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Diastereoselective conjugate addition of Grignard reagents to a homochiral fumaramide derived from Oppolzer's sultam

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Dedicated to Professor David Crout, University of Warwick, UK, to mark the occasion of his retirement

Abstract—Conjugate addition of Grignard reagents to *N*,*N*′-fumaroylbis[(2*R*)-bornane-10,2-sultam] **1** occurred with moderate to high levels of diastereoselectivity. Diastereomeric excesses were estimated by analysis of the ^{1}H NMR spectra of the succinamide mixtures and enantiomeric excesses from ^{19}F NMR spectra of the bis Mosher esters of the diols produced by reductive cleavage of the succinamides. Saponification of the succinamides gave the corresponding (*R*)-succinic acids with ees up to 92% showing that addition of the Grignard reagents takes place selectively on the *re*-face of **1**.

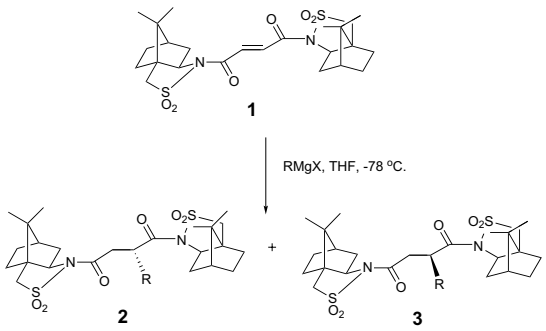
1. Introduction

Asymmetric conjugate addition reactions to α,β-unsaturated organic compounds are one of the most useful methods for producing β-substituted products stereoselectively.[1] The introduction of chirality using a chiral auxiliary is a useful way of producing a wide variety of optically active organic compounds. Oppolzer et al. reported the diastereoselective conjugate addition of Grignard reagents to *N*-enoylsultams.[2] *N*,*N*′-Fumaroylbis[(2*R*)-bornane-10,2-sultam] **1**,[3] is readily available from Oppolzer's (2*R*)-bornane-10,2-sultam.[4] The C_2 symmetrical fumaramide **1** containing two of Oppolzer's camphorsultam moieties has previously been used in cycloaddition and dihydroxylation reactions.[3,5,6] However no examples of conjugate additions to **1** have been reported.

We report the diastereoselective conjugate addition of a series of Grignard reagents to fumaramide **1**. It was intended to hydrolyse the succinamide products **2** and **3** to yield the corresponding enantiomerically enriched substituted succinic acids. Substituted succinic acids **6** are important intermediates in organic synthesis. They are building blocks for the synthesis of enantiomerically pure β-substituted β-amino acids.[7] They also have a role as structural components of natural products.[8]

2. Results and discussion

The fumaramide **1** was prepared from fumaroyl chloride and commercially available (2*R*)-(−)-2,10-camphorsultam.[3] We first established that 3.5 equiv of Grignard reagents were required for successful conjugate addition. Using these conditions the fumaramide **1** was treated with a series of Grignard reagents derived from alkyl bromides and chlorides to produce a mixture of diastereomers **2** and **3** (Scheme 1 and Table 1). The extent of diastereofacial differentiation was determined in all cases except for the benzyl derivative **19** by analysis of the ^{1}H NMR spectra of the crude reaction mixtures. The ABX system of the succinamide protons resonated at different chemical shifts for each pair of diastereomers (except for the benzylsuccinamide). The ABX system of the major diastereomer was consistently at a lower



Scheme 1.

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Table 1. Conjugate addition to fumaramide **1**

Entry	RMgX	Isolated yield (%)	Dr[a] (major/minor)	De (%)
1	R = ethyl	76	81:19 (**7/8**)	62
2	R = isopropyl	89	66:34 (**9/10**)	32
3	R = propyl	69	68:32 (**11/12**)	36
4	R = butyl	76	77:23 (**13/14**)	54
5	R = cyclohexyl	87	66:34 (**15/16**)	34
6	R = octyl	62	76:24 (**17/18**)	52
7	R = benzyl	78	N/A (**19**)	N/A
8	R = isobutyl	87	72:28 (**20/21**)	44
9	R = hexyl	80	76:24 (**22/23**)	53
10	R = cyclohexyl methyl	75	69:31 (**24/25**)	38

[a] Diastereomeric ratios were determined by ^{1}H 400 MHz NMR spectra of the crude reaction mixtures.

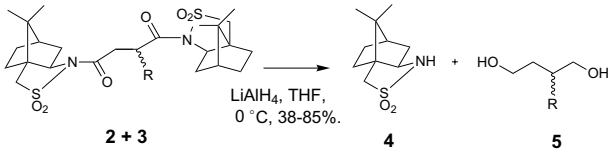
δ value than the minor diastereomer. Integration of the signals gave an estimate of the diastereomeric excess. The moderate diastereoselectivity observed did permit the separation and characterisation of individual diastereomers **2**, **3** (except for benzyl derivative **19**). The methyl, phenyl and allyl Grignard reagents reacted with **1** to produce the direct 1,2-addition products. Oppolzer et al. observed the same result with the methyl Grignard reagent on *N*-enoylsultams.[2]

The number of equivalents of Grignard reagent appears to have a considerable effect on the reaction outcome. This is due to the importance of chelation by magnesium as discussed by Oppolzer et al.[2] More than 3 equiv of Grignard reagent are required to effect the addition to fumaramide **1**. One is required for chelation to the O atoms of the C=O and SO_2 groups at each end and the C=O adopts a *cis*-conformation with the C=C. This forces the camphor rings to block the *si*-face. The third equivalent then delivers its alkyl group in a 1,4-manner from the *re*-face and the addition proceeds via a six-membered cyclic mechanism.[2] There was no difference in the reactivity of Grignard reagents prepared from alkyl bromides or chlorides.

If chelation of the magnesium does not occur, comparative semi-empirical PM3 and ab initio STO 3 21G calculations suggest that at 193 K four conformations of **1** can exist.[9] There are two symmetrical and two unsymmetrical species with the symmetrical conformations making up 96% and the nonsymmetrical conformations 4% of the total. The initial diastereomeric excesses estimated from ^{1}H NMR spectra of compounds **2** and **3** showed moderate diastereoselectivity. The existence of these other conformations could explain the moderate values obtained.

In order to confirm the results obtained from the NMR spectra of the products from the conjugate addition we decided to make the 2-substituted diols **5** by reduction of the succinamides with lithium aluminium hydride (Scheme 2). This reaction produced the diols **5** and camphorsultam **4**, which were separated by column chromatography. The camphorsultam **4** was recovered in 90–95% yield and showed no loss of enantiomeric excess. The absolute configuration of each of the diols **26**, **27**, **28** and **30** was determined to be (*R*) by comparison of the specific rotations with those reported in the literature. This agrees with the postulated model system with attack on the *re*-face of **1**.

A more accurate method than specific rotations was desirable for determining the enantiomeric excesses of the diols produced. GC on chiral columns was not possible as the diols were not volatile enough. Attempts



Scheme 2.

