Synthesis of (+)-Brefeldin-A

Andrew J. Carnell,[a] Guy Casy,[a] Gilles Gorins,[a] Arefeh Kompany-Saeid,[a] Ray McCague,[b] Horacio F. Olivo,[a] Stanley M. Roberts[a] and Andrew J. Willetts[c]
[a] *Department of Chemistry, Exeter University, Exeter, Devon EX4 4QD, UK*
[b] *Chiroscience Ltd., Science Park, Cambridge CB4 4WE, UK*
[c] *Department of Biological Sciences, Exeter University, Exeter, Devon EX4 4QG, UK*

Two routes to (+)-brefeldin A have been investigated. In one the bicyclic ketone **2** was transformed into the hydroxy lactone **7**. Subsequent reduction, opening of the heterocyclic ring and epimerization furnished the aldehyde **13**. Further steps towards the natural product from this late stage intermediate **13** were not investigated. In the second route, the readily available hydroxy lactone **17** was converted into the enone **22**. Conjugate addition of the requisite cuprate reagent to this enone afforded the 3,4-disubstituted cyclopentanone **24** which was converted into brefeldin-A **29** in five steps.

(+)-Brefeldin-A is a naturally occurring antibiotic that has attracted considerable attention because of the range of its biological activity[1] and a number of synthetic routes to this material have been explored.[2,3]

We envisaged two new approaches to this natural product (Fig. 1). Both routes set up the relative stereochemistry at C-4 and C-5 at an early stage in the synthesis and in this way differ from the prescribed pathways.

The first route utilized a 7-substituted bicyclo[3.2.0]hept-2-en-6-one. Based on earlier work,[4] we foresaw that functionalization of the double bond could be easily achieved in a stereocontrolled fashion and that Baeyer–Villiger oxidation would provide the oxygen atom of the 4-hydroxy group of brefeldin-A. Opening of the lactone ring would give *cis*-disposed one carbon atom and four carbon atom side chains which could be equilibrated to the thermodynamically favoured *trans*-arrangement using base. Extension of the two side-chains and formation of the lactone ring was to provide the natural product. In such a lengthy route high yields would be needed at each stage.

The second route started from 4-hydroxy-2-oxabicyclo-[3.3.0]oct-7-en-3-one, a starting material that is easy to prepare in optically active form.[5] Such γ-lactones have been used previously by ourselves[6] and by others[7] in the synthesis of biologically interesting compounds. Conversion of the bicyclic lactone into a 4-substituted cyclopentenone would precede a conjugate addition of an organometallic reagent which, by analogy with Corey's earlier work,[3] should give the correct relative stereochemistry at C-5 and C-9 by steric approach control. Selective reduction of the ketone carbonyl group and ring closure would quickly provide the naturally occurring macrocyclic lactone.[8]

Attempted Synthesis of Brefeldin-A by Route 1.—Chlorination of 5-bromopentanoic acid gave a good yield of the dihalogenoacyl chloride 1. Treatment of this compound with triethylamine in the presence of freshly distilled cyclopentadiene gave the bicyclic compounds **2** which were reductively dechlorinated under very mild conditions to give a good yield of the desired ketone **3** (Scheme 1). The bromine atom in the latter compound was exchanged for a methoxy group using silver tetrafluoroborate in methanol with ultrasonication. Bromohydrin formation took place with great selectivity on the ether **4** to give compound **5** in 72% yield; a small amount (17%) of the C-7 epimer was formed under the reaction conditions.

Peracetic acid oxidation of the ketone **5** was highly regio-

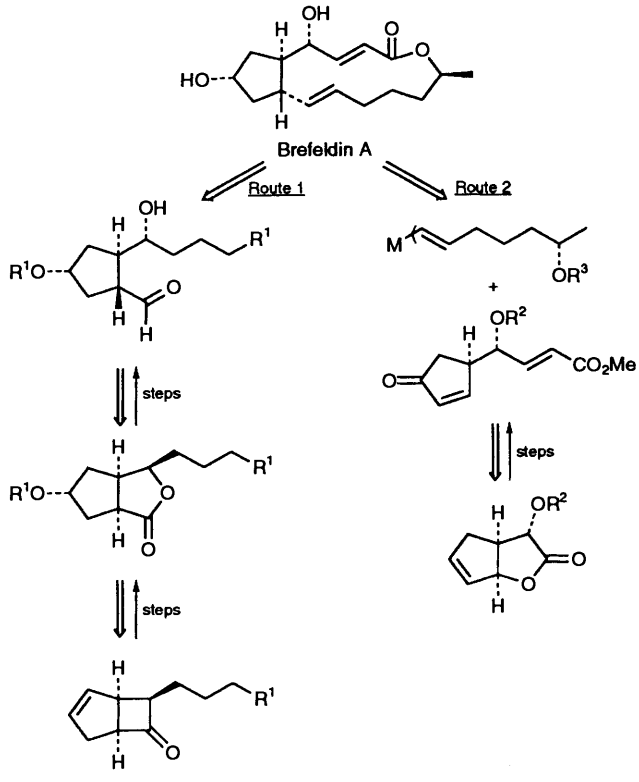
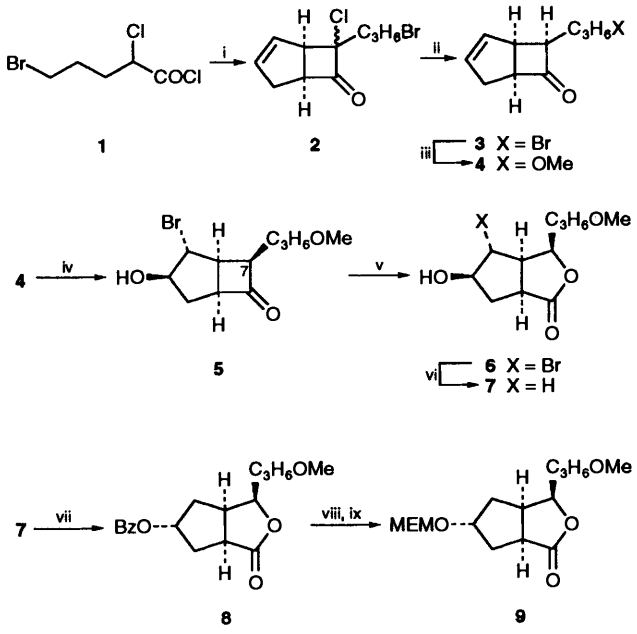


