Pergamon

Tetrahedron Vol. 51, No. 21, pp. 6061-6070, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00264-2

Total Synthesis of Balanol, Part 1. Enantioselective Synthesis of the Hexahydroazepine Ring via Chiral Epoxides and Aziridines

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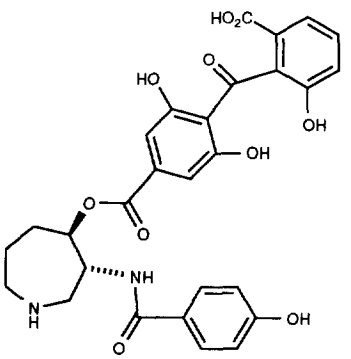
Abstract: Three different routes to the hexahydroazepine unit of the natural products balanol (**1**) and ophiocordin (**2**) are described. The common starting material is the chiral epoxy alcohol **3** which is converted to the balanol degradation product **10** (Scheme 1) or to suitably protected derivatives thereof: **15** (Scheme 2) and **19** (Scheme 3). A key step in the first route is the acid-catalysed ring-opening of bicyclic aziridine **8** which proceeds in good chemical yield (71% isolated) and with remarkable regioselectivity (98:2 in favour of the desired regioisomer).

Balanol (**1**) is a natural product isolated from the fungus *Verticillium balanoides* and shows remarkable inhibitory properties towards protein kinase C.[1] Compound **1** and its regioisomer ophiocordin, **2**, an antifungal antibiotic[2] from the fungus *Cordyceps ophioglossoides*, have recently been the subjects of synthetic studies,[3] an important aspect of which is the development of procedures sufficiently flexible to allow access to a range of non-natural analogs suitable for screening.



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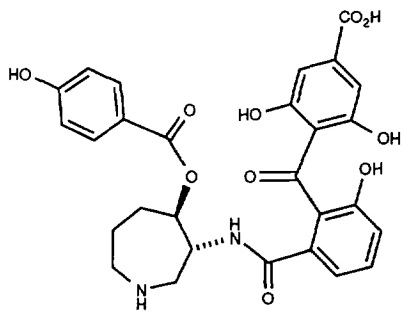

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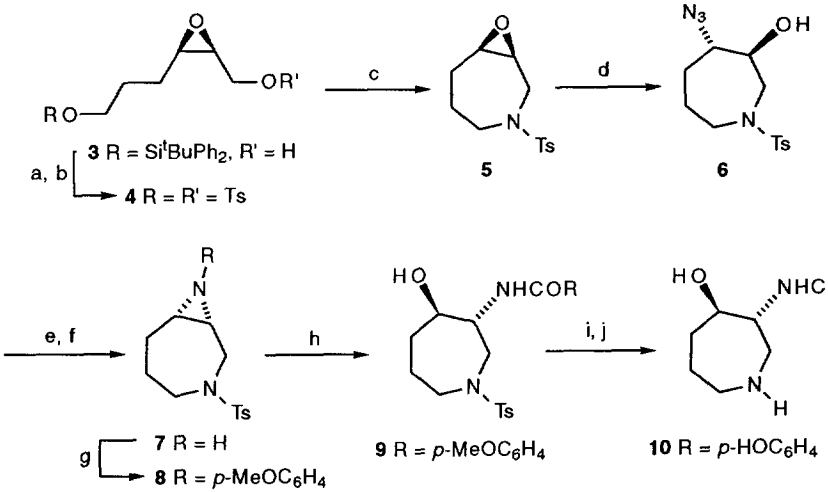
In this paper we present three different routes to the hexahydroazepine portion of **1** and **2**, with the readily available chiral epoxide **3** as a common precursor. The first route (Scheme 1) illustrates our long-standing interest in the chemistry of chiral aziridines[4] and is characterised by the unexpectedly high regioselectivity observed in the ring-opening of bicyclic aziridine **8**.

The epoxy alcohol **3** (obtained in 90% *e.e.* [5] via Sharpless asymmetric epoxidation[6]) was converted to ditosylate **4** in two operations, the second requiring use of *N*-tosylimidazole[7] in the presence of Bu_4NF.[8] The *cis* geometry of **4** facilitated ring closure to the desired seven-membered ring, particularly when cesium carbonate[9] was used together with *p*-toluenesulfonamide to give **5**. Crude yields were near-quantitative, and

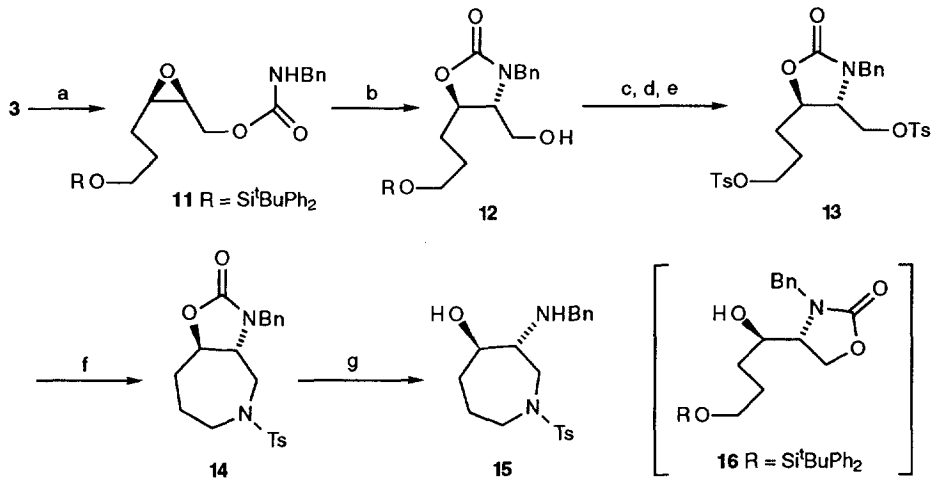
analytically pure **5** could be isolated in 88% yield after flash chromatography and recrystallisation; the recrystallisation did not enhance the *e.e.* to any observable extent.[10] When **5** was reacted with LiN_3 in hot DMF, azido alcohol **6** was produced with remarkably high regioselectivity (97:3 ratio of separable isomers).



