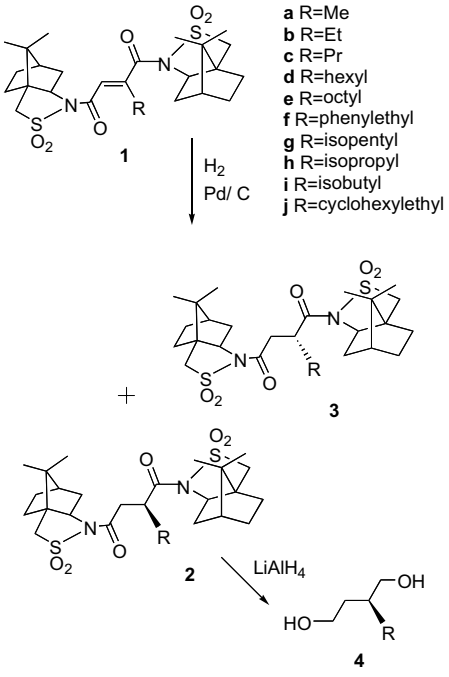
doi:10.1016/j.tetasy.2004.11.023



Scheme 1.

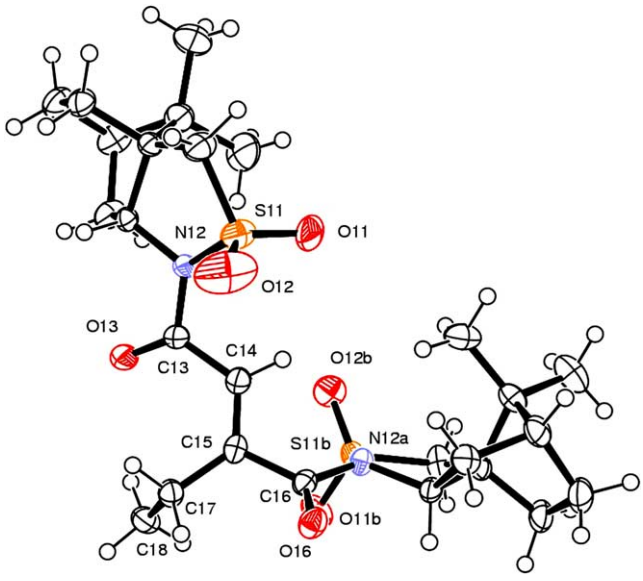


Figure 1. ORTEP diagram of compound **1b**. The view is normal to the olefin plane, with 50% probability ellipsoids for the non-H atoms and arbitrary sized spheres for the H-atoms.

to reach completion compared with **1a–c**, which were complete overnight. The isopropyl **1h** and isobutyl **1g** derivatives could only be hydrogenated partially even after two weeks and the cyclohexylethyl derivative did not hydrogenate at all. This may be due to steric effects.

X-ray crystal structures were determined for the ethyl derivative **1b** (Fig. 1) and the corresponding succinamide **2b** (Fig. 2). From a consideration of the space-filling views of **1b** shown in Figure 3, it can been seen that the olefinic carbon atom C(15) is less sterically hindered from the *re*-face than from the *si*-face. Moreover, the olefinic H-atom is also more accessible from this face. Given the caveat that the solution conformation may differ from that in the solid phase, it is reasonable to assume that this sterically less crowded *re*-face interacts more easily with the catalyst surface, and hence explains the formation of the major product **2b**.

The succinamide mixtures **2** and **3** (**a–g**) were separated by column chromatography leading to single diastereomers **2** and **3** (**a–g**) by analysis of ^{1}H NMR spectra.

The reduction of succinamides **2a–e** produced 2-substituted butane-1,4-diols **4a–e**. A small amount of each diol was converted into its Mosher's diesters. Estimation of de's by analysis of the ^{19}F NMR spectra of the Mosher's diesters provided figures that correlated well with the initial values (Table 1).

3. Natural product synthesis

We have applied our methodology towards the synthesis of a number of pyrrolidine natural products. In 1995, Veith et al. reported[8] the isolation of five *N*-alkylated 3-methylpyrrolidines. Methods for the preparation of enantiomerically pure pyrrolidines substituted exclusively at the 3-position are scarce. We have synthesised

Table 1. Hydrogenation of fumaramides **1** to the corresponding succinamides **2** and **3**

Entry	R	Yield (%)	Dr[a] (major/minor)	De[a] (%) (^{1}H NMR)	De[b] (%) (^{19}F NMR)
1	Methyl (**1a**)	100	89:11 (**2a/3a**)	77	81[c]
2	Ethyl (**1b**)	96	94:6 (**2b/3b**)	88	78
3	Propyl (**1c**)	98	90:10 (**2c/3c**)	80	75
4	Hexyl (**1d**)	98	93:7 (**2d/3d**)	85	85
5	Octyl (**1e**)	94	89:11 (**2e/3e**)	78	75
6	Phenylethyl (**1f**)	100	90:10 (**2f/3f**)	80	—
7	Isopentyl (**1g**)	100	90:10 (**2g/3g**)	79	—
8	Isopropyl (**1h**)	50	74:26[d]	—	—
9	Isobutyl (**1i**)	30	84:16[d]	—	—
10	Cyclohexylethyl (**1j**)	No product	—	—	—

[a] Diastereomeric ratios were determined by ^{1}H 400 MHz NMR spectra of the crude reaction mixtures.
[b] Both (*R*)- and (*S*)-bis Mosher's esters of each diol were synthesised and analysed by ^{19}F NMR spectra.
[c] Determined from HPLC analysis of the dianilide.
[d] Incomplete reaction.

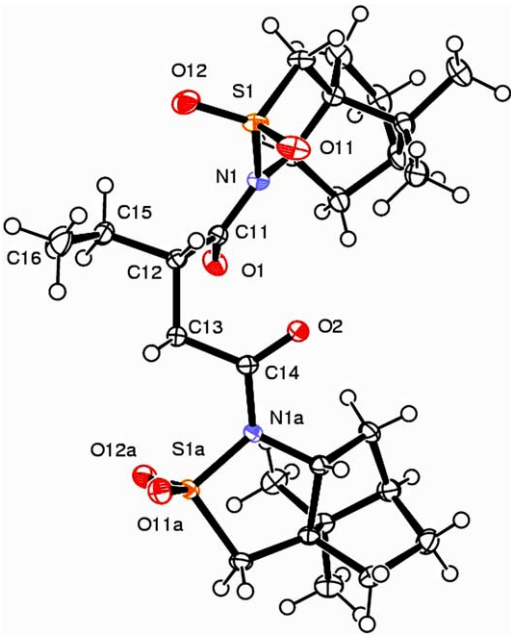


Figure 2. ORTEP diagram of compound **2b**. Ellipsoids are plotted at the 50% probability level, with H atoms shown as arbitrary spheres.

