Total synthesis of balanol: a potent protein kinase C inhibitor of fungal origin

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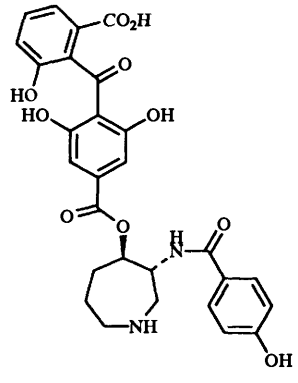
The total synthesis of the fungal metabolite balanol, a potent inhibitor of protein kinase C, is described. The synthesis includes a novel synthesis of 3-amino-4-hydroxyazepanes *via* a directed ring expansion of 3-bromopiperidin-4-ones.

Balanol **1** is a structurally novel inhibitor of protein kinase C, a family of phospholipid dependent serine/threonine protein kinases which play an important role in cell growth, signal transduction and differentiation.[1] The activated enzyme[2] has been implicated in many diseases, such as cancer, inflammation and HIV infection; therefore inhibitors of protein kinase C may be therapeutic.[3] Balanol **1** was initially isolated by workers at Sphinx Pharmaceuticals from *Verticillium balanoides*[4,5] and more recently from species of *Fusarium*[6] by a team at Nippon Roche. Synthetic interest in balanol is intense, owing to its chemical structure, biological activity and its low availability from natural sources. As our synthetic route was nearing completion, the total synthesis of balanol was recently reported by workers at Sphinx,[7] and by the Nicolaou group.[8] Here we describe a new synthesis of balanol with novel routes to the hexahydroazepine (azepane) and benzophenone portions.



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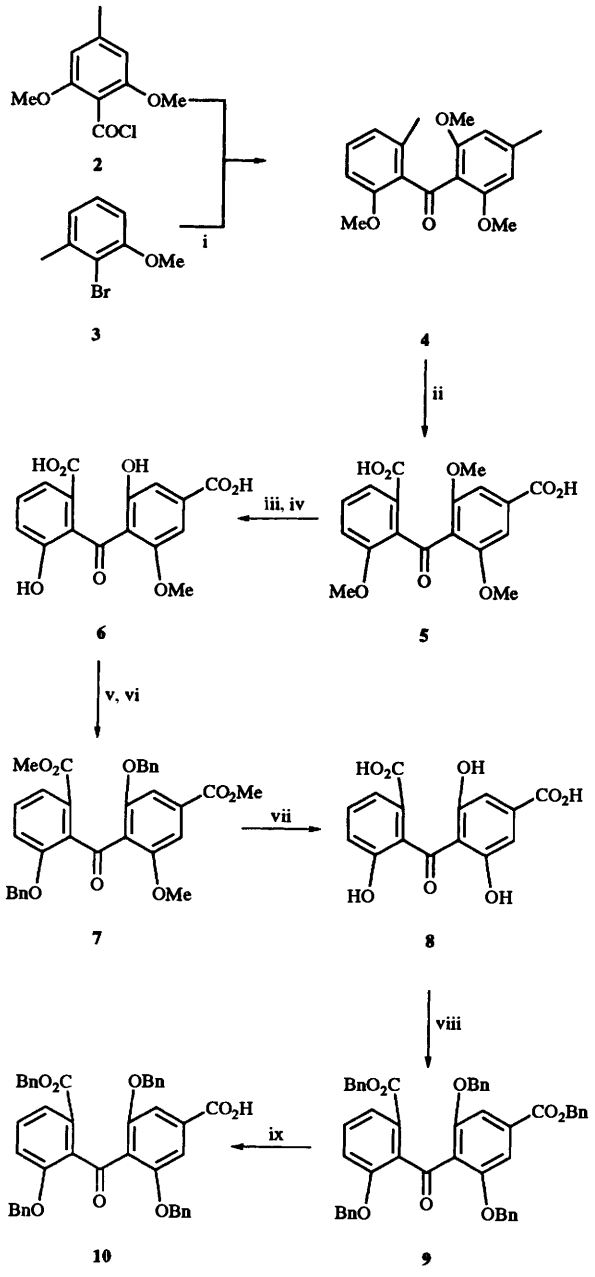
Results and discussion

The key disconnection for the synthesis of balanol is the ester bond joining the azepane and the benzoic acid. This implies that preparation of suitably protected benzophenone and azepane portions, which would be coupled together to form the ester bond, could then be deprotected to give balanol **1**.

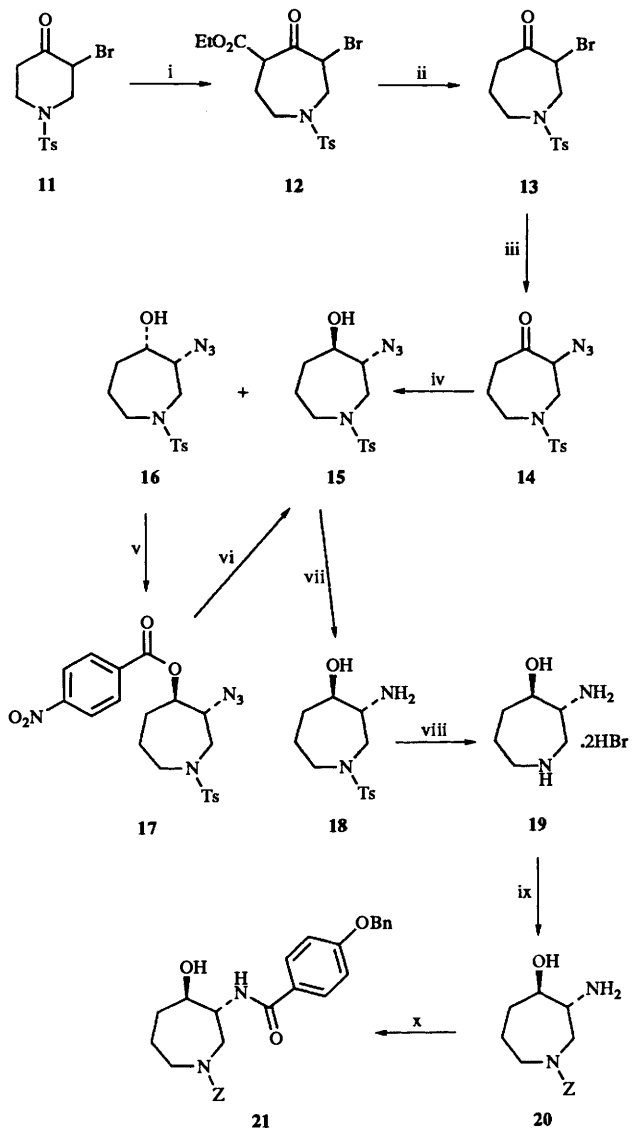
The synthesis of the benzophenone portion started from 2,6-dimethoxy-4-methylbenzoyl chloride[9] **2** and 2-bromo-3-methoxytoluene[10] **3** which were readily prepared from commercially available 3,5-dimethoxytoluene and 2-amino-3-methoxytoluene respectively, in 86 and 85% yield. Formation of the Grignard reagent of **3** and reaction of this with **2** gave the hindered benzophenone **4** in 80% yield. Oxidation of the methyl groups of **4** using potassium permanganate gave the diacid **5** in 38% yield. The diacid **5** had limited solubility and was quantitatively converted into the dimethyl ester. Treatment of this dimethyl ester with boron tribromide gave **6** in 95% yield with only small amounts of **8** being detected. Further demethylation of **6** to give the triphenolic diacid **8** directly was problematic and treatment of **6** with boron tribromide and a host of other demethylating agents yielded only traces of **8**. Possibly once **6** has been formed, its insolubility and ability to complex with reagents hinders the final demethylation. This problem was overcome by re-esterification of **6** to give the dimethyl ester followed by benzylation of the phenolic groups to give **7** in 74% overall yield. Treatment of **7** with boron tribromide in dichloromethane gave the desired triphenolic diacid **8** in 52% yield and **6** in 41% yield which could be recycled. In this case, the demethylation occurred competitively with the more hindered benzyl groups, which, since they are more labile than the methoxy group, are then subsequently removed. Complete demethylation of the dimethyl ester of **6** under the above conditions was unsuccessful, only ester hydrolysis being observed. The triphenolic diacid **8** was converted into the pentabenzyl compound **9** in 42% yield selective hydrolysis of which gave **10** in 91% yield. This compound was identical spectroscopically with an authentic sample prepared by a different route.[7d,8] The tetrabenzyl compound **10** is suitably protected for activation and coupling to a protected portion of the azepane **21** to give balanol.