*Scheme 1. (a) p-TsCl, NEt_3, DMAP, CH_2Cl_2, 91% (b) N-tosylimidazole, Bu_4NF, THF, 74% (c) p-$TolSO_2NH_2$, Cs_2CO_3, DMF, room temp., 88% (d) LiN_3, DMF, 90°C, 87% (e) MsCl, NEt_3, CH_2Cl_2, 96% (f) $LiAlH_4$, THF, 50°C, 88% (g) p-$MeOC_6H_4COCl$, NEt_3, CH_2Cl_2, 86% (h) pTsOH, H_2O, THF, room temp., 71% (i) BCl_3, CH_2Cl_2, room temp. (j) Na(Hg), Na_2HPO_4, MeOH, reflux, 67% overall from **10**.*

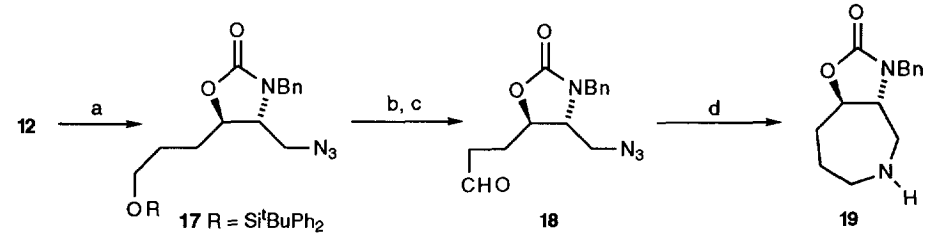
The major regioisomer was obtained analytically pure in 87% yield and a single recrystallisation afforded material[10] of >96% *e.e.* Although **6** possesses the wrong regiochemistry for the synthesis of **1** and **2**, it is obviously an attractive precursor to non-natural congeners. (Investigation of the detailed structural features of **5**, via molecular modelling, X-ray crystallography, and high-field NMR spectroscopy, as well as results of a study of its ring-opening by a range of nucleophiles will be the subjects of a separate report).[11] The regiochemical problem posed by **6** was solved by transformation[12] to aziridine **8** which, in direct analogy to **5**, underwent near-exclusive ring-opening[13] at C-4 (98:2 ratio of regioisomers, 71% isolated yield of **9**; we have also observed[11] that a number of other oxygen and nitrogen nucleophiles attack **8** with excellent C-4 selectivity). For comparison, compound **9** was then converted in two steps[14, 15] to **10**, a known degradation product of balanol.[1]

Our second route to a suitably protected derivative of the heterocyclic component of balanol and ophiocordin is shown in Scheme 2. Epoxide **3** was now elaborated to the 2-oxazolidinone **12** in two operations, the second of which (**11** to **12**) presumably involves an *in situ* acyl transfer[16] within the initially-formed **16** (which was never isolated). Similar behaviour for a related *cis* epoxyurethane has been reported by Roush.[16] Conversion of **12** to ditosylate **13** was followed by ring closure under very mild conditions[9] to the required hexahydroazepine **14** (55% yield for the one-pot, two-step, transformation of **13**; the structure of **14** has been confirmed by X-ray crystallography[11]). Recrystallisation at this point yielded material[10] of >99% *e.e.* and hydrolysis furnished enantiomerically pure **15**.



Scheme 2. (a) BnN=C=O, NEt3, CH2Cl2, 90% (b) NaH, THF, room temp., 90% (c) p-TsCl, NEt3, CH2Cl2, 97% (d) Bu4NF, THF, 0°C, 90% (e) p-TsCl, NEt3, DMAP, CH2Cl2, 88% (f) p-TolSO2NH2, Cs2CO3,, DMF, room temp., 55% (g) LiOH, THF, H2O, EtOH, reflux, 98%.

The sequence shown in Scheme 3 has so far been carried out with racemic material only, the reason being the capricious behaviour of the ring-closure/reduction stage which transforms **18** to **19**.



Scheme 3. (a) PPh3, CBr4, LiN3, DMF, room temp., 92% (b) Bu4NF, THF, 0°C, 93% (c) PCC, NaOAc, mol. sieves, CH2Cl2, 70% (d) PPh3, toluene, then NaBH4, MeOH, ca. 50%.

Racemic **12** was converted in three operations[17] and good overall yield (60%) to azido aldehyde **18**, which was expected to be a suitable substrate for cyclisation via an intramolecular Staudinger reaction followed by *in situ* reduction of the intermediate cyclic imine.[18] However, while conversion of **18** usually appeared to be complete according to TLC, obtention of **19** was plagued by irreproducibility and (according to ^{1}H NMR and MS) formation of the corresponding "dimer" (14-membered ring). In the best cases, **19** could be isolated in *ca.* 50% yield (structure confirmed by conversion to *rac*-**14**). Due to these difficulties, we made no attempt to repeat the sequence using optically active materials.

In conclusion, we note that others have described[3a, b, d] the preparation of the benzophenone fragment of balanol and ophiocordin (in itself a synthetic challenge due to the sterically congested nature of the ketone) and the conversion of our intermediates such as **7** and **14** to the natural products will be reported separately.[11]

Acknowledgements. We thank *Astra Draco AB* and the *Swedish Natural Science Research Council* for financial support. We are also indebted to Prof. D. R. Williams (Indiana University) for provision of experimental procedures relevant to Scheme 3, and to Magnus Karlsson (Astra Draco AB) for mass spectra.