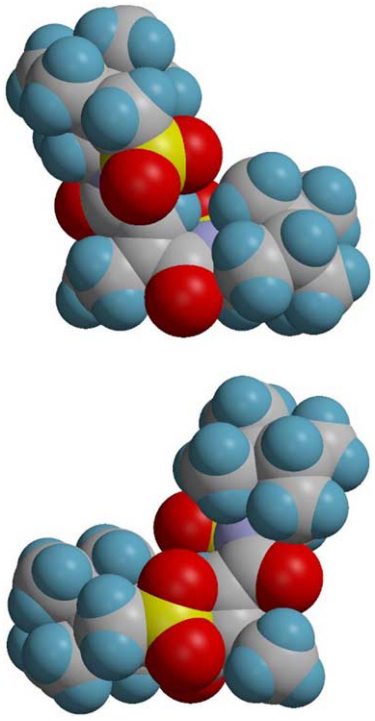
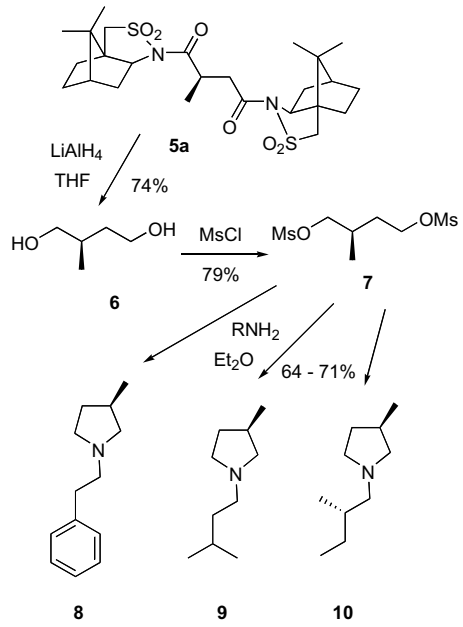


Figure 3. Space filling plot of compound **1b**. Viewed normal to the *re*-face of the olefin (top view) and the *si*-face (bottom view). The olefinic C=C bond is vertical in both views.

three of these alkaloids from the antipode of methyl derivative **2a** (Scheme 2). Column chromatography or crystallisation provided succinamide **5a** in good yield with >98% diastereomeric excess by ^{1}H NMR spectra analysis. To confirm this the diastereomer was hydrolysed to 2-methylsuccinic acid. This was converted into the dianilide and chiral HPLC analysis showed no trace of



Scheme 2.

the minor enantiomer. Reduction of **5a** produced diol **6**, which was mesylated in good yield. The mesylate **7** was stirred over 2–4 days with the appropriate amine and the homochiral final products **8**–**10** were isolated by column chromatography.

4. Conclusions

An asymmetric heterogeneous hydrogenation method has been developed for the synthesis of enantiomerically pure 2-substituted butane-1,4-diols and succinic acids. This methodology has been applied to natural product synthesis of pyrrolidine alkaloids.

5. Experimental

5.1. General experimental

All reactions were carried out under nitrogen with anhydrous solvents unless otherwise stated. Tetrahydrofuran and diethyl ether were dried by distillation from sodium benzophenone immediately before use. Toluene and dichloromethane were dried by distillation from CaH_2 immediately before use. Reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained on a Bruker DPX-400 spectrometer. Chemical shifts are given relative to chloroform ($\delta_H = 7.27$) and ($\delta_C = 77.0$) as internal standards unless otherwise stated. All coupling constants are reported in Hertz (Hz). Infra red spectra were recorded on either a Nicolet Impact 410 FT-IR or Perkin–Elmer 500 spectrometer. Mass spectra were obtained on a Jeol JMS700 or a VG updated MS902 spectrometer, using the

electron impact method unless otherwise stated. Combustion analysis was carried out using an Elemental Analyser MOD 1106. All of the thin layer chromatography plates used were Merck aluminium oxide 60 F_{254} neutral (type E) with layers of 0.2 mm thickness or Merck silica gel 60 F_{254} with layers of 0.25 mm thickness. The plates were visualised by illumination with UV light or permanganate solution. Optical rotations were recorded on a Polaar 2000 polarimeter with path length 10 cm. $[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}.

5.2. Substituted fumaric acids

Isopentyl-, cyclohexylethyl- and phenylethyl-fumaric esters were prepared as described.[7] The remaining substituted fumaric acids were made by modification of the route of Akhtar et al.[6]

Sodium (1.1 equiv) was dissolved in dry ethanol. Ethyl acetoacetate (1.0 equiv) was added dropwise over 10 min, the solution stirred for an additional 5 min and, after addition of KI (0.1 equiv), the appropriate alkyl bromide (1.3 equiv) was added slowly dropwise. Following the addition, the reaction was heated at reflux overnight and was then allowed to cool. The solution was poured into water and extracted with diethyl ether (5×200 mL). The combined organic extracts were washed with water and dried over $MgSO_4$. The solvent was removed in vacuo and the resultant oil purified by distillation. To a vigorously stirred solution of the appropriate ester (1.0 equiv) in dry diethyl ether was slowly added bromine (2.0 equiv) and the solution was heated at reflux for 3 h. The mixture was washed with 10% sodium thiosulfate and then with brine. The solvent was removed under pressure to give the dibromide as a pale yellow oil. The dibromide was added slowly to a solution of ethanol containing potassium hydroxide (5.7 equiv) with rapid stirring. The mixture was heated at reflux for 30 min and the solvent removed in vacuo. After addition of water, the solution was acidified to pH 1 using concd HCl and extracted with diethyl ether (4×200 mL). The organic extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The products were purified by recrystallisation.

5.2.1. Hexylfumaric acid. This was prepared in 10% yield on a 76 mmol scale by the above method and gave mp 172–174 °C; IR (KBr, cm^{-1}) 2930, 1712; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (3H, t, $J = 7.0$, CH_3CH$_2$), 1.16–1.34 (6H, m), 1.34–1.38 (2H, m), 2.64 (2H, t, $J = 7.3$, CH_2C=C), 6.57 (1H, s, CH=C); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.2, 22.3, 27.4, 28.9, 28.9, 31.3, 127.1, 147.4, 167.1, 168.4; HR-CIMS *m*/*z* 201.1128 (M+H)$^+$ (calcd for $C_{10}H_{17}O_4$ requires 201.1127).

5.2.2. Octylfumaric acid. This was prepared in 10% yield on a 76 mmol scale by the above method and gave mp 125–128 °C; IR (KBr, cm^{-1}) 2927, 1710; ^{1}H NMR (400 MHz, MeOH-d_4) δ 0.80 (3H, t, $J = 7.0$, CH_3CH$_2$), 1.10–1.30 (10H, m), 1.32–1.42 (2H, m), 2.64 (2H, t, $J = 7.5$, CH_2C=C), 4.79 (2H, br s, $2 \times$ OH), 6.60 (1H, s, CH=C); ^{13}C NMR (100 MHz, MeOH-d_4) δ 14.8, 24.1, 29.0, 30.7 (×2), 30.8, 31.1, 33.4, 128.2, 149.8, 169.3, 170.5; HR-CIMS *m*/*z* 229.1441 (M+H)$^+$ (calcd for $C_{12}H_{21}O_4$: 229.1440). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.1; H, 8.8. Found: C, 63.1; H, 8.8.

5.3. Diethyl cyclohexylethylfumarate

This was prepared in 43% yield on a 20 mmol scale by the method of Cooke.[7] IR (KBr, cm^{-1}) 2952, 1721; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86–0.96 (2H, m, $2 \times$ cyclohexane-H), 1.10–1.35 (11H, m, $5 \times$ cyclohexane-H, $2 \times$ CH_3CH$_2$O), 1.61–1.76 (6H, m, $4 \times$ cyclohexane-H, CH_2CH), 2.76–2.80 (2H, m, CH_2C=C), 4.17–4.26 (4H, m, $2 \times$ CH$_3$CH_2O), 6.69 (1H, s, CH=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 25.6, 26.3, 26.6, 33.1, 36.7, 38.0, 60.5, 61.4, 125.9, 148.9, 165.7, 167.0; HR-EIMS *m*/*z* 282.1829 M$^+$ (calcd for $C_{16}H_{26}O_4$: 282.1831).