The synthesis of the azepane portion of balanol started from commercially available piperidin-4-one. *N*-Tosylation under standard conditions followed by bromination gave **11** in 80% overall yield. The tosyl group was chosen to protect the nitrogen as this group was more stable to the bromination conditions and subsequent stages than carbamates and all compounds containing the tosyl group were crystalline. It was expected that the tosyl group would have to be removed and replaced by a more labile group after the requisite functional group manipulations had been completed so that deprotection at the final stage of the balanol synthesis would not be problematic.

The regiospecific homologation of unhindered α-bromo ketones using ethyl diazoacetate and boron trifluoride–diethyl ether has been reported.[11] The observed regioselectivity of homologation has been demonstrated to be due to a combination of steric and electronic factors.[11] The electron-withdrawing effect of the α-bromo substituent suppresses the migration of the carbon atom bearing it and the steric effect of the bromine atom enhances this selectivity of migration. This



Scheme 1 *Reagents and conditions:* i, Mg, THF, **2** (80%); ii, $KMnO_4$, pyridine (aq.) (38%); iii, $SOCl_2$, MeOH; iv, BBr_3, CH_2Cl_2 (95% from **5**); v, $SOCl_2$, MeOH; vi, NaH, BnBr, DMF (74% from **6**); vii, BBr_3, CH_2Cl_2 (52%); viii, NaH, BnBr, DMF (42%); ix, Na_2CO_3 (aq.), EtOH (91%)



Scheme 2 *Reagents and conditions:* i, N_2CHCO_2Et, BF_3–Et_2O, CH_2Cl_2 (71%); ii, HCl (aq), dioxane (90%); iii, NaN_3, AcOH, DMF (73%); iv, $NaBH_4$, EtOH (88%); v, PPh_3, DIAD, THF, *p*-nitrobenzoic acid (84%); vi, NaOH (aq.), MeOH, dioxane (99%); vii, $LiAlH_4$, THF (85%); viii, HBr (aq.) (68%); ix, Et_3N, CH_2Cl_2, 18-crown-6, benzyl chloroformate (88%); x, 4-(benzyloxy)benzoyl chloride, Et_3N, CH_2Cl_2 (65%)

sort of regiospecific homologation has not been applied previously to unsymmetrical ketones present in heterocyclic systems. A novel use of this type of ring expansion was demonstrated in the conversion of **11** into **12** using ethyl diazoacetate under Lewis acid conditions, which proceeded in 71% yield. As predicted, insertion of the methylene was selective for the unhindered side of the ketone, with none of the other regioisomer being observed. Hydrolysis and decarboxylation of **12** gave **13** in 90% yield. Reaction of **13** with sodium azide resulted in nucleophilic displacement of bromide by azide to give **14** in 73% yield. Reduction of **14** with sodium boranuide ($NaBH_4$) gave a *cis*:*trans* (2.4:1) mixture of azido alcohols **16** and **15** which were easily separable by chromatography giving **15** in 26% and **16** in 62% yields, respectively. Conversion of the major unwanted *cis* isomer **16** into the *trans* isomer **15** proceeded in 84% yield using a Mitsunobu[12] inversion *via* the *p*-nitrobenzoate **17** followed by hydrolysis. The *trans* relationship of the hydroxy and azido groups in **15** was unambiguously established by X-ray crystallography at this stage as shown in Fig. 1. Treatment of **15** with lithium aluminium hydride gave the 3-amino-4-hydroxyazepane **18** in 85% yield. At this stage, the *N*-tosyl group had to be replaced by a group that would be more easily removed in the final stage of the synthesis. Removal of the *N*-tosyl group was effected in 68% yield using aqueous hydrobromic acid to give **19**. Selective protection of the secondary amino group in **19** proceeded in 88% yield using benzyl chloroformate in the presence of 18-crown-6 to give **20**. Reaction of **20** under standard conditions with 4-(benzyloxy)benzoyl chloride gave **21** in 65% yield, which is a suitably protected azepane portion of balanol to be coupled to **10** following activation. The enantiomers of **21** were resolved by forming their Mosher's esters[13] **22** followed by chromatography and hydrolysis to give both enantiomers of **21** in

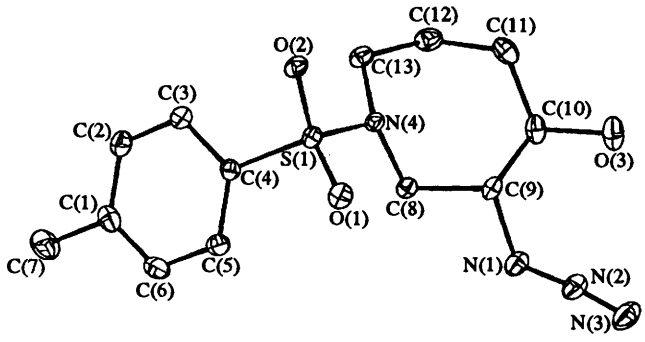
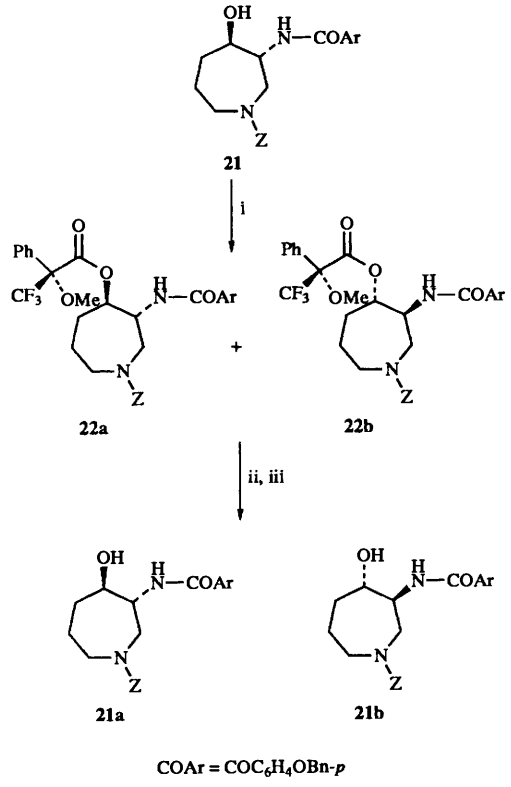


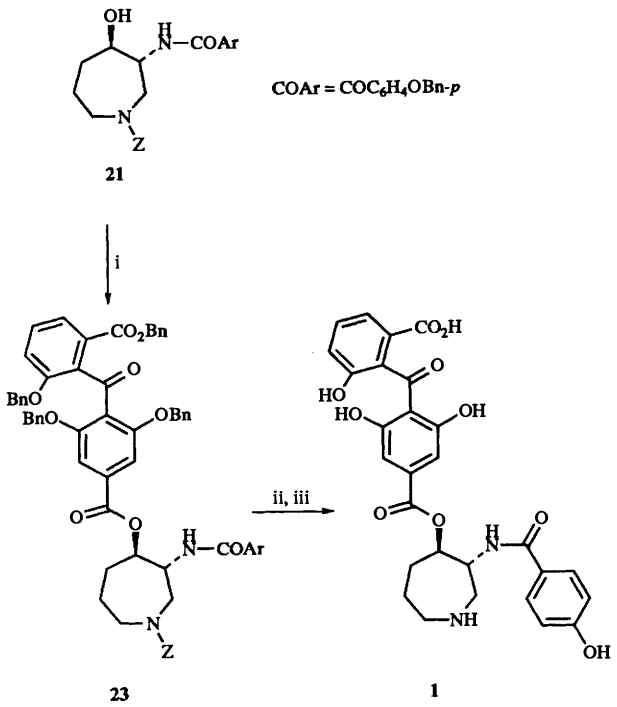
Fig. 1 X-Ray structure of compound **15**