EXPERIMENTAL

General remarks. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL 300 spectrometer ($CDCl_3$/TMS unless otherwise stated). IR spectra were obtained on a Perkin-Elmer 1600 FT-IR instrument. Specific rotation values were measured on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a VG Autospec-Q instrument equipped with an electrospray interface. Elemental analyses were performed by Analytische Laboratorien, Gummersbach, Germany. Tetrahydrofuran (THF) was distilled under nitrogen from Na/benzophenone; methanol was distilled under nitrogen from magnesium turnings; methylene chloride, triethylamine, and dimethylformamide (DMF) were distilled under nitrogen from calcium hydride. Silica gel for flash chromatography was purchased from Grace-Amicon.

Epoxy alcohol **3** was obtained according to the literature procedure[5] for preparation of the enantiomer, with the exception that (+)-diethyltartrate was used as the source of chirality. The *e.e.* of **3**, which showed $[\alpha]_D^{19}$ -2.5 (*c* = 1.0, CH_2Cl_2), was determined to be 90% by chiral HPLC analysis of the corresponding acetate.[10] ^1H NMR: δ 1.05 (s, 9H); 1.60 - 1.76 (m, 4H); 1.99 (dd, J = 7, 2; 1H, O*H*); 3.02 (td, J = 6, 4; 1H); 3.16 (td, J = 6, 4; 1H); 3.65 - 3.85 (m, 4H); 7.34 - 7.48 (m, 6H); 7.62 - 7.68 (m, 4H). ^{13}C NMR: 19.2, 24.2, 26.9, 29.4, 56.7, 57.0, 60.8, 63.2, 127.7, 129.7, 133.6, 135.5, 135.6. IR: 3600 - 3200, 2930, 2856, 1427, 1111 cm^{-1}. Anal. Calc. for $C_{22}H_{30}O_3Si$: C, 71.35%; H, 8.11. Found: C: 71.19; H, 8.01.

Ditosylate **4**. (i) Epoxy alcohol **3** (9.825 g, 26.55 mmol) was dissolved with stirring under nitrogen in dry CH_2Cl_2 (300 mL) and cooled in an ice-bath. Triethylamine (7.4 mL, 53.1 mmol), DMAP (0.100 g) and *p*-TsCl (6.57 g, 34.49 mmol) were added and the mixture was stirred at room temperature for 14 h. Water (150 mL) was added, the aqueous phase was extracted with CH_2Cl_2 (50 mL) and the combined organics were washed with brine, dried over Na_2SO_4, and concentrated to give a residue which was purified by flash chromatography (silica gel, ether/pentane, 1/4 to 1/2 gradient) to afford the monotosylated derivative of **3** as a colorless oil (12.69 g, 91%). $[\alpha]_D^{19}$ -10.6 (*c* = 1.08, CH_2Cl_2); ^1H NMR: 1.04 (s, 9H); 1.48 - 1.74 (m, 4H); 2.43, s, 3H); 2.99 (ddd, J = 6.5, 5.5, 4.5; 1H); 3.15 (td, J = 6.5, 4.5; 1H); 3.67 (td, J = 6, 2; 2H); 4.06 (dd, J = 11, 6; 1H); 4.19 (dd, J = 11, 4.5; 1H); 7.28 and 7.80 (AA'BB', J_{AB} = 8.2; 4H); 7.32 - 7.46 (m, 6H); 7.61 - 7.69 (m, 4H); ^{13}C NMR: 19.2, 21.7, 24.5, 26.8, 29.4, 53.2, 56.4, 63.0, 68.2, 127.7, 128.0, 129.7, 130.0, 133.7, 135.5, 145.1; IR: 2930, 1369, 1178, 1111.

(ii) The product from above (12.3 g, 23.47 mmol) was dissolved with stirring under nitrogen in dry THF (90 ml) and *N*-tosylimidazole (26 g, 117 mmol) was added. After 10 min a solution of tetrabutylammonium fluoride (TBAF, 1M in THF, 23.5 mL, 23.5 mmol) was added dropwise over 65 min. The resultant mixture was stirred at room temp. for 2 h and diluted with ether (150 mL). The solution was washed with brine (50 mL), dried over Na_2SO_4 and the solvents were removed *in vacuo*. Flash chromatography (EtOAc/CH_2Cl_2, 1/29) separated unreacted *N*-tosylimidazole (16.9 g) and afforded **4** as a viscous colorless oil (7.65 g, 74%). $[\alpha]_D^{19}$ -4.4 (*c* = 1.1, CH_2Cl_2); ^1H NMR: 1.30 - 1.42 (m, 1H); 1.52 - 1.68 (m, 1H); 1.74 - 1.87 (m, 2H); 2.44 (s, 6H); 2.92 (td, J = 4.5, 7.5; 1H); 3.13 (app. q, J = 4.5; 1H); 3.95 - 4.13 (m, 4H); 7.34 and 7.77 (2xAA'BB', J_{AB} = 8; 8H); ^{13}C NMR: 21.6, 23.9, 26.0,. 53.0, 55.6, 67.7, 69.5, 127.8, 127.9, 129.9,

130.0, 132.4, 132.7, 144.9, 145.3; IR: 2960, 1359, 1174; Anal. Calc. for $C_{20}H_{24}O_7S_2$: C, 54.54%; H, 5.45. Found: C, 54.36; H, 5.43.