5.4. General procedure for the hydrolysis of isopentyl-, cyclohexylethyl- and phenylethyl-fumarate into 2-substituted fumaric acids

A solution of KOH (4 equiv) in ethanol/water (1:1) was added to the appropriate diethyl ester (1 equiv) and the mixture heated at reflux overnight. The reaction mixture was concentrated, taken up in water (30 mL) and extracted with diethyl ether (2×20 mL). The aqueous layer was acidified to pH 1 using concd HCl and extracted with diethyl ether (3×50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo.

5.5. General procedure 1 for the synthesis of 2-substituted fumaramides

(1*S*,2*R*)-(−)-2,10-Camphorsultam (2 equiv) in toluene was added dropwise to a suspension of NaH (60% in mineral oil, 3 equiv) in dry toluene and the mixture was stirred at 0 °C for 2 h. The appropriate fumaric acid (1 equiv) was heated at reflux with thionyl chloride (6 equiv) overnight and the excess thionyl chloride was removed in vacuo. The resultant acid chloride was taken up in dry toluene (15 mL) and added to the camphorsultam mixture dropwise at 0 °C. The mixture was stirred at room temperature overnight. Saturated aqueous ammonium chloride was added and the mixture poured into saturated aqueous ammonium chloride, extracted with toluene (3×100 mL) and the organic layers washed with brine. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo.

5.6. General procedure 2 for the synthesis of 2-substituted fumaramides

To a solution of (1*S*,2*R*)-(−)-2,10-camphorsultam (2 equiv) in dry DCM (15 mL) were added DCC (2.4 equiv), DMAP (0.3 equiv) and the appropriate fumaric acid (1 equiv) at 0 °C. The mixture was stirred at 0 °C for 3 h, then allowed to warm to room temperature overnight. The separated dicyclohexylurea was removed by filtration and washed with cold DCM. The filtrate was washed sequentially with 4% NaOH

(2 × 15 mL), 3% HCl (30 mL) and water (until neutral). The organic layer was dried over Na_2SO_4 and concentrated in vacuo.

5.6.1. *N,N′*-Bis[(2*R*)-bornane-10,2-sultam]-2-methyl-fumaramide 1a. Mesaconic acid (0.50 g, 3.84 mmol) was treated following general procedure 2 to produce a beige foam, which was triturated using ethanol to give **1a** (1.57 g, 50%) as a beige powder; mp 239–240 °C; $[\alpha]_D = -117$ (*c* 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 2970, 1678, 1331, 1138; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, s, CH_3), 0.99 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.34–1.46 (4H, m), 1.57 (3H, s, CH_3C=C), 1.89–1.97 (6H, m), 2.02–2.29 (4H, m), 3.38–3.54 (4H, m, 2 × CH_2SO_2), 3.93 (1H, dd, $J = 4.9$, 7.6, CHN), 4.01 (1H, app t, $J = 6.6$, CHN), 6.88 (1H, s, CH=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 19.8, 20.7, 21.0, 21.1, 26.4, 26.5, 32.7, 33.0, 38.1, 38.5, 44.6, 45.0, 47.7, 48.4, 48.5, 52.9, 53.2, 64.8, 65.2, 124.5 147.8, 162.8, 170.3; HR-FABMS m/z 525.2094 $(M+H)^+$ (calcd for $C_{25}H_{37}N_2O_6S_2$: 525.2093). Anal. Calcd for $C_{25}H_{37}N_2O_6S_2$: C, 57.1; H, 6.7; N, 5.3. Found: C, 57.1; H, 6.8; N, 5.4.

5.6.2. *N,N′*-Bis[(2*S*)-bornane-10,2-sultam]-2-methyl-fumaramide. Mesaconic acid (1.30 g, 10 mmol) and (1*R*,2*S*)-camphorsultam (4.31 g, 20 mmol) were treated following general procedure 1 to produce a beige foam, which was triturated using ethanol to produce *N,N′*-bis[(2*S*)-bornane-10,2-sultam]-2-methylfumaramide (2.67 g, 51%) as a beige powder; mp 214–216 °C. Spectral data were identical to **1a**.

5.6.3. *N,N′*-Bis[(2*R*)-bornane-10,2-sultam]-2-ethyl-fumaramide 1b. Ethylfumaric acid (0.27 g, 1.87 mmol) was treated following general procedure 2 and recrystallised from ethanol to produce **1b** (1.33 g, 32%) as cream needles; mp 194–195 °C; $[\alpha]_D = -103$ (*c* 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 2959, 1684, 1337, 1135; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, s, CH_3), 0.97 (3H, s, CH_3), 1.13 (3H, t, $J = 7.5$, CH_3CH_2), 1.17 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.33–1.46 (4H, m), 1.85–1.97 (6H, m), 2.04–2.21 (4H, m), 2.73 (1H, dq, $J = 7.4$, 14.7, CH_3CH), 2.88 (1H, dq, $J = 7.5$, 15.0, CH_3CH), 3.34–3.49 (4H, m, 2 × CH_2SO_2), 3.93 (1H, dd, $J = 4.9$, 7.7, CHN), 4.02 (1H, app t, $J = 6.2$, CHN), 6.87 (1H, s, CH=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 19.8 (×2), 20.8, 21.0, 23.2, 26.4, 26.5, 32.8, 32.9, 38.2, 38.5, 44.6, 44.9, 47.8, 48.2, 48.5, 52.9, 53.4, 64.8, 65.3, 124.8, 153.1, 162.7, 169.9; HR-FABMS *m/z* 539.2247 $(M+H)^+$ (calcd for $C_{26}H_{39}O_6N_2S_2$: 539.2250). Anal. Calcd for $C_{26}H_{39}O_6N_2S_2$: C, 57.9; H, 7.1; N, 5.2. Found: C, 58.1; H, 7.1; N, 4.9.

5.6.4. *N,N′*-Bis[(2*R*)-bornane-10,2-sultam]-2-propyl-fumaramide 1c. Propylfumaric acid (1.0 g, 6.20 mmol) was treated following general procedure 1 and recrystallised from ethanol to produce **1c** (0.76 g, 24%) as beige plates; mp 190–193 °C; $[\alpha]_D = -88$ (*c* 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 2961, 1683, 1340, 1135; ^1H NMR (400 MHz; $CDCl_3$) δ 0.94–0.98 (9H, m, CH_3CH_2, 2 × CH_3), 1.18 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.33–1.43 (4H, m), 1.53–1.60 (2H, m, CH_2CH_3), 1.89–1.98 (6H, m), 2.04–2.19 (4H, m), 2.69–2.84 (2H, m, $CH_2CH_2CH_3$), 3.38–3.52 (4H, m, 2 × CH_2SO_2), 3.93 (1H, dd, $J = 5.0$, 7.7, CHN), 4.02 (1H, app t, $J = 6.2$, CHN), 6.90 (1H, s, CH=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.8, 19.9, 20.8, 21.0, 21.8, 26.5 (×2), 31.8, 32.8, 33.0, 38.3, 38.5, 44.7, 44.9, 47.8, 48.3, 48.5, 52.9, 53.4, 64.9, 65.4, 125.3, 151.9, 162.9, 170.0; HR-FABMS *m/z* 553.2407 $(M+H)^+$ (calcd for $C_{27}H_{41}O_6N_2S_2$: 553.2406). Anal. Calcd for $C_{27}H_{41}O_6N_2S_2$: C, 58.5; H, 7.4; N, 5.1. Found: C, 58.6; H, 7.3; N, 5.1.