Scheme 3 *Reagents and conditions:* i, acid chloride of (*S*)-(-)-MTPA, CH_2Cl_2, Et_3N, DMAP; ii, chromatography (96% from **21**); iii, KOH, MeOH (100%)

96% overall yield and in >99% ee. The enantiomeric purity was checked relative to the racemate using chiral chromatography. This separation allowed access to both enantiomerically pure forms of balanol in a similar manner to that previously described.[7a] Compound **21** was identical with an authentic sample prepared by a different route.[8]

Activation of **10** by the method of Mukaiyama,[14] as employed in the Nicolaou synthesis[8] of balanol followed by coupling to **21** gave **23** which was identical spectroscopically with an authentic sample.[8] Hydrogenolysis of **23** with palladium black in aqueous acetic acid–ethyl acetate gave balanol **1** as a major product. In our hands the use of THF as a co-solvent under similar conditions to Nicolaou during the deprotection step gave rise to quantities of *N*-hydroxybutylbalanol. This side reaction was avoided by replacing the THF with ethyl acetate. Purification of **1** using reverse phase HPLC gave pure balanol **1** identical by HPLC, MS and NMR with an authentic sample of balanol.[8]



Scheme 4 *Reagents and conditions:* i, **10**, 2-chloro-l-methylpyridinium iodide, DMAP, Et_3N, CH_2Cl_2 (37%); ii, H_2, Pd black, HOAc, EtOAc, H_2O; iii, HPLC (53% from **23**)

Experimental

Mps were determined using an Electrothermal apparatus and are uncorrected. IR spectra were recorded on a Nicolet 20SXB spectrophotometer. ^1H NMR spectra were obtained using a Varian VXR400 instrument (400 MHz), δ values quoted are relative to internal TMS and J values are given in Hz. Mass spectra were measured with either a Varian VG 7070E or Finnegan TSQ 700 spectrometer. Flash chromatography was performed using Sorbsil C 60 (40–60 μm mesh) silica gel. Analytical thin layer chromatography was carried out on 0.25 mm precoated silica gel plates (E. Merck Kieselgel 60 F_{254}) and compounds were visualised using UV fluorescence, ethanolic phosphomolybdic acid or aqueous potassium permanganate.

2,6-Dimethoxy-4-methylphenyl 2-methoxy-6-methylphenyl ketone 4

A suspension of magnesium turnings (0.6 g, 25 mmol) in THF (2 cm^3) under an atmosphere of nitrogen was treated with 1,2-dibromoethane (0.14 cm^3). The mixture was slowly stirred and heated to reflux whilst a solution of 2-bromo-3-methoxytoluene **3** (5.03 g, 25 mmol) in THF (20 cm^3) was added dropwise. The mixture was heated at reflux for 1 h, allowed to cool to room temperature and then filtered to remove any traces of magnesium. To this Grignard reagent a solution of 2,6-dimethoxy-4-methylbenzoyl chloride **3** (5.25 g, 25 mmol) in THF (20 cm^3) was added dropwise, the temperature of the mixture being kept at *ca.* 25 °C. The mixture was stirred at room temperature for 30 min after which the solvent was removed under reduced pressure to give a pale red syrup which was treated with saturated aq. NH_4Cl (200 cm^3) and ethyl acetate (150 cm^3). The layers were separated and the aqueous layer was extracted with ethyl acetate (50 cm^3). The combined organic layer and extracts were washed with 5% aq. $NaHCO_3$ (3 × 100 cm^3) and brine (100 cm^3) dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield a yellow solid (7.2

g). This was recrystallised from ethanol to yield **4** (6.0 g, 80%) as a white solid, mp 132–133 °C (Found: C, 71.8; H, 6.6. $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.7%); ν_{max}(KBr)/cm^{-1} 1670s (CO); δ_H($CDCl_3$) 2.31 (3 H, s, Me), 2.34 (3 H, s, Me), 3.58 (3 H, s, 6-OMe), 3.66 (6 H, s, 2′- and 6′-OMe), 6.34 (2 H, s, 3′- and 5′-H), 6.67 (1 H, d, *J* 8), 6.78 (1 H, d, *J* 8) and 7.16 (1 H, t, *J* 8, 4-H); *m/z* 301 (MH^+).

4-Carboxy-2,6-dimethoxyphenyl 2-carboxy-6-methoxyphenyl ketone 5

To a stirred solution of potassium permanganate (28 g, 3 equiv.) in water (160 cm^3) and pyridine (160 cm^3) at *ca.* 100 °C, aq. NaOH (20%; 4 cm^3) was added. To this stirred mixture a solution of **4** (17.67 g, 16.98 mmol) in pyridine (90 cm^3) was added dropwise followed by water (90 cm^3). The mixture was heated at reflux for 1 h after which further quantities of potassium permanganate (28 g, 3 equiv.) were added hourly to it, stirring and heating being continued, until a total of 208 g, 24 equiv. had been added. The hot reaction mixture was filtered through Celite and the filter cake was washed with water (4 × 150 cm^3) and pyridine (50 cm^3). The filtrate was cooled on ice and acidified to pH 1 by the addition of concentrated aq. HCl; any precipitated solid was filtered off. The acidic aqueous filtrate was treated with NaCl (200 g) and extracted with ethyl acetate (6 × 400 cm^3). The combine/extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure and the residue treated with diethyl ether to give **5** (8.1 g, 38%) as a white solid, mp 253–256 °C (Found: C, 59.1; H, 4.5. $C_{18}H_{16}O_8$·0.25H_2O requires C, 59.25; H, 4.4%); ν_{max}(KBr)/cm^{-1} 3400br and 2900br (OH), 1690s (CO); δ_H(CD_3SOCD_3) 3.59 (3 H, s, 6-OMe), 3.64 (6 H, s, 2′- and 6′-OMe), 7.17 (2 H, s, 3′- and 5′-H), 7.22 (1 H, d, *J* 8), 7.29 (1 H, d, *J* 8) and 7.46 (1 H, t, *J* 8, 4-H); *m/z* 361 (MH^+).

4-Carboxy-2-hydroxy-6-methoxyphenyl 2-carboxy-6-hydroxyphenyl ketone 6

To a stirred solution of **5** (1.01 g, 2.8 mmol) in methanol (25 cm^3), thionyl chloride (1.17 cm^3, 16 mmol) was added dropwise and the mixture heated at reflux for 2 h. The mixture was allowed to cool to room temperature and then evaporated to dryness. Treatment of the residue with toluene (2 × 20 cm^3) and removal of the solvent gave a white solid (1.09 g) which was dissolved in dichloromethane (37 cm^3) and the resulting solution was cooled to −60 °C. To the solution at −60 °C boron tribromide in dichloromethane (1 mol dm^{-3}; 31 cm^3) was added dropwise and the mixture was allowed to warm to room temperature with stirring for 18 h. The mixture was cooled to 0 °C and water (50 cm^3) was added dropwise to it. The mixture was allowed to warm to room temperature and any precipitated solid was removed by filtration. The layers were separated and the aqueous layer was adjusted to pH 4 by the addition of aq. $NaHCO_3$ (5%) and the aqueous layer was re-extracted with ethyl acetate (2 × 50 cm^3). The solid removed by the previous filtration was dissolved in the combined organic extracts and the solution dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield **6** (0.9 g, 95%) as a pale yellow solid, mp 262–265 °C (Found C, 57.8; H, 3.7. $C_{16}H_{12}O_8$ requires C, 57.8; H, 3.6%); ν_{max}(KBr)/cm^{-1} 3490br, 3415br and 2900br (OH), 1680s and 1635s (CO); δ_H(CD_3SOCD_3) 3.49 (3 H, s, 6′-OMe), 6.90 (1 H, s), 7.05 (1 H, s), 7.08 (1 H, d, *J* 8), 7.32 (1 H, t, *J* 8, 4-H), 7.39 (1 H, d, *J* 8), 9.90 (1 H, br s, OH) and 12.75 (1 H, br s; OH); *m/z* 333 (MH^+).

