Diastereoselective addition of chiral azomethine ylides to cyclic α,β-unsaturated *N*-enoylbornanesultams

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Doubly diastereoselective 1,3-dipolar cycloaddition reactions of chiral non-racemic azomethine ylides to cyclic five- and six-membered α,β-unsaturated *N*-enoylbornanesultams were carried out. When suitable solvents were used, the fused bicyclic adducts formed were obtained in good diastereoselectivity. Moreover, a change of the absolute configuration of the starting ylide precursor reversed the diastereoselectivity of some such reactions. Cleavage of the chiral auxiliary of the cycloadducts furnished amino alcohols and a β-amino ester. The latter was transformed into a known precursor of an antibacterial compound.

Introduction

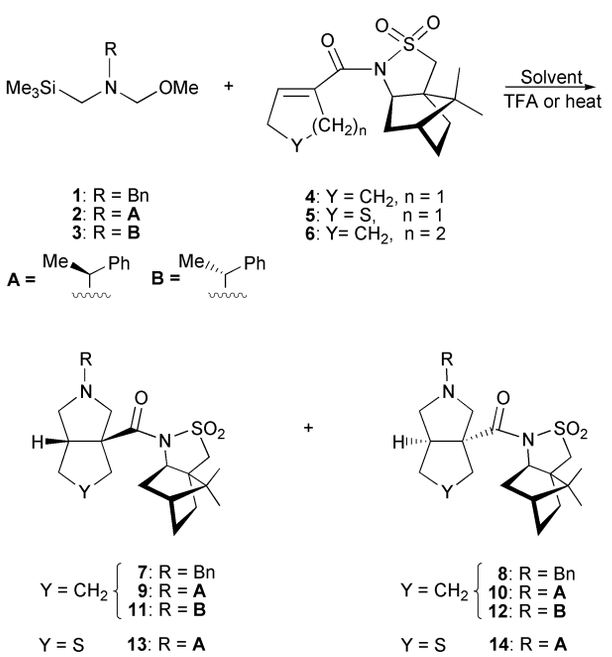
One of the most powerful reactions for the construction of substituted five-membered heterocyclic compounds is the 1,3-dipolar cycloaddition reaction.[1] When an ylide containing a heteroatom reacts with dipolarophiles, up to four new chiral centers are created in one step. Moreover, when either the dipolarophile or the ylide is chiral and non-racemic, diastereofacial selectivity is expected.[2] For example, achiral nonstabilized azomethine ylides react with α,β-unsaturated acyl moieties attached to chiral auxiliaries with varying degrees of facial selectivity to give substituted pyrrolidines.[3] The diastereofacial selectivity can often be improved, if both the reacting partners are chiral. We have recently studied acyclic dipolarophiles attached to chiral auxiliaries in reactions with non-racemic azomethine ylides, derived from enantiomerically pure phenylethylamine.[4] When such and other types of chiral ylides are used, the induction of facial selectivity is generally small to moderate.[4–6] This can probably be explained by minor interactions between the chiral *N*-substituent of the ylide and the substituent(s) of the dipolarophile.

Azomethine ylides have previously been used in intermolecular 1,3-dipolar cycloadditions to non-racemic bicyclic lactams and cyclopent-1-enecarboxylic acid methyl ester.[6,7] However, azomethine ylide additions to monocyclic five- and six-membered α,β-unsaturated acyl derivatives attached to chiral auxiliaries have, to our knowledge, not been investigated. Some derivatives of the resulting azabicyclo[3.3.0]octanes have been found to exhibit antibacterial activity.[7] Furthermore, the cycloadducts can be used for further transformation into enantiopure amino alcohols and β-amino acids.

We now present singly and doubly diastereoselective 1,3-dipolar cycloadditions of azomethine ylides, both achiral and chiral, to cyclic dipolarophiles attached to (2*R*)-(−)-bornanesultam.

Results and discussion

When an excess of the achiral azomethine ylide precursor **1** was treated with a catalytic amount (~1 mol%) of trifluoroacetic acid (TFA) in the presence of the dipolarophile **4** (Scheme 1) in THF at room temperature, a mixture of the cycloadducts **7** and **8** was obtained in a low diastereomeric ratio (dr = 60 : 40)



Scheme 1 1,3-Dipolar cycloadditions of achiral or chiral azomethine ylide precursors **1**–**3** to cyclic dipolarophiles **4**–**6**.

(Table 1, entry 5). In contrast to our earlier studies with acyclic dipolarophiles,[3a] these experiments had to be performed in the presence of only a trace of TFA, because no conversion occurred at higher concentrations (20–50 mol% of TFA). Moreover, the reactions were slower, less stereoselective and more sensitive to the reaction conditions than those with acyclic dipolarophiles.

It has been shown earlier that, compared with α-unsubstituted α,β-unsaturated dipolarophiles attached to bornanesultam, α-substituted examples show reduced reactivity and diastereoselectivity in other cycloaddition reactions.[8] In the latter case, the α-substituent is expected to force the alkene moiety out of the plane of the carbonyl group. The resulting loss of conjugation is thought to be partly responsible for the reduced reactivity of α-substituted acryloyl compounds.[8a]

A change of the solvent in the reaction of the dipolarophile **4** with the ylide from **1** could have an effect on the diastereo-

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Table 1 Diastereomeric ratio in the 1,3-dipolar cycloaddition of azomethine ylides derived from **1**–**3** to dipolarophiles **4** and **5**

Entry[a,b]	Precursor	Dipolarophile	Solvent	Temp./°C	Dr (major : minor)
1	**1**	**4**	Xylene	110	40 : 60 (**7** : **8**)[c]
2	**1**	**4**	Dioxane	Reflux	52 : 48 (**7** : **8**)[c]
3	**1**	**4**	CCl_4	Reflux	41 : 59 (**7** : **8**)[c]
4	**1**	**4**	DMF	100	54 : 46 (**7** : **8**)[c]
5	**1**	**4**	THF	20	60 : 40 (**7** : **8**)[c]
6	**1**	**4**	Acetone	Reflux	52 : 48 (**7** : **8**)[c]
7	**1**	**4**	CH_3CN	Reflux	57 : 43 (**7** : **8**)[c]
8	**1**	**4**	Toluene	Reflux	41 : 59 (**7** : **8**)[c]
9	**1**	**4**	CH_2Cl_2	Reflux	57 : 43 (**7** : **8**)[c]
10	**2**	**4**	Xylene	110	20 : 80 (**9** : **10**)[d]
11	**2**	**4**	Dioxane	Reflux	25 : 75 (**9** : **10**)[d]
12	**2**	**4**	CCl_4	Reflux	20 : 80 (**9** : **10**)[d]
13	**2**	**4**	DMF	100	30 : 70 (**9** : **10**)[d]
14	**2**	**4**	THF	20	32 : 68 (**9** : **10**)[d]
15	**2**	**4**	Acetone	Reflux	32 : 68 (**9** : **10**)[d]
16	**2**	**4**	CH_3CN	Reflux	32 : 68 (**9** : **10**)[d]
17	**2**	**4**	Toluene	Reflux	22 : 78 (**9** : **10**)[d]
18	**2**	**4**	CH_2Cl_2	Reflux	32 : 68 (**9** : **10**)[d]
19	**3**	**4**	Xylene	110	48 : 52 (**11** : **12**)[c]
20	**3**	**4**	Dioxane	Reflux	57 : 43 (**11** : **12**)[c]
21	**3**	**4**	CCl_4	Reflux	43 : 57 (**11** : **12**)[c]
22	**3**	**4**	DMF	100	68 : 32 (**11** : **12**)[c]
23	**3**	**4**	THF	20	75 : 25 (**11** : **12**)[c]
24	**3**	**4**	Acetone	Reflux	73 : 27 (**11** : **12**)[c]
25	**3**	**4**	CH_3CN	Reflux	74 : 26 (**11** : **12**)[c]
26	**3**	**4**	Toluene	Reflux	55 : 45 (**11** : **12**)[c]
27	**3**	**4**	CH_2Cl_2	Reflux	82 : 18 (**11** : **12**)[c]
28	**2**	**5**	Xylene	110	25 : 75 (**13** : **14**)[c]
29	**2**	**5**	CH_2Cl_2	20	23 : 77 (**13** : **14**)[c]