Table 2. Reduction of succinamides **2+3** yielding diols **5**

Entry	2-Substituted diol	Isolated yield (%)	Ee (%)[a]	Configuration[b]
1	Ethyl (**26**)	44	73	(*R*)[11]
2	Isopropyl (**27**)	43	29	(*R*)[12]
3	Propyl (**28**)	46	36	(*R*)[12]
4	Butyl (**29**)	56	56	
5	Cyclohexyl (**30**)	38	33	(*R*)[c]
6	Octyl (**31**)	79	54	
7	Benzyl (**32**)	75	90	
8	Isobutyl (**33**)	85	50	
9	Hexyl (**34**)	75	60	

[a] Enantiomeric excesses were determined by synthesis of both (*R*)- and (*S*)-bis Mosher's esters of each diol and were analysed by ^{19}F NMR spectra.
[b] Compared with specific rotations reported in the literature.
[c] (*S*) previously reported with opposite sign.[13]

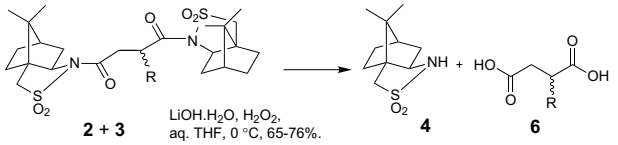
Table 3. Saponification of succinamides **2+3** yielding 2-substituted succinic acids **6**

Entry	2-Substituted diacid	Isolated yield (%)	Ee (%)[a]	Configuration
1	Ethyl	65	63	(*R*)[14]
2	Propyl	71	52[b]	(*R*)[15]
3	Butyl	67	72[b]	(*R*)[16]
4	Benzyl	71	92[c]	(*R*)[17]
5	Hexyl	65	37	(*R*)[18]

[a] Enantiomeric excesses were determined by chiral HPLC of dianilide derived from diacid.
[b] Not resolved by chiral HPLC, % ee based on specific rotation of substituted succinic acid compared with literature value.
[c] Diacid converted into dimethyl ester.

to trifluoroacetylate the diols resulted in mainly mono-trifluoroacetate products in crude mixtures that could not be purified. In another approach racemic 2-methylbutane-1,4-diol was converted into the dibenzoate[10] but this could not be resolved on the chiral HPLC columns available. Synthesis of the (*R*)- and (*S*)-bis Mosher esters of the substituted diols **5** was carried out. Integration of the fluorine signals in the ^{19}F NMR spectra allowed us to determine the enantiomeric excesses of the diols (Table 2). The results obtained were generally in good agreement with the results from the ^{1}H NMR studies on the initial conjugate addition.

Saponification of some of the succinamide products **2** and **3** yielded the corresponding enantiomerically enriched substituted succinic acids **6** (Scheme 3 and Table 3). Their absolute configuration was confirmed as (*R*) by comparison of the specific rotations with those reported in the literature.



Scheme 3.

3. Conclusion

We have developed methodology for the preparation of a range of substituted butane-1,4-diols and substituted succinic acids in moderate enantiomeric excess apart from (2*R*)-benzylsuccinic acid, which was obtained in high 92% ee. (2*R*)-Benzylsuccinic acid has been shown to be an inhibitor of carboxypeptidase A.[19]

4. Experimental

4.1. 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 and 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 residual chloroform ($\delta_H = 7.27$) and ($\delta_C = 77.2$) as internal standards unless otherwise stated. All coupling constants are reported in hertz (Hz). Infrared spectra were recorded on either a Nicolet Impact 410 FT-IR or Perkin Elmer 500 spectrometer. 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, permanganate, or vanillin 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}.

4.2. *N,N′*-Bis[(2*R*)-bornane-10,2-sultam]fumaramide 1[3]

This was prepared in 81% yield on a 3.34 mmol scale by the method of Bauer et al.[3] and gave mp 246 °C (lit.[3] 247–248 °C); $[\alpha]_D = -133.5$ (*c* 1.18, $CHCl_3$) [lit.[3] −135.6 (*c* 1.18, $CHCl_3$)].

4.3. General procedure for the 1,4-addition of Grignard reagents to *N,N′*-bis[(2*R*)-bornane-10,2-sultam]fumaramides 1 (Table 1)

The Grignard reagent (3.5 equiv) in diethyl ether was added dropwise to a stirred solution of *N,N′*-bis[(2*R*)-bornane-10,2-sultam]fumaramide **1** (1 equiv) in dry THF under N_2 at −78 °C. After 3 h at −78 °C the reaction mixture was quenched with satd aq NH_4Cl soln and then poured onto satd aq NH_4Cl soln. The product was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure.

4.3.1. (2*R*)-7 and (2*S*)-*N,N′*-Bis[(2*R*)-bornane-10,2-sultam]-2-ethylsuccinamide 8. Ethyl magnesium bromide (7.0 mL of a 2 M solution in Et_2O, 14 mmol) was added dropwise to *N,N′*-bis[(2*R*)-bornane-10,2-sultam]fumaramide **1** (2.0 g, 4.0 mmol) in dry THF (20 mL) as above to produce a residue, which was chromatographed

[SiO_2, EtOAc–hexane (1:1)] to give (2*R*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-ethylsuccinamide **7** (1.0 g, 56%) and (2*S*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-ethylsuccinamide **8** (0.35 g, 17%) as plates.

7 (Major): mp 196–199 °C; $[\alpha]_D = -98$ (*c* 1.2, EtOAc); IR (KBr, cm^{-1}) 2965, 1687, 1330, 1164; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93–0.96 (9H, m, 2×CH_3 and CH_3CH_2), 1.13, 1.15 (3H, s, CH_3), 1.24–1.42 (4H, m), 1.61–1.70 (1H, m), 1.78–1.98 (8H, m), 2.05–2.18 (3H, m), 2.85 (1H, dd, *J* = 4.4 and 17.0, CH*H*CHC=O), 3.31 (1H, dd, *J* = 9.0 and 17.0, CH*H*CHC=O), 3.40–3.49 (5H, m, 2×CH_2SO_2 and CH_2CHC=O), 3.86 (1H, t, *J* = 8.0, C*H*N), 3.95 (1H, t, *J* = 6.3, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 20.3 (×2), 21.2, 21.3, 26.0, 26.8 (×2), 33.2, 33.3, 36.0, 38.8, 39.0, 42.7, 45.0, 45.1, 48.1 (×2), 48.7, 48.9, 53.3, 53.4, 65.6, 65.7, 170.0, 174.0; HR-EIMS *m*/*z* 540.2329 (M^+) (calcd for $C_{26}H_{40}N_2O_6S_2$: 540.2328). Anal. Calcd for $C_{26}H_{40}N_2O_6S_2$: C, 57.75; H, 7.5; N, 5.2. Found: C, 57.5; H, 7.4; N, 5.1%.