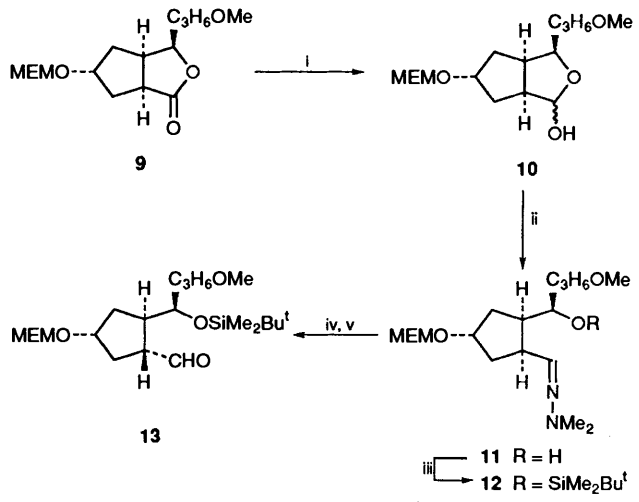
Fig. 1

selective giving mainly the required lactone **6** (48.5%) which could be separated from the small amount of the isomeric 2-oxabicyclo[3.3.0]octan-3-one (4.5%) that was formed. The major isomer was hydrodebrominated using tributyltin hydride in warm toluene and the product **7** was subjected to a Mitsunobu reaction to give the benzoate **8** in 83% yield from the lactone **6**. Hydrolysis of the ester group and protection of the resultant alcohol as the methoxyethoxymethyl (MEM) derivative gave the lactone **9** in 78% overall yield.

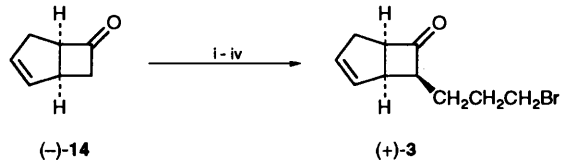
Reduction of the lactone **9** with diisobutylaluminium hydride gave the lactols **10** (Scheme 2) and these compounds reacted with *N*,*N*-dimethylhydrazine to give the hydrazone **11** which was further protected as the *tert*-butyldimethylsilyl ether **12**. Regeneration of the aldehyde unit (46% yield) and DBU-catalysed epimerization (84% yield) gave the required aldehyde



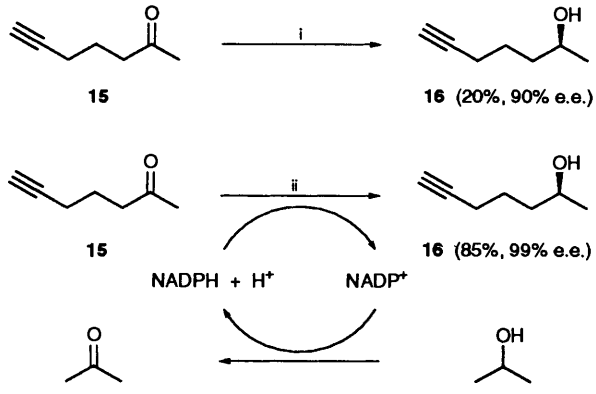
Scheme 1* *Reagents and conditions:* i, Et_3N, excess, C_5H_5, hexane, 0–5 °C, 16 h, 54%; ii, Zn (2 equiv.), NH_4Cl (2.5 equiv.), MeOH, 0 °C, 3 h, 40 min., 77%; iii, $AgBF_4$, MeOH, ultrasound, 40 °C, 6 h, 73%; iv, *N*-bromoacetamide, acetone–H_2O (4 : 1), room temp., 16 h, 72% plus 17% of C-7 epimer; v, $MeCO_2H$, H_2O_2, 0–5 °C, 4 h, 53% total yield; vi, Bu_3SnH, AIBN, toluene, 60 °C, 2 h, 90%; vii, PPh_3, diethyl azodicarboxylate, $PhCO_2H$, THF, room temp., 40 min., 92%; viii, 2% K_2CO_3, MeOH, room temp., 1 h, 87%; ix, $MeOCH_2CH_2OCH_2Cl$, Pr^i_2EtN, CH_2Cl_2, 16 h, 89%