5.6.5. *N,N′*-Bis[(2*R*)-bornane-10,2-sultam]-2-hexyl-fumaramide 1d. Hexylfumaric acid (0.50 g, 2.50 mmol) was treated following the general procedure 2 and the resultant mixture chromatographed [SiO_2, ethyl acetate/hexane (2:3)] to produce **1d** (0.35 g, 23%) as a white powder; mp 85–88 °C; $[\alpha]_D = -103$ (*c* 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 2958, 1682, 1338, 1134; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, $J = 6.8$, CH_3CH_2), 0.96 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.25–1.36 (3H, m), 1.37–1.60 (9H, m), 1.88–1.98 (6H, m), 2.04–2.18 (4H, m), 2.71 (1H, dt, $J = 5.2$, 12.6, CHHC=C), 2.83 (1H, dt, $J = 5.2$, 12.6, CHHC=C), 3.38–3.52 (4H, m, 2 × CH_2SO_2), 3.92 (1H, dd, $J = 5.0$, 7.6, CHN), 4.02 (1H, app t, $J = 6.2$, CHN), 6.88 (1H, s, CH=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.8, 19.9, 20.8, 21.0, 22.5, 26.5 (×2), 28.3, 29.6, 29.9, 31.5, 32.8, 32.9, 38.2, 38.5, 44.7, 44.9, 47.8, 48.3, 48.5, 52.9, 53.4, 64.8, 65.4, 125.0, 152.1, 162.7, 170.0; HR-FABMS *m/z* 595.2870 $(M+H)^+$ (calcd for $C_{30}H_{46}N_2O_6S_2$: 595.2876). Found: C, 60.5; H, 7.9; N, 4.7. Found C, 60.6; H, 7.8; N, 4.7.

5.6.6. *N,N′*-Bis[(2*R*)-bornane-10,2-sultam]-2-octyl-fumaramide 1e. Octylfumaric acid (0.50 g, 2.19 mmol) was treated following general procedure 2 and the resultant mixture chromatographed [SiO_2, ethyl acetate/hexane (1:2)] to produce **1e** (1.13 g, 41%) as a white powder; mp 68–70 °C; $[\alpha]_D = -91.5$ (*c* 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 2927, 1682, 1338, 1134; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, $J = 6.4$, CH_3CH_2), 0.96 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.24–1.54 (19H, m), 1.89–1.98 (6H, m), 2.04–2.19 (4H, m), 2.72 (1H, dt, $J = 5.6$, 12.6, CHHC=C), 2.83 (1H, dt, $J = 5.6$, 12.6, CHHC=C), 3.38–3.52 (4H, m, 2 × CH_2SO_2), 3.93 (1H, dd, $J = 4.9$, 7.5, CHN), 4.02 (1H, app t, $J = 6.2$, CHN), 6.89 (1H, s, CH=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.8, 19.9, 20.8, 21.0, 22.6, 26.4, 26.5, 28.3, 29.2, 29.9, 31.8, 32.8, 32.9, 38.2, 38.5, 44.6, 44.9, 47.8, 48.2, 48.5, 52.9, 53.4, 64.8, 65.4, 125.0, 152.1, 162.7, 170.0; HR-FABMS *m/z* 623.3192 $(M+H)^+$ (calcd for $C_{30}H_{46}N_2O_6S_2$: 623.3189). Anal. Calcd for $C_{30}H_{46}N_2O_6S_2$: C, 61.7; H, 8.1; N, 4.5. Found: C, 61.8; H, 8.1; N, 4.7.

5.6.7. *N,N′*-Bis[(2*R*)-bornane-10,2-sultam]-2-phenyl-ethylfumaramide 1f. Phenylethylfumaric acid (0.50 g, 2.3 mmol) was treated following general procedure 2 to produce a beige foam, which was chromatographed [SiO_2, ethyl acetate/hexane (1:2)] to produce **1f** (0.61 g, 44%) as an off-white powder; mp 179–180 °C; $[\alpha]_D = -102$ (*c* 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 2963,

1688, 1329, 1163; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.27–1.47 (4H, m), 1.82–1.98 (6H, m), 2.04–2.19 (4H, m), 2.78 (1H, dt, J = 4.4, 12.4, CHHC=C), 2.92 (1H, dt, J = 4.8, 12.8, CHHC=C), 2.98–3.14 (2H, m), 3.39–3.54 (4H, m, 2 × CH_2SO$_2$), 3.93 (1H, dd, J = 5.2, 7.2, CHN), 4.05 (1H, app t, J = 6.0, CHN), 6.96 (1H, s, CH=C), 7.15–7.18 (1H, m, Ar), 7.24–7.26 (4H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8 (×2), 20.8, 21.0, 26.4, 26.5, 32.1, 32.8, 32.9, 34.5, 38.2, 38.5, 44.7, 44.9, 47.8, 48.3, 48.5, 52.9, 53.4, 64.8, 65.4, 125.6, 125.8, 128.2, 128.5, 138.1, 141.6, 162.5, 169.9; HR-FABMS m/z 615.2562 $(M+H)^+$ (calcd for $C_{32}H_{43}N_2O_6S_2$: 615.2563). Anal. Calcd for $C_{32}H_{42}N_2O_6S_2$: C, 62.5; H, 6.9; N, 4.6. Found: C, 62.4; H, 7.0; N, 4.6.

5.6.8. *N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-isopentylfumaramide 1g. Isopentylfumaric acid (0.50 g, 2.69 mmol) was treated following general procedure 2 to produce a beige foam, which was chromatographed [SiO_2, ethyl acetate/hexane (1:1)] to produce **1g** (0.71 g, 46%) as an off-white powder; mp 112–115°C; $[\alpha]_D$ = −232 (c 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 2925, 1682, 1337, 1167; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.91 (6H, m, (CH_3)$_2$CH), 0.96 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.30–1.65 (7H, m), 1.88–1.95 (6H, m), 2.09–2.22 (4H, m), 2.72 (1H, dt, J = 4.8, 12.4, CHHC=C), 2.85 (1H, dt, J = 5.2, 12.0, CHHC=C), 3.38–3.52 (4H, m, 2 × CH_2SO$_2$), 3.93 (1H, dd, J = 4.8, 7.2, CHN), 4.02 (1H, app t, J = 6.0, CHN), 6.88 (1H, s, CHC=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 19.9, 20.8, 21.0, 22.1, 22.4, 26.5 (×2), 28.0, 28.4, 32.8, 33.0, 37.0, 38.2, 38.5, 44.7, 44.9, 47.8, 48.2, 48.5, 52.9, 53.4, 64.8, 65.4, 125.0, 152.3, 162.7, 170.1; HR-CIMS m/z 581.2714 $(M+H)^+$ (calcd for $C_{29}H_{45}N_2O_6S_2$: 581.2719).