2-Hydroxy-6-methoxycarbonylphenyl 2-hydroxy-6-methoxy-4-methoxycarbonylphenyl ketone

To a stirred solution of **6** (5.64 g, 17 mmol) in methanol (200 cm^3) thionyl chloride (12 cm^3, 165 mmol) was added dropwise. The mixture was heated at reflux for 3 h, after which it was allowed to cool to room temperature and then evaporated to dryness to give a light brown crystalline solid. This was then treated first with toluene (2 × 20 cm^3) which was evaporated under reduced pressure and then with diethyl ether to give a cream crystalline solid (6.13 g, 100%), mp 154–156 °C (Found C, 59.8; H, 4.5. $C_{16}H_{16}O_8$ requires C, 60.0; H, 4.5%); ν_{max}(KBr)/cm^{-1} 3450br (OH), 1725s and 1710s (CO); δ_H($CDCl_3$) 3.46 (3 H, s, 6′-OMe), 3.52 (3 H, s, CO_2Me), 3.83 (3 H, s, CO_2Me), 6.94 (1 H, s), 7.12 (1 H, d, *J* 8), 7.30 (1 H, s), 7.38 (1 H, t, *J* 8, 4-H), 7.44 (1 H, d, *J* 8); *m/z* 361 (MH^+).

2-Benzyloxy-6-methoxycarbonylphenyl 2-benzyloxy-6-methoxy-4-methoxycarbonylphenyl ketone 7

To a stirred solution of 2-hydroxy-6-methoxycarbonylphenyl 2-hydroxy-6-methoxy-4-methoxycarbonylphenyl ketone (6.13 g, 17 mmol) in dry DMF (120 cm^3) at 0 °C NaH (60% in oil; 2.04 g, 51 mmol) was added during 3 min. After the mixture had been allowed to warm to room temperature with stirring over 1 h benzyl bromide (6.5 cm^3, 51 mmol) was added to it and the reaction mixture was heated at 65 °C for 2 h. After the mixture had been cooled to 0 °C it was treated with methanol (10 cm^3) and then evaporated under reduced pressure; the residue was then treated with ice water (400 cm^3) and extracted with diethyl ether (2 × 150 cm^3). The combined extracts were dried ($MgSO_4$) filtered and evaporated under reduced pressure to yield a yellow solid. Treatment of this with diethyl ether gave **7** (7 g, 74%) as a cream solid, mp 155–158 °C (Found C, 71.1; H, 5.1. $C_{32}H_{28}O_8$ requires C, 71.1; H, 5.2%); ν_{max}(KBr)/cm^{-1} 1730s and 1670s (CO); δ_H($CDCl_3$) 3.64 (3 H, s, 6′-OMe), 3.70 (3 H, s, CO_2Me), 3.95 (3 H, s, CO_2Me), 4.75 (2 H, s, OCH_2Ph), 4.86 (2 H, s, OCH_2Ph), 6.94 (3 H, m), 7.05 (2 H, m), 7.10 (1 H, s) and 7.15–7.35 (9 H, m); *m/z* 541 (MH^+).

4-Carboxy-2,6-dihydroxyphenyl 2-carboxy-6-hydroxyphenyl ketone 8

To a stirred solution of **7** (6 g, 11.1 mmol) in dichloromethane (150 cm^3) at −60 °C boron tribromide in dichloromethane (1 mol dm^{-3}; 122 cm^3) was added dropwise during 45 min. The reaction mixture was allowed to warm to room temperature after which it was kept at ambient temperature for 2 days. It was then cooled to 10 °C, treated dropwise with water (150 cm^3) and stirred at room temperature for 1 h. The layers were separated and the aqueous layer adjusted to pH 4 by the addition of solid $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (2 × 100 cm^3) and the combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield a yellow solid. The residue was purified by column chromatography on silica, eluting with methanol–dichloromethane (5:95, v/v), to give **8** (1.85 g, 52% uncorrected) as a light yellow solid, mp 222–225 °C (Found C, 56.3; H, 3.2. $C_{15}H_{10}O_8$ requires C, 56.6; H, 3.2%); ν_{max}(KBr)/cm^{-1} 3500br, 3100br, 2900br and 2600br (OH), 1700s and 1640s (CO); δ_H(CD_3SOCD_3) 6.69 (2 H, s, 2′- and 6′-H), 7.06 (1 H, d, *J* 8), 7.27 (1 H, t, *J* 8, 4-H) and 7.48 (1 H, d, *J* 8; *m/z* 318 (M^+). A quantity of **6** was also recovered (1.5 g, 41%) which could be recycled.

2-Benzyloxy-6-benzyloxycarbonylphenyl 2,6-dibenzyloxy-4-benzyloxycarbonylphenyl ketone 9

To a stirred solution of **8** (0.4 g, 1.26 mmol) in dry DMF (30 cm^3) at 0 °C NaH (60% in oil; 0.3 g, 7.56 mmol) was added portionwise and the mixture was allowed to warm to room temperature with stirring for 1 h. After treatment with benzyl bromide (0.9 cm^3, 7.57 mmol), the mixture was heated at 65 °C for 20 h. The mixture was cooled to 0 °C and treated with a further quantity of NaH (0.15 g, 3.78 mmol) after which it was stirred at room temperature for 30 min, and then treated with benzyl bromide (0.9 cm^3, 7.57 mmol). After being heated at 65 °C for a further 4 h, the mixture was cooled to 0 °C and

treated with methanol (10 cm^3); it was then evaporated under reduced pressure. The residue was treated with water (60 cm^3) and then extracted with ethyl acetate (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was chromatographed on a Dynamax silica column (20 mm × 300 mm) eluting with heptane–ethyl acetate (85:15, v/v) to yield **9** (0.4 g, 42%) as a white solid, mp 127–130 °C (Found C, 77.9; H, 5.1. $C_{50}H_{40}O_8$ requires C, 78.1; H, 5.2%); ν_{max}(KBr)/cm^{-1} 1720s and 1680s (CO); δ_H($CDCl_3$) 4.70 (2 H, s, 6-OCH_2Ph), 4.78 (4 H, s, 2′- and 6′-OCH_2Ph), 5.12 (2 H, s, 2-CO_2CH_2Ph), 5.38 (2 H, s, 4′-CO_2CH_2Ph), 6.82 (2 H, m), 6.95 (1 H, d, *J* 8) and 7.01–7.48 (27 H, m); *m/z* 769 (MH^+).