Scheme 2* *Reagents and conditions:* i, Bu^i_2AlH, CH_2Cl_2, −78 °C, 1 h, 89%; ii, Me_2NNH_2, TsOH·H_2O (5 mol %), 3 h reflux, 100%; iii, TBDMS-OTf, Et_3N, CH_2Cl_2, 83%; iv, $Cu(OAc)_2$, THF–H_2O (1 : 1), room temp., 28 h, 46%; v, DBU, DMF, N_2, 2 h, 84%



Scheme 3 *Reagents and conditions:* i, Me_2NNH_2, 60 °C, 2 h, 100%; ii, Pr^i_2NLi, Et_2O, 0 °C, 40 min then $Br(CH_2)_3Br$ −70 °C→5 °C, 2 h; iii, 1 mol dm^{-3} HCl, THF (1 : 1), 1 h, 3% from (−)-**14**; iv, 1 mol dm^{-3} NaOH, 72 h, 35%



Scheme 4 *Reagents and conditions:* i, Baker's yeast, sucrose, H_2O; ii, TabDH, Tris buffer

13. The structure of this compound was elucidated by NMR spectroscopy.

A number of difficulties had been experienced along this first synthetic route. Two modest yields were troublesome, first the Baeyer–Villiger oxidation (Scheme 1, step iv, 48.5%) and the regeneration of the aldehyde group (Scheme 2, step iv, 46%). Secondly, the obtention of quantities of optically active starting material was unsuccessful. For example, in a model study (using the 'wrong' enantiomer), optically active ketone (−)-**14**† was converted into the bromo ketone (+)-**3** as outlined in Scheme 3[9] but the overall yield was ≤1%. Obviously, further experimentation could have led to a marked improvement in this yield but this research was not undertaken.

Thirdly, the functional group at the terminus of the C(4)-side chain needed modification and the C(2)–C(3) double bond had yet to be introduced. This meant that we were faced with several more tricky steps in what had become a protracted synthesis. Hence we turned our attention to the second route where many of these difficulties could be more easily resolved.

Synthesis of (+)-*Brefeldin-A by Route 2.*—For the second route, we required the optically pure alkynol **16**. Thus, hept-6-yn-2-one **15** was enantioselectively reduced using the alcohol dehydrogenase from *Thermoanaerobium brockii* (TabDH) in high optical purity and excellent yield in a process that is much cleaner and efficient than the prescribed biotransformation using baker's yeast (Scheme 4).[10]

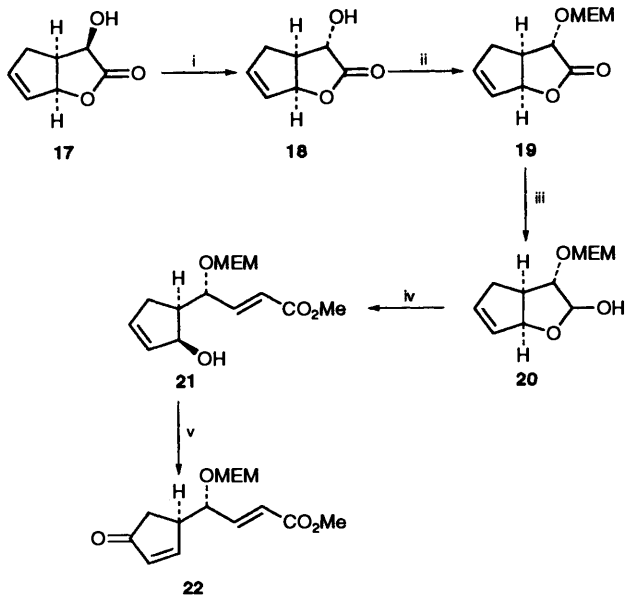
It is noteworthy that the resolution of racemic hept-6-yn-2-ol using lipases was not as effective as the dehydrogenase-catalysed reaction for the production of optically active material.[8]

The alcohol **16** was protected as the *tert*-butyldimethylsilyl ether before being converted into the stannane **23**.