[a] Compound **1**, **2** or **3** (0.21 mmol) was added to a solution of **4** or **5** (0.07 mmol) in the solvent (0.2 ml) specified and trifluoroacetic acid (0.001 mmol), at 0.25 h intervals in four portions at the temperature specified. After 0.5 h, Na_2CO_3 (aq. sat., 3 ml) was added and the mixture was diluted with EtOAc (5 ml). The organic phase was dried ($MgSO_4$) and concentrated. Diastereomeric ratios were determined for the crude products. [b] Complete conversion was not achieved here, but occurred in reactions performed on a larger scale, as described in the Experimental section. [c] Determined by GC analyses. [d] Determined by ^1H NMR integration.

selectivity (Table 1). Reversed facial selectivity was observed in some solvents (compare entries 1, 3 and 8 with entries 2, 4–7 and 9). When performing this reaction at a high temperature, *e.g.* in xylene at 110 °C, we noticed that an acid catalyst such as TFA was not a prerequisite for azomethine ylide generation. Smaller amounts of the azomethine ylide precursor were consumed, and higher yields were obtained under acid-free conditions (see Experimental section).

All of the reactions studied so far (entries 1–9, Table 1) involved the achiral ylide **1** and took place with low diastereoselectivity. In order to increase this selectivity, we treated the dipolarophile **4** with the ylide enantiomers obtained from the phenylethylamine-derived precursors **2** and **3**. Most of these reactions resulted in improved diastereoselectivity, but reversed facial selectivity was observed in some of them. For example, when the reaction was performed in refluxing CH_2Cl_2 in the presence of either one of the ylide precursors **2** or **3**, the facial selectivity switched from a preference for the diastereomer **10** (dr **9** : **10**, 32 : 68) to **11** (dr **11** : **12**, 82 : 18) (entries 18 and 27, Table 1). The significant effect observed here (Fig. 1) of the chiral phenylethylamine-derived azomethine ylides is in sharp contrast to our earlier results obtained with the same ylides in reactions with acyclic dipolarophiles.[4] The non-racemic ylide derived from **2** reacted with the dihydrothiophene **5** under the same conditions as in entry 10, to afford a diastereomeric mixture of the cycloadducts **13** and **14** (1 : 3, entry 28). We tried, without success, to make the six-membered cyclic dipolarophile **6** react with a large excess of either enantiomer of the chiral azomethine ylides derived from **2** and **3** under a variety of conditions. Only trace amounts (1–4% conversion) of two diastereomeric cycloadducts were produced. However, they were obtained in good diastereoselectivity (up to 85 : 15 dr).

The optimal conditions for achieving high diastereoselectivity were different for each set of reactants. Using such conditions (see Experimental section) we also performed the

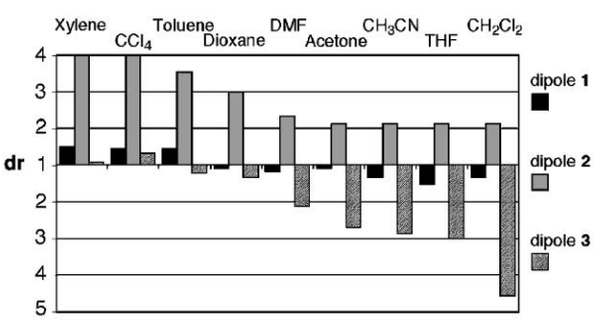
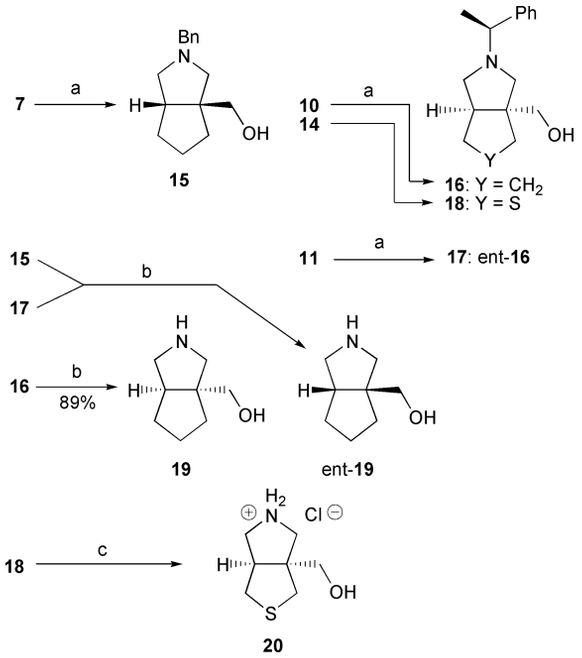


Fig. 1 Diastereomeric ratio (dr) as a function of solvent and dipole precursor used (**1**, **2** or **3**) in the reaction with **4**. Negative bars mean an excess of diastereomer **7** or **11** and positive bars mean an excess of diastereomer **8**, **10** or **12**.

1,3-dipolar cycloaddition reactions on a larger scale. Thus, the crude mixture of the diastereomeric cycloadducts **7** and **8** (obtained from **1** and **4** in THF), **9** and **10** or **13** and **14** (obtained from **2** and **4** or **2** and **5**, respectively, in xylene at 110 °C), was separated on silica gel to give the individual diastereomers, all in >200 : 1 diastereomeric ratio (dr). Thus, the major cycloadducts **7**, **10** and **14** were obtained in 54, 59 and 56% isolated yield, respectively. The diastereomers **11** and **12**, obtained from **3** and **4** in THF, were not separable on silica gel. Fortunately, one recrystallisation of the crude mixture from cyclohexane afforded the major diastereomer **11** (>200 : 1 dr) in 58% isolated yield. The minor diastereomer **12** could not be isolated in a diastereomerically pure form. The sultam auxiliary of the major diastereomeric cycloadducts **7**, **10**, **11** and **14** was then cleaved off as shown in Scheme 2 to give the amino alcohols **15**–**18** (88–99% yield) along with the recovered bornanesultam (97–99%).