8 (Minor): mp 115–117 °C; $[\alpha]_D = -104$ (*c* 1.2, EtOAc); IR (KBr, cm^{-1}) 2962, 1693, 1333, 1134; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94–0.98 (12H, m, 3×CH_3 and CH_3CH_2), 1.15 (3H, s, CH_3), 1.31–1.44 (4H, m), 1.51–1.58 (1H, m), 1.84–2.16 (11H, m), 3.00 (1H, dd, *J* = 5.0 and 17.0, CH*H*CHC=O), 3.14 (1H, dd, *J* = 8.7 and 17.0, CH*H*CHC=O), 3.35–3.51 (5H, m, 2×CH_2SO_2 and CH_2CHC=O), 3.82–3.92 (2H, m, 2×C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 20.3, 20.4, 21.0, 21.2, 24.5, 26.8, 26.9, 33.2, 33.3, 38.2, 38.4, 38.7, 42.8, 45.0 (×2), 48.1, 48.2, 48.8, 48.9, 53.2, 53.5, 65.5, 65.7, 170.2, 174.2; HR-FABMS *m*/*z* 541.2405 (M^+) (calcd for $C_{26}H_{40}N_2O_6S_2$: 541.2406). Anal. Calcd for $C_{26}H_{40}N_2O_6S_2$: C, 57.75; H, 7.5; N, 5.2. Found: C, 57.6; H, 7.45; N, 5.2%.

4.3.2. (2*R*)-9 and (2*S*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-isopropylsuccinamide 10. Isopropyl magnesium chloride (2.7 mL of a 2 M solution in Et_2O, 5.5 mmol) was added dropwise to *N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]fumaramide **1** (0.8 g, 1.6 mmol) in dry THF (20 mL) as above. A portion of the residue (0.14 g) was chromatographed [SiO_2, EtOAc–hexane (1:1)] to give (2*R*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-isopropylsuccinamide **9** (81 mg, 58%) and (2*S*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-isopropylsuccinamide **10** (43 mg, 31%) as plates.

9 (Major): mp 74–78 °C; $[\alpha]_D = -142$ (*c* 0.7, EtOAc); IR (KBr, cm^{-1}) 2962, 1691, 1330, 1134; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, d, *J* = 7.0, CH_3CHCH_3), 0.92, 0.96 (3H, s, CH_3), 1.02 (3H, d, *J* = 6.8, CH_3CHCH_3), 1.15 (6H, s, 2×CH_3), 1.24–1.42 (4H, m), 1.83–1.89 (6H, m), 2.00–2.18 (4H, m), 2.27–2.31 (1H, m, CH_2CHC=O), 2.80 (1H, dd, *J* = 3.7 and 17.0, CH*H*CHC=O), 3.26 (1H, dd, *J* = 9.6 and 17.0, CH*H*CHC=O), 3.40–3.49 (4H, m, 2×CH_2SO_2), 3.86 (1H, t, *J* = 5.0, C*H*N), 3.95 (1H, t, *J* = 5.4, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 20.3 (×2), 21.2 (×2), 21.3, 26.9 (×2), 30.6, 32.1, 33.2, 33.3, 38.7, 39.1, 45.0 (×2), 47.1, 48.1 (×2), 48.6, 48.9, 53.3, 53.5, 65.7 (×2), 170.3, 173.8; HR-FABMS *m*/*z* 555.2565 (M^+) (calcd for $C_{27}H_{42}N_2O_6S_2$: 555.2563).

10 (Minor): mp 256–258 °C; $[\alpha]_D = -83$ (*c* 0.7, EtOAc); IR (KBr, cm^{-1}) 2965, 1693, 1324, 1137; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92–0.96 (9H, m, CH_3 and 2×CH_3), 1.00–1.02 (3H, m, CH_3), 1.15, 1.26 (3H, s, CH_3), 1.28–1.44 (4H, m), 1.83–1.89 (6H, m), 1.95–2.05 (3H, m), 2.15–2.20 (1H, m), 2.29–2.33 (1H, m, CH_2CHC=O), 2.95 (1H, dd, *J* = 3.9 and 17.0, CH*H*CHC=O), 3.12 (1H, dd, *J* = 10.0 and 17.0, CH*H*CHC=O), 3.31–3.36 (1H, m, CH_2CHC=O), 3.39–3.50 (4H, m, 2×CH_2SO_2), 3.82–3.86 (1H, app t, *J* = 6.3, C*H*N), 3.90–3.92 (1H, app t, *J* = 6.3, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 18.8, 20.3, 20.5, 21.0, 21.3, 21.7, 26.8, 26.9, 28.7, 33.2, 33.3, 34.3, 38.5, 38.7, 45.0, 46.4, 48.1, 48.2, 48.8, 48.9, 53.2, 53.5, 65.6, 65.7, 170.5, 173.8; HR-CIMS (isobutane) *m*/*z* 555.2563 (calcd for $C_{27}H_{42}N_2O_6S_2$: 555.2563). Anal. Calcd for $C_{27}H_{42}N_2O_6S_2$: C, 58.5; H, 7.6; N, 5.05. Found: C, 58.45; H, 7.5; N, 5.0%.

4.3.3. (2*R*)-11 and (2*S*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-propylsuccinamide 12. Propyl magnesium bromide (3.5 mL of a 1 M solution in Et_2O, 3.4 mmol) was added dropwise to *N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]fumaramide **1** (0.5 g, 1.0 mmol) in dry THF (20 mL) as above to produce a residue, which was chromatographed [SiO_2, EtOAc–hexane (1:1)] to give (2*R*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-propylsuccinamide **11** (0.23 g, 43%) and (2*S*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-propylsuccinamide **12** (0.14 g, 26%) as plates.

11 (Major): mp 198–200 °C; $[\alpha]_D = -90$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2960, 1685, 1335, 1133; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.2, CH_2CH_3), 0.96, 0.98 (3H, s, CH_3), 1.16, 1.17 (3H, s, CH_3), 1.31–1.43 (6H, m), 1.55–1.60 (3H, m), 1.73–1.77 (1H, m), 1.86–1.89 (5H, m), 2.07–2.19 (3H, m), 2.86 (1H, dd, *J* = 4.5 and 17.2, CH*H*CHC=O), 3.32 (1H, dd, *J* = 8.9 and 17.2, CH*H*CHC=O), 3.41–3.51 (5H, m, 2×CH_2SO_2 and CH_2CHC=O), 3.87 (1H, t, *J* = 7.4, C*H*N), 3.95 (1H, t, *J* = 6.2, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 19.9 (×2), 19.9, 20.8, 20.9, 26.4 (×2), 32.8, 32.9, 34.5, 36.0, 38.4, 38.6, 41.1, 44.7 (×2), 47.7 (×2), 48.3, 48.5, 52.9, 53.0, 65.2 (×2), 169.6, 173.8; HR-FABMS *m*/*z* 577.2380 $(M+Na)^+$ (calcd for $C_{27}H_{42}N_2O_6S_2Na$: 577.2382). Anal. Calcd for $C_{27}H_{42}N_2O_6S_2$: C, 58.5; H, 7.6; N, 5.05. Found: C, 58.2; H, 7.6; N, 5.0%.