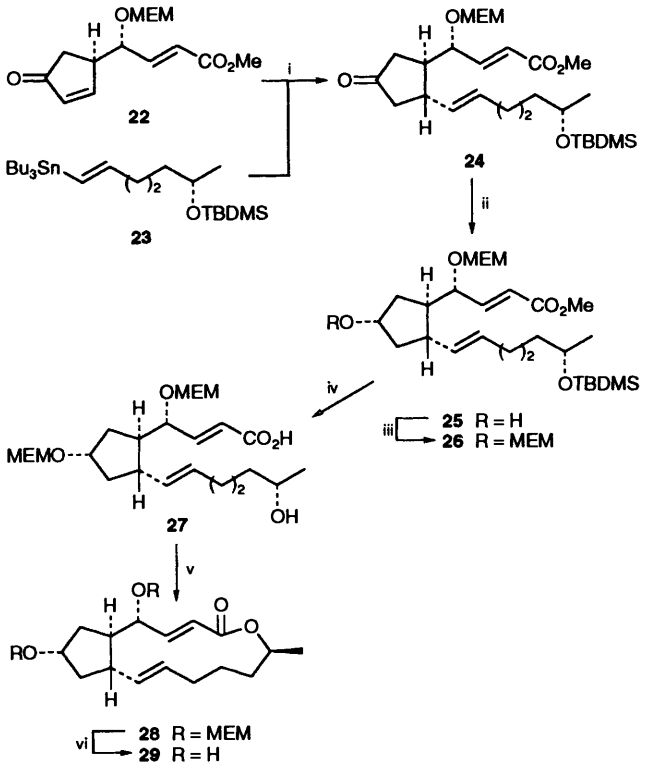
The required *exo*-hydroxy lactone **18** was prepared from the readily available *endo*-hydroxy lactone **17** (Scheme 5) and was protected as the methoxyethoxymethyl ether **19** by treatment with methoxyethoxymethyl chloride in dry dichloromethane using Hunig's base as the proton sponge. The ether **19** was treated with diisobutylaluminium hydride (2 equiv.) in tetrahydrofuran to afford the lactol **20** in quantitative yield. The lactol was subjected to a Wittig reaction using methyl triphenylphosphoranylideneacetate in toluene. In order to avoid formation of undesired cyclic ether resulting from over reaction, the temperature was maintained at 95 °C. Under these conditions an 80% yield of the α,β-unsaturated methyl ester **21** was obtained. The rearrangement and oxidation of the cyclopentenol **21** to the corresponding cyclopentenone **22** was

* In Schemes 1 and 2 the compounds which are described therein are racemic but only one enantiomer is shown for convenience.

† The ketone (−)-**14** was a gift from Glaxo Research and Development.



Scheme 5 *Reagents and conditions:* i, Ph_3P, $ClCH_2CO_2H$, DEAD, THF, 20 h, room temp.; then thiourea, EtOH, 2 h, heat, 84%; ii, $MeOCH_2CH_2OCH_2Cl$, Pr^i_2EtN, CH_2Cl_2, 24 h, 91%; iii, Bu^i_2AlH, THF, −78 °C, 2 h, 100%; iv, methyl (triphenylphosphoranylidene)-acetate, toluene, 95 °C, 6 h, 80%; v, pyridinium chlorochromate, toluene-*p*-sulfonic acid, CH_2Cl_2, 12 h, 60%



Scheme 6 *Reagents and conditions:* i, Compound **23**, MeLi, CuCN, THF, −78 °C, 0.5 h, 87%; ii, Bu^i_2AlH, THF, −78 °C, 1 h, 50% or K-Selectride, THF, −78 °C, 1 h, 63%; iii, methoxyethoxymethyl chloride, Pr^i_2NEt, CH_2Cl_2, 12 h, 87%; iv, 1 mol dm^{-3} HCl, THF, 14 h and LiOH, MeOH, H_2O, 10 h, 100%; v, 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 6 h and, 4-(*N*,*N*-dimethylamino)pyridine, toluene, reflux, 14 h, 80%; vi, $TiCl_4$, CH_2Cl_2, 0 °C, 2 h, 85%

achieved in one pot using Baeckstrom's conditions[11] (60% yield).

Conjugate addition of the cuprate reagent derived from **23** to the enone **22** (Scheme 6) attached the lower side chain with complete stereocontrol, the attack being directed on the α face of the enone by the ester-containing side chain. The success of this conjugate addition (87% yield) proved to be crucial for the completion of brefeldin-A construction as it enabled substantial quantities of compound **24** to be obtained. Reduction of the ketone **24** using potassium Selectride afforded a 63% yield of the hydroxy compound **25** along with 22% of the undesired epimer. This mixture was separated by chromatography and the alcohol **25** was protected as its methoxyethoxymethyl ether **26** in 85% yield.

The *tert*-butyldimethylsilyl group was removed and the ester group hydrolysed with aqueous lithium hydroxide to give the hydroxy acid **27**. Lactonisation was achieved using Yamaguchi's conditions. Thus, after activation of the carboxylic acid function, treatment with 4-(*N*,*N*-dimethylamino)-pyridine, using high dilution conditions, afforded 80% yield of diprotected brefeldin-A **28**. Removal of both methoxyethoxymethyl groups gave (+)-brefeldin-A in 85% yield. This compound was identical in terms of m.p., ^1H and ^{13}C NMR spectra with an authentic sample of the natural product.

The new route to (+)-brefeldin-A from the hydroxy lactone **17** comprises 12 steps and illustrates how careful choice of enzymatically prepared chiral synthons can dramatically ease a difficult task.

Other enzymatic transformations are under study in our laboratories and their use in the synthesis of natural products will be reported in due course.