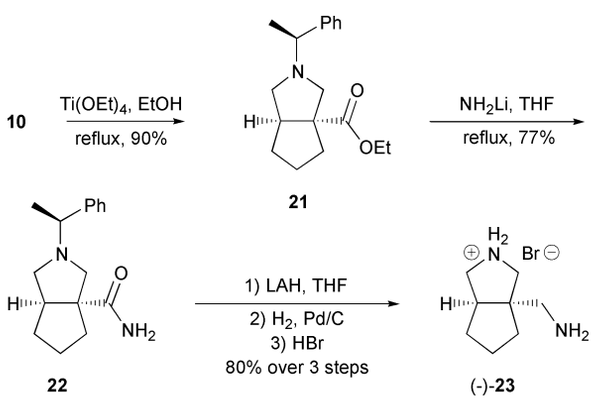
Hydrogenation of the benzyl group of **15** and the phenylethyl groups of **16** and **17**, using Pd/C, furnished the enantiomers **19**



Scheme 2 Reductive cleavage of the chiral auxiliary and preparation of amino alcohols **19**–**20**. (a) (i) $LiAlH_4$, THF; (ii) H_3O^+, 88–99%; (b) Pd/C, H_2; (c) (i) $ClCOOCH(Cl)CH_3$, 1,8-bis(dimethylamino)-naphthalene; (ii) methanol, reflux; (iii) MeOH, HCl (aq.) (77% over 3 steps).

and *ent*-**19**. The phenylethyl group of the sulfur-containing compound **18** could not be removed under the same conditions. Only unreacted starting material could be recovered, along with small amounts of the corresponding desulfurised compound (**18** with Y = H_2 instead of S) as judged by GC-MS analysis. Catalyst poisoning by the divalent sulfur was a probable reason why **18** was unreactive towards hydrogenation.[9] However, an alternative reagent, α-chloroethyl chloroformate,[10] accomplished the removal of the phenylethyl group of **18** to give compound **20** (77% yield) after methanolysis and hydrolysis.

In order to confirm the configuration of the stereocenters in the cycloadducts **7**–**12**, we converted the major diastereomer **10**, obtained from the reaction of the ylide **2** with the dipolarophile **4**, in a few steps (Scheme 3) to compound (−)-**23**, a known synthetic precursor of an antibacterial compound.[7]



Scheme 3 Preparation of (−)-**23**.

Ethanolysis[11] of compound **10** [$Ti(OEt)_4$, EtOH, reflux] afforded the ester **21** (90%). Aminolysis through treatment in THF under reflux, with an excess of lithium amide, furnished the corresponding amide **22** in 77% yield. This amide was reduced with LAH, which yielded the corresponding primary amine. Without further purification, this was subjected to hydrogenation of the phenylethyl group (H_2, Pd/C). The resulting diamine was treated with aqueous HBr to give the known[7] salt (−)-**23** in 80% overall yield, $[\alpha]_D^{25} = -1.0$ (*c* 5.8, MeOH). Thus, our sample of (−)-**23** had the same configuration as that of the previously prepared (−)-**23**, lit.[7] $[\alpha]_D^{24} = -0.9$ (*c* 49, MeOH). The configurations of the compounds **7** and **11** could then be determined by comparison of the sign of optical rotation of *ent*-**19** (Scheme 2) obtained from **7** and **11** with that of compound **19** prepared from **10**. The absolute configurations of the diastereomeric bicyclic adducts **13** and **14** were not determined, but were assumed to be as shown (Scheme 1), provided that the dihydrothiophene **5** reacted with the azomethine ylide derived from **2** in the same fashion as the cyclopentenoic derivative **4**. This assumption was supported by the ^1H NMR chemical shifts of **13** and **14**, which showed the same pattern of relative positions of the signals as the shifts of samples of **9** and **10**. Other data of **13** and **14** also had the same relative values as those observed for samples of **9** and **10** (see Experimental section).

We wished to explain the reversed stereoselectivity obtained when letting the cyclopentenecarboxamide **4** react with either the ylide from **2** or its enantiomer **3**. Hence, we also investigated the reaction of **2** with two achiral cyclic dipolarophiles, cyclopent-1-enecarboxylic acid ethyl ester and 2,5-dihydrothiophene-3-carboxylic acid methyl ester, using the conditions in entry 29 (Table 1). Two separable diastereomeric cycloadducts were formed in both cases (64 : 36 dr). Both major adducts were formed with the same sense of π-facial selectivity as that observed in the reactions of the ylide derived from **2** with the corresponding chiral dipolarophile **4** or **5**. This indicates that there was an interaction in the transition state between the five- membered cyclic framework and the chiral phenylethyl moiety of the ylide, resulting in a discrimination of one of the π-faces of the dipolarophile.

The results described above show that the chirality of the ylide is more important than that of the dipolarophile for achieving high diastereoselectivity in ylide additions to cyclic alkenoyl derivatives attached to bornanesultam.

In summary, we have demonstrated that five-membered cycloalkenylcarbonyl derivatives attached to (2*R*)-(−)-bornanesultam can serve as dipolarophiles in reactions with both chiral and achiral azomethine ylides, giving fused bicyclic heterocycles. A good diastereoselectivity and a high yield can be obtained with the correct choice of reaction conditions. The cycloadducts are potential building blocks for further manipulation into natural alkaloids, chiral ligands and auxiliaries, suitable for use in enantioselective reactions. The utility of the reactions studied here has been demonstrated by the synthesis of the known[7] enantiomerically pure (−)-**23**.

Experimental

All chemicals were used as received unless otherwise stated. THF (K, benzophenone), xylene, dioxane, acetone, acetonitrile, toluene, CH_2Cl_2 (all CaH_2) were distilled from the indicated drying agents. Other solvents were used as recieved. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DMX 250 (250 MHz ^1H and 62.9 MHz ^{13}C) instrument. Preparative liquid chromatography was performed on straight phase silica gel (Merck 60, 230–400 mesh, 0.040–0.063 mm) using an increasing concentration of distilled ethyl acetate in distilled cyclohexane as eluent. GC analyses were carried out using a capillary column EC-5, 30 m, 0.32 mm id, d_f = 0.25μm, carrier gas N_2. The elemental analyses (C, H, N) were performed by Mikro Kemi AB, SE-752 28 Uppsala, Sweden. Boiling points are uncorrected and given as air bath temperatures (bath temp./mbar) in a bulb to bulb (Büchi GKR-51) apparatus. Optical rotations were measured (10^{-1} deg cm^2 g^{-1}) with a Perkin-Elmer 241 MC polarimeter in a 1 dm cell. Mass spectra were recorded on a Saturn 2000 instrument, coupled to a Varian 3800 GC instrument. Compounds **1**, **2** and **3** were prepared using the procedure reported by Hosomi *et al.*[12] The work up procedure

followed another alternative method.[6b] Compound **6**[13] was obtained following the procedure for the preparation of **4** described below.

