Synthesis of the 1,4-diazepan-2-one moiety of liposidomycins

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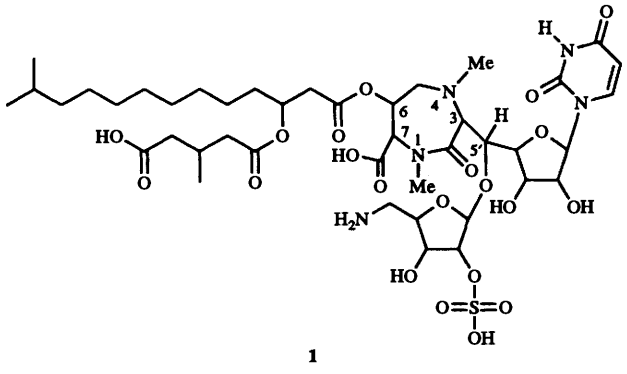
The two stereoisomers **12** and **16** of 1,4-dimethyl-1,4-diazepan-2-one, a central feature of liposidomycins, have been synthesized starting from L-ascorbic acid and sarcosine

The liposidomycins are a family of novel lipid-containing nucleoside antibiotics that were recently found in the culture filtrate and mycelia of *Streptomyces griseosporeus*.[1] These antibiotics, which have unique biological activity and structures, inhibit the formation of the lipid intermediate in bacterial peptidoglycan synthesis with three orders of magnitude greater activity than that of tunicamycin; they also have extremely high specificity.[2,3] The structures of liposidomycins A,[4] B(**1**)[2] and C, proposed on the basis of degradation



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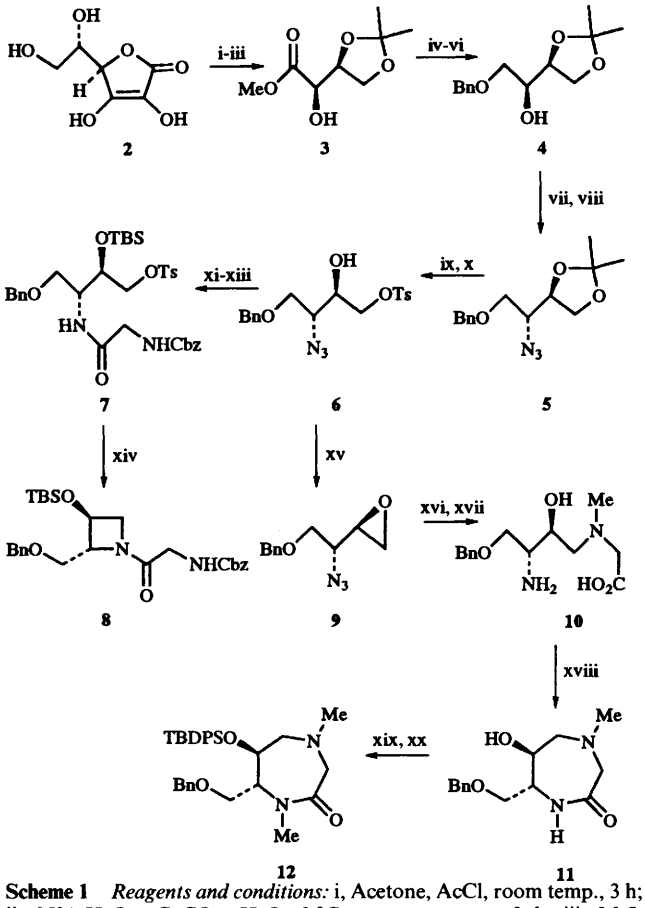
and spectroscopic studies are identical except for slight variations in the lipid portion. However, six stereogenic centres in the lipid and diazepanone moieties remain unassigned. Here we report synthetic studies related to the 1,4-diazepan-3-one part of the liposidomycins.