2-Benzyloxy-6-benzyloxycarbonylphenyl 2,6-dibenzyloxy-4-carboxyphenyl ketone 10

To a stirred mixture of **9** (0.4 g, 0.52 mmol) in ethanol (30 cm^3), a solution of Na_2CO_3 (0.24 g, 1.04 mmol) in water (30 cm^3), was added and the mixture heated at reflux for 4 h. The mixture was allowed to cool to room temperature after which the ethanol was removed under reduced pressure. Water (150 cm^3) was added to the residue and the solution adjusted to pH 1 by the addition of concentrated aq. HCl. The aqueous mixture was then extracted with ethyl acetate (3 × 50 cm^3) and the combined extracts were dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure to yield a pale yellow solid. Trituration of this with diethyl ether gave **10** (320 mg, 91%) as a white solid, mp 132–134 °C; δ_H($CDCl_3$) 4.72 (2 H, s, 6-OCH_2Ph), 4.80 (4 H, s, 2′- and 6′-OCH_2Ph), 5.14 (2 H, s, 2′-CO_2CH_2Ph), 6.85 (2 H, d, *J* 8), 6.97 (1 H, d, *J* 8), 7.05–7.08 (4 H, m), 7.13 (2 H, t, *J* 8, 4-H) and 7.18–7.34 (16 H, m); *m/z* 679 (MH^+). Spectroscopic data of **10** were identical with those reported.[7d,8]

3-Bromo-1-(4′-methylphenylsulfonyl)piperidin-4-one 11

To a solution of 1-(4′-methylphenylsulfonyl)piperidin-4-one (262.2 g, 1.036 mol) in dichloromethane (6.5 dm^3) at −5 °C, a solution of bromine (51.8 cm^3, 1.004 mol) in dichloromethane (1 dm^3) was added dropwise during 2 h. The temperature of the mixture was maintained between −4 and −2 °C during the first 90 min of the addition and allowed to rise to 0 °C during the last 30 min. The resulting solution was allowed to warm to room temperature with stirring over 1 h. Saturated aq. $NaHCO_3$ (2 dm^3) was added to the reaction mixture followed by water (2 dm^3) and the resulting biphasic system was stirred for 30 min; the layers were then separated. The organic phase was extracted with aq. $NaHCO_3$ (2.5 dm^3) and then dried, ($MgSO_4$), filtered and evaporated under reduced pressure to give **11** (340 g, 98%) as a white solid, mp 129–134 °C (Found: C, 43.2; H, 4.2; N, 4.3. $C_{12}H_{14}BrNO_3S$ requires C, 43.4; H, 4.25; N, 4.2%); ν_{max}(KBr)/cm^{-1} 1735s (CO), 1340s and 1160s (SO_2); δ_H($CDCl_3$) 2.45 (3 H, s, 4′-Me), 2.66 (1 H, dddd, *J* 14.8, 8.9, 5.7 and 1.2, 5-H_{ax}), 2.96 (1 H, ddd, *J* 14.8, 5.7 and 4.5, 5-H_{eq}), 3.25 (1 H, dddd, *J* 12.4, 8.9, 4.5 and 1.2, 6-H_{ax}), 3.36 (1 H, ddd, *J* 12.8, 8.4 and 1.2, 2-H_{ax}), 3.65 (1 H, dtd, *J* 12.4, 5.7 and 1.8, 6-H_{eq}), 3.98 (1 H, ddd, *J* 12.8, 5.1 and 1.8, 2-H_{eq}), 4.55 (1 H, ddd, *J* 8.4, 5.1 and 1.2, 3-H), 7.36 (2 H, d, *J* 8, 3′- and 5′-H) and 7.7 (2 H, d, *J* 8, 2′- and 6′-H); *m/z* 331 and 333 (M^+).

3-Bromo-5-ethoxycarbonyl-1-(4′-methylphenylsulfonyl)azepan-4-one 12

To a solution of **11** (25.1 g, 75.6 mmol) in dichloromethane (822 cm^3) at −5 °C under nitrogen, a solution of boron trifluoride–diethyl ether (9.96 cm^3, 79.3 mmol) in dichloromethane (117 cm^3) was added dropwise over 15 min, the temperature of the mixture being kept between −5 and −3 °C. The solution was stirred at −5 °C for 20 min after which a solution of ethyl diazoacetate (9.93 cm^3, 94.4 mmol) in dichloromethane (117 cm^3) was added dropwise to it during 20 min, the temperature of the solution being maintained between −5 and −2 °C during the addition. The solution was allowed to warm to room temperature for 90 min, after which it was diluted with water (234 cm^3) and then stirred at room temperature for 25 min. The layers were separated and the organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a pale yellow oily solid which was crystallised from ethyl acetate to yield **12** (22.4 g, 71%) as a colourless solid, mp 165–167 °C (Found: C, 45.6; H, 4.75; N, 3.2. $C_{16}H_{20}BrNO_5S$ requires C, 45.9; H, 4.8; N, 3.3%); ν_{max}(KBr)/cm^{-1} 1740s and 1710s (CO), 1340s and 1160s (SO_2); δ_H($CDCl_3$) 1.26 (3 H, t, CH_3CH_2O), 2.05 (1 H, dtd, *J* 14.7, 12.1 and 4.9, 6-H_b), 2.20 (1 H, dq, *J* 14.7 and 2.9, 6-H_a), 2.45 (3 H, s, 4′-Me), 2.81 (1 H, ddd, *J* 14.0, 12.1 and 2.9, 7-H_b), 3.07 (1 H, dd, *J* 15.3 and 11.0, 2-H_b), 4.00 (1 H, dddd, *J* 14.0, 4.9, 2.9 and 0.9, 7-H_a), 4.02 (1 H, dd, *J* 12.1 and 2.9, 5-H_a), 4.19 (2 H, q, CH_3CH_2O), 4.27 (1 H, m, *J* 15.3, 6.5 and 0.9, 2-H_a), 4.45 (1 H, dd, *J* 11.0 and 6.5, 3-H), 7.34 (2 H, d, *J* 8, 3′- and 5′-H) and 7.67 (2 H, d, *J* 8, 2′-and 6′-H); *m/z* 418 and 420 (MH^+).

3-Bromo-1-(4′-methylphenylsulfonyl)azepan-4-one 13

To a suspension of **12** (45.4 g, 0.109 mol) in 1,4-dioxane (680 cm^3) at 80 °C aq. HCl (3 mol dm^{-3}; 364 cm^3) was added during 10 min. The resulting solution was heated at reflux for 7 h, cooled to room temperature and kept for 16 h. After this it was evaporated under reduced pressure to give a pale brown solid which was dissolved in ethyl acetate (650 cm^3) and the solution washed with water (2 × 50 cm^3) and brine (50 cm^3) dried (Na_2SO_4), filtered, and evaporated under reduced pressure to afford a pale brown crystalline solid. This was recrystallised from diisopropyl ether to give **13** (33.9 g, 90%) as a colourless crystalline solid, mp 104–106 °C (Found: C, 45.2; H, 4.7; N, 4.0 $C_{13}H_{16}BrNO_3S$ requires C, 45.1; H, 4.7; N, 4.05%); ν_{max}(KBr)/cm^{-1} 1710s (CO), 1340s and 1160s (SO_2); δ_H($CDCl_3$) 1.87 (1 H, m, 6-H_b), 1.96 (1 H, m, 6-H_a), 2.45 (3 H, s, 4′-Me), 2.56 (1 H, ddd, *J* 12.4, 6.8 and 2.6, 5-H_b), 2.77 (1 H, ddd, *J* 13.7, 11.7 and 3.4, 7-H_b), 2.88 (1 H, td, *J* 12.4 and 3.4, 5-H_a), 3.05 (1 H, dd, *J* 15.1 and 11.0, 2-H_b), 4.0 (1 H, dt, *J* 13.7 and 3.8, 7-H_a), 4.24 (1 H, ddd, *J* 15.1, 6.4 and 1.10, 2-H_a), 4.38 (1 H, dd, *J* 11.0 and 6.4, 3-H), 7.34 (2 H, d, *J* 8, 3′- and 5′-H) and 7.67 (2 H, d, *J* 8, 2′- and 6′-H); *m/z* 346 and 348 (MH^+).