N-(1-Cyclopent-1-en-1-ylcarbonyl)-(2′*R*)-bornane-10,2-sultam 4

Thionyl chloride (5 ml, 68.5 mmol) was added to a solution of cyclopent-1-enecarboxylic acid (2.4 g, 21.4 mmol) in CH_2Cl_2 (20 ml). The solution was allowed to reflux for 2 hours followed by concentration *in vacuo* to give the corresponding acid chloride. MeMgBr (3 M in diethyl ether, 6.7 ml, 20.1 mmol) was added to a 0 °C solution of (2*R*)-(−)-bornane-10,2-sultam (4.3 g, 20.0 mmol) in THF (150 ml). After 0.5 h the acid chloride in THF (20 ml) was slowly added and the solution was allowed to stir for 1 h. Addition of NH_4Cl (aq. sat., 100 ml) was followed by dilution with EtOAc (200 ml). The organic phase was extracted with 2 M NaOH (2 × 100 ml), dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue [SiO_2, EtOAc–cyclohexane (10–>60%) as eluent] yielded compound **4** (5.5 g, 17.8 mmol, 89%) as a colourless solid in >99% purity (GC). Mp 148–150 °C, $[\alpha]_D^{25} = -65.7$ (*c* 0.40, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, s), 1.23 (3H, s), 1.31–1.46 (2H, m), 1.83–2.09 (7H, m), 2.43–2.82 (4H, m), 3.40 (1H, d, *J* = 13.6 Hz), 3.51 (1H, d, *J* = 13.6 Hz), 4.05 (1H, dd, *J* = 4.9, 7.3 Hz), 6.68–6.74 (1H, m). ^{13}C NMR ($CDCl_3$) δ 19.8, 21.2, 22.5, 26.4, 32.5, 33.1, 34.0, 38.3, 45.1, 47.6, 47.9, 53.5, 65.5, 137.8, 144.3, 167.3. MS (EI): *m*/*z* (%) 310 [30, (M + H)$^+$], 95 (100). Found: C, 62.2; H, 7.6; N, 4.6. Calc. for $C_{16}H_{23}NO_3S$: C, 62.1; H, 7.5; N, 4.5%.

N-(2,5-Dihydro-3-thienylcarbonyl)-(2′*R*)-bornane-10,2-sultam 5

Following the same procedure for the preparation of **4** the title compound (5.7 g, 17.4 mmol, 94%) was obtained as a colourless solid from (2*R*)-(−)-bornane-10,2-sultam (4.0 g, 18.6 mmol) and 2,5-dihydrothiophene-1-carboxylic acid (2.6 g, 20.0 mmol) which was prepared from the corresponding methyl ester[14] (*via* hydrolysis, NaOH–H_2O–MeOH). Mp 171–173 °C, $[\alpha]_D^{25} = -98.1$ (*c* 0.59, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, s), 1.22 (3H, s), 1.30–1.47 (2H, m), 1.82–2.10 (5H, m), 3.42 (1H, d, *J* = 13.7 Hz), 3.53 (1H, d, *J* = 13.7 Hz), 3.83–4.20 (5H, m), 6.71–6.76 (1H, m). ^{13}C NMR ($CDCl_3$) δ 19.8, 21.2, 26.4, 33.1, 38.0, 38.2, 39.7, 45.1, 47.7, 48.0, 53.5, 65.5, 136.4, 140.2, 165.7. MS (EI): *m*/*z* (%) 327 (80, M$^+$), 263 (50), 113 (100). Found: C, 55.2; H, 6.4; N, 4.3. Calc. for $C_{15}H_{21}NO_3S_2$: C, 55.0; H, 6.5; N, 4.3%.

N-[(3a*S*,6a*S*)-2-Benzyloctahydrocyclopenta[*c*]pyrrol-3a-ylcarbonyl]-(2*R*)-bornane-10,2-sultam 7 and *N*-[(3a*R*,6a*R*)-2-benzyloctahydrocyclopenta[*c*]pyrrol-3a-ylcarbonyl]-(2*R*)-bornane-10,2-sultam 8

N-Benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine (**1**, 780 mg, 3.3 mmol) was added to a solution of **4** (500 mg, 1.6 mmol) in a 5 mM solution of TFA–THF (5 ml) over a period of 1.5 h. After an additional 0.25 h NH_4Cl (aq. sat., 25 ml) was added followed by EtOAc (50 ml). The organic phase was washed with Na_2CO_3 (aq. sat., 25 ml), dried ($MgSO_4$), filtered and concentrated at 130 °C, 1 mbar. The residue which consisted of two diastereomers **7** and **8** in a 60 : 40 ratio (GC) was purified by column chromatography [SiO_2, EtOAc–cyclohexane (5–60% as eluent)] to give the two individual pure diastereomers **7** (381 mg, 0.86 mmol, 54%) and **8** (230 mg, 0.52 mmol, 32%). Both diastereomers were obtained as colourless solids in >200 : 1 diastereomeric ratio (GC).

7 (Major): mp 92–94 °C, $[\alpha]_D^{25} = -23.4$ (*c* 0.41, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.89 (6H, s), 1.20–2.23 (14H, m), 2.34 (1H, d, *J* = 10.4 Hz), 2.92 (1H, t, *J* = 8.4 Hz), 3.29–3.49 (5H, m), 3.61 (1H, d, *J* = 12.9 Hz), 3.89 (1H, dd, *J* = 4.8, 7.6 Hz), 7.21–7.32 (5H, m). ^{13}C NMR ($CDCl_3$) δ 19.9, 20.0, 26.5, 26.7, 31.4, 32.4, 35.9, 38.5, 43.9, 47.5, 47.8, 48.1, 53.1, 59.7, 60.4, 63.4, 64.4, 66.3, 126.8, 128.2, 128.7, 138.9, 176.8. MS (EI): *m*/*z* (%) 443 [18, (M + H)$^+$], 379 (30), 352 (5), 229 (5), 200 (100), 91 (68). Found: C, 68.0; H, 7.8; N, 6.4. Calc. for $C_{25}H_{34}N_2O_3S$: C, 67.8; H, 7.7; N, 6.3%.

8 (Minor): mp 158–160 °C, $[\alpha]_D^{25} = -37.7$ (*c* 0.45, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, s), 1.13 (3H, s), 1.30–1.50 (4H, m), 1.71–2.45 (11H, m), 2.76 (1H, d, *J* = 9.7 Hz), 3.13 (1H, d, *J* = 9.7 Hz), 3.27–3.38 (1H, m), 3.40 (1H, d, *J* = 13.3 Hz), 3.42 (2H, s), 3.70 (1H, d, *J* = 13.3 Hz), 3.95 (1H, dd, *J* = 4.4, 7.6 Hz), 7.18–7.34 (5H, m). ^{13}C NMR ($CDCl_3$) δ 19.9, 20.5, 26.6, 26.9, 32.6, 33.0, 38.5, 38.8, 44.1, 47.1, 47.8, 48.1, 53.4, 59.2, 59.9, 63.1, 63.7, 66.6, 126.8, 128.1, 128.5, 139.2, 176.1. MS (EI): *m*/*z* (%) 443 [14, (M + H)$^+$], 379 (25), 352 (4), 229 (7), 200 (100), 91 (99). Found: C, 67.6; H, 7.8; N, 6.4. Calc. for $C_{25}H_{34}N_2O_3S$: C, 67.8; H, 7.7; N, 6.3%.