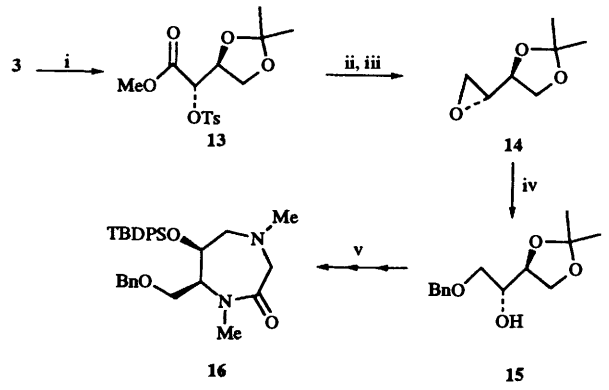
Because of the biological activity of benzodiazepanones their synthesis is well documented[5] although, until recently, this was not true of the chiral monocyclic diazepanone ring system when Knapp *et al.* reported the synthesis in racemic form of the 1,4-diazepan-3-one system.[6] Spada *et al.* also synthesized an optically active ribosyl-substituted 1,4-diazepan-3-one although the procedure was tedious.[7] Both syntheses employed intramolecular imine formation for the elaboration of the ring system, and neither is suitable for the total synthesis of liposidomycins. For the total synthesis of liposidomycins, the synthetic scheme must (*i*) give all four possible stereoisomers of the diazepanone ring moiety and (*ii*) control the stereochemistry at C-3 of the diazepanone ring and at C-5′ of the uridine portion. Since the addition of the enolate of an appropriately protected diazepanone to uridine-5′-aldehyde appears to be the most promising route for connection of the diazepanone and uridine moieties, the 1,4-diazepan-2-ones, **12** and **16**, having a 7-alkoxymethyl group were chosen as the target molecules rather than the 7-carboxy compound.

The synthesis began with L-ascorbic acid **2** and proceeded to methyl threonate **3** (65% yield over three steps; Scheme 1).[8] Compound **3** was reduced with sodium boranuide and the resultant monoacetonide tetraol[9] was converted into the monobenzyl ether **4** by stannylene acetal. Tosylation of **4** followed by reaction with sodium azide in dimethylformamide



Scheme 1 *Reagents and conditions:* i, Acetone, AcCl, room temp., 3 h; ii, 35% H_2O_2, $CaCO_3$, H_2O, 0 °C to room temp., 3 h; iii, MeI, $NaHCO_3$, $AcNMe_2$, room temp., 2 days (65%, 3 steps); iv, $NaBH_4$, EtOH, 0 °C to room temp. (83%); v, $(Bu)_2SnO$, MeOH, reflux, 5 h; vi, BnBr, DMF, 70–80 °C (90%, 2 steps); vii, TsCl, pyridine, 0 °C, 12 h (95%); viii, NaN_3, DMF, 70–80 °C, 12 h (90%); ix, 1 mol dm^{-3} aq. HCl, MeCN (87%); x, TsCl, pyridine, 0 °C, 15 h (75%); xi, TBSCl, imidazole, DMF (89%); xii, H_2, Pd–C, EtOAc (92%); xiii, $CbzNHCH_2CO_2H$, DCC, CH_2Cl_2; 0 °C, 2 h (88%); xiv, K_2CO_3, DMF, 40 °C, 10 h (50%); xv, K_2CO_3, MeOH, room temp. (85%); xvi, $MeNHCH_2CO_2H$, Et_3N, MeOH, reflux, 10 h (83%); xvii, H_2, Pd–C, MeOH (72%); xvii, DCC, CH_2Cl_2, 0 °C, 15 h (71%); xix, TBDPSCl, imidazole, DMF (83%); xx, MeI, NaH DMF (76%)

(DMF) gave the azidobenzyl ether **5**. Deprotection of the isopropylidene group in **5** afforded a diol, which upon selective tosylation gave the monotosylate **6**. Hydroxyl protection of **6** as a TBS ether and the reduction of the azido group then produced an amino compound, which upon treatment with Cbz-glycine in the presence of 1,3-dicyclohexylcarbodiimide (DCC) furnished the peptide **7**. Surprisingly, however, attempted cyclization of **7** by treatment with potassium carbonate in DMF at 40 °C in order to induce intramolecular substitution provided the unwanted four-membered ring azetidine **8** (50%); the ^1H NMR