Bicyclic epoxide **5**. Cesium carbonate (10.84 g, 33.26 mmol) was added to a solution of *p*-toluenesulfonamide (2.85 g, 16.64 mmol) in dry DMF (400 mL) and the mixture was stirred under nitrogen at room temp. for 3 h. A solution of **4** (6.1 g, 13.86 mmol) in DMF (40 mL) was added dropwise over 4.5 h and the resultant solution stirred for 24 h. The solvent was evaporated at reduced pressure and the residue partitioned between ether (100 mL) and water (50 mL). The aqueous phase was extracted with ether (50 mL) and EtOAc (50 mL) and the combined organics were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (CH_2Cl_2/ether, 30/1) to give **5** as a white solid (2.45 g, 88%). Recrystallisation from toluene/pentane afforded crystals with mp 77 - 78°C. This material showed $[\alpha]_D^{19}$ +7.8 (*c* = 1.2, CH_2Cl_2) and was of 90% *e.e.*[10] ^1H NMR (C_6D_6) : 1.12 - 1.51 (m, 4H); 1.92 (s, 3H); 2.49 (td, J = 12, 4.5, 1H); 2.58 (td, J = 4, 5; 1H); 2.80 (dd, J = 14, 6; 1H); 2.91 (td, J = 4, 6; 1H); 3.18 (dtd, J = 12, 4, 1; 1H); 3.65 (ddd, J = 14, 4, 1; 1H); 6.80 and 7.63 (AA'BB', J_{AB} = 8; 4H). ^{13}C NMR: 21.5, 24.0, 27.7, 48.3, 50.9, 54.3, 55.0, 127.1, 129.7, 136.3, 143.4; IR:2922, 1330, 1156; Anal. Calc. for $C_{13}H_{17}NO_3S$: C, 58.43%; H, 6.37; N, 5.24. Found: C, 58.26; H, 6.31; N, 5.24.

Azido alcohol **6**. Lithium azide (1.26 g, 25.84 mmol) was added to a solution of **5** (1.7 g, 6.46 mmol) in dry DMF (55 mL) and the mixture was stirred at 90°C under nitrogen for 48 h. The solvent was evaporated at reduced pressure and the residue partitioned between water (30 mL) and ether (50 mL). The aqueous phase was extracted with ether (2 x 50 mL) and the combined organics were washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (ether/pentane, 3/2) to give **6** as a white solid (90% *e.e.*[10]). Recrystallisation (EtOAc/pentane, 1/4) gave 1.5 g of needles, m.p. 119 - 120°C. This material was of 99% *e.e.*[10] and showed $[\alpha]_D^{19}$ +4.5 (*c* = 1.00, CH_2Cl_2). ^1H NMR: 1.72 - 2.05 (m, 4H); 2.43 (s, 3H); 3.01 (d, J = 6; 1H, O*H*); 3.06 (m, 1H); 3.27 (dd, J = 12, 3.5; 1H); 3.33 (dd, J = 12, 5.5; 1H); 3.48 (dt, J = 12, 6; 1H); 3.57 (m, 1H); 3.70 (m, 1H); 7.32 and 7.67 (AA'BB', J_{AB} = 8.3; 4H); ^{13}C NMR: 21.5, 23.4, 26.2, 48.0, 49.2, 67.0, 73.1, 126.9, 129.8, 135.3, 143.7; IR: 3524, 2096, 1328, 1157; Anal. Calc. for $C_{13}H_{18}N_4O_3S$: C, 50.32%; H, 5.81; N, 18.06. Found: C, 50.38; H, 5.77; N, 18.12.

Aziridine **7**. (i) Azido alcohol **6** (0.92 g, 2.96 mmol) was dissolved with stirring under nitrogen in dry CH_2Cl_2 (40 mL) and the solution was cooled to 0°C. Triethylamine (0.82 mL, 5.92 mmol) was added, followed by mesyl chloride (0.43 mL, 4.44 mmol) and the resultant mixture was stirred at 0°C for 2 h. The mixture was diluted with CH_2Cl_2 (40 mL) and then washed with brine, dried (Na_2SO_4) and the solvent was removed. Flash chromatography of the residue (CH_2Cl_2/ether, 29/1) afforded the azido mesylate as a viscous oil which crystallised as needles (mp. 111 - 112°C) upon trituration with ether. Yield: 1.11 g, 96%. $[\alpha]_D^{19}$ +44.2 (*c* = 1.00, CH_2Cl_2); ^1H NMR: 1.75 - 2.00 (m, 4H); 2.42 (s, 3H); 3.15 (m, 1H); 3.17 (s, 3H); 3.30 (m, 1H); 3.47 (dd, J = 12.5, 6; 1H); 3.53 (dd, J = 12.5, 4; 1H); 3.65 (ddd, J = 9.5, 7.2, 2.5; 1H); 4.56 (ddd, J = 7.2, 6, 4; 1H); 7.31 and 7.67 (AA'BB', J_{AB} = 8.3; 4H); ^{13}C NMR: 21.5, 23.7, 26.9, 38.4, 47.8, 48.1, 65.0, 81.2, 127.1, 129.9, 135.2, 143.8; IR: 2107, 1340, 1175, 1159.

(ii) The azido mesylate from above (1.01 g, 2,6 mmol) was dissolved with stirring (at 0°C) under nitrogen in THF (200 mL) and $LiAlH_4$ (0.296 g, 7.8 mmol) was added in small portions. The mixture was then heated at 50°C for 3 h and cooled to 0°C before saturated aqueous Na_2SO_4 solution (300 µl) was added. Ether (50 mL) was added, the mixture was stirred at room temp. overnight, solid Na_2SO_4 was added, and the mixture was stirred for another hour. The mixture was evaporated to dryness and the residue flash chromatographed (EtOAc/MeOH, 9/1) to give **7** as a crystalline solid, mp. 154 - 155°C. Yield: 0.61 g, 88%. $[\alpha]_D^{19}$ -5.0 (*c* =

0.80, CH_2Cl_2); ^1H NMR: 1.10 (b, 1H; N*H*); 1.30 - 1.40 (m, 1H); 1.60 - 1.85 (m, 2H) 2.15 - 2.30 (m, 2H); 2.41 (s, 3H); 2.45 (m, 1H); 2.50 - 2.64 (m, 2H); 3.73 (bm, 1H); 4.15 (bm, 1H); 7.28 and 7.65 (AA'BB', J_{AB} = 8.5; 4H). The spectrum is temperature-dependent, due to aziridine nitrogen inversion. ^{13}C NMR: 21.5, 27.0, 29.5, 33.0, 33.6, 51.6, 52.3, 127.0, 129.7, 136.4, 143.2; IR: 3332, 3312, 2945, 1332, 1162. Anal. Calc. for $C_{13}H_{18}N_2O_2S$: C, 58.62%; H, 6.81; N, 10.52. Found: C, 58.56; H, 6.77; N, 10.50.