N-{(3a*S*,6a*S*)-2-[(1*R*)-1-Phenylethyl]octahydrocyclopenta[*c*]-pyrrol-3a-ylcarbonyl}-(2*R*)-bornane-10,2-sultam 11

The title compound was prepared from compound **4** (700 mg, 2.26 mmol) and (*R*)-*N*-(1-phenylethyl)-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)amine (**3**, 1.68 g, 6.68 mmol) following the same procedure as for the preparation of **7** and **8** with the following exception. The crude product mixture consisting of two diastereomers (inseparable on silica gel) in a 75 : 25 ratio (GC) was recrystallised from cyclohexane (60 ml) which furnished **11** (601 mg, 1.32 mmol, 58%) as a colourless solid in >99% de (GC) and in chemical purity >99% (GC). Mp 217–219 °C, $[\alpha]_D^{25} = +5.7$ (*c* 0.53, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, s), 1.18 (3H, s), 1.25 (3H, dd, *J* = 6.5 Hz), 1.27–2.25 (15H, m), 2.74 (1H, t, *J* = 8.5 Hz), 3.07 (1H, q, *J* = 6.5 Hz), 3.25–3.40 (1H, m), 3.42 (2H, s), 3.80 (1H, d, *J* = 10.3 Hz), 3.94 (1H, dd, *J* = 5.0, 7.2 Hz), 7.16–7.30 (5H, m). ^{13}C NMR ($CDCl_3$) δ 19.8, 20.4, 23.1, 26.5, 26.7, 31.3, 32.4, 35.5, 38.5, 44.0, 47.2, 47.9, 48.3, 53.2, 59.7, 62.6, 63.3, 64.7, 66.3, 126.7, 126.9, 128.2, 145.6, 177.3. MS (EI): *m*/*z* (%) 457 [14, (M + H)$^+$], 442 (25), 393 (37), 243 (7), 214 (100), 105 (63). Found: C, 68.7; H, 8.0; N, 6.2. Calc. for $C_{26}H_{36}N_2O_3S$: C, 68.4; H, 8.0; N, 6.1%.

N-{(3a*R*,6a*R*)-2-[(1*S*)-1-Phenylethyl]octahydrocyclopenta[*c*]-pyrrol-3a-ylcarbonyl}-(2*R*)-bornane-10,2-sultam 10 and *N*-{(3a*S*,6a*S*)-2-[(1*S*)-1-phenylethyl]octahydrocyclopenta-[*c*]pyrrol-3a-ylcarbonyl}-(2*R*)-bornane-10,2-sultam 9

To a 110 °C solution of compound **4** (1.5 g, 4.85 mmol) in xylene (mixture of *o*-, *m*-, *p*-isomers, 20 ml) was added (*S*)-*N*-(1-phenylethyl)-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)-amine (**2**, 2.1 g, 8.4 mmol) over a period of 2 h. Full conversion was achieved after an additional 10 min. The crude product mixture, consisting of the two diastereomers **10** and **9** in a 80 : 20 ratio (NMR), was worked up using the same protocol as for the work up of **7** and **8**. This afforded the two individual diastereomers **10** (1.32 g, 2.89 mmol, 59%) and **9** (0.45 g, 0.99 mmol, 20%), both as colourless solids in >99% purity (GC). The compounds **10** and **9** were diastereomerically pure according to NMR analyses.

10 (Major): mp 117–119 °C, $[\alpha]_D^{25} = -74.3$ (*c* 0.54, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, s), 1.11 (3H, s), 1.30 (3H, d, *J* = 6.6 Hz), 1.32–1.49 (4H, m), 1.70–2.15 (9H, m), 2.40 (1H, dd, *J* = 4.0, 8.7 Hz), 2.47–2.56 (1H, m), 2.72 (1H, d, *J* = 10.0 Hz), 2.91 (1H, d, *J* = 10.0 Hz), 3.18 (1H, q, *J* = 6.6 Hz), 3.25–3.35 (1H, m), 3.37 (2H, s), 3.94 (1H, dd, *J* = 4.3, 7.4 Hz), 7.15–7.33 (5H, m). ^{13}C NMR ($CDCl_3$) δ 19.9, 20.5, 22.8, 26.5, 26.6, 32.7 (2 ×C), 38.2, 38.8, 44.2, 46.7, 47.7, 48.0, 53.4, 58.8, 61.7, 63.3, 64.0, 66.7, 126.7, 127.0, 128.1, 145.5, 176.3. MS (EI): *m*/*z* (%) 457 [25, (M + H)$^+$], 441 (100), 392 (20), 242 (14), 213 (95), 105 (83). Found: C, 68.7; H, 8.1; N, 6.2. Calc. for $C_{26}H_{36}N_2O_3S$: C, 68.4; H, 8.0; N, 6.1%.

9 (Minor): mp 118–121 °C, $[\alpha]_D^{25} = -37.1$ (*c* 0.52, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, s), 0.88 (3H, s), 1.31 (3H, d, *J* = 6.6 Hz), 1.32–2.19 (14H, m), 2.40 (1H, d, *J* = 10.6 Hz), 2.95 (1H, t, *J* = 8.4 Hz), 3.08 (1H, q, *J* = 6.6 Hz), 3.15 (1H, d, *J* = 10.6 Hz), 3.28 (1H, d, *J* = 13.6 Hz), 3.34 (1H, d, *J* = 13.6 Hz), 3.34–3.45

(1H, m), 3.87 (1H, dd, J = 4.9, 7.6 Hz), 7.15–7.27 (5H, m). ^{13}C NMR ($CDCl_3$) δ 19.8, 20.6, 22.8, 26.3, 26.6, 31.6, 32.5, 36.9, 38.7, 44.0, 47.2, 47.8, 47.9, 53.1, 58.9, 62.8, 63.6, 64.9, 66.5, 126.6, 127.0, 128.2, 145.1, 176.7. MS (EI): *m*/*z* (%) 457 [90, (M + H)$^+$], 442 (37), 393 (25), 242 (10), 213 (100), 105 (75). Found: C, 68.4; H, 7.9; N, 6.2. Calc. for $C_{26}H_{36}N_2O_3S$: C, 68.4; H, 8.0; N, 6.1%.