12 (Minor): mp 187–189 °C; $[\alpha]_D = -88$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2960, 1687, 1336, 1136; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.2, CH_2CH_3), 0.95–0.97 (6H, m, 2×CH_3), 1.15, 1.25 (3H, s, CH_3), 1.31–1.51 (7H, m), 1.78–1.93 (7H, m), 1.96–2.16 (4H, m), 3.00 (1H, dd, *J* = 5.2 and 17.0, CH*H*CHC=O), 3.13 (1H, dd, *J* = 8.6 and 17.0, CH*H*CHC=O), 3.39–3.51 (5H, m, 2×CH_2SO_2 and CH_2CHC=O), 3.83–3.86 (1H, app t, *J* = 6.3, C*H*N), 3.88–3.91 (1H, app t, *J* = 6.3, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.3, 20.4, 20.5, 21.0, 21.2, 26.8, 26.9, 33.2 (×2), 33.3, 33.4, 38.5, 38.7, 41.2, 45.0 (×2), 48.1, 48.2, 48.8, 48.9, 53.2, 53.5,

65.5, 65.7, 170.1, 174.4; HR-FABMS m/z 555.2563 $(M+H)^+$ (calcd for $C_{27}H_{42}N_2O_6S_2$: 555.2563). Anal. Calcd for $C_{27}H_{42}N_2O_6S_2$: C, 58.5; H, 7.6; N, 5.05. Found: C, 58.2; H, 7.7; N, 5.0%.

4.3.4. (2*R*)-13 and (2*S*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-butylsuccinamide 14. Butyl magnesium chloride (1.7 mL of a 2 M solution in Et_2O, 3.43 mmol) was added dropwise to *N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-fumaramide **1** (0.5 g, 1 mmol) in dry THF (20 mL) as above to produce a residue, which was chromatographed [SiO_2, EtOAc–hexane (1:1)] to give (2*R*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-butylsuccinamide **13** (0.28 g, 56%) and (2*S*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-butylsuccinamide **14** (0.1 g, 20%) as plates.

13 (Major): mp 73–75 °C; $[\alpha]_D = -75$ (*c* 0.88, EtOAc); IR (KBr, cm^{-1}) 2960, 1690, 1333, 1135; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, $J = 7.2$, CH_2CH_3), 0.95, 0.96 (3H, s, CH_3), 1.15, 1.16 (3H, s, CH_3), 1.23–1.42 (8H, m), 1.52–1.62 (1H, m), 1.72–1.76 (1H, m), 1.85–1.88 (6H, m), 2.05–2.18 (4H, m), 2.85 (1H, dd, $J = 2.3$ and 17.2, CH*H*CHC=O), 3.31 (1H, dd, $J = 9.0$ and 17.2, CH*H*CHC=O), 3.40–3.50 (5H, m, $2\times CH_2SO_2$ and CH_2CHC=O), 3.84–3.88 (1H, app t, $J = 6.3$, C*H*N), 3.94 (1H, t, $J = 6.3$, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.3 (×2), 21.2, 21.3, 22.9, 26.8 (×2), 29.1, 32.5, 33.2 (×2), 36.4, 38.8, 39.0, 41.6, 45.0 (×2), 48.1 (×2), 48.7, 48.8, 53.3 (×2), 65.6 (×2), 170.0, 174.2; HR-FABMS m/z 591.2535 $(M+Na)^+$ (calcd for $C_{28}H_{44}N_2O_6S_2Na$: 591.2539). Anal. Calcd for $C_{28}H_{44}N_2O_6S_2$: C, 59.1; H, 7.5; N, 4.9. Found: C, 59.0; H, 7.7; N, 4.95%.

14 (Minor): mp 131–133 °C; $[\alpha]_D = -82$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2960, 1695, 1331, 1134; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, $J = 6.6$, CH_2CH_3), 0.97, 0.98, 1.17 (3H, s, CH_3), 1.24–1.50 (13H, m), 1.86–1.90 (6H, m), 1.98–2.18 (4H, m), 3.01 (1H, dd, $J = 5.0$ and 17.0, CH*H*CHC=O), 3.15 (1H, dd, $J = 8.5$ and 17.0, CH*H*CHC=O), 3.41–3.53 (5H, m, $2\times CH_2SO_2$ and CH_2CHC=O), 3.86 (1H, t, $J = 7.1$, C*H*N), 3.91 (1H, t, $J = 7.3$, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.3, 20.4, 20, 21.2, 23.0, 26.8, 26.9, 29.4, 31.0, 33.2, 33.3, 38.4, 38.5, 38.7, 41.5, 45.0 (×2), 48.1, 48.2, 48.8, 48.9, 53.3, 53.5, 65.5, 65.7, 170.1, 174.4; HR-FABMS m/z 569.2717 $(M+H)^+$ (calcd for $C_{28}H_{44}N_2O_6S_2$: 569.2719). Anal. Calcd for $C_{28}H_{44}N_2O_6S_2$: C, 59.1; H, 7.8; N, 4.9. Found: C, 58.9; H, 8.0; N, 4.75%.

4.3.5. (2*R*)-15 and (2*S*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-cyclohexylsuccinamide 16. Cyclohexyl magnesium chloride (6.8 mL of a 2 M solution in Et_2O, 13.7 mmol) was added dropwise to *N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]fumaramide **1** (2.0 g, 3.9 mmol) in dry THF (20 mL) as above to produce a crude mixture of diastereoisomers. A portion (0.5 g) was chromatographed [SiO_2, EtOAc–hexane (1:1)] to give (2*R*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-cyclohexylsuccinamide **15** (0.28 g, 56%) and (2*S*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-cyclohexylsuccinamide **16** (0.11 g, 22%) as plates.

15 (Major): mp 180–183 °C; $[\alpha]_D = -80$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2927, 1686, 1333, 1134; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86–1.42 (20H, m), 1.60–1.73 (6H, m), 1.84–1.89 (7H, m), 2.00–2.18 (4H, m), 2.83 (1H, dd, $J = 4.0$ and 17.0, CH*H*CHC=O), 3.25 (1H, dd, $J = 9.3$ and 17.0, CH*H*CHC=O), 3.39–3.55 (5H, m, $2\times CH_2SO_2$ and CH_2CHC=O), 3.86 (1H, app t, $J = 6.3$, C*H*N), 3.94 (1H, t, $J = 6.2$, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3 (×2), 21.0, 21.2, 26.4, 26.8 (×2), 27.0, 28.7, 31.4, 33.1, 33.3, 38.8, 39.0 (×2), 40.8, 45.0, 48.1, 48.6 (×2), 48.8 (×2), 53.3, 53.4, 65.6, 65.7, 170.2, 173.6. Anal. Calcd for $C_{30}H_{46}N_2O_6S_2$: C, 60.6; H, 7.8; N, 4.7. Found: C, 60.4; H, 7.9; N, 4.7%.