5.6.9. *N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-isopropylfumaramide 1h. Isopropylfumaric acid (2.0 g, 12.7 mmol) was treated following general procedure 1 to produce an orange syrup, which was triturated from ethanol to give **1h** (0.25 g, 4%) as an off-white powder; mp 224–225 °C; $[\alpha]_D$ = −132 (c 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 2963, 1682, 1335, 1138; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.15 (3H, d, J = 6.9, CH_3CH), 1.18 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.30 (3H, d, J = 7.0, CH_3CH), 1.34–1.47 (4H, m), 1.88–1.98 (6H, m), 2.04–2.18 (4H, m), 3.38–3.53 (4H, m, 2 × CH_2SO$_2$), 3.85 (1H, septet, J = 7.0, CH(CH$_3$)$_2$), 3.95 (1H, dd, J = 4.9, 7.7, CHN), 4.02 (1H, dd, J = 5.2, CHN), 6.75 (1H, s, CH=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 19.8, 19.9, 20.8, 21.1, 23.3, 26.4, 26.5, 29.0, 32.8, 33.0, 38.4, 38.6, 44.7, 44.9, 47.8 (×2), 48.1, 48.5, 53.0, 53.4, 64.9, 65.3, 123.9, 157.1, 162.7, 168.3; HR-FABMS m/z 553.2403 $(M+H)^+$ (calcd for $C_{27}H_{41}N_2O_6S_2$: 553.2406). Anal. Calcd for $C_{27}H_{40}N_2O_6S_2$: C, 58.7; H, 7.3; N, 5.1. Found: C, 58.7; H, 7.4; N, 5.1.

5.6.10. *N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-isobutylfumaramide 1i. Isobutylfumaric acid (1.00 g, 5.81 mmol) was treated following general procedure 1 to produce an off-white powder, which was crystallised from ethanol to give **1i** (1.49 g, 45%) as white needles; mp 193–195 °C; $[\alpha]_D$ = −103 (c 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 2962, 1682, 1336, 1167; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94–1.02 (12H, m, (CH_3)$_2$CH, 2 × CH_3), 1.18 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.32–1.47 (4H, m), 1.86–1.98 (7H, m), 2.03–2.20 (4H, m), 2.74 (2 H, d, J = 7.1, CH_2CH), 3.38–3.52 (4H, m, 2 × CH_2SO$_2$), 3.87 (1H, dd, J = 5.0, 7.6, CHN), 3.92 (1H, app t, J = 6.2, CHN), 6.96 (1 H, s, CH=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 19.9, 20.8, 20.9, 22.4, 23.0, 26.5, 28.2, 32.8, 32.9, 38.0, 38.2, 38.5, 44.7, 44.8, 47.8 (×2), 48.2, 48.5, 52.9, 53.4, 64.9, 65.5, 126.6, 151.1, 162.8, 170.0; HR-FABMS m/z 567.2564 $(M+H)^+$ (calcd for $C_{28}H_{43}N_2O_6S_2$: 567.2563). Anal. Calcd for $C_{28}H_{43}N_2O_6S_2$: C, 59.3; H, 7.5; N, 4.9. Found: C, 59.3; H, 7.3; N, 5.0.

5.6.11. *N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-cyclohexylethylfumaramide 1j. Cyclohexylethylfumaric acid (0.50 g, 2.21 mmol) was treated following general procedure 2 to produce a beige foam, which was chromatographed [SiO_2, ethyl acetate/hexane (1:1)] to give **1j** (0.91 g, 66%) as an orange syrup; $[\alpha]_D$ = −154 (c 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 2925, 1684, 1337, 1135; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.26–1.54 (10H, m), 1.60–1.74 (7H, m), 1.89–1.98 (6H, m), 2.04–2.17 (4H, m), 2.72 (1H, dt, J = 4.4, 12.0, CH$_2$CHHC=C), 2.85 (1H, dt, J = 5.2, 12.4, CH$_2$CHHC=C), 3.38–3.52 (4H, m, 2 × CH_2SO$_2$), 3.93 (1H, dd, J = 4.8, 7.2, CHN), 4.02 (1H, app t, J = 6.4, CHN), 6.87 (1H, s, CH=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 19.9, 20.8, 21.0, 26.3, 26.5 (×2), 26.6, 27.6, 32.8, 33.0 (×2), 35.5, 38.0, 38.2, 38.5, 44.7, 44.9, 47.8, 48.3, 48.5, 52.9, 53.4, 64.8, 65.4, 124.9, 152.6, 162.7, 170.0; HR-FABMS m/z 621.3033 $(M+H)^+$ (calcd for $C_{32}H_{49}N_2O_6S_2$: 621.3032).

5.7. General procedure for the hydrogenation of 2-substituted fumaramides

A solution of the fumaramide (1 equiv) in dry toluene (60 mL) containing 10% Pd/C (0.12 equiv) was shaken under 7 bar H_2 at 25 °C using a Baskerville hydrogenator. The mixture was then filtered through Celite and the solvent removed in vacuo to give a mixture of diastereoisomers, which were separated by column chromatography.

5.7.1. (2*S*)-2a and (2*R*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-methylsuccinamide 3a. *N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-methylfumaramide **1a** (1.00 g, 1.90 mmol) was hydrogenated overnight as above and the resultant mixture chromatographed [SiO_2, ethyl acetate/hexane (1:1)] to produce **2a** (0.94 g, 94%) and **3a** (0.06 g, 6%) as white plates.

Compound **2a** (major): mp 200–202 °C; $[\alpha]_D$ = −119 (c 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 2958, 1684, 1331, 1163; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, s, CH_3), 0.98 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.18 (3H, d, J = 6.8, CH_3CH), 1.31–1.44 (4H,

m), 1.84–1.93 (6H, m), 1.95–2.13 (4H, m), 2.92 (1H, dd, $J = 4.7$, 17.3, CHHCHC=O), 3.23 (1H, dd, $J = 9.4$, 17.3, CHHCHC=O), 3.39–3.55 (5H, m, $2\times$ CH_2SO_2, $CH_2CHC{=}O$), 3.84 (1H, dd, $J = 5.2$, 7.5, CHN), 3.90 (1H, dd, $J = 5.0$, 7.7, CHN); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 19.9, 20.0, 20.5, 20.8, 26.4, 26.5, 32.7, 32.8, 35.7, 37.9, 38.2, 40.4, 44.6 (×2), 47.7 (×2), 48.5 (×2), 52.8, 53.0, 65.0, 65.2, 169.5, 174.7; HR-FABMS *m/z* 527.2222 $(M+H)^+$ (calcd for $C_{25}H_{39}N_2O_6S_2$: 527.2250). Anal. Calcd for $C_{25}H_{38}N_2O_6S_2$: C, 56.9; H, 7.3; N, 5.3. Found: C, 56.8; H, 7.2; N, 5.3.