Scheme 2 *Reagents and conditions:* i, TsCl, pyridine, 0 °C (90%); ii, $NaBH_4$, EtOH, 0 °C, 30 min, then room temp., 12 h; iii, K_2CO_3, MeOH, room temp. (63%, 2 steps); iv, BnONa, DMF, 50 °C, 3 h (88%); v, same as vii–x and xv–xx in Scheme 1 (16% yield from **15**)

spectrum of this clearly showed a triplet at 5.61 ppm attributable to the proton on the nitrogen of a NHCBz group. Changes in the reaction conditions failed to give the desired diazepanone ring. Since, in addition, the free amine obtained by the removal of Cbz group of **7** failed to provide the desired diazepanone and selective *N*-methylation of the peptide linkage of **7** prior to the cyclization failed to give the mono-*N*-methyl product, the synthetic plan was modified. Thus, protection of the hydroxy group of **6** proceeded well with *tert*-butyldimethylsilyl chloride but subsequent attempted substitution of the tosyloxy group with sarcosine, sarcosine methyl ester or glycine methyl ester failed to provide the desired compound. Presumably the bulky TBS ether prevents an S_N2 reaction. The hydroxy tosylate **6** was, therefore, converted into the epoxide **9**. Nucleophilic opening of the epoxide ring of **9** with sarcosine in refluxing methanol in the presence of triethylamine proceeded, as expected, *via* attack at the primary carbon to give an azidocarboxylic acid (83%), the subsequent catalytic hydrogenation of which afforded the amino acid **10**. Cyclization of **10** with DCC in methylene dichloride at 0 °C for 15 h provided the desired 1,4-diazepan-2-one **11** (71%). The protection of the hydroxy group of **11** and subsequent *N*-methylation with methyl iodide and sodium hydride finally provided one of our target compounds, **12** (76%), accompanied by an ammonium salt (*ca.* 10%) resulting from the quaternization of N-4. The salt could be converted into compound **12** (56%) by dequaternization with sodium benzenethiolate in DMSO at 110 °C for 10 h. Synthesis of the other target molecule **16** was accomplished through a similar synthetic route from the same starting material as that for **12** (see Scheme 2). The tosylate **13**, obtained from **3**, was converted into the epoxide **14** by reduction and subsequent treatment with potassium carbonate. Epoxide ring opening of **14** by treatment with sodium phenolate in DMF proceeded well to afford the benzyl ether **15**, the conversion of which into **16** was carried out in overall 16% yield by following the procedure for the conversion of **4** into **12**. Thus, we have developed a flexible synthetic route to the chiral 1,4-diazepan-3-one ring system. The enantiomers of the diazepanones **12** and **16** can also be prepared from D-isoascorbic acid. We are currently pursuing the stereocontrolled addition of the enolates of **12** and **16** to uridine-5′-aldehyde.

Experimental

The amino acid 10

A solution of the azido epoxide **9** (180 mg, 0.82 mmol) and sarcosine (81 mg, 0.90 mmol) in methanol (10 cm^3) in the presence of triethylamine (1 cm^3) was heated under reflux for 10 h, after which the mixture was evaporated and the residue purified by flash chromatography (methanol–ethyl acetate, 4:1) to provide the azidocarboxylic acid as a colourless liquid (210 mg, 83%). This azidocarboxylic acid (163 mg, 0.53 mmol) in methanol (10 cm^3) was hydrogenated at 15 psi for 4 h and then filtered through Celite. The filtrate was evaporated and the residue purified by flash chromatography (methanol) to give the amino acid **10** as a colourless liquid (108 mg, 72%); δ_H(300 MHz; $CDCl_3$) 2.29 (3 H, s), 2.64–2.74 (2 H, m), 3.07 (2 H, br s), 3.45 (1 H, m), 3.70 (2 H, m), 3.96 (1 H, m), 4.47 (2 H, br s), 6.20–6.70 (4 H, br s) and 7.19–7.38 (5 H, m); δ_C(75.3 MHz; $CDCl_3$) 43.5, 55.0, 59.7, 61.9, 66.0, 68.3, 73.2, 128.0, 128.6, 138.0 and 176.4; $[\alpha]_D/10^{-1}$ deg cm^2 g^{-1} +13.5 (*c* 0.18 in $CHCl_3$).