Experimental

IR spectra were recorded on a Perkin-Elmer 881 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 250 spectrometer at 250 and 62.8 MHz respectively using deuteriochloroform as the solvent. All chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are quoted in Hz. The m.p.s were determined on a capillary apparatus. $[\alpha]_D$ Values, in units of 10^{-1} deg cm^2 g^{-1}, were recorded on an Optical Activity Ltd AA 1000 polarimeter. Solvents were distilled prior to use. Tetrahydrofuran (THF) and ether were distilled from sodium metal/benzophenone under nitrogen. Methylene dichloride (CH_2Cl_2) and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride under nitrogen. Toluene was distilled from calcium hydride under nitrogen and stored over 4A molecular sieves. Flash chromatography was carried out using silica gel 60 H (Merck 7385). Thin-layer chromatography (TLC) was performed on Merck 60F-254 (Merck 5715) glass-backed silica gel plates with visualisation by UV light (254 nm), phosphomolybdic acid (solution in ethanol), or potassium permanganate (aqueous solution). All new compounds were homogeneous by TLC analysis using the solvent systems employed in the purification process.

5-Bromo-2-chlorovaleryl Chloride **1**.—5-Bromovaleric acid (20 g, 0.11 mol) was stirred in thionyl chloride (65.4 g, 0.55 mol, 40 cm^3) and benzene (19 cm^3) at 80 °C for 90 min after which the solution was allowed to cool to room temperature. *N*-Chlorosuccinimide (29 g, 0.22 mol) was added to the solution which was then heated at reflux for 2 h. The solution was allowed to cool to room temperature and the residual succinimide was filtered off washing with carbon tetrachloride. The thionyl chloride and benzene were evaporated from the filtrate and washings under reduced pressure before vacuum distillation of the crude residue gave the desired acid chloride **1** (22.5 g, 87%), b.p. 76 °C/0.5 mmHg; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1790 (C=O); δ_H(60 MHz) 4.90–4.45 (1 H, m, 2-H), 3.70–3.40 (2 H, m, 2 × 5-H), 2.70–1.80 (4 H, m, 2 × 3-H and 2 × 4-H).

7-(3-*Bromopropyl*)-7-*chlorobicyclo*[3.2.0]*hept*-2-*en*-6-*one* **2**.—A solution of the acid chloride **1** (15 g, 64 mmol) in dry hexane (20 cm^3) was added dropwise to a stirred solution of triethylamine (13.4 g, 0.13 mol, 18.3 cm^3) and cyclopentadiene (72.6 g, 1.1 mol, 91 cm^3) in hexane (74 cm^3) at 0–5 °C under a nitrogen atmosphere. The resultant mixture was stirred at that temperature for 4.5 h after which water (110 cm^3) was added to it and the layers separated. The organic layer was washed with 2 mol dm^{-3} hydrochloric acid (70 cm^3), dilute aqueous sodium hydrogen carbonate (70 cm^3) and brine (2 × 70 cm^3) and then dried ($MgSO_4$), and evaporated under reduced pressure. The crude red oil was purified by chromatography [CH_2Cl_2–petroleum (b.p. 60–80 °C) (1:9)] to give an inseparable mixture of two epimeric ketones **2** in the ratio 9:1 (9 g, 54%) as a colourless oil. For the major epimer ν_{max}/cm^{-1} 3065, 2965, 2922, 2854 and 1778 (C=O); δ_H 6.06–5.76 (2 H, m, 2-H and 3-H), 4.27 (1 H, ddd, *J* 9.0, 7.5, 1.5, 5-H), 3.72–3.64 (1 H, m, 1-H), 3.52–3.33 (2 H, m, 2 × 3′-H), 2.71 (1 H, d, *J* 17.0, 4_{endo}-H), 2.48 (1 H, dddd, *J* 17.5, 9.0, 3.5, 2.0, 4_{exo}-H) and 2.36–1.88 (4 H, m, 2 × 1′-H and 2 × 3′-H); δ_C 206.0 (C=O), 136.9 and 128.0 (CHCH), 82.8 (C-7), 59.4 (C-5), 54.65 (C-1), 34.05 and 33.0 (C-3′ and C-4), 30.35 and 27.4 (C-1′ and C-2′); *m*/*z* (CI) 267, 265, 263 (M^+ + H), 266, 264, 262 (M), 229, 227 (M − Cl) and 185–183 (M − Br); (Found: M^+, 261.9760. $C_{10}H_{12}ClO^{79}Br^{35}$ requires *M*, 261.9760). For the minor epimer δ_H 5.95–5.60 (2 H, m, 2-H and 3-H), 4.10–3.90 (1 H, m, 5-H), 3.70–3.25 (3 H, m, 1-H and 2 × 3′-H), 2.70 (1 H, d, *J* 14.0, 4_{endo}-H), 2.40 (1 H, m, 4_{exo}-H), 2.25–1.90 (4 H, m, 2 × 1′-H and 2 × 2′-H). It was assumed that the major epimer corresponds to the *endo*-bromopropyl ketone.