Aziridine **8**. Triethylamine (1.05 mL) and a solution of *p*-anisoyl chloride (0.51 g, 3 mmol) in CH_2Cl_2 (4 mL) were added to an ice-cold solution of **7** (0.67 g, 2.5 mmol) in CH_2Cl_2 (40 mL) under nitrogen. The mixture was allowed to reach room temp. and was stirred for 15 h before dilution with CH_2Cl_2 (50 mL) and addition of water. The aqueous phase was extracted with CH_2Cl_2 (30 mL) and the combined organics were washed with brine (2 x 30 mL), dried over Na_2SO_4, and stripped down to yield a residue which was purified by flash chromatography (EtOAc/pentane, 1/2 to 2/3 gradient, then ether/CH_2Cl_2, 1/19). The acyl aziridine **8** was obtained as a viscous pale yellow oil (0.867 g, 86%). $[\alpha]_D^{19}$ -27.8 (*c* = 0.46, CH_2Cl_2); ^1H NMR: 1.70 - 1.83 (m, 2H); 1.95 (m, 1H); 2.17 (m, 1H); 2.35 (s, 3H); 2.69 (td, J = 6.5, 4; 1H); 2.86 (td, J = 6.5, 4; 1H); 3.19 (m, 1H); 3.31 (m, 1H); 3.48 (dd, J = 15, 6.5; 1H); 3.86 (s, 3H); 3.89 (dd, J = 15, 4; 1H); 6.86 and 7.85 (AA'BB', J_{AB} = 8.5; 4H); 7.23 and 7.64 (AA'BB', J_{AB} = 8.3; 4H); ^{13}C NMR: 21.4, 25.7, 28.2, 40.0, 40.4, 48.8, 51.6, 55.4, 113.6, 125.3, 127.0, 129.7, 131.1, 136.5, 143.3, 163.2, 178.5; IR: 2925, 1666, 1603, 1577, 1510, 1443, 1256, 1166, 1091.

Compound **9**. Acylaziridine **8** (0.097 g, 0.242 mmol) was dissolved with stirring in a mixture of THF (6 mL) and water (4 mL). To this solution was added *p*-toluenesulfonic acid (0.050 g) and the mixture was stirred for 12 h at room temp. The THF was removed on the rotary evaporator, the remaining aqueous solution was diluted with saturated aqueous $NaHCO_3$ solution (10 mL) and the mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organics were washed with brine, dried over Na_2SO_4, and stripped down to yield a residue which was purified by flash chromatography (EtOAc/ether, 1/1). Compound **9** was obtained as colorless crystals (mp. 237 - 239°C, after recrystallisation from THF/pentane). Yield: 0.072 g, 71%. $[\alpha]_D^{19}$ +32.6 (*c* = 0.42, DMSO); ^1H NMR (DMSO-d_6): 1.55 (m, 2H); 1.85 (m, 2H); 2.37 (s, 3H); 3.02 (m, 1H); 3.21 (m, 3H); 3.68 (m, 1H); 3.80 (s, 3H); 3.84 (m, 1H); 4.84 (d, J = 4.5; O*H*); 6.99 and 7.83 (AA'BB', J_{AB} = 8.5; 4H); 7.39 and 7.65 (AA'BB', J_{AB} = 8; 4H); 7.91 (d, J = 7.5; N*H*); ^{13}C NMR (DMSO-d_6): 21.0, 21.8, 31.0, 47.2, 48.3, 55.4, 56.0, 71.8, 113.4, 126.91, 126.98, 129.2, 129.9, 135.3, 143.2, 161.5, 165.6. IR: 3600 - 3200, 2924, 1607, 1534, 1508, 1333, 1255, 1160.

Conversion of **9** *to* **10**. Compound **9** (0.046 g, 0.1 mmol) was dissolved under nitrogen in dry CH_2Cl_2 (10 mL) and stirred at -78°C during addition of boron trichloride (1M in CH_2Cl_2, 0.13 mL, 0.13 mmol). The resultant mixture was allowed to reach room temp. and was then stirred overnight. Methanol (10 mL) was added and the resultant mixture concentrated. Fresh methanol was added to the residue and the solution concentrated once more to give a crude product (0.034 g) which was used directly in the next step.

The crude product from above was dissolved with stirring in methanol (10 mL) and Na_2HPO_4 (0.142 g, 1 mmol) was added, followed by freshly prepared 6% sodium amalgam (0.40 g). The mixture was stirred rapidly and heated under reflux overnight, then the hot solvent was decanted. Concentration gave a residue which was purified by flash chromatography (EtOH/H_2O/AcOH, 4/1/1) to yield **10** (0.017 g, 67% based on **9**) with spectral data in excellent agreement with those reported.[1]