1,4-Diazepan-2-one 11

A solution of the amino acid **10** (93 mg, 0.32 mmol) and DCC (93 mg, 0.45 mmol) in methylene dichloride (5 cm^3) was stirred at 0 °C for 15 h. The urea was filtered off and the filtrate was evaporated. Flash chromatography (ethyl acetate–methanol, 9:1) of the residue afforded the diazepanone **11** as a colourless liquid (60 mg, 71%); δ_H(300 MHz; $CDCl_3$; *J*/Hz) 2.32 (1 H, br s), 2.46 (3 H, s), 2.72 (1 H, dd, *J* 7.7 and 13.5), 3.06 (1 H, dd, *J* 3.3 and 13.5), 3.23 and 3.51 (2 H, ABq, *J* 15.4), 3.58 (1 H, m), 3.66 (1 H, dd, *J* 3.9 and 9.7), 3.74 (1 H, dd, *J* 5.4 and 9.7), 3.86 (1 H, m), 4.54 (2 H, s), 5.93 (1 H, br s) and 7.30–7.40 (5 H, m); δ_C(75.3 MHz; $CDCl_3$) 44.60, 56.76, 61.98, 63.81, 67.31, 69.17, 73.63, 128.30, 128.52, 129.06, 137.88 and 174.89; $[\alpha]_D/10^{-1}$ deg cm^2 g^{-1} +46.7 (*c* 0.12 in $CHCl_3$) [Found: *m/z* (HRMS), 264.1450. Calc. for $C_{14}H_{20}N_2O_3$; M^+, 264.1474].

1,4-Dimethyl-1,4-diazepanone 12

Sodium hydride (50% oil dispersion; 170 mg, 3.5 mmol) was added to a stirred solution of the TBDPS ether (356 mg, 0.71 mmol) of **11** in DMF (5 cm^3). The resulting solution was stirred at 0 °C for 2 h before the addition of methyl iodide (111 mg, 0.78 mmol). After being stirred for 1 h, the reaction mixture was diluted with diethyl ether and then filtered through Celite. The filtrate was evaporated and the residue flash chromatographed (hexane–ethyl acetate, 1:1) to afford the diazepanone **12** as a colourless liquid (279 mg, 76%); δ_H(300 MHz; $CDCl_3$; *J*/Hz) 1.07 (9 H, s), 2.28 (3 H, s), 2.51 (1 H, d, *J* 13.0), 2.77 (1 H, dd, *J* 4.9 and 13.0), 2.90 (3 H, s), 3.30 (1 H, m), 3.39 and 3.55 (2 H, ABq, *J* 16.5), 3.63 (1 H, dd, *J* 6.1 and 9.7), 3.71 (1 H, dd, *J* 7.4 and 9.7), 4.22–4.37 (3 H, m) and 7.12–7.72 (15 H, m); δ_C(75.3 MHz; $CDCl_3$) 19.13, 27.02, 37.96, 45.59, 60.29, 62.53, 65.30, 69.77, 70.51, 73.01, 127.86, 128.13, 128.22, 128.34, 128.81, 130.41, 130.53, 133.72, 133.92, 136.38, 136.47, 138.35 and 174.00; $[\alpha]_D/10^{-1}$ deg cm^2 g^{-1} +25.5 (*c* 0.44 in $CHCl_3$) [Found: *m/z* (HRMS), 517.2900. Calc. for $C_{31}H_{41}N_2O_3Si$; $(M + H)^+$, 517.2886].

Acknowledgements

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