7-endo-(3-*Bromopropyl*)*bicyclo*[3.2.0]*hept*-2-*en*-6-*one* **3**.—A solution of the ketone **2** as the C-7 epimeric mixture (ratio 9:1) (5 g, 19 mmol) in methanol (13 cm^3) was added dropwise to a stirred solution of zinc dust (2.48 g, 37.95 mmol) and ammonium chloride (2.54 g, 47.42 mmol) in methanol (20 cm^3) at 0 °C. The mixture was stirred at 0 °C for 5.5 h and then filtered through a Celite bed, washing with methanol. The methanol was evaporated under reduced pressure. The residue was dissolved in dichloromethane (20 cm^3) and the solution filtered evaporated under reduced pressure. The crude residue was purified by chromatography [petroleum (b.p. 40–60 °C)–Et_2O (9:1)] to give the title compound **3** (3.33 g, 77%) as a colourless oil; ν_{max}/cm^{-1} 3042, 2925, 2854 and 1764 (C=O); δ_H 5.94–5.70 (2 H, m, 2-H and 3-H), 3.85–3.74 (1 H, m, 5-H), 3.67–3.52 (1 H, m, 1-H), 3.51–3.31 (3 H, m, 7-H and 2 × 3′-H), 2.63 (1 H, d br, *J* 17.0, 4_{endo}-H), 2.38 (1 H, dddd, *J* 17.0, 9.5, 3.0, 2.0, 4_{exo}-H) and 2.05–1.46 (4 H, m, 2 × 1′-H and 2 × 2′-H); δ_C 214.3 (C=O), 135.1 and 129.3 (CH=CH), 63.9 (C-7), 59.5 (C-5), 44.6 (C-1), 34.0 (C-4), 33.1 (C-3′), 30.8 and 23.85 (C-1′ and C-2′) (Found: C, 52.2; H, 5.6. $C_{10}H_{13}BrO$ requires C, 52.42; H, 5.72%).

7-endo-(3-*Methoxypropyl*)*bicyclo*[3.2.0]*hept*-2-*en*-6-*one* **4**.—A solution of the bromopropyl ketone **3** (200 mg, 0.87 mmol) in methanol (4.6 cm^3) was sonicated with silver tetrafluoroborate (340 mg, 1.74 mmol) for 6 h. The methanol was decanted off and the residual solid washed several times with dichloromethane. The organic solution was washed with brine (4 × 5 cm^3), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude residue was purified by chromatography [petroleum–EtOAc (9:1)] to give the title compound **4** (114 mg, 73%) as a colourless oil; ν_{max}/cm^{-1} 3020, 2932, 2862, 1768 (C=O) and 1605 (C=C); δ_H 5.83–5.64 (2 H, m, 2-H and 3-H), 3.70 (1 H, br t, *J* 8.0, 5-H), 3.60–3.44 (1 H, m, 1-H), 3.43–3.20 (6 H, m, 7-H, 2 × 3′-H and CH_3), 2.54 (1 H, d br, *J* 17.0, 4_{endo}-H), 2.29 (1 H, dddd, *J* 17.0, 9.5, 1.5, 4_{exo}-H) and 2.20–1.90 (4 H, m, 2 × 1′-H and 2 × 2′-H); δ_C 214.9 (C=O), 134.7 and 129.6 (C-2 and C-3), 72.3 (C-3′), 64.7 (C-7), 59.2 (C-5), 58.3 (CH_3), 42.2 (C-1), 33.9 (C-4), 27.6 and 21.7 (C-1′ and C-2′); *m*/*z* (CI) 181 (M^+ + H, 100%), 197 (M + OH, 60) and 149 (M − OMe, 20) (Found: M^+ + H, 181.1229. $C_{11}H_{16}O_2$ requires *M* + H, 181.1228).

2-exo-*Bromo*-3-endo-*hydroxy*-7-endo-(3-*methoxypropyl*)-*bicyclo*[3.2.0]*heptan*-6-*one* **5**.—The methoxypropyl ketone **4** (4.51 g, 25.0 mmol) was dissolved in a mixture of acetone–water (4:1; 196 cm^3) and *N*-bromoacetamide (3.25 g, 23.5 mmol) was added portionwise to the stirred solution. The reaction mixture was stirred at room temperature for 10 h after which water (50 cm^3) was added to it and the acetone was evaporated under reduced pressure. The aqueous residue was extracted with ether (3 × 30 cm^3) and the combined organic extracts were washed with 10% (w/v) aqueous sodium sulfite (2 × 20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The crude oil was purified by chromatography [petroleum–EtOAc (7:3)] to give an inseparable mixture of the ketone **5** and the C-7 epimer (6.14 g, 89%) in the ratio 5.6:1. For the ketone **5**: ν_{max}/cm^{-1} 3595, 3433, 2938, 2874, 2835 and 1774 (C=O); δ_H 4.48 (1 H, br d, 3-H), 4.22 (1 H, s, 2-H), 3.72–3.60 (1 H, m, 5-H), 3.42–3.20 (7 H, m, 7-H, 1-H, 2 × 3′-H and CH_3), 2.31 (1 H, ddd, *J* 14.0, 9.0, 4.2, 4_{exo}-H), 2.20 (1 H, br d, *J* 14.0, 4_{endo}-H) and 1.86–1.50 (5 H, m, OH, 2 × 1′-H and 2 × 2′-H); δ_C 213.6 (C=O), 81.2 (C-3), 72.3 (C-3′), 63.4 and 60.3 (C-7 and C-5), 58.1 (CH_3), 53.6 (C-2), 44.2 (C-1), 34.5 (C-4), 27.7 and 22.7 (C-1′and C-2′); *m*/*z* (CI) 279, 277 (M^+ + H, 100%, 93%) 296, 294 (M + NH_4, 19) and 197 (M − Br, 63) (Found: M^+ + H, 277.0417. $C_{11}H_{17}{}^{79}BrO_3$ requires M + H, 277.0439); for the epimeric ketone: (observable signals) δ_H 4.56 (1 H, br d, *J* 4.0, 3-H), 4.30 (1 H, s, 2-H), 2.91 (1 H, dd, *J* 7.5, 4.0, 1-H), 2.44 (1 H, ddd, *J* 14.0, 9.0, 4.2, 4_{exo}-H) and 2.15 (1 H, br d, *J* 14.00, 4_{endo}-H); δ_C 215.1 (C=O), 81.8 (C-3), 72.1 (C-3′), 65.4 and 60.3 (C-7 and C-5), 58.1 (CH_3), 57.8 (C-2), 46.35 (C-1), 37.0 (C-4), 27.15 and 27.1 (C-1′ and C-2′).