16 (Minor): mp 244–246 °C; $[\alpha]_D = -84$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2929, 1684, 1327, 1136; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96–1.43 (21H, m), 1.56–2.19 (16H, m), 2.97 (1H, dd, $J = 4.1$ and 17.0, CH*H*CHC=O), 3.11 (1H, dd, $J = 9.7$ and 16.8, CH*H*CHC=O), 3.29–3.31 (1H, m, CH_2CHC=O), 3.39–3.51 (4H, m, $2\times CH_2SO_2$), 3.84 (1H, app t, $J = 6.2$, C*H*N), 3.92 (1H, app t, $J = 6.2$, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 20.5, 21.0, 21.3, 26.6, 26.7, 26.8 (×2), 27.1, 28.7, 32.1, 33.2, 33.4, 35.2, 38.6, 38.7, 38.9, 45.0, 45.1, 46.4, 48.1 (×2), 48.7, 48.9, 53.2, 53.5, 65.6, 65.8, 170.4, 173.6; HR-FABMS m/z 595.2878 $(M+H)^+$ (calcd for $C_{30}H_{46}N_2O_6S_2$ 595.2876). Anal. Calcd for $C_{30}H_{46}N_2O_6S_2$: C, 60.6; H, 7.8; N, 4.7. Found: C, 60.65; H, 7.9; N, 4.8%.

4.3.6. (2*R*)-17 and (2*S*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-octylsuccinamide 18. Octyl magnesium bromide (6.8 mL of a 2 M solution in Et_2O, 13.7 mmol) was added dropwise to *N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-fumaramide **1** (2.0 g, 3.9 mmol) in dry THF (20 mL) as above to produce a crude mixture of diastereoisomers. A portion (0.5 g) was chromatographed [SiO_2, EtOAc–hexane (1:1)] to give (2*R*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-octylsuccinamide **17** (0.39 g, 78%) and (2*S*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-octylsuccinamide **18** (93 mg, 19%) as plates.

17 (Major): mp 160–163 °C; $[\alpha]_D = -76$ (*c* 1.2, EtOAc); IR (KBr, cm^{-1}) 2923, 1683, 1331, 1134; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, $J = 7.1$, CH_2CH_3), 0.95, 0.96 (3H, s, CH_3), 1.15, 1.16 (3H, s, CH_3), 1.23–1.42 (19H, m), 1.73–1.79 (1H, m), 1.85–1.88 (5H, m), 2.05–2.15 (3H, m), 2.85 (1H, dd, $J = 4.6$ and 17.1, CH*H*CHC=O), 3.30 (1H, dd, $J = 9.0$ and 17.1, CH*H*CHC=O), 3.44–3.50 (5H, m, $2\times CH_2SO_2$ and CH_2CHC=O), 3.84–3.87 (1H, app t, $J = 6.3$, C*H*N), 3.94 (1H, t, $J = 6.3$, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 20.3 (×2), 21.2, 21.3, 23.0, 26.8 (×2), 26.9, 29.6, 29.7, 29.9, 32.2, 32.9, 33.2, 33.3, 36.4, 38.8, 38.9, 41.7 (×2), 45.1, 48.1 (×2), 48.7, 48.8, 53.3, 53.4, 65.6, 65.7, 170.0, 174.2; HR-EIMS m/z 624.3260 (M^+) (calcd for $C_{32}H_{52}N_2O_6S_2$: 624.3267). Anal. Calcd for $C_{33}H_{52}N_2O_6S_2$: C, 61.5; H, 8.4; N, 4.5. Found: C, 61.5; H, 8.3; N, 4.5%.

18 (Minor): $[\alpha]_D = -83$ (*c* 1.2, EtOAc); IR (KBr, cm^{-1}) 2932, 1678, 1332, 1134; ^1H NMR (400 MHz, $CDCl_3$)

δ 0.87 (3H, t, $J = 7.0$, CH_2CH_3), 0.96, 0.97 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.26–1.49 (21H, m), 1.85–2.18 (10H, m), 3.00 (1H, dd, $J = 5.1$ and 17.0, CH*H*CHC=O), 3.14 (1H, dd, $J = 8.5$ and 17.0, CH*H*CHC=O), 3.40–3.52 (5H, m, $2\times CH_2SO_2$ and CH_2CHC=O), 3.85 (1H, app t, $J = 6.2$, C*H*N), 3.90 (1H, app t, $J = 6.2$, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.9, 20.0, 20.5, 20.8, 22.6, 26.4, 26.5, 26.9, 29.2, 29.3, 29.5, 30.9, 31.8, 32.8, 32.9, 38.0, 38.1, 38.3, 41.1, 44.6 (×2), 47.7, 47.8, 48.4, 48.5, 52.9, 53.1, 65.1, 65.3, 169.8, 174.0; HR-FABMS m/z 647.3166 $(M+Na)^+$ (calcd for $C_{32}H_{52}N_2O_6S_2Na$: 647.3165).

4.3.7. (2*R*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-benzylsuccinamide 19. Benzyl magnesium chloride (7.0 mL of a 2 M solution in Et_2O, 14 mmol) was added dropwise to *N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]fumaramide **1** (2.0 g, 4.0 mmol) in dry THF (20 mL) as above to produce a mixture, which was chromatographed [SiO_2, EtOAc–hexane (1:1)] to give *N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-[(2*R*)-benzyl]succinamide **19** (1.7 g, 71%) as plates, mp 191–193 °C; $[\alpha]_D = -70$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2958, 1685, 1333, 1135; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92, 0.93 (3H, s, CH_3), 0.98, 1.07 (3H, s, CH_3), 1.22–1.37 (4H, m), 1.80–1.86 (6H, m), 2.00–2.06 (4H, m), 2.67 (1H, dd, $J = 9.4$ and 13, ArCCH*H*), 2.74 (1H, dd, $J = 5.2$ and 17.5 CH*H*CHC=O), 3.22 (1H, dd, $J = 7.5$ and 13, ArCCH*H*), 3.32 (1H, dd, $J = 8.3$ and 17.4, CH*H*CHC=O), 3.42–3.51 (4H, m, $2\times CH_2SO_2$), 3.82–3.87 (3H, m), 7.17–7.37 (5H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3 (×2), 21.2, 21.3, 26.8 (×2), 33.2, 33.3, 36.3, 38.8 (×2), 43.6, 45.0 (×2), 48.1 (×2), 48.7, 48.8, 53.2 (×2), 53.4, 65.5, 65.6, 127.1, 128.9 (×2), 129.8 (×2), 138.2, 169.9, 173.5; HR-EIMS m/z 602.2487 M^+ (calcd for $C_{31}H_{42}N_2O_6S_2$: 602.2484). Anal. Calcd for $C_{31}H_{42}N_2O_6S_2$: C, 61.8; H, 7.0; N, 4.65. Found: C, 61.6; H, 7.1; N, 4.6%.

4.3.8. (2*R*)-20 and (2*S*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-isobutylsuccinamide 21. Isobutyl magnesium bromide (6.8 mL of a 2 M solution in Et_2O, 13.7 mmol) was added dropwise to *N*,*N*′-bis[(2*R*)bornane-10,2-sultam]fumaramide **1** (2.0 g, 3.9 mmol) in dry THF (20 mL) as above to produce a mixture of diastereoisomers. A portion (0.5 g) was chromatographed [SiO_2, EtOAc–hexane (1:1)] to give (2*R*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-isobutylsuccinamide **20** (0.16 g, 32%) and *(2S)*-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-isobutylsuccinamide **21** (96 mg, 19%) as plates.