Compound **3a** (minor): mp 218–220 °C; $[\alpha]_D = -75$ (*c* 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 2960, 1685, 1327, 1165; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, s, C*H*$_3$), 0.97 (3H, s, C*H*$_3$), 1.15 (3H, s, C*H*$_3$), 1.16 (3H, s, C*H*$_3$), 1.29 (3H, d, $J = 7.1$, C*H*$_3$CH), 1.33–1.42 (4H, m), 1.79–1.94 (6H, m), 2.05–2.18 (4H, m), 2.78 (1H, dd, $J = 4.1$, 17.2, CH*H*CHC=O), 3.38–3.56 (6H, m, $2\times$ C*H*$_2$SO$_2$, CH$_2$C*H*C=O, CH*H*CHC=O), 3.86 (1H, dd, $J = 5.1$, 7.7, C*H*N), 3.95 (1H, app t, $J = 6.4$, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 19.8, 20.8 (×2), 26.4 (×2), 32.7, 32.8, 36.1, 38.1, 38.4, 44.6 (×2), 47.7, 48.3, 48.5, 52.8, 52.9, 65.1, 65.2, 169.3, 174.2; HR-FABMS *m/z* 527.2248 $(M+H)^+$ (calcd for $C_{25}H_{39}N_2O_6S_2$ 527.2250).

5.7.2. (2*R*)-5a and (2*S*)-*N*,*N*′-Bis[(2*S*)-bornane-10,2-sultam]-2-methylsuccinamide 5b. *N*,*N*′-Bis[(2*S*)-bornane-10,2-sultam]-2-methylfumaramide (1.00 g, 1.90 mmol) was hydrogenated overnight as above and the resultant mixture chromatographed [SiO_2, ethyl acetate/hexane (1:1)] to produce **5a** (0.70 g, 70%) and **5b** (0.03, 3%) as white plates.

Compound **5a** (major): mp 202–203 °C; $[\alpha]_D = +119$ (c 1.18, $CHCl_3$). Spectral data were identical to enantiomer **2a**.

Compound **5b** (minor): mp 218–219 °C; $[\alpha]_D = +75$ (*c* 1.18, $CHCl_3$). Spectral data were identical to enantiomer **3a**.

5.7.3. (2*S*)-2b and (2*R*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-ethylsuccinamide 3b.[4] *N*,*N*′-Bis[(2*S*)-bornane-10,2-sultam]-2-ethylfumaramide **1b** (0.35 g, 0.65 mmol) was hydrogenated overnight as above and the resultant mixture chromatographed [SiO_2, ethyl acetate/hexane (1:1)] to produce **2b** (0.27 g, 77%) and **3b** (0.01, 3%) as white plates.

Compound **2b** (major): mp 114–117 °C (lit.[4] 115–117 °C); $[\alpha]_D = -103$ (*c* 1.2, EtOAc) [lit.[4] −104 (*c* 1.2, EtOAc)].

Compound **3b** (minor): $[\alpha]_D = -98$ (*c* 1.2, EtOAc) [lit.[4] −98 (*c* 1.2, EtOAc)].

5.7.4. (2*S*)-2c and (2*R*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-propylsuccinamide 3c.[4] *N*,*N*′-Bis[(2*S*)-bornane-10,2-sultam]-2-propylfumaramide **1c** (0.45 g, 0.81 mmol) was hydrogenated overnight as above and the resultant mixture chromatographed [SiO_2, ethyl acetate/hexane (1:1)] to produce **2c** (0.36 g, 81%) and **3c** (0.01, 3%) as white plates.

Compound **2c** (major): mp 188–190 °C (lit.[4] 187–189 °C); $[\alpha]_D$ −90 (*c* 1.0, EtOAc) [lit.[4] −88 (*c* 1.0, EtOAc)].

Compound **3c** (minor): $[\alpha]_D$ −96 (*c* 1.0, EtOAc) [lit.[4] −90 (*c* 1.0, EtOAc)].

5.7.5. (2*S*)-2d and (2*R*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-hexylsuccinamide 3d.[4] *N*,*N*′-Bis[(2*S*)-bornane-10,2-sultam]-2-hexylfumaramide **1d** (0.37 g, 0.62 mmol) was hydrogenated over 2 d as above and the resultant mixture chromatographed [SiO_2, ethyl acetate/hexane (1:1)] to produce **2d** (0.35 g, 94%) and **3d** (0.02, 6%) as white plates.

Compound **2d** (major): mp 80–82 °C (lit.[4] 76–78 °C); $[\alpha]_D = -68$ (*c* 1.0, EtOAc) [lit.[4] −66 (*c* 1.0, EtOAc)].

Compound **3d** (minor): $[\alpha]_D = -64$ (*c* 1.0, EtOAc) [lit.[4] −60 (*c* 1.0, EtOAc)].

5.7.6. (2*S*)-2e and (2*R*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-octylsuccinamide 3e.[4] *N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-octylfumaramide **1e** (0.22 g, 0.35 mmol) was hydrogenated over 7 d as above and the resultant mixture chromatographed [SiO_2, ethyl acetate/hexane (1:1)] to produce **2e** (0.18 g, 81%) as white plates and **3e** (0.01, 3%) as a colourless oil.

Compound **2e** (major): $[\alpha]_D = -68$ (*c* 1.0, EtOAc) [lit.[4] −66 (*c* 1.0, EtOAc)]. New data: mp 164–166 °C.

Compound **3e** (minor): $[\alpha]_D = -73$ (*c* 1.2, EtOAc) [lit.[4] −76 (*c* 1.2, EtOAc)].

5.7.7. (2*S*)-2f and (2*R*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-phenylethylsuccinamide 3f. *N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-phenylethylfumaramide **1f** (0.20 g, 0.33 mmol) was hydrogenated overnight as above and the resultant mixture chromatographed [SiO_2, ethyl acetate/hexane (1:2)] to produce **2f** (0.18 g, 86%) and **3f** (0.02 g, 10%) as white plates.

Compound **2f** (major): mp 154–155 °C; $[\alpha]_D = -80$ (*c* 1.18, $CHCl_3$); (Found: C, 62.3; H, 7.2; N, 4.6; $C_{32}H_{44}N_2O_6S_2$ requires C, 62.3; H, 7.2; N, 4.5); IR (KBr, cm^{-1}) 2963, 1688, 1329, 1163; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, s, C*H*$_3$), 0.90 (3H, s, C*H*$_3$), 1.07 (3H, s, C*H*$_3$), 1.18 (3H, s, C*H*$_3$), 1.24–1.38 (4H, m), 1.69–2.14 (12H, m), 2.52–2.67 (2H, m, C*H*$_2$Ar), 2.99 (1H, dd, $J = 5.2$, 17.0, CH*H*C=O), 3.13 (1H, dd, $J = 8.3$, 17.0, CH*H*C=O), 3.32–3.45 (5H, m, $2\times$ C*H*$_2$SO$_2$, C*H*C=O), 3.77 (1H, dd, $J = 5.2$, 7.2, C*H*N), 3.84 (1H, dd, $J = 4.8$, 7.2, C*H*N), 7.06–7.13 (3H, m, Ar), 7.16–7.19 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.0, 20.5, 20.8, 26.4 (×2), 32.7 (×2), 32.9, 33.3, 38.0 (×2), 38.2, 41.1, 44.6, 47.7 (×2), 48.5 (×2), 52.8, 53.0, 62.8, 65.1, 65.2, 125.8, 128.2, 128.4, 141.4, 169.5, 173.5; HR-EIMS *m/z*

616.2639 M^+ (calcd for $C_{32}H_{44}N_2O_6S_2$: 616.2641). Anal. Calcd for $C_{32}H_{44}N_2O_6S_2$: C, 62.3; H, 7.2; N, 4.5. Found: C, 62.3; H, 7.2; N, 4.6.