6-exo-*Bromo*-7-endo-*hydroxy*-4-endo-(3-*methoxypropyl*)-3-*oxabicyclo*[3.3.0]*octan*-2-*one* **6**.—A mixture of the ketone **5** and the C-7 epimer (ratio, 5.6:1 respectively) (6.143 g, 0.022 mol) was oxidized with peracetic acid over 4 h. Work-up and chromatography [petroleum–EtOAc (1:1)] gave a separable mixture of the lactone **6** and 6-*exo*-bromo-7-*endo*-hydroxy-4-*endo*-(1′-methoxypropyl)-2-oxabicyclo[3.3.0]octan-3-one (over-all yield 3.32 g, 52%) in the ratio 10:1, respectively. For the lactone **6** m.p. 106–107 °C, spectral data were as follows ν_{max}/cm^{-1} 3593, 3435, 2935 and 1768 (C=O); δ_H 4.64–4.52 (1 H, m, 4-H), 4.37–4.28 (1 H, q, *J* 4.0, 7-H), 4.13 (1 H, t, *J* 4.0, 6-H), 3.52–3.38 (2 H, m, 2 × 3′-H), 3.36–3.23 (4 H, m, 5-H and CH_3), 3.16 (1 H, dt, *J* 9.5, 2.5, 1-H), 3.10 (1 H, br s, OH), 2.50 (1 H, ddd, *J* 14.0, 9.5, 5.0, 8_{exo}-H), 2.11 (1 H, dt, *J* 14.0, 3.0, 8_{endo}-H), 2.00–1.60 (4 H, m, 2 × 1′-H and 2 × 2′-H); δ_C 179.5 (C=O), 80.9 and 79.3 (C-4 and C-7), 71.9 (C-3′), 58.6 (CH_3), 52.5 and 52.0 (C-6 and C-1), 43.8 (C-5), 35.0 (C-8), 28.2 and 26.5 (C-1′ and C-2′); *m*/*z* (CI) 230 (M^+ + NH_4 − HBr, 100%), 295 and 293 (M + H, 18) (Found: M^+, 292.0310. $C_{11}H_{17}{}^{79}BrO_4$ requires *M*, 292.0310) (Found: C, 44.8; H, 5.7. $C_{11}H_{17}BrO_4$ requires C, 45.07; H, 5.85%).

7-exo-*Benzoyloxy*-4-endo-(3-*methoxypropyl*)-3-*oxabicyclo*-[3.3.0]*octan*-2-*one* **8**.—A catalytic amount of azoisobutyronitrile (5 mg, 0.32 mmol) and tributyltin hydride (4.68 g, 16.08 mmol, 4.33 cm^3) were added to a stirred solution of the bromohydrin **6** (3.152 g, 10.72 mmol) in dry toluene (54 cm^3). The reaction mixture was stirred at 60 °C for 2 h after which it was allowed to cool to room temperature. The toluene was evaporated under reduced pressure and the residue partitioned between hexane (100 cm^3) and acetonitrile (100 cm^3). The acetonitrile fraction was extracted with hexane (3 × 10 cm^3) and the combined hexane fractions were washed with aceto-

nitrile (3 × 10 cm^3). The combined acetonitrile fractions were washed with hexane (2 × 10 cm^3) and evaporated under reduced pressure to give an orange oil which was purified by filtration through flash silica (Et_2O then EtOAc) to give 7-*endo*-hydroxy-4-*endo*-(3-methoxypropyl)-3-oxabicyclo[3.3.0]octan-2-one (2.06 g, 90%) as a colourless oil; ν_{max}/cm^{-1} 3605, 3065, 2944 and 1763 (C=O); δ_H 4.55–4.44 (1 H, m, 4-H), 4.30–4.17 (1 H, m, 7-H), 3.44–3.20 (5 H, m, CH_3 and 2 × 3'-H), 3.01 (1 H, dt, *J* 7.0, 2.5, 1-H), 2.93–2.79 (1 H, m, 5-H), 2.75 (1 H, br s, OH), 2.10–1.95 (2 H, m, 2 × 8-H) and 1.90–1.50 (6 H, m, 2 × 6-H, 2 × 1'-H and 2 × 2'-H); δ_C 180.7 (C=O), 81.2 (C-4), 72.6 (C-7), 72.1 (C-3'), 58.4 (CH_3), 45.0 (C-1), 41.0 (C-5), 38.8 (C-8), 34.5 (C-6), 28.4 and 26.4 (C-1' and C-2'), *m/z* (CI) 215 (M^+ + H, 100%), 232 (M + NH_4, 22) and 196 (M − OH, 10) (Found: M^+ + H, 215.1283. $C_{11}H_{18}O_4$ requires *M* + H, 215.1283).