20 (Major): mp 239–241 °C; $[\alpha]_D = -76$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2958, 1685, 1333, 1164; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.96 (12H, m), 1.15, 1.16 (3H, s, CH_3), 1.20–1.46 (5H, m), 1.59–1.69 (2H, m), 1.84–1.92 (6H, m), 2.05–2.19 (4H, m), 2.86 (1H, dd, $J = 5.2$ and 17.2, CH*H*CHC=O), 3.26 (1H, dd, $J = 8.4$ and 17.2, CH*H*CHC=O), 3.40–3.57 (5H, m, $2\times CH_2SO_2$ and CH_2CHC=O), 3.84–3.88 (1H, app t, $J = 6.3$, C*H*N), 3.94 (1H, t, $J = 6.3$, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3 (×2), 21.2, 21.3, 21.9, 23.6, 26.1, 26.8 (×2), 33.2, 33.3, 36.5, 38.8, 38.9, 40.0, 41.6, 45.1 (×2), 48.1 (×2), 48.7, 48.8, 53.3, 53.4, 65.7 (×2), 170.0, 174.6; HR-FABMS m/z 591.2536 $(M+Na)^+$ (calcd for $C_{28}H_{44}N_2O_6S_2Na$: 591.2539). Anal. Calcd for $C_{28}H_{44}N_2O_6S_2$: C, 59.1; H, 7.8; N, 4.9. Found: C, 59.1; H, 7.75; N, 4.9%.

21 (Minor): mp 208–210 °C; $[\alpha]_D = -80$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2960, 1685, 1336; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.97 (12H, m), 1.15, 1.25 (3H, s, CH_3), 1.29–1.43 (5H, m), 1.61–1.68 (2H, m), 1.73–1.80 (1H, m), 1.84–1.89 (6H, m), 1.94–2.16 (4H, m), 3.00 (1H, dd, $J = 5.5$ and 17.0, CH*H*CHC=O), 3.09 (1H, dd, $J = 7.9$ and 17.0, CH*H*CHC=O), 3.39–3.54 (5H, m, $2\times CH_2SO_2$ and CH_2CHC=O), 3.84 (1H, app t, $J = 6.2$, C*H*N), 3.88 (1H, app t, $J = 6.2$, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 20.4, 20.9, 21.2, 22.0, 23.5, 26.0, 26.8, 26.9, 33.2, 33.3, 38.4, 38.5, 38.7, 39.7, 40.0, 45.0 (×2), 48.1, 48.2, 48.8, 48.9, 53.3, 53.5, 65.6, 65.7, 170.1, 174.5; HR-FABMS m/z 591.2540 $(M+Na)^+$ (calcd for $C_{28}H_{44}N_2O_6S_2Na$: 591.2539). Anal. Calcd for $C_{28}H_{44}N_2O_6S_2$: C, 59.1; H, 7.8; N, 4.9. Found: C, 59.05; H, 7.9; N, 4.9%.

4.3.9. (2*R*)-22 and (2*S*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-hexylsuccinamide 23. Hexyl magnesium bromide (6.8 mL of a 2 M solution in Et_2O, 13.7 mmol) was added dropwise to *N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-fumaramide **1** (2.0 g, 3.9 mmol) in dry THF (20 mL) as above to produce a mixture of diastereoisomers. A portion (0.5 g) was chromatographed [SiO_2, EtOAc–hexane (1:1)] to give (2*R*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-hexylsuccinamide **22** (0.31 g, 62%) and (2*S*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-hexylsuccinamide **23** (89 mg, 18%) as plates.

22 (Major): mp 164–166 °C; $[\alpha]_D = -60$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2960, 1685, 1330, 1164; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, $J = 7.0$, CH_2CH_3), 0.96, 0.97 (3H, m, CH_3), 1.16, 1.17 (3H, s, CH_3), 1.24–1.48 (11H, m), 1.54–1.62 (4H, m), 1.71–1.78 (1H, m), 1.85–1.92 (5H, m), 2.06–2.18 (4H, m), 2.86 (1H, dd, $J = 4.6$ and 17.1, CH*H*CHC=O), 3.31 (1H, dd, $J = 9$ and 17.1, CH*H*CHC=O), 3.45–3.55 (4H, m, $2\times CH_2SO_2$), 3.86 (1H, app t, $J = 6.3$, C*H*N), 3.95 (1H, t, $J = 6.3$, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 19.7 (×2), 20.6, 20.7, 22.3, 26.2, 26.3, 28.9, 31.4 (×2), 32.3, 32.6, 32.7, 35.8, 38.2, 38.3, 41.1, 44.5 (×2), 47.5 (×2), 48.1, 48.2, 52.7, 52.8, 65.0, 65.1, 169.4, 173.6; HR-FABMS m/z 597.3033 $(M+H)^+$ (calcd for $C_{30}H_{48}N_2O_6S_2$: 597.3032). Anal. Calcd for $C_{30}H_{48}N_2O_6S_2$: C, 60.4; H, 8.1; N, 4.7. Found: C, 60.2; H, 8.1; N, 4.7%.

23 (Minor): mp 76–78 °C; $[\alpha]_D = -66$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2958, 1693, 1333, 1134; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, $J = 6.9$, CH_2CH_3), 0.95, 0.97 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.20–1.48 (14H, m), 1.58 (4H, s), 1.85–1.94 (6H, m), 1.98–2.16 (4H, m), 3.00 (1H, dd, $J = 5.1$ and 17.0, CH*H*CHC=O), 3.14 (1H, dd, $J = 8.5$ and 17.0, CH*H*CHC=O), 3.39–3.52 (4H, m, $2\times CH_2SO_2$), 3.85 (1H, t, $J = 6.2$, C*H*N), 3.90 (1H, t, $J = 6.2$, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.8, 20.0, 20.5, 20.8, 22.5, 26.4 (×2),

26.8, 29.1, 30.9, 31.5, 32.7, 32.8, 37.9, 38.0, 38.2, 41.1, 44.6 (×2), 47.7 (×2), 48.4, 48.5, 52.8, 53.0, 65.1, 65.2, 169.7, 173.9; HR-FABMS m/z 619.2855 $(M+Na)^+$ (calcd for $C_{30}H_{48}N_2O_6S_2Na$: 619.2852). Anal. Calcd for $C_{30}H_{48}N_2O_6S_2$: C, 60.4; H, 8.1; N, 4.7. Found: C, 60.55; H, 8.3; N, 4.6%.

4.3.10. (2*R*)-24 and (2*S*)-*N*,*N*′-Bis[(2*R*)-bornane-10,2-sultam]-2-cyclohexylhexylmethylsuccinamide 25. Cyclohexylmethyl magnesium bromide (6.8 mL of a 2 M solution in Et_2O, 13.7 mmol) was added dropwise to *N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]fumaramide **1** (2.0 g, 3.9 mmol) in dry THF (20 mL) as above to produce a mixture of diastereoisomers. A portion (0.5 g) was chromatographed [SiO_2, EtOAc–hexane (1:1)] to give (2*R*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-cyclohexylmethylsuccinamide **24** (0.28 g, 56%) and (2*S*)-*N*,*N*′-bis[(2*R*)-bornane-10,2-sultam]-2-cyclohexylmethylsuccinamide **25** (94 mg, 19%) as plates.