Compound **3f** (minor): $[\alpha]_D = -44$ (*c* 1.18, $CHCl_3$); IR (KBr, cm^{-1}) 2971, 1688, 1329, 1163; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (6H, s, $2\times CH_3$), 1.08 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.16–1.35 (4H, m), 1.76–1.90 (7H, m), 1.95–2.11 (5H, m), 2.57 (2H, t, $J = 8.4$, CH_2Ar), 2.88 (1H, dd, $J = 5.0$, 17.0, CHHC=O), 3.24–3.43 (6H, m, $2\times CH_2SO_2$, CHHC=O, CHC=O), 3.78 (1H, dd, $J = 5.2$, 7.6, CHN), 3.85 (1H, app t, $J = 6.4$, CHN), 7.07–7.09 (3H, m, Ar), 7.15–7.18 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.9, 26.4 (×2), 32.8, 32.9, 33.0, 34.3, 35.9, 38.4, 38.6, 41.3, 44.6, 47.7, 48.4, 48.5, 52.9, 53.0, 65.3, 125.9, 128.4 (×2), 141.3, 169.4, 173.3; HR-EIMS *m/z* 616.2643 M^+ (calcd for $C_{32}H_{44}N_2O_6S_2$: 616.2641).

5.7.8. (2*S*)-2g and (2*R*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-isopentylsuccinamide 3g. *N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-isopentylfumaramide **1g** (0.35 g, 0.60 mmol) was hydrogenated overnight as above and the resultant mixture chromatographed [SiO_2, ethyl acetate/hexane (1:1)] to produce **2g** (0.30 g, 84%) as white plates and **3g** (0.02, 6%) as a colourless oil.

Compound **2g** (major): mp 102–104 °C; $[\alpha]_D = -94$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2959, 1691, 1331, 1135; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85–0.87 (6H, m, $(CH_3)_2CH$), 0.95 (3H, s, CH_3), 0.96 (3H, s, CH_3), 1.14 (3H, s, CH_3), 1.16–1.56 (12H, m), 1.81–1.88 (6H, m), 1.93–2.15 (4H, m), 2.98 (1H, dd, $J = 4.8$, 17.2, CHHC=O), 3.13 (1H, dd, $J = 8.4$, 17.2, CHHC=O), 3.33–3.51 (5H, m, $2\times CH_2SO_2$, CHC=O), 3.84 (1H, dd, $J = 5.2$, 7.6, CHN), 3.90 (1H, dd, $J = 5.2$, 7.6, CHN); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 20.0, 20.5, 20.8, 22.3, 22.4, 26.4 (×2), 28.0, 28.8, 32.7, 32.8, 35.9, 38.0, 38.1, 38.2, 41.4, 44.6, 47.7 (×2), 48.4, 48.5, 52.8, 53.0, 65.1, 65.2, 169.7, 173.9; HR-CIMS *m/z* 583.2873 $(M+H)^+$ (calcd for $C_{29}H_{47}N_2O_6S_2$: 583.2876).

Compound **3g** (minor): $[\alpha]_D = -86$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2959, 1691, 1331, 1135; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83–0.86 (6H, m, $(CH_3)_2CH$), 0.96 (3H, s, CH_3), 0.97 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.18–1.51 (7H, m), 1.52–1.79 (2H, m), 1.85–1.93 (6H, m), 2.05–2.18 (4H, m), 2.84 (1H, dd, $J = 4.4$, 17.2, CHHC=O), 3.31 (1H, dd, $J = 9.2$, 17.2, CHHC=O), 3.37–3.52 (5H, m, $2\times CH_2SO_2$, CHC=O), 3.86 (1H, dd, $J = 5.2$, 7.6, CHN), 3.94 (1H, app t, $J = 6.4$, CHN); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.7, 20.9, 22.3, 22.4, 26.4, 28.0, 30.3, 32.7, 32.9, 35.4, 36.0, 38.4, 38.5, 41.4, 44.6, 47.7 (×2), 48.3, 48.4, 52.9, 53.0, 65.2, 65.3, 169.6, 173.7; HR-CIMS *m/z* 583.2874 $(M+H)^+$ (calcd for $C_{29}H_{47}N_2O_6S_2$: 583.2876).

5.7.9. (2*S*)-Methylbutane-1,4-diol 4a.[9] This was prepared using the succinamide mixture **2a** and **3a** in 91% yield on a 1.44 mmol scale by the method of Reid et al.[4] and gave $[\alpha]_D = -11.4$ (*c* 0.7, MeOH) [lit.[9] −13.4, (*c* 0.7, MeOH)]; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, d, $J = 6.9$, CH_3CH), 1.55–1.67 (2H, m, OCH_2CH_2), 1.78–1.86 (1H, m, CH), 2.71 (2H, br s, $2\times OH$), 3.42–3.47 (1H, m, CHCHHOH), 3.51 (1H, dd, $J = 7.4$, 10.4, CHCHHOH), 3.64–3.81 (2H, m, $CHCH_2OH$).

5.7.10. (2*S*)-Ethylbutane-1,4-diol 4b.[10] This was prepared using the succinamide mixture **2b** and **3b** in 68% yield on a 1.50 mmol scale by the method of Reid et al.[4] and gave $[\alpha]_D = -0.6$ (*c* 3.5, MeOH) [lit.[10] −0.6, (*c* 3.76, MeOH)]; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, $J = 7.4$, CH_3CH_2), 1.23–1.38 (2H, m, CH_3CH_2), 1.50–1.59 (2H, m, CH_2CH_2OH), 1.62–1.70 (1H, m, $CHCH_2$), 3.42–3.46 (1H, dd, $J = 6.9$, 10.8, CHCHHOH), 3.58–3.63 (2H, m, CH_2CH_2OH), 3.71–3.76 (1H, m, CHCHH OH).

5.7.11. (2*S*)-Propylbutane-1,4-diol 4c.[10] This was prepared using the succinamide mixture **2c** and **3c** in 87% yield on a 1.33 mmol scale by the method of Reid et al.[4] and gave $[\alpha]_D = -2.7$ (*c* 3.0, MeOH) [lit.[10] −3.1, (*c* 3.18, MeOH)]; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, $J = 6.9$, CH_3CH_2), 1.19–1.37 (4H, m, $CH_3CH_2H_2$), 1.54–1.72 (3H, m, $CHCH_2CH_2O$), 3.03 (2H, br s, $2\times OH$), 3.45 (1H, dd, $J = 7.0$, 10.7, CHCHHOH), 3.61–3.67 (2H, m, CH_2CH_2OH), 3.72–3.79 (1H, m, CHCHHOH).

5.7.12. (2*S*)-Hexylbutane-1,4-diol 4d.[4] This was prepared using the succinamide mixture **2d** and **3d** in 68% yield on a 0.60 mmol scale by the method of Reid et al.[4] and gave $[\alpha]_D = -2.0$ (*c* 1.0, EtOAc) [lit.[4] for enant. +2, (*c* 1.0, EtOAc)]; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, $J = 5.6$, CH_3CH_2), 1.25 (10H, app br s), 1.50–1.57 (3H, m, $CHCH_2CH_2OH$), 3.39–3.43 (1H, dd, $J = 7.0$, 10.6, CHCHHOH), 3.57–3.66 (2H, m, CH_2CH_2OH), 3.70–3.75 (1H, m, CHCHHOH).