A solution of the above *endo*-hydroxy lactone (586 mg, 2.74 mmol) in dry tetrahydrofuran (10 cm^3) was stirred with triphenylphosphine (831 mg, 4.11 mmol) and benzoic acid (502 mg, 4.11 mmol). Diethyl azodicarboxylate (647 mm^3,* 4.11 mmol) was slowly added to the reaction mixture which was then stirred at room temperature for 40 min. The tetrahydrofuran was evaporated under reduced pressure and dichloromethane (30 cm^3) was added to the residue. The organic solution was washed with saturated aqueous sodium hydrogen carbonate (3 × 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The crude residue was purified by chromatography [CH_2Cl_2–petroleum (b.p. 40–60 °C)–Et_2O; 5:4:1] to give the title compound **8** (808 mg, 92%); δ_H(60 Mz) 8.2–8.0 (2 H, m, Ar), 7.8–7.5 (3 H, m, Ar), 5.7–5.5 (1 H, m, 7-H), 4.8–4.5 (1 H, m, 4-H), 3.8–3.0 (7 H, m, CH_3O, 2 × 1'-H, 1-H and 5-H), 2.6–2.3 (2 H, m, 2 × 8-H), 2.2–1.6 (6 H, m, 2 × 1'-H, 2 × 2'-H and 2 × 6-H). This compound was used for the following step without further characterization.

7-exo-*Methoxyethoxymethoxy*-4-endo-(3-*methoxypropyl*)-3-*oxabicyclo*[3.3.0]*octan*-2-*one* **9**.—The benzoate ester **8** (808 mg, 2.54 mmol) was stirred with a solution of 2% (w/v) potassium carbonate in methanol (10 cm^3) at room temperature for 1 h. Saturated aqueous ammonium chloride (2 cm^3) was added to the mixture and the methanol evaporated under reduced pressure. The aqueous residue was extracted with dichloromethane (3 × 10 cm^3), back extracting with water (3 × 2 cm^3) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the 7-*exo*-hydroxy compound (476 mg, 81%).

A solution of the *exo*-hydroxy lactone (602 mg, 2.81 mmol) in dry dichloromethane (7 cm^3) was stirred with diisopropylamine (1.5 cm^3, 8.43 mmol) and 2-methoxyethoxymethyl chloride (MEM-Cl) (485 mm^3, 4.22 mmol) was slowly added to the mixture . After the mixture had been stirred overnight, further MEM-Cl (323 mm^3, 1 equiv.) was added to the reaction mixture which was then stirred for a further 5 h. After this, the mixture was diluted with dichloromethane (10 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (3 × 3 cm^3) and water (3 × 3 cm^3), the combined organic phases being back extracted with additional dichloromethane (3 × 2 cm^3). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure and the crude residue was purified by chromatography [Et_2O–petroleum (b.p. 40–60 °C) (9:1)] to give the title compound **9** (673 mg, 79%) as a colourless oil; ν_{max}/cm^{-1} 2934, 2893 and 1762 (C=O); δ_H 4.56 (2 H, s, OCH_2O), 4.48 (1 H, dt, *J* 8.0, 5.0, 4-H), 4.22–4.13 (1 H, m, 7-H), 3.62–3.42 (4 H, m, OCH_2CH_2O), 3.39–3.26 [5 H, m, 2 × 3'-H and $(CH_2)_3OCH_3$], 3.23 [3 H, s, $O(CH_2)_2CH_3$], 3.16–2.90 (2 H, m, 1-H and 5-H), 2.11–1.98 (2 H, m, 2 × 8-H) and 1.90–1.40 (6 H, m, 2 × 1'-H, 2 × 2'-H and 2 × 6-H); δ_C 182.0 (C=O), 94.0 (OCH_2O), 80.45 (C-4), 78.35 (C-7), 72.0, 71.75 and 67.05 (OCH_2CH_2O and C-3'), 59.0 and 58.5 (2 × CH_3), 45.1 (C-1), 42.9 (C-5), 35.5 (C-8), 32.1 (C-6), 28.1 and 26.3 (C-1' and C-2'); *m/z* (CI) 320 (M^+ + NH_4, 100%) and 303 (M + H, 25) (Found: M^+ + NH_4, 320.2073. $C_{15}H_{26}O_6$ requires M + NH_4, 320.2073).

7-exo-*Methoxyethoxymethoxy*-4-endo-(3-*methoxypropyl*)-3-*oxabicyclo*[3.3.0]*octan*-2-*ol* **10**.—A solution of diisobutylaluminium hydride (1.0 mol dm^{-3} solution in toluene; 3.5 cm^3, 3.5 mmol) was added dropwise to a stirred solution of the lactone **9** (673 mg, 2.23 mmol) in dry dichloromethane (11 cm^3) at −70 °C. The reaction mixture was stirred for 0.5 h after which methanol (3 cm^3) was added dropwise to it, the temperature being maintained at −70 °C. The reaction mixture was allowed to warm to room temperature when it was filtered through Celite to remove the white precipitate. The filtrate was