24 (Major): mp 214–216 °C; $[\alpha]_D = -60$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2924, 1685, 1334, 1164; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87–0.96 (8H, m), 1.07–1.18 (8H, m), 1.24–1.42 (6H, m), 1.60–1.76 (7H, m), 1.84–1.93 (5H, m), 2.05–2.19 (5H, m), 2.85 (1H, dd, $J = 5.3$ and 17.2, CH*H*CHC=O), 3.25 (1H, dd, $J = 8.2$ and 17.2, CH*H*CHC=O), 3.41–3.50 (4H, m, $2\times CH_2SO_2$), 3.71 (1H, m, CH_2CHC=O), 3.87 (1H, app t, $J = 6.4$, C*H*N), 3.93 (1H, t, $J = 6.3$, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3 (×2), 21.3 (×2), 26.4, 26.6, 26.8, 26.9 (×2), 32.6, 33.2, 33.3, 34.1, 35.5, 36.7, 38.8, 38.9, 39.2, 40.4, 45.1 (×2), 48.1 (×2), 48.7, 48.8, 53.3, 53.4, 65.7 (×2), 170.0, 174.8; HR-FABMS m/z 609.3032 $(M+H)^+$ (calcd for $C_{31}H_{48}N_2O_6S_2$: 609.3032). Anal. Calcd for $C_{31}H_{48}N_2O_6S_2$: C, 61.15; H, 7.95; N, 4.6. Found: C, 61.0; H, 8.2; N, 4.7%.

25 (Minor): mp 101–103 °C; $[\alpha]_D = -86$ (*c* 1.0, EtOAc); IR (KBr, cm^{-1}) 2935, 1687, 1328, 1136; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (8H, m), 1.11–1.44 (14H, m) 1.58–1.89 (12H, m), 1.98–2.18 (5H, m), 2.99 (1H, dd, $J = 5.4$ and 17.0, CH*H*CHC=O), 3.10 (1H, dd, $J = 7.8$ and 17.0, CH*H*CHC=O), 3.39–3.55 (5H, m, $2\times CH_2SO_2$ and CH_2CHC=O), 3.85 (1H, t, $J = 6.2$, C*H*N), 3.90 (1H, t, $J = 6.2$, C*H*N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 20.0, 20.5, 20.7, 26.0, 26.1, 26.4 (×2), 26.5 (×2) 32.3, 32.7, 32.8, 33.7, 34.9, 38.0, 38.1, 38.3 (×2), 38.5, 44.5, 44.6, 47.7, 48.4 (×2), 52.8, 53.0, 65.1, 65.2, 169.6, 174.2; HR-FABMS m/z 609.3031 $(M+H)^+$ (calcd for $C_{31}H_{48}N_2O_6S_2$: 609.3032). Anal. Calcd for $C_{31}H_{48}N_2O_6S_2$: C, 61.15; H, 7.95; N, 4.6. Found: C, 61.3; H, 8.0; N, 4.7%.

4.4. General procedure for the reduction of 2-substituted succinamides 2 and 3 into 2-substituted butane-1,4-diols 5 (Table 2)

The 2-substituted succinamide mixture **2** and **3** (0.5 g) in dry THF (10 mL) was added dropwise to a stirred solution of lithium aluminium hydride (5 equiv) in dry THF (50 mL) under N_2 at 0 °C. After 3 h at 0 °C the reaction mixture was quenched with satd aq NH_4Cl soln (2 mL). The mixture was filtered and concentrated under reduced pressure.

4.4.1. (2*R*)-Ethylbutane-1,4-diol 26.[11] Using **7**+**8** (0.8 g, 1.5 mmol) gave a mixture of diol and chiral sultam (0.72 g), which was chromatographed [SiO_2, acetone–hexane (1:1)] to give (2*R*)-ethylbutane-1,4-diol **26** (0.08 g, 39%) as a colourless oil. $[\alpha]_D = +12$ (*c* 1.5, $CHCl_3$) [lit.[10] +14.3 (*c* 1.5, $CHCl_3$)]; IR (NaCl, cm^{-1}) 3332, 2925, 1018; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, $J = 7.4$, CH_2CH_3), 1.25–1.43 (2H, m, CH_2CH_3), 1.55–1.62 (2H, m, CH_2CH_2OH), 1.67–1.76 (1H, m, C*H*), 3.00 (2H, br s, OH), 3.49 (1H, dd, $J = 6.7$ and 10.8, CHCH*H*OH), 3.63–3.68 (2H, m, CH_2CH_2OH), 3.76–3.81 (1H, m, CHCH*H*OH).

4.4.2. (2*R*)-Isopropylbutane-1,4-diol 27.[12] Using **9**+**10** (0.5 g, 0.9 mmol) gave a mixture (0.24 g), which was chromatographed [SiO_2, acetone–hexane (2:3)] to give (2*R*)-isopropylbutane-1,4-diol **27** (0.05 g, 43%) as a colourless oil; $[\alpha]_D = -3.3$ (*c* 1.0, MeOH) [lit.[11] −10 (*c* 1.0, MeOH)]; IR (NaCl, cm^{-1}) 3332, 2958, 1466, 1044; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, $J = 7.2$, $CHCH_3$), 0.89 (3H, d, $J = 7.2$, $CHCH_3$), 1.44–1.61 (2H, m, CH_2CH_2OH), 1.68–1.79 (2H, m, CH_3CHCH), 3.20 (2H, br s, OH), 3.54 (1H, dd, $J = 7.8$ and 10.6, CHCH*H*OH), 3.60–3.70 (2H, m, CH_2CH_2OH), 3.77–3.82 (1H, m, CHCH*H*OH).

4.4.3. (2*R*)-propylbutane-1,4-diol 28.[12] Using **11**+**12** (0.5 g, 0.9 mmol) gave a mixture (0.18 g), which was chromatographed [SiO_2, acetone–hexane (1:1)] to give (2*R*)-propylbutane-1,4-diol **28** (0.06 g, 46%) as a colourless oil. $[\alpha]_D = -1$ (*c* 1.1, MeOH) [lit.[11] −3.6 (*c* 2.12, MeOH)]; IR (NaCl, cm^{-1}) 3320, 2929, 1466, 1039; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, $J = 6.9$, CH_2CH_3), 1.21–1.37 (4H, m, $CH_3CH_2CH_2$), 1.55–1.75 (3H, m, $CHCH_2CH_2OH$), 2.63 (2H, br s, OH), 3.49 (1H, dd, $J = 7.0$ and 10.8, CHCH*H*OH), 3.64–3.71 (2H, m, CH_2CH_2OH), 3.76–3.81 (1H, m, CHCH*H*OH).