5.7.13. (2*S*)-Octylbutane-1,4-diol 4e.[4] This was prepared using the succinamide mixture **2e** and **3e** in 58% yield on a 1.00 mmol scale by the method of Reid et al.[4] and gave $[\alpha]_D = -0.8$ (*c* 0.2, EtOH) [lit.[4] +0.5, (*c* 0.2, EtOH)]; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.6$, CH_3CH_2), 1.25–1.30 (15H, m), 1.51–1.72 (2H, m, CH_2CH_2OH), 3.44 (1H, dd, $J = 7.0$, 10.7, CHCHHOH), 3.59–3.64 (2H, m, CH_2CH_2OH), 3.73–3.78 (1H, m, CHCHHOH).

5.7.14. (2*R*)-Methylbutane-1,4-diol 6.[11] This was prepared using (2*R*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-methyl-succinamide **5** in 74% yield on a 2.27 mmol scale by the method of Reid et al.[4] and gave $[\alpha]_D = +14$ (*c* 1.0, MeOH) [lit.[14] +13.2 (*c* 1.0, MeOH)]. Spectral data were identical to enantiomer **4a**.

5.7.15. (2*R*)-Methyl-1,4-bis[(methoxysulfonyloxy)]butane 7.[12] This was prepared in 79% yield on a 4.61 mmol scale by the method of Feringa et al.[12] ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, d, $J = 6.8$, CH_3CH), 1.64–1.72 (1H, m, $CHHCH_2O$), 1.90–1.98 (1H, m, $CHHCH_2O$), 2.08–2.16 (1H, m, $CHCH_3$), 3.02 (6H, s, $2\times CH_3S$), 4.07–4.16 (2H, m, $CHCH_2O$), 4.25–4.36 (2H, m, CH_2CH_2O).

5.7.16. (*R*)-3-Methyl-*N*-(2-phenylethyl)-pyrrolidine 8.[5] This was prepared in 67% yield on a 4.15 mmol scale by the method of Zheng et al.[5] and gave $[\alpha]_D = -2.0$ (*c* 1.0, EtOH) [lit.[5] −1.87 (*c* 1.0, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, d, $J = 6.8$, 6-CH_3), 1.26–1.36 (1H, m, 3-CH), 1.95–2.04 (2H, m, 4-CH_2), 2.15–2.26 (1H, m, 5-CHH), 2.42–2.48 (1H, m, 5-CHH), 2.57–2.78 (5H, m, 2′-CH_2, 1′-CH_2, 2-CHH), 2.83–2.87 (1H, m, 2-CHH), 7.07–7.22 (5H, m, Ar); HR-CIMS *m*/*z* 190.1597 $(M+H)^+$ (calcd for $C_{13}H_{19}N$: 190.1596).

5.7.17. (*R*)-3-Methyl-*N*-(3-methylbutyl)-pyrrolidine 9.[5] This was prepared in 71% yield on a 7.30 mmol scale by the method of Zheng et al.[5] and gave $[\alpha]_D = -2.0$ (*c* 1.0, EtOH) [lit.[5] −1.8 (*c* 1.0, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (6H, d, $J = 6.4$, 4′- and 5′-CH_3), 1.02 (3H, d, $J = 6.8$, 6-CH_3), 1.09–1.44 (3H, m, 3′-CH, 2′-CH_2), 1.49–1.63 (1H, m, 3-C*H*), 1.93–2.05 (2H, m, 4-CH_2), 2.20–2.29 (1H, m, 5-CH*H*), 2.33–2.47 (3H, m, 5-CH*H*, 1′-CH_2), 2.66–2.71 (1H, m, 2-CH_2), 2.83 (1H, dd, $J = 7.6$, 8.8, 2-CH_2); HR-CIMS *m*/*z* 156.1749 $(M+H)^+$ (calcd for $C_{10}H_{21}N$: 156.1752).

5.7.18. (3*R*,2′*S*)-3-Methyl-*N*-(2-methylbutyl)-pyrrolidine 10.[5] This was prepared in 64% yield on a 5.76 mmol scale by the method of Zheng et al.[5] and gave $[\alpha]_D = +22$ (*c* 1.0, EtOH) [lit.[5] +17.5 (*c* 0.94, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83–0.91 (6H, m, 4′- and 5′-CH_3), 1.01 (3H, d, $J = 6.8$, 6-CH_3), 1.26–1.31 (2H, m, 3-C*H*, 3′-CH*H*), 1.50–1.55 (2H, m, 3′-CH*H*, 2′-C*H*), 1.92–2.03 (2H, m, 4-CH_2), 2.18–2.27 (3H, m, 5-CH_2, 1′-CH*H*), 2.32–2.38 (1H, m, 1′-CH*H*), 2.61–2.67 (1H, m, 2-CH*H*), 2.76 (1H, dd, $J = 7.6$, 8.8, 2-CH*H*); HR-CIMS *m*/*z* 155.1677 (M^+) (calcd for $C_{10}H_{21}N$: 155.1674).

5.8. General procedure for the conversion of 2-substituted butane-1,4-diols into Mosher diesters

A mixture of diol (~20 mg), (*R*)- or (*S*)-Mosher acid (2.5 equiv) and DMAP (1 equiv) in dry DCM (2 mL) was placed under N_2. EDCI (5 equiv) was added and the mixture was stirred at room temperature over 24 h, quenched using 5% citric acid (2 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with sodium hydrogen carbonate (10 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo.

5.9. X-ray structure analyses for compounds 1b and 2b

Data were collected on an Enraf-Nonius KappaCCD diffractometer, running under Nonius Collect software, and using graphite monochromated X-radiation ($\lambda = 0.71073$ Å). Data sets were collected at temperatures of 150 and 100 K, respectively, for **1b** and **2b**. Typically scan angles of 1–2° were used, with integration times of 50–100 s per image. Precise unit cell dimensions were determined by post-refinement of the setting angles of a large proportion of the data set. The frame images were integrated using Denzo(SMN)[13] and the resultant raw intensity files processed using a locally modified version of DENZOX.[14] Absorption corrections, either by gaussian quadrature,[15] based on the measured crystal faces, or by a semi-empirical correction[16] were applied to the data sets. Data were then sorted and merged using SORTAV,[17] and structures were solved by direct methods (SIR92).[18] Solvent molecules were present, water in the case of **1b**, and ethanol for **2b**. Refinement with SHELXL97–2[19] using full-matrix least-squares on F^2 and all the unique data converged without problems for both structures. All non-H atoms were allowed anisotropic thermal motion. Aliphatic C–H hydrogen atoms were included at calculated positions, with C–H = 0.96 Å, and were refined with a riding model and with U_{iso} set to 1.2 times that of the attached C-atom. Absolute configurations were confirmed by the refinement of the Flack absolute structure parameter, which refined to zero within error. Thermal ellipsoid plots were obtained using the program ORTEP-3 for Windows[20] All calculations were carried out using the WinGX package[21,22] of crystallographic programs.

Crystallographic data (excluding structure factors) for both structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 250740 and 250741. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44-(0)1223–336033 or email: deposit@ccdc.cam.ac.uk].

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