3-Azido-1-(4′-methylphenylsulfonyl)azepan-4-one 14

To a solution of **13** (33.9 g, 97.9 mmol) in dry DMF (750 cm^3) under argon, acetic acid (11.2 cm^3) and then sodium azide (12.7 g, 0.195 mol) were added. The resulting suspension was stirred at room temperature for 3.5 h and then kept at room temperature for 16 h. Upon dilution of the mixture with water (1.875 dm^3) an oily solid separated and this was extracted with ethyl acetate (1 × 900 cm^3, 3 × 300 cm^3). The combined extracts were washed with brine (225 cm^3) dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield a yellow viscous liquid which crystallised when kept at room temperature. Recrystallisation of this from *tert*-butyl methyl ether gave **14** (21.9 g, 73%) as a white crystalline solid, mp 88 °C (Found: C, 50.3; H, 5.15; N, 17.8. $C_{13}H_{16}N_4O_3S$ requires C, 50.6; H, 5.2; N, 18.1%); ν_{max}(KBr)/cm^{-1} 2090s (N_3), 1710s (CO), 1340s and 1160s (SO_2); δ_H($CDCl_3$) 1.89 (1 H, dddd, *J* 14.8, 8.2, 6.5 and 4.2, 6-H_b), 1.95 (1 H, m, 6-H_a), 2.45 (3 H, s, 4′-Me), 2.64 (1 H, ddd, *J* 13.8, 9 and 4.2, 5-H_b), 2.69 (1 H, ddd, *J* 13.8, 8.2 and 4.2, 5-H_a) 3.02 (1 H, ddd, *J* 13.7, 8.2 and 4.2, 7-H_b), 3.04 (1 H, dd, *J* 14.8 and 8.7, 2-H_b), 3.68 (1 H, dddd, *J* 13.7, 6.5, 4.2 and 1, 7-H_a), 3.78 (1 H, ddd, *J* 14.8, 5.3 and 1, 2-H_a), 4.21 (1 H, dd, *J* 8.7 and 5.3), 7.34 (2 H, d, *J* 8, 3′- and 5′-H) and 7.68 (2 H, d, *J* 8, 2′- and 6′-H).

***trans*-3-Azido-1-(4′-methylphenylsulfonyl)azepan-4-ol 15 and *cis*-3-azido-1-(4′-methylphenylsulfonyl)azepan-4-ol 16**

To a suspension of **14** (21.8 g, 70.7 mmol) in ethanol (220 cm^3)

at 0 °C sodium boranuide (2.67 g, 70.06 mmol) was added portionwise over 10 min. The resulting clear solution was stirred at 2–5 °C for 15 min after which it was cooled in an ice–water bath whilst water (670 cm^3) was added to it followed by aq. HCl (1 mol dm^{-3}; 110 cm^3), added dropwise over 10 min as the mixture was allowed to warm to *ca.* 20 °C. The mixture was then stirred at *ca.* 20 °C for 15 min after which it was further diluted with water (440 cm^3) to give separation of a yellow oil which was extracted with ethyl acetate (1 × 440 cm^3, 3 × 220 cm^3). The combined extracts were washed with brine (2 × 55 cm^3), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The products were purified on SiO_2 eluting with *tert*-butyl methyl ether–pentane (**1**:1, v/v to 7:3, v/v): to give **16** (13.5 g, 62%) as a white solid, mp 87–90 °C (Found: C, 50.15; H, 5.75; N, 18.15. $C_{13}H_{18}N_4O_3S$ requires C, 50.31; H, 5.85; N, 18.05%); ν_{max}(KBr)/cm^{-1} 3510br (OH), 2940s (N_3), 1340s and 1160s (SO_2); δ_H($CDCl_3$) 1.73 (2 H, m, 6-H), 1.98 (2 H, m, 5-H), 2.05 (1 H, dd, *J* 3.6 and 1.2, -OH), 2.45 (3 H, s, 4′-Me), 2.93 (1 H, dt, *J* 12.4 and 5.9, 7-H_b), 3.08 (1 H, dd, *J* 14.4 and 9.6, 2-H_b), 3.61 (2 H, m, 2-H_a and 7-H_a), 3.78 (1 H, ddd, *J* 9.6, 3.9 and 3.3, 3-H), 4.1 (1 H, br m, 4-H), 7.34 (2 H, d, *J* 8, 3′- and 5′-H) and 7.68 (2 H, d, *J* 8, 2′- and 6′-H); and **15** (5.7 g, 26%) as a white solid, mp 67–70 °C (Found: C, 50.2; H, 5.8; N, 18.1. $C_{13}H_{18}N_4O_3S$ requires C, 50.3; H, 5.85; N, 18.05%); ν_{max}(KBr)/cm^{-1} 3510br (OH), 2940s (N_3), 1340s and 1160s (SO_2); δ_H($CDCl_3$) 1.54 (1 H, m, 6-H_b), 1.78 (1 H, m, 6-H_a), 1.96 (2 H, m, 5-H), 2.22 (1 H, d, *J* 3.9, OH), 2.45 (3 H, s, 4′-Me), 2.82 (1 H, dd, *J* 14.8 and 9, 2-H_b), 3.01 (1 H, ddd, *J* 12.2, 6.5 and 3.5, 7-H_b), 3.48 (2 H, m, 4-H and 7-H_a), 3.53 (1 H, dd, *J* 9 and 3.6, 3-H), 3.66 (1 H, ddd, *J* 14.8, 3.6 and 0.9, 2-H_a), 7.34 (2 H, d, *J* 8, 3′- and 5′-H) and 7.68 (2 H, d, *J* 8, 2′- and 6′-H).

trans-3-Azido-1-(4′-methylphenylsulfonyl)-4-(4″-nitrobenzoyloxy)azepane 17

To a solution of triphenylphosphine (17.6 g, 67.1 mmol) in dry THF (330 cm^3) at 5 °C, DIAD (diisopropylazodicarboxylate; 13.9 cm^3, 67.1 mmol) was added dropwise during 10 min while the temperature of the mixture was kept at 5–10 °C. A thick cream suspension formed which was stirred for a further 15 min and to this 4-nitrobenzoic acid (11.2 g, 67 mmol) and **16** (13.4 g, 43.2 mmol) were added. The resulting yellow solution was allowed to warm to room temperature as it was stirred for 1 h and then kept at room temperature for 16 h. After this the mixture was evaporated under reduced pressure and the residue stirred with *tert*-butyl methyl ether (170 cm^3) to yield a cream solid. The product was crystallised from *tert*-butyl methyl ether to give **17** (16.9 g, 85%) as colourless crystals, mp 164–168 °C (Found: C, 52.3; H, 4.6; N, 15.1. $C_{20}H_{21}N_5O_6S$ requires C, 52.3; H, 4.6; N, 15.2%); ν_{max}(KBr)/cm^{-1} 2105s (N_3), 1720s (CO), 1530s and 1350w (NO_2), 1330s and 1160s (SO_2); δ_H($CDCl_3$) 1.70 (1 H, m, 6-H_b), 2.06 (3 H, m, 5-H and 6-H_a), 2.45 (3 H, s, 4′-Me), 2.82 (1 H, dd, *J* 15 and 10, 2-H_b), 2.97 (1 H, ddd, *J* 12.3, 6.6 and 3.5, 7-H_b), 3.64 (1 H, ddd, *J* 12.3, 9.8 and 6.6, 7-H_a), 3.76 (1 H, ddd, *J* 15, 4.2 and 1, 2-H_a), 4.02 (1 H, ddd, *J* 10, 8.4 and 4.2, 3-H), 5.0 (1 H, ddd, *J* 10, 8.4 and 2.9, 4-H), 7.34 (2 H, d, *J* 8, 3′- and 5′-H), 7.7 (2 H, d, *J* 8, 2′- and 6′-H), 8.25 (2 H, d, *J* 8, 3″- and 5″-H) and 8.33 (2 H, d, *J* 8, 2″- and 6″-H).