N-{(3a*S*,6a*R*)-5-[(1*S*)-1-Phenylethyl]hexahydro-1*H*-thieno-[3,4-*c*]pyrrol-3a-ylcarbonyl}-(2*R*)-bornane-10,2-sultam 14 and *N*-{(3a*R*,6a*S*)-5-[(1*S*)-1-phenylethyl]hexahydro-1*H*-thieno-[3,4-*c*]pyrrol-3a-ylcarbonyl}-(2*R*)-bornane-10,2-sultam 13

Following the procedure described for the preparation of **9** and **10**, compounds **5** (5.38 g, 16.4 mmol) and (*S*)-*N*-(1-phenylethyl)-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)amine (**2**, 5.4 g, 21.5 mmol) gave the two diastereomeric products **14** and **13** in a 75 : 25 ratio (GC). The mixture was purified by flash column chromatography [SiO_2, EtOAc–cyclohexane (10–>50% as eluent)] to give the individual diastereomers **14** and **13**, each compound in >200 : 1 diastereomeric ratio (GC). The major diastereomer **14** and the minor diastereomer **13** were further purified through recrystallisations from heptane–EtOAc (95 : 5) and heptane, respectively, to give chemically and diastereomerically pure **14** (4.34 g, 9.1 mmol, 56%) and **13** (1.70 g, 3.6 mmol, 22%) as colourless solids.

14 (Major): mp 139–141 °C, $[a]_D^{25}$ = −81.3 (*c* 0.51, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, s), 1.08 (3H, s), 1.32 (3H, d, J = 6.6 Hz), 1.32–1.51 (2H, m), 1.80–2.05 (5H, m), 2.43 (1H, dd, J = 5.5, 9.0 Hz), 2.52–2.65 (2H, m), 2.88–3.08 (4H, m), 3.30 (1H, q, J = 6.6 Hz), 3.39 (2H, s), 3.54 (1H, d, J = 12.6 Hz), 3.68–3.80 (1H, m), 3.90–3.97 (1H, m), 7.17–7.31 (5H, m). ^{13}C NMR ($CDCl_3$) δ 19.8, 20.2, 22.4, 26.6, 32.4, 36.7, 38.4, 41.8, 43.9, 47.8, 48.3, 50.6, 53.2, 56.8, 59.0, 63.7, 66.3, 68.2, 126.9 (2 × C), 128.2, 144.8, 174.1. MS (EI): *m*/*z* (%) 475 [80, (M + H)$^+$], 460 (100), 370 (7), 231 (26), 105 (73). Found: C, 63.2; H, 7.3; N, 6.0. Calc. for $C_{25}H_{34}N_2O_3S_2$: C, 63.3; H, 7.2; N, 5.9%.

13 (Minor): mp 144–147 °C, $[a]_D^{25}$ = −10.6 (*c* 0.74, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.80 (3H, s), 0.87 (3H, s), 1.31 (3H, d, J = 6.6 Hz), 1.31–1.47 (2H, m), 1.79–2.08 (5H, m), 2.13 (1H, t, J = 8.4 Hz), 2.37 (1H, d, J = 10.6 Hz), 2.52 (1H, dd, J = 1.9, 11.8 Hz), 2.96 (1H, dd, J = 6.6, 11.8 Hz), 3.12 (2H, s), 3.15–3.23 (2H, m), 3.27 (1H, d, J = 13.6 Hz), 3.34 (1H, d, J = 13.6 Hz), 3.41 (1H, d, J = 10.6 Hz), 3.79–3.91 (2H, m), 7.15–7.27 (5H, m). ^{13}C NMR ($CDCl_3$) δ 19.8, 20.6, 22.5, 26.6, 32.4, 37.0, 38.6, 40.4, 43.9, 47.8, 48.0, 52.1, 53.0, 57.6, 63.1, 64.5, 66.6, 67.2, 126.7, 127.0, 128.2, 144.8, 174.6. MS (EI): *m*/*z* (%) 475 [74, (M + H)$^+$], 460 (100), 370 (8), 231 (37), 105 (100). Found: C, 63.4; H, 7.4; N, 6.0. Calc. for $C_{25}H_{34}N_2O_3S_2$: C, 63.3; H, 7.2; N, 5.9%.

General method for reductive removal of bornanesultam

A solution of one of the cycloadducts in THF (0.11 mmol ml^{-1}) was added dropwise to a stirred solution of $LiAlH_4$ (3 mol equivalents) in THF (0.33 mmol ml^{-1}) at 0 °C. The reaction was then allowed to reach room temperature and after 0.5 h HCl (aq., 1 M, 35 ml per mmol substrate) was added followed by EtOAc (100 ml per mmol substrate). The organic phase was extracted with HCl (1 M, 2 × 35 ml per mmol substrate), dried ($MgSO_4$), filtered and concentrated to give recovered bornanesultam in 97–99% yield and purity >99% (GC). The aqueous phase was basified (6 M NaOH) and extracted with EtOAc (3 × 50 ml per mmol substrate). The organic phase was dried ($MgSO_4$), filtered and concentrated to yield the crude alcohol. Distillation furnished the pure alcohol in the yields specified for each compound below.

{(3a*R*,6a*R*)-2-[(1*S*)-1-Phenylethyl]octahydrocyclopenta[*c*]-pyrrol-3a-yl}methanol 16

Compound **10** (0.62 g, 1.37 mmol) when subjected to the general method for reductive removal of bornanesultam, furnished alcohol **16** (0.315 g, 1.28 mmol, 93%) as a colourless oil in >99% purity (GC). Bp 140 °C, 1.4 mbar, $[a]_D^{25}$ = −53.7 (*c* 0.54, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.05–1.70 (7H, m), 1.30 (3H, d, J = 6.6 Hz), 2.02 (1H, d, J = 8.9 Hz), 2.25–2.38 (1H, m), 2.84 (1H, t, J = 8.8 Hz), 3.02–3.15 (2H, m), 3.32 (1H, dd, J = 0.9, 9.4 Hz), 3.67 (1H, d, J = 9.4 Hz), 4.10 (1H, br s), 7.12–7.26 (5H, m). ^{13}C NMR ($CDCl_3$) δ 23.0, 24.9, 31.5, 33.8, 45.0, 54.8, 61.3, 62.3, 64.9, 71.6, 126.9, 127.0, 128.4, 144.6. MS (EI): *m*/*z* (%) 246 [100, (M + H)$^+$], 230 (75), 105 (8). Found: C, 78.3; H, 9.6; N, 5.9. Calc. for $C_{16}H_{23}NO$: C, 78.3; H, 9.4; N, 5.7%.

{(3a*S*,6a*S*)-2-[(1*R*)-1-Phenylethyl]octahydrocyclopenta[*c*]-pyrrol-3a-yl}methanol 17

Compound **11** (0.52 g, 1.13 mmol) when subjected to the general method for reductive removal of bornanesultam, furnished alcohol **17** (0.275 g, 1.12 mmol, 99%) as a colourless oil in >99% purity (GC). $[a]_D^{25}$ = +57.2 (*c* 0.52, MeOH). All other data were identical to those for the enantiomer described above.