4.4.4. (2*R*)-Butylbutane-1,4-diol 29. Using **13**+**14** (0.5 g, 0.9 mmol) gave a mixture (0.17 g), which was chromatographed [SiO_2, acetone–hexane (2:3)] to give (2*R*)-butylbutane-1,4-diol **29** (73 mg, 56%) as a colourless oil. $[\alpha]_D = -1$ (*c* 1.5, EtOH); IR (NaCl, cm^{-1}) 3410, 2946, 1466, 1041; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, $J = 6.8$, CH_2CH_3), 1.21–1.34 (6H, m), 1.52–1.73 (3H, m, $CHCH_2CH_2OH$), 3.39 (2H, br s, OH), 3.45 (1H, dd, $J = 6.8$ and 10.4, CHCH*H*OH), 3.60–3.65 (2H, m, CH_2CH_2OH), 3.73–3.78 (1H, m, CHCH*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 23.1, 29.5, 31.6, 36.0, 39.6, 61.2, 66.5; HR-CIMS m/z (isobutane) 147.1384 (MH^+) (calcd for $C_8H_{18}O_2$: 147.1385).

4.4.5. (2*R*)-Cyclohexylbutane-1,4-diol 30 Using **15**+**16** (0.5 g, 0.8 mmol) gave a mixture (0.44 g), which was chromatographed [SiO_2, acetone–hexane (2:3)] to give

(2*R*)-cyclohexylbutane-1,4-diol **30** (53 mg, 38%) as a colourless oil. $[\alpha]_D = -7.6$ (*c* 0.5, EtOH); IR (NaCl, cm^{-1}) 3336, 2921, 1448, 1041; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95–1.74 (14H, m), 3.52 (1H, dd, $J = 6.8$ and 17.6, CHCH*H*OH), 3.56–3.62 (1H, m, CH_2CH*H*OH), 3.66 (1H, dd, $J = 4.0$ and 10.8, CHCH*H*OH), 3.73–3.78 (1H, m, CH_2CH*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 26.7 (×2), 30.0, 30.1, 33.4, 40.1, 45.0, 61.7, 64.8; HR-FABMS *m*/*z* 173.1541 (MH^+) (calcd for $C_{10}H_{20}O_2$ 173.1542).

4.4.6. (2*R*)-Octylbutane-1,4-diol 31. Using **17+18** (0.6 g, 1.0 mmol) gave a mixture (0.45 g), which was chromatographed [SiO_2, acetone–hexane (2:3)] to give 2*R*-octylhexylbutane-1,4-diol **31** (0.15 g, 79%) as a colourless oil. $[\alpha]_D = +0.5$ (*c* 0.2, EtOH); IR (NaCl, cm^{-1}) 3328, 2924, 1465, 1041; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, $J = 7.0$, CH_2CH_3), 1.26–1.33 (15H, m), 1.57–1.77 (2H, m, CH_2CH_2OH), 2.62 (2H, br s, OH), 3.52 (1H, dd, $J = 6.8$ and 10.7, CHCH*H*OH), 3.68–3.73 (2H, m, CH_2CH_2OH), 3.79–3.85 (1H, m, CHCH*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 27.1, 29.3, 29.5, 29.9, 31.7, 31.9, 35.8, 39.3, 61.3, 66.4; HR-EIMS *m*/*z* 202.1934 (M^+) (calcd for $C_{12}H_{26}O_2$: 202.1933).

4.4.7. (2*R*)-Benzylbutane-1,4-diol 32. Using **19** (0.6 g, 1.0 mmol) gave a mixture (0.60 g), which was chromatographed [SiO_2, acetone–hexane (2:3)] to give (2*R*)-benzylbutane-1,4-diol **32** (0.15 g, 75%) as a colourless oil. $[\alpha]_D = +6.6$ (*c* 1.5, EtOAc); IR (NaCl, cm^{-1}) 3348, 2927, 1603, 1454, 1043; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56–1.75 (2H, m, $ArCH_2CH$), 1.97–2.01 (1H, m, $ArCH_2CH$), 2.40 (2H, br s, OH), 2.53–2.74 (2H, m, CH_2CH_2OH), 3.47–3.52 (1H, m, CHCH*H*OH), 3.62–3.68 (2H, m, CH_2CH_2OH), 3.75–3.80 (1H, m, CHCH*H*OH), 7.16–7.30 (5H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.6, 38.6, 41.6, 61.5, 66.0, 126.4, 128.8, 129.5, 140.7; HR-EIMS *m*/*z* 162.1046 (M^+) (calcd for $C_{11}H_{16}O_2$: 162.1045).

4.4.8. (2*R*)-Isobutylbutane-1,4-diol 33. Using **20+21** (0.5 g, 0.9 mmol) gave a mixture (0.45 g), which was chromatographed [SiO_2, acetone–hexane (2:3)] to give (2*R*)-isobutylbutane-1,4-diol **33** (0.11 g, 85%) as a colourless oil. $[\alpha]_D = +2.4$ (*c* 4.2, EtOAc); IR (NaCl, cm^{-1}) 3334, 2954, 1468, 1039; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (6H, t, $J = 6.4$. CH_3CHCH_3), 1.04–1.25 (2H, m, CH_3CHCH_2), 1.50–1.75 (4H, m), 3.42 (1H, dd, $J = 7.2$ and 10.8, CHCH*H*OH), 3.56 (2H, br s, OH), 3.61–3.66 (2H, m, CH_2CH_2OH), 3.74–3.79 (1H, m, CHCH*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 22.8, 25.2, 30.1, 37.1, 41.1, 61.0, 66.5; HR-CIMS (isobutane) *m*/*z* 147.1386 (MH^+) (calcd for $C_8H_{18}O_2$: 147.1385).

4.4.9. (2*R*)-Hexylbutane-1,4-diol 34. Using **22+23** (0.54 g, 0.9 mmol) gave a mixture (0.38 g), which was chromatographed [SiO_2, EtOAc–hexane (1:1)] to give (2*R*)-hexylbutane-1,4-diol **34** (0.12 g, 75%) as a colourless oil. $[\alpha]_D = +2$ (*c* 1.0, EtOAc); IR (NaCl, cm^{-1}) 3320, 2925, 1466, 1043; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 7.0$. CH_2CH_3), 1.27 (10H, br s), 1.52–1.73 (3H, m, $CHCH_2CH_2OH$), 3.27 (2H, br s, OH), 3.46 (1H, dd, $J = 7.0$ and 10.7, CHCH*H*OH), 3.61–3.67 (2H, m, CH_2CH_2OH), 3.74–3.80 (1H, m, CHCH*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 23.0, 27.4, 30.0, 32.2 (×2), 36.2, 39.8, 61.5, 66.7; HR-FABMS *m*/*z* 175.1697 (MH^+) (calcd for $C_{10}H_{22}O_2$: 175.1698).

4.5. General procedure for the conversion of 2-substituted butane-1,4-diols 5 into Mosher diesters

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

4.6. General procedure for the saponification of succinamides 2 and 3

Aqueous (30%) H_2O_2 (4.8 equiv) and $LiOH{\cdot}H_2O$ (2.4 equiv) was added at 0 °C to a solution of substituted succinamide **2** and **3** (1 mol equiv) in THF/H_2O (4:1, 0.15 M). The mixture was stirred at 0 °C for 7 h, saturated aqueous Na_2SO_3 was added and the mixture was extracted with ethyl acetate (2×10 mL). The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give recovered auxiliary. The aqueous layer was then acidified with 1 M HCl to pH 1 and extracted with ethyl acetate (2×10 mL). The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to produce the diacid (Table 3).

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