Conversion of *trans*-3-azido-1-(4′-methylphenylsulfonyl)-4-(4″-nitrobenzoyloxy)azepane 17 into *trans*-3-azido-1-(4′-methylphenylsulfonyl)azepan-4-ol 15

To a suspension of **17** (16.9 g, 36.8 mmol) in methanol (750 cm^3) and 1,4-dioxane (190 cm^3) was added aq. NaOH (2% w/v; 150 cm^3) at room temperature. The suspension was stirred at room temperature for 5 h; a clear solution was obtained after 3 h. The solution was kept at room temperature for 16 h, after which it was evaporated under reduced pressure to give an oily residue which was stirred with ethyl acetate (460 cm^3) and water (460 cm^3). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 230 cm^3). The combined organic layer and extracts were washed with brine (2 × 50 cm^3), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a viscous liquid, which crystallised with time to give **15** (11.3 g, 99%) mp 66–70 °C, identical with **15** as prepared above.

trans-3-Amino-1-(4′-methylphenylsulfonyl)azepan-4-ol 18

To a solution of **15** (16.9 g, 54.5 mmol) in dry THF (270 cm^3) at 0 °C under nitrogen, a solution of lithium aluminium hydride in THF (1 mol dm^{-3}; 27.3 cm^3, 27.3 mmol) was added dropwise during 10 min, while the temperature of the mixture was kept at 0–2 °C. After the mixture had been allowed to warm to room temperature it was stirred for 45 min. Water (30 cm^3) was then added dropwise during 10 min to the mixture with cooling (ice–water bath) followed by aq. Na_2CO_3 (275 cm^3; 20% w/v). The mixture was diluted with water (2 dm^3) and extracted with ethyl acetate (1 × 1 dm^3, 3 × 450 cm^3) and the combined extracts were washed with brine (2 × 150 cm^3), dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a colourless oil which crystallised with time. The product was recrystallised from *tert*-butyl methyl ether to give **18** (13.1 g, 85%) as colourless crystals, mp 93–96 °C (Found: C, 54.8; H, 7.05; N, 9.6. $C_{13}H_{20}N_2O_3S$ requires C, 54.9; H, 7.1; N, 9.85%); ν_{max}(KBr)/cm^{-1} 3360br (OH), 3100br and 2930br (NH_2), 1330s and 1150s (SO_2); δ_H($CDCl_3$) 1.64 (2 H, m, 6-H), 1.94 (2 H, m, 5-H), 2.45 (3 H, s, 4′-Me), 2.76 (1 H, td, *J* 8.1, 8.1 and 3.5, 3-H), 2.86 (1 H, dd, *J* 14.2 and 8.1, 2-H_b), 3.18 (1 H, ddd, *J* 12.6, 6.1 and 4.4, 7-H_b), 3.22 (1 H, m, 7-H_a), 3.29 (1 H, ddd, *J* 9.8, 8.1 and 2.4, 4-H), 3.49 (1 H, ddd, *J* 14.2, 3.5 and 0.6, 2-H_a), 7.31 (2 H, d, *J* 8, 3′- and 5′-H) and 7.66 (2 H, d, *J* 8, 2′- and 6′-H); *m*/*z* 285 (MH^+).

trans-3-Aminoazepan-4-ol dihydrobromide 19

A suspension of **18** (13.0 g, 45.7 mmol) in aq. HBr (48%; 130 cm^3) was stirred and heated to reflux at which temperature the resulting yellow solution was kept for 3 h. The solution was then cooled to room temperature and kept for 16 h after which it was diluted with ice–water (260 cm^3) and then extracted with *tert*-butyl methyl ether (1 × 160 cm^3, 2 × 40 cm^3). The aqueous layer was concentrated under reduced pressure to give an oily yellow solid which was crystallised from ethanol to yield **19** (9.09 g, 68%) as a white crystalline solid, mp 215 °C (decomp.) (Found: C, 24.5; H, 5.6; N, 9.4. $C_6H_{16}Br_2N_2O$ requires C, 24.7; H, 5.5; N, 9.4%); ν_{max}(KBr)/cm^{-1} 3420br, 3230br and 2900br; δ_H(CD_3SOCD_3) 1.6–1.65 (3 H, m), 1.79–1.81 (1 H, m), 1.95–2.05 (1 H, m), 3.05–3.2 (3 H, m), 3.65 (1 H, br), 5.75 (1 H, br), 8.18 (3 H, br) and 9.1 (1 H, br).

trans-3-Amino-1-benzyloxycarbonylazepan-4-ol 20

To a stirred suspension of **19** (9.01 g, 30.9 mmol) in dry dichloromethane (230 cm^3) at room temperature under nitrogen, triethylamine (21.5 cm^3) was added followed by 18-crown-6 (16.3 g, 61.7 mmol). The mixture was stirred at room temperature for 20 min and the resulting clear solution cooled to 5 °C and benzyl chloroformate (4.97 cm^3, 33.9 mmol) was added dropwise during 10 min. The mixture was stirred at room temperature for 5 h, allowed to stand at room temperature for 16 h and then concentrated under reduced pressure to give a pale yellow oily solid which was stirred with ethyl acetate (330 cm^3) and aq. Na_2CO_3 (10% w/v; 220 cm^3). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 110 cm^3). The combined organic extracts were washed with aq. Na_2CO_3 (10% w/v 110 cm^3) and saturated aq. KBr (2 × 55 cm^3), dried (Na_2SO_4), filtered and the mixture was concentrated under reduced pressure to give a pale yellow oily solid. Crystallisation from *tert*-butyl methyl ether gave **20**

(7.19 g, 88%) as a colourless crystalline solid, mp 78–80 °C (Found: C, 63.7; H, 7.8; N, 10.7. $C_{14}H_{20}N_2O_3$ requires C, 63.6; H, 7.6; N, 10.6%); ν_{max}(KBr)/cm^{-1} 3350br, 3270br and 2900br, 1700s (CO); δ_H($CDCl_3$) 1.48 (1 H, m, 6-H_b), 1.61 (1 H, m, 6-H_a) 1.96 (2 H, m, 5-H), 2.66 ($\frac{1}{2}$ H, dt, *J* 9,9 and 3.7, 3-H), 2.70 ($\frac{1}{2}$ H, dt, *J* 9,9 and 3.7, 3-H), 2.87 ($\frac{1}{2}$ H, dd, *J* 14.4 and 9, 2-H_b), 2.97 ($\frac{1}{2}$ H, dd, *J* 14.4 and 9, 2-H_b), 3.22 ($1\frac{1}{2}$ H, m, 7-H_b and 4-H), 3.33 ($\frac{1}{2}$ H, ddd, *J* 13.6, 5.9 and 4.3, 7-H_b), 3.53 ($\frac{1}{2}$ H, ddd, *J* 13.6, 9.9 and 5.9, 7-Ha), 3.66 ($\frac{1}{2}$ H, ddd, *J* 13.6, 9.9 and 5.9, 7-Ha), 3.71 ($\frac{1}{2}$ H, dd, *J* 14.5 and 3.8, 2-H_a), 3.79 ($\frac{1}{2}$ H, dd, *J* 14.5 and 3.8, 2-H_a), 5.12, 5.17 (AB system, 2 H, *J* 12, PhCH_2) and 7.28–7.4 (5 H, m, Ar); *m*/*z* 265 (MH^+).

trans-3-[4-(Benzyloxy)benzamido]-1-benzyloxycarbonylazepan-4-ol 21

To a stirred suspension of **20** (3.09 g, 11 mmol) in dichloromethane (60 cm^3) at 0 °C, triethylamine (2.28 cm^3, 16.4 mmol) was added. While the temperature of the mixture was maintained at *ca.* 0 °C, 4-(benzyloxy)benzoyl chloride (3.02 g, 11 mmol) in dichloromethane (30 cm^3) was added dropwise after which the mixture was stirred at *ca.* 0 °C for a further 3 h. The mixture was then evaporated under reduced pressure and the residue dissolved in ethyl acetate (500 cm^3). The resulting solution was washed with water (2 × 60 cm^3) and brine (1 × 60 cm^3), dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield a viscous yellow oil. Chromatography of the oil on silica, eluting with *tert*-butyl methyl ether gave a colourless viscous oil, crystallisation of which from diisopropyl ether gave **21** (3.29 g, 63%) as a colourless solid, mp 132–134 °C (Found: C, 70.8; H, 6.4; N, 5.8. $C_{28}H_{30}N_2O_5$ requires C, 70.9; H, 6.4; N, 5.9%); ν_{max}(KBr)/cm^{-1} 3330br (OH), 2950br (NH) and 1700s (CO); δ_H($CDCl_3$) 1.66 (1 H, m, 6-H_b), 1.78–2.0 (3 H, m, 5- and 6-H_a), 2.78 (1 H, ddd, *J* 14, 13 and 4, 7-H_b), 3.35 (1 H, dd, *J* 15 and 5, 2-H_b), 3.78 (1 H, ddd, *J* 10, 6 and 2, 4-H), 4.07–4.23 (3 H, m, 2-H_a, 3-H and 7-H_a), 5.12 (2 H, s, OCH_2Ph), 5.14, 5.21 (AB system, 2 H, *J* 12, PhCH_2), 5.46 (1 H, br, s, OH), 7.02 (2 H, d, *J* 8, Ar), 7.28–7.47 (10 H, m, Ar), 7.82 (2 H, d, *J* 8, Ar) and 8.83 (1 H, br d, NH); *m*/*z* 475 (MH^+). Spectroscopic data of **21** were identical with those reported.[8]