[(3a*S*,6a*S*)-2-Benzyloctahydrocyclopenta[*c*]pyrrol-3a-yl]-methanol 15

Compound **7** (0.355 g, 0.80 mmol) when subjected to the general method for reductive removal of bornanesultam, furnished alcohol **15** (0.174 g, 0.75 mmol, 94%) as a colourless oil in 99% purity (GC). Bp 130 °C, 0.8 mbar, $[a]_D^{25}$ = −15.6 (*c* 0.39, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.11–1.28 (1H, m), 1.41–1.73 (5H, m), 1.85 (1H, t, J = 8.4 Hz), 2.07 (1H, d, J = 9.1 Hz), 2.40–2.52 (1H, m), 2.89 (1H, d, J = 9.1 Hz), 3.15 (1H, t, J = 8.6 Hz), 3.37 (1H, dd, J = 1.0, 9.5 Hz), 3.53 (2H, s), 3.64 (1H, d, J = 9.5 Hz), 3.72 (1H, br s), 7.19–7.36 (5H, m). ^{13}C NMR ($CDCl_3$) δ 25.0, 31.5, 33.8, 45.4, 55.1, 59.7, 62.0, 63.9, 71.1, 127.0, 128.3, 128.6, 138.4. MS (EI): *m*/*z* (%) 232 [87, (M + H)$^+$], 214 (2), 140 (32), 91 (100). Found: C, 77.5; H, 9.2; N, 6.1. Calc. for $C_{15}H_{21}NO$: C, 77.9; H, 9.2; N, 6.0%.

{(3a*S*,6a*R*)-5-[(1*S*)-1-Phenylethyl]hexahydro-1*H*-thieno[3,4-*c*]-pyrrol-3a-yl}methanol 18

Compound **14** (0.50 g, 1.05 mmol) when subjected to the general method for reductive removal of bornanesultam, furnished alcohol **18** (0.243 g, 0.92 mmol, 88%) as a colourless oil in 99% purity (GC). Bp 150 °C, 0.8 mbar, $[a]_D^{25}$ = −83.3 (*c* 0.97, MeOH). ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, d, J = 6.6 Hz), 2.00 (1H, t, J = 8.2 Hz), 2.42 (1H, d, J = 8.2 Hz), 2.47–2.51 (1H, m), 2.53 (1H, d, J = 12.1 Hz), 2.60 (1H, d, J = 12.1 Hz), 2.70 (1H, dq, J = 2.4, 7.5 Hz), 2.86 (1H, d, J = 8.5 Hz), 2.92 (1H, dd, J = 7.2, 12.0 Hz), 3.13 (1H, d, J = 8.8 Hz), 3.21 (1H, q, J = 6.6 Hz), 3.49 (1H, dd, J = 1.0, 9.5 Hz), 3.76 (1H, d, J = 9.5 Hz), 4.05 (1H, br s), 7.19–7.35 (5H, m). ^{13}C NMR ($CDCl_3$) δ 22.9, 37.5, 39.3, 49.0, 59.5, 60.0, 61.4, 64.6, 70.0, 126.8, 127.1, 128.4, 144.7. MS (EI): *m*/*z* (%) 263 (17, M$^+$), 248 (100), 158 (11), 105 (30). Found: C, 68.7; H, 8.0; N, 5.3. Calc. for $C_{15}H_{21}NOS$: C, 68.4; H, 8.0; N, 5.3%.

(3a*R*,6a*R*)-Octahydrocyclopenta[*c*]pyrrol-3a-ylmethanol 19

To a solution of **16** (250 mg, 1.02 mmol) in MeOH (5 ml) 10% Pd/C (70 mg) was added. The suspension was allowed to stir at room temperature under hydrogen for 15 h. The Pd/C was filtered off and the residue was concentrated to give **19** (129 mg, 0.91 mmol, 89%) as a semi-solid in >99% purity (GC). $[a]_D^{25}$ = +13.9 (*c* 1.27, MeOH, free base). ^{1}H NMR (D_2O, HCl salt) δ 1.45–1.90 (6H, m), 2.45–2.58 (1H, m), 2.97 (1H, dd, J = 6.9, 12.1 Hz), 3.05 (1H, d, J = 12.2 Hz), 3.40 (1H, d, J = 12.2 Hz), 3.45–3.58 (3H, m). ^{13}C NMR (D_2O, HCl salt) δ 25.0, 31.5, 35.0, 45.2, 52.1, 54.3, 56.0, 67.1. MS (EI, free base): *m*/*z* (%) 142 [100, (M + H)$^+$], 123 (7), 111 (4). Found: C, 54.0; H, 9.1; N, 7.9. Calc. for $C_8H_{15}NO{\cdot}HCl$: C, 54.1; H, 9.1; N, 7.9%.

(3a*S*,6a*S*)-Octahydrocyclopenta[*c*]pyrrol-3a-ylmethanol *ent*-19

Following the same procedure for the preparation of **19**, compounds **15** and **17** furnished *ent*-**19**. $[a]_D^{25} = -14.3$ (*c* 1.25, MeOH, free base). All other data were identical to those for the enantiomer **19**.

(3a*S*,6a*R*)-Hexahydro-1*H*-thieno[3,4-*c*]pyrrol-3a-ylmethanol hydrochloride 20

The title compound was prepared following a procedure similar to that reported by Bonjoch *et al.*[15] To a solution of **18** (140 mg, 0.53 mmol) and 1,8-bis(dimethylamino)naphthalene (250 mg, 1.17 mmol) in dry 1,2-dichloroethane (20 ml) at 0 °C 1-chloroethyl chloroformate (0.29 ml, 2.66 mmol) was slowly added. After 0.25 h the solution was allowed to stir overnight at room temperature. The reaction was then heated at reflux for 3 h followed by cooling and addition of HCl (aq., 1 M, 20 ml) and CH_2Cl_2 (50 ml). The organic phase was extracted with HCl (aq., 1 M, 20 ml) and Na_2CO_3 (aq., sat., 30 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated followed by purification of the residue by flash chromatography [SiO_2, EtOAc–cyclohexane (5–50%)]. Without further purification the resulting carbamate–carbonate intermediate was dissolved in MeOH (10 ml) and refluxed (1 h) followed by addition of HCl (3 M, 4 ml). Reflux for 2 h followed by concentration, gave **20** (80.0 mg, 0.41 mmol, 77%) as a colourless solid in >98% purity (GC, free base). Recrystallisation from MeOH–EtOAc furnished **20** in >99% purity. Mp 156–158 °C, $[a]_D^{25} = 0.0$ (*c* 2.1, MeOH). ^{1}H NMR (D_2O) δ 2.65–2.74 (2H, m), 2.81 (1H, d, *J* = 12.5 Hz), 2.85–2.96 (1H, m), 3.02 (1H, dd, *J* = 6.5, 12.2 Hz), 3.08 (1H, dd, *J* = 8.0, 11.8 Hz), 3.16 (1H, d, *J* = 12.2 Hz), 3.53 (1H, d, *J* = 12.2 Hz), 3.62 (2H, s), 3.64 (1H, dd, *J* = 8.2, 12.0 Hz). ^{13}C NMR (D_2O) δ 36.4, 39.4, 48.9, 51.4, 53.7, 60.4, 65.6. MS (EI, free base): *m*/*z* (%) 159 (100, M^+), 142 (11), 128 (60). Found: C, 42.7; H, 7.1; N, 7.0. Calc. for $C_7H_{13}NOS{\cdot}HCl$: C, 43.0; H, 7.2; N, 7.2%.