Epoxyurethane **11**. Epoxy alcohol **3** (11.57 g, 31.27 mmol) was dissolved with stirring under nitrogen in dry CH_2Cl_2 (450 mL). Triethylamine (8,7 mL, 62.54 mmol) and benzyl isocyanate (5.8 mL, 46.90 mmol) were

added and the mixture was stirred overnight. Saturated aqueous NH_4Cl solution (50 mL) was added, and the organic phase was washed with 5% HCl solution (50 mL) and then with brine (2 x 50 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a residue which was purified by flash chromatography (ether/pentane, 1/2). There was obtained 14.2 g (90%) of **11** as a viscous pale yellow oil. $[\alpha]_D^{19}$ -7.5 (*c* = 1.00, CH_2Cl_2); ^1H NMR: 1.08 (s, 9H); 1.62 - 1.88 (m, 4H); 3.02 (td, J = 6.5, 4; 1H); 3.19 (td, J = 4, 7; 1H); 3.72 (m, 2H); 4.04 (dd, J = 12, 7; 1H); 4.38 (d, J = 6; 2H); 4.39 (dd, J = 12, 4; 1H); 5.10 (bt, N*H*); 7.23 - 7.47 (m, 11H); 7.62 -7.70 (m, 4H); ^{13}C NMR: 19.2, 24.6, 26.8, 29.5, 45.1, 54.2, 56.3, 63.2, 63.4, 127.49, 127.53, 127.66, 128.7, 129.6, 133.7, 135.5, 138.2, 156.1; IR: 3336, 3069, 2930, 2857, 1728, 1530, 1427, 1244, 1111.

Oxazolidinone **12**. Epoxy urethane **11** (4.4 g, 8.74 mmol) was dissolved with stirring under nitrogen in dry THF (400 mL) and the solution cooled to 0°C. Sodium hydride (0.839 g, 35 mmol) was added portionwise and the resultant mixture was stirred at room temp for 8 h, recooled to 0°C and saturated aqueous NH_4Cl solution was added. The separated aqueous phase was extracted with ether (2 x 50 mL) and the combined organics were washed with brine (50 mL), dried over Na_2SO_4, and stripped down to leave a residue which was flash chromatographed (EtOAc/pentane, 1/2) to afford **12** as a colorless oil (3.96 g, 90%). $[\alpha]_D^{19}$ +41.5 (*c* = 0.60, CH_2Cl_2); ^1H NMR: 1.03 (s, 9H); 1.50 - 1.79 (m, 5H, incl. O*H*); 3.25 (td, J = 3.5, 6; 1H); 3.48 (m, 1H); 3.65 (m, 3H); 4.38 (q, J = 6; 1H); 4.35 and 4.63 (AB, J = 15; 2H); 7.28 - 7.47 (m, 11H); 7.64 (m, 4H); ^{13}C NMR: 19.2, 26.8, 27.4, 31.4, 46.8, 61.0, 61.7, 63.1, 75.9, 127.7, 127.9, 128.1, 129.0, 129.7, 133.7, 135.5, 136.4, 158.4; IR: 3600 - 3200, 2931, 1728, 1449, 1244, 1106. (During the course of the reaction, analytical TLC showed the temporary presence of a third component presumed to be **16**).

Ditosylate **13**. (i) *p*TsCl (2.9 g, 15.22 mmol) and triethylamine (4.25 mL, 30.45 mmol) were added to an ice-cooled solution of **12** (5.1 g, 10.15 mmol) in dry CH_2Cl_2 under nitrogen.The mixture was stirred for 17 h at room temp. and water (30 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (30 mL) and the combined organics were washed with saturated aqueous NH_4Cl (2 x 30 mL) and brine (30 mL). After drying over Na_2SO_4, the organic phase was concentrated and the residue purified by flash chromatography (EtOAc/pentane, 1/4) to give the tosylate of **12** (viscous oil, 6.46 g, 97%). $[\alpha]_D^{19}$ +22.5 (*c* = 1.80, CH_2Cl_2); ^1H NMR: 1.02 (s, 9H); 1.45 - 1.69 (m, 4H); 2.45 (s, 3H); 3.25 (q, J = 4.5; 1H); 3.60 (m, 2H); 3.86 (dd, J = 9.2, 4.5; 1H); 3.89 (dd, J = 9.2, 4.5; 1H); 4.08 (q, J = 4.5; 1H); 3.87 and 4.75 (AB, J = 12.5; 2H); 7.15 - 7.20 (m, 2H); 7.28 - 7.45 (m, 11H); 7.58 - 7.64 (m, 4H); 7.73 (AA' of AA'BB', J_{AB} = 8.3; 2H); ^{13}C NMR: 19.2, 21.7, 26.8, 27.2, 31.4, 46.4, 58.0, 62.9, 67.3, 75.6, 127.7, 127.9, 128.15, 128.20, 129.0, 129.7, 130.1, 132.1, 133.6, 135.2, 135.5, 145.6,157.4; IR: 2947, 1739, 1595, 1303, 1178.

(ii) The product from above (4.3 g, 6.54 mmol) was dissolved with stirring under nitrogen in dry THF (300 mL) and cooled to 0°C. A solution of tetrabutylammonium fluoride (1M in THF, 7.2 mL, 7.2 mmol) was added dropwise and the mixture stirred for 4 h at 0°C. Water (50 mL) was added and the separated aqueous phase was extracted with ether (50 mL). The combined organics were washed with brine (50 mL), dried over Na_2SO_4 and the solvents were removed to give a residue which was purified by flash chromatography (EtOAc/pentane, 8/3). There was obtained 2.46 g (90%) of the relevant monotosylated diol as a colorless oil. $[\alpha]_D^{19}$ +21.4 (*c* = 1.10, EtOAc); ^1H NMR: 1.50 - 1.68 (m, 4H); 1.62 (br, O*H*); 2.46 (s, 3H); 3.35 (q, J = 4.5; 1H); 3.59 (m, 2H); 3.95 (dd, J = 10, 4.5; 1H); 4.00 (dd, J = 10, 4.5; 1H); 4.23 (q, J = 4.5; 1H); 3.96 and 4.73 (AB, J = 15; 2H); 7.12 - 7.20 (m, 2H); 7.29 - 7.33 (m, 3H); 7.36 and 7.72 (AA'BB', J_{AB} = 8.3; 4H); ^{13}C NMR: 21.7, 27.4, 31.3, 46.4, 58.1, 61.7, 67.2, 75.7, 127.9, 128.12, 128.19, 128.9, 130.1, 132.0, 135.2, 145.6, 157.4; IR: 3600 - 3200, 2946, 1728, 1365, 1177.