Separation of the enantiomers of 21

To a solution of **21** (170 mg, 0.36 mmol), triethylamine (0.1 cm^3, 0.72 mmol) and DMAP (4-dimethylaminopyridine; 44 mg, 0.36 mmol) in dichloromethane (5 cm^3), the acid chloride derived from (*S*)-(-)-MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid; 113 mg, 0.45 mmol] in dichloromethane (2 cm^3) was added dropwise at room temperature. The mixture was stirred at room temperature for 16 h after which it was evaporated under reduced pressure. The residue was chromatographed on silica eluting with ethyl acetate–pentane (1:3 v/v) to give the enantiomerically pure Mosher's esters **22a** (120 mg, 48%); *m*/*z* 691 (MH^+), and **22b** (120 mg, 48%); *m*/*z*; 691 (MH^+). Both **22a** and **22b** appear as a *ca.* 3:1 rotameric mixture by ^{1}H NMR. Separate solutions of both **22a** (120 mg, 0.17 mmol) and **22b** (120 mg, 0.17 mmol) in methanol (5 cm^3) were stirred and treated with aq. KOH (1 mol dm^{-3}; 2 cm^3). Each reaction mixture was stirred at room temperature for 16 h and then diluted with diethyl ether (30 cm^3) and water (20 cm^3). The organic layer was separated and evaporated under reduced pressure to yield a colourless gum, treatment of which with diisopropyl ether gave, as white solids, **21a** (80 mg, 100%), mp 113–114 °C, and **21b** (80 mg, 100%), mp 116–118 °C. Both **21a** and **21b** were identical spectroscopically with **21**. The enantiomeric purity of **21a** and **21b** was assessed relative to racemic **21** using chiral chromatography on a Chiral Pack AD column (4.6 mm × 250 mm) eluting with ethanol–heptane (15:85, v/v) which showed **21a** and **21b** both to be >99% enantiomerically pure.

Protected balanol 23

To a stirred solution of **10** (180 mg, 0.265 mmol), triethylamine (0.74 cm^3, 5.3 mmol) and DMAP (16.4 mg, 0.133 mmol) in dichloromethane (9 cm^3), 2-chloro-1-methylpyridinium iodide (88 mg, 0.345 mmol) was added and the mixture stirred at room temperature for 1 h. Compound **21** (125 mg, 0.26 mmol) was added to the mixture which was then, stirred at room temperature for 20 h and finally heated at reflux for 2 h. After being cooled to room temperature the mixture was evaporated under reduced pressure and the residue dissolved in ethyl acetate (20 cm^3). The resulting solution was washed with aq. $NaHCO_3$ (5%; 2 × 50 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification of the residue on silica eluting with ethyl acetate–dichloromethane (5:95, v/v) gave **23** (0.11 g, 37%) as a glass; *m*/*z* 1135 (MH^+); δ_H($CDCl_3$) as a *ca.* 3:1 rotameric mixture 1.6–2.1 (4 H, m), 2.9 (1 H, m), 3.4 (1 H, m), 4.08–4.16 (2 H, m), 4.67 (2 H, s, OCH_2Ph), 4.7–4.88 (1 H, m), 4.82, 4.85 (2 H, AB system, *J* 12, OCH_2Ph), 5–5.15 (1 H, m), 5.04 (2 H, s, OCH_2Ph), 5.1 (4 H, s, OCH_2Ph), 5.26 (2 H, s, OCH_2Ph), 6.82 (2 H, d, *J* 8, Ar), 6.88–6.95 (4 H, m, Ar), 7.0–7.45 (32 H, m, Ar), 7.72 and 7.79 (*ca.* 3:1, 2 H, d, *J* 8, Ar). Spectroscopic data were identical with those reported;[8] the presence of rotamers precludes the exact assignment of all resonances.

Balanol 1

A solution of **23** (106 mg, 0.093 mmol) in ethyl acetate–acetic acid–water (19 cm^3, 16:2:1, v/v) was treated with palladium black (10.6 mg) under an atmosphere of hydrogen. The reaction mixture was initially warmed to 50 °C and then stirred at room temperature for 4 h. After this the mixture was filtered and fresh catalyst (10.6 mg) added, to the filtrate; the reaction mixture was then placed under a fresh atmosphere of hydrogen and stirred at room temperature for 24 h. The catalyst was filtered off and washed with a solvent mixture (16 cm^3) as used for the reaction. The mixture was concentrated and the residue was chromatographed on a Dynamax C_{18} column (20 × 300 mm) eluting with acetonitrile–water–trifluoroacetic acid (20:80:0.1, v/v) to give **1** (27 mg, 53%) as a light yellow powder; *m*/*z* 551 (MH^+); δ_H(CD_3OD) 1.84–2.12 (4 H, br m, 5- and 6-H), 3.42–2.98 (4 H, br m, 2- and 7-H), 4.32 (1 H, br m, 3-H), 5.29 (1 H, m, 4-H), 6.76 (2 H, d, *J* 8.7, 4′- and 6′-H), 6.80 (1 H, d, *J* 7.8, 11″-H), 6.92 (2 H, s, 3″- and 7″-H), 7.17 (1 H, t, *J* 7.8, 12″-H), 7.25 (1 H, d, *J* 7.8, 13″-H) and 7.60 (2 H, d, J 8.7, 3′-, 7′-H). Spectroscopic data were identical with those reported.[8]

X-Ray crystal structure determination of *trans*-3-azido-1-(4′-methylphenylsulfonyl)hexahydroazepan-4-ol 15

A single crystal of compound **15** (from *tert*-butyl methyl ether, appoximate size 0.18 × 0.28 × 0.16 mm), mounted in a Lindemann tube, was used for X-ray data collection.

Crystal data. $C_{13}H_{18}N_4O_3S$, M = 310.37, colourless prisms, orthorhombic, space group $Pn2_1a$, a = 8.7030(9), b = 11.3280(13), c = 15.097(2) Å (by least squares refinement of the setting angles for 250 reflections within θ = 2.25–27.16 °), V = 1488.4(3) Å^{-3}, Z = 4, D_c = 1.385 g cm^{-3}, T = 120 K, μ(Mo-Kα) = 2.33 cm^{-1}, F(000) = 656.

Data collection, structure solution and refinement. Data were collected on a FAST TV Area detector diffractometer following previously described methods.[15] From the ranges scanned, 6059 data were recorded (2.25 < θ < 27.16 °; index ranges $-10 \leqslant h \leqslant 10$, $-13 \leqslant k \leqslant 9$, $-18 \leqslant l \leqslant 10$) and merged to give 2618 unique [R(int) = 0.0532]. The structure was solved by direct methods[16] and refined on F_o^2 by full matrix least squares[17] using all unique data corrected for Lorentz and polarisation factors. All non-hydrogen atoms were anisotropic. The hydrogen atoms were inserted in idealised positions with U_{iso} set at 1.5 times U_{eq} of the parent. The weighting scheme

used was $w = 1/[\sigma^2(F_o)^2 + (0.0612P)^2]$, where $P = [\max(F_o)^2 + 2(F_c)^2]/3$; this gave satisfactory agreement analysis. Final R_1 (on F) and R_{w2} (on F_o^2) values were 0.0473 and 0.1067 for all 2616 data and 191 parameters. The corresponding R values were 0.0424 and 0.1008 for 2323 data with $I > 2\sigma(I)$. Sources of scattering factors are given in ref. 17.

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