Ethyl (3a*R*,6a*R*)-2-[(1*S*)-1-phenylethyl]octahydrocyclopenta[*c*]-pyrrole-3a-carboxylate 21

$Ti(OEt)_4$ (2.5 g, 11.0 mmol) was added to a solution of **10** (1.0 g, 2.19 mmol) in EtOH (99.5%, 5 ml). After reflux for 3 h, the solvent was evaporated off and the residue was purified by column chromatography [SiO_2, EtOAc–cyclohexane (0–80% as eluent)]. After distillation, compound **21** (570 mg, 1.98 mmol, 90%) was obtained as a colourless oil in >99% purity (GC) along with recovered bornanesultam (458 mg, 2.13 mmol, 97%) in >99% purity. Bp 130 °C, 0.9 mbar, $[a]_D^{25} = -70.0$ (*c* 0.65, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, *J* = 7.0 Hz), 1.32 (3H, d, *J* = 6.1 Hz), 1.45–2.05 (6H, m), 2.38 (1H, d, *J* = 9.4 Hz), 2.47–2.55 (2H, m), 2.75 (1H, d, *J* = 9.4 Hz), 2.79–2.89 (1H, m), 3.13 (1H, q, *J* = 6.2 Hz), 4.11 (2H, q, *J* = 7.0 Hz), 7.15–7.35 (5H, m). ^{13}C NMR ($CDCl_3$) δ 14.2, 23.4, 26.8, 34.0, 38.6, 47.0, 59.2, 59.5, 60.4, 62.8, 64.8, 126.7, 127.0, 128.2, 146.0, 177.3. MS (EI): *m*/*z* (%) 288 [10, $(M + H)^+$], 272 (100), 244 (12), 182 (15), 105 (20). Found: C, 75.5; H, 8.8; N, 5.0. Calc. for $C_{18}H_{25}NO_2$: C, 75.2; H, 8.8; N, 4.9%.

(3a*R*,6a*R*)-2-[(1*S*)-1-Phenylethyl]octahydrocyclopenta[*c*]-pyrrole-3a-carboxamide 22

NH_2Li (250 mg, 10.9 mmol) was added to a solution of **21** (440 mg, 1.53 mmol) in THF (4 ml). After 6 h of reflux, MeOH–H_2O was added. The mixture was diluted with EtOAc (50 ml) and extracted with HCl (1 M, 2 × 40 ml). The pooled aqueous phase was made basic with NaOH (6 M) and extracted with EtOAc (100 + 50 ml). The organic phase was dried ($MgSO_4$) and concentrated. Flash column chromatography [SiO_2, EtOAc–cyclohexane (10–80% as eluent)] furnished **22** (305 mg, 1.18 mmol, 77%) as a colourless solid in >99% purity (GC). Mp 125–126 °C, $[a]_D^{25} = -2.6$ (*c* 1.68, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, d, *J* = 6.6 Hz), 1.38–1.78 (6H, m), 2.03 (1H, d, *J* = 9.4 Hz), 2.17–2.33 (1H, m), 2.63 (1H, q, *J* = 7.6 Hz), 2.96 (1H, t, *J* = 8.8 Hz), 3.24 (1H, q, *J* = 6.5 Hz), 3.45 (1H, d, *J* = 9.4 Hz), 5.78 (1H, br s), 7.22–7.36 (5H, m), 7.58 (1H, br s). ^{13}C NMR ($CDCl_3$) δ 22.9, 24.8, 31.2, 31.6, 49.2, 58.7, 60.2, 62.3, 64.5, 126.7, 127.2, 128.4, 144.8, 180.8. MS (EI): *m*/*z* (%) 259 [97, $(M + H)^+$], 243 (100), 214 (10), 153 (62), 105 (67). Found: C, 74.8; H, 8.7; N, 10.9. Calc. for $C_{16}H_{22}N_2O$: C, 74.4; H, 8.6; N, 10.8%.

(3a*S*,6a*R*)-Octahydrocyclopenta[*c*]pyrrol-3a-ylmethylamine dihydrobromide (−)-23

Compound **22** (251 mg, 0.97 mmol) dissolved in THF (5 ml) was added to a 0 °C solution of $LiAlH_4$ (111 mg, 2.9 mmol) in THF (2 ml). The reaction was allowed to reach room temperature for 0.2 h followed by heating at reflux for 0.5 h. Addition of H_2O (0.5 ml), filtration, rinsing the solid collected with ether and concentration of the filtrate furnished the corresponding primary amine (222 mg, 0.91 mmol, 94%) as a semi solid in >99% purity (GC). ^{1}H NMR (2 × HCl salt, D_2O, * denotes peaks arising from a minor conformer) δ 1.45–1.89 (6H, m), 1.70 (3H, d, *J* = 6.9 Hz), 2.05–2.20* (0.3H, m), 2.38–2.50 (0.7H, m), 2.63–2.73 (1H, m), 3.01–3.50 (4H, m), 3.74* (0.3 H, d, *J* = 11.0 Hz), 4.09 (0.7H, d, *J* = 12.2 Hz), 4.35–4.45 (1H, m), 7.42–7.55 (5H, m). ^{13}C NMR (2 × HCl salt, D_2O, * denotes peaks arising from a minor conformer) δ 18.4, 24.4, 26.0*, 30.0, 33.1*, 35.9, 36.0*, 46.1*, 46.6, 46.7, 52.2, 52.3*, 58.3, 59.6*, 61.1, 62.2*, 66.5, 67.8*, 128.8, 128.9*, 130.0, 130.7, 136.0. MS (EI, free base): *m*/*z* (%) 245 [100, $(M + H)^+$], 229 (9), 139 (12), 110 (30). Without any further purification this primary amine was dissolved in MeOH (3 ml), 10% Pd/C (50 mg) was added and the resulting suspension was allowed to stir over night under an atmosphere of hydrogen. The Pd/C was filtered off and rinsed with MeOH. HBr (0.5 ml, 48%) was added followed by concentration of the solution. This furnished (−)-**23** (236 mg, 0.78 mmol, 80%) as a red–brown solid, pure according to NMR analysis. Recrystallisation from MeOH–EtOAc gave colourless crystals of (−)-**23**. $[a]_D^{25} = -1.0$ (*c* 5.8, MeOH), lit.[7] $[a]_D^{24} = -0.9$ (*c* 49.5, MeOH). MS (EI, free base): *m*/*z* (%) 141 [100, $(M + H)^+$], 123 (7). All other data agreed with those reported for the enantiomer.[7]

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