(iii) The product from above (2.5 g, 6 mmol) was dissolved with stirring in dry CH_2Cl_2 (100 mL). To the solution were added triethylamine (2.5 mL, 18 mmol), *p*-TsCl (1.7 g, 9 mmol) and DMAP (0.020 g). The mixture was stirred at room temp. for 18 h, and water (30 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (30 mL) and the combined organics were washed with saturated aqueous NH_4Cl (2 x 30 mL) and brine (30 mL). After drying of the organic phase (Na_2SO_4) the solvent was removed and the residue flash chromatographed (ether/pentane, 4/1, then ether) to afford ditosylate **13** (3.0 g, 88%) as a highly viscous oil. $[\alpha]_D^{19}$ +25.7 (*c* = 2.00, CH_2Cl_2); ^1H NMR: 1.50 - 1.80 (m, 4H); 2.44 (s, 3H); 2.46 (s, 3H); 3.28 (q, J = 5; 1H); 3.95 (m, 5H incl. A of AB); 4.14 (q, J = 5; 1H); 4.71 (B of AB, J = 15; 1H); 7.15 - 7.21 (m, 2H); 7.30 - 7.41 (m, 7H); 7.74 (2 x AA' of AA'BB', J_{AB} = 8.3 and 8.3; 4H); ^{13}C NMR: 21.6, 21.7, 24.2, 30.9, 46.4, 58.0, 66.9, 69.3, 74.9, 127.8, 127.9, 128.1, 128.3, 129.0, 129.9, 130.1, 131.9, 132.6, 135.0, 145.0, 145.7, 157.0.; IR: 2920, 1729, 1597; Anal. Calc. for $C_{28}H_{31}NO_8S_2$: C, 58.64%; H, 5.41. Found: C, 58.58; H, 5.38.

Bicyclic oxazolidinone **14**. *p*-Toluenesulfonamide (1.3 g, 7.68 mmol) was stirred under nitrogen in dry DMF (100 mL) and cesium carbonate (5 g, 15.35 mmol) was added. The mixture was stirred at room temp. for 2 h before being diluted by addition of DMF (400 mL). A solution of **13** (4.0 g, 6.98 mmol) in DMF (40 mL) was added dropwise over 6 h and the resultant solution stirred for 20 h. The solvent was removed by distillation at reduced pressure and the solid residue was partitioned between water (50 mL) and ether (100 mL). The separated aqueous phase was extracted with ether (50 mL), EtOAc (50 mL) and the combined organics were washed with brine, dried ($MgSO_4$) and concentrated to give a residue which was purified by flash chromatography (ether/pentane, 8/2). This gave the desired product contaminated with unreacted *p*-toluenesulfonamide, which was removed by a second chromatography (EtOAc/CH_2Cl_2, 1/29) to yield **14** (1.54 g, 55%) as a white solid of 90% *e.e.*[10] Recrystallisation from EtOAc/pentane (1/3) gave fine needles (mp. 146 - 147°C). This material showed $[\alpha]_D^{19}$ -64.9 (*c* = 1.05, CH_2Cl_2) and was of >99% *e.e.*[10] ^1H NMR: 1.55 (m, 1H); 1.81 (m, 2H); 2.28 (m, 1H); 2.44 (s, 3H); 2.79 (m, 1H); 3.12 (dd, J = 10, 9.5; 1H); 3.23 (dd, J = 10, 5; 1H); 3.37 (td, J = 9.5, 5; 1H); 3.49 (m, 1H); 4.33 (ddd, J = 11.5, 9.5, 3.5; 1H); 4.23 and 4.54 (AB, J = 15; 2H); 7.23 - 7.39 (m, 7H); 7.51 (AA' of AA'BB', J_{AB} = 8.3; 2H); ^{13}C NMR: 21.6, 25.7, 29.9, 45.5, 47.4, 47.8, 60.7, 78.1, 126.9, 128.2, 128.3, 128.9, 129.9, 135.28, 135.32, 143.8, 158.3; IR: 2924, 1770, 1335, 1160; Anal. Calc. for $C_{21}H_{24}N_2O_4S$: C, 63.00%; H, 6.00; N, 7.00. Found: C, 62.75; H, 5.98; N, 6.92.

Amino alcohol **15**. Oxazolidinone **14** (0.329 g, 0.822 mmol) was dissolved with stiring in a mixture of 50% aqueous ethanol (30 mL) and THF (10 mL). Lithium hydroxide 0.592 g, 24.67 mmol) was added and the resultant mixture heated under reflux overnight. The organic solvents were removed at reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (2 x 40 mL). The combined organics were washed with brine, dried over $MgSO_4$ and the solvent was removed to afford NMR-spectroscopically pure **15** as a viscous oil (0.301 g, 98%). The analytical sample was obtained by flash chromatography (EtOAc). $[\alpha]_D^{19}$ -43.6 (*c* = 0.72, CH_2Cl_2); ^1H NMR: 1.52 - 1.68 (m, 2H); 1.82 - 2.02 (m, 2H); 2.41 (s, 3H); 2.55 (td, J = 7.5, 4; 1H); 2.95 (dd, J = 14.5, 7.5; 1H); 3.11 - 3.34 (m, 3H); 3.53 (dd, J = 14.5, 4; 1H); 3.75 and 4.00 (AB, J = 13; 2H); 7.23 - 7.38 (m, 7H); 7.63 (AA' of AA'BB'; J_{AB} = 8; 2H); ^{13}C NMR: 21.5, 23.6, 30.8, 46.5, 48.5, 51.2, 64.5, 75.2, 126.9, 127.1, 128.3, 128.5, 129.7, 135.8, 139.9, 143.3; IR: 3600 - 2500; Anal. Calc. for $C_{20}H_{26}N_2O_3S$: C, 64.14%; H, 6.99; N, 7.48. Found: C, 64.11; H, 6.82; N, 7.40.

Oxazolidinone **17**. Racemic primary alcohol **12** (3 g, 5.96 mmol) was dissolved with stirring under nitrogen in dry DMF (50 mL). Triphenylphosphine (3.13 g, 11.93 mmol) was added, followed by lithium azide (1.46

g, 29.82 mmol). The mixture was stirred for 10 min before addition of carbon tetrabromide (3.95 g, 11.92 mmol). The mixture became yellow and was stirred overnight at room temperature. The solvent was then distilled off at reduced pressure and the residue partitioned between ether (100 mL) and water (50 mL). The separated aqueous phase was extracted with ether (50 mL) and the combined organics were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was purified by flash chromatography (ether/pentane, 2/3) to yield the azide as a pale yellow oil. (2.9 g, 92%). ^{1}H NMR: 1.03 (s, 9H); 1.58 - 1.70 (m, 2H); 3.23 (td, J = 5, 4; 1H); 3.32 (dd, J = 12, 4; 1H) 3.41 (dd, J = 12, 5; 1H); 3.65 (m, 2H); 4.18 and 4.78 (AB, J = 15; 2H); 4.24 (td, J = 5, 4; 1H); 7.29 - 7.42 (m, 11H); 7.60 - 7.69 (m, 4H); IR: 2930, 2108, 1750, 1427, 1111.

Azido aldehyde **18**. (i) To an ice-cooled solution of **17** (2.9 g, 5.51 mmol) in dry THF (100 mL) under nitrogen was added a 1M solution of tetrabutylammonium fluoride (6 mL, 6mmol) and the resultant mixture was stirred for 2 h at 0°C. The solution was diluted with ether (50 mL) and then washed with water. The separated aqueous phase was extracted with EtOAc (50 mL) and the combined organics were washed with brine, dried over $MgSO_4$ and the solvents were removed to leave a residue which was purified by flash chromatography (EtOAc/ether, 2/8). There was obtained 1.54 g (93%) of the azido alcohol as a colorless oil. ^{1}H NMR: 1.65 - 1.79 (m, 5H, incl. O*H*); 3.28 (td, J = 5, 4; 1H); 3.36 (dd, J = 12, 4; 1H); 3.46 (dd, J = 12, 5; 1H) 3.65 (m, 2H); 4.15 and 4.78 (AB, J = 15; 2H); 4.28 (td, J = 6.5, 5; 1H); 7.28 - 7.40 (m, 5H); ^{13}C NMR: 27.5, 31.4, 46.6, 51.4, 58.8, 61.9, 76.7, 128.0, 128.2, 129.0, 135.5, 157.6; IR: 3600 - 3200, 2960, 2090, 1610.

(ii) The azido alcohol from above (0.112 g, 0.386 mmol) was dissolved with stirring under nitrogen in dry CH_2Cl_2 (10 mL). Freshly activated and powdered 4Å molecular sieves were added followed by sodium acetate (0.063 g) and recrystallised PCC (0.1 g, 0.463 mmol) and the mixture was stirred at room temp. for 3 h. The mixture was filtered through a short pad of silica gel and the filtrate concentrated to give the crude aldehyde which was purified by flash chromatography (EtOAc/pentane, 2/3). There was obtained **18** (0.078 g, 70%) as an oil. ^{1}H NMR: 1.70 - 1.82 (m, 1H); 1.88 - 2.00 (m, 1H); 2.66 (t, J = 7; 2H); 3.26 (ddd, J = 5, 4, 4; 1H); 3.38 (dd, J = 13, 4; 1H); 3.47 (dd, J = 13, 5; 1H); 4.17 and 4.78 (AB, J = 15; 2H); 4.27 (ddd, J = 9, 5, 4; 1H); 7.27 - 7.40 (m, 5H); 9.77 (s, 1H); ^{13}C NMR: 27.0, 38.9, 46.6, 51.2, 58.8, 75.6, 128.0, 128.3, 129.0, 135.4, 157.3, 200.3; IR: 2945, 2105, 1725.

Bicyclic oxazolidinone **19**. To a solution of aldehyde **18** (0.045 g, 0.156 mmol) in dry toluene (40 mL) under nitrogen was added triphenylphosphine (0.0615 g, 0.234 mmol) and the mixture was stirred for 48 h at room temp. and then at 80°C for 16 h. The solution was cooled to 0°C before addition of $NaBH_4$ (0.059 g, 1.56 mmol) and methanol (5 mL). The resulting solution was stirred at room temp. for 1 h, then acetone (1 mL) and silica gel were added. The mixture was stirred for 10 min and then concentrated to give a residue which was flash chromatographed (EtOAc/methanol, 19/1) to afford **19** as a colorless oil (0.020 g, 52%). ^{1}H NMR: 1.44 - 1.60 (m, 2H); 1.70 - 1.90 (m, 2H, 2.35 (app. t, J = 12; 1H); 2.63 (m, 2H); 3.04 (m, 2H); 4.12 and 4.71 (AB, J = 15; 2H); 4.45 (m, 1H); 7.28 - 7-38 (m, 5H); ^{13}C NMR: 23.7, 32.1, 46.5, 46.9, 51.3, 59.9, 78.0, 127.9, 128.0, 128.8, 136.0, 158.2. (Structure further proved by conversion (*p*-TsCl, NEt3; CH_2Cl_2) to *rac* **14** identical in all respects, except for specific rotation, with the material described above). The 14-membered ring "dimer" corresponding to **19** was also isolated, and showed *m/z* 493 (MH^+ for $C_{28}H_{36}N_4O_4$) in the MS.

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(*Received in UK* 23 *March* 1995; *accepted* 31 *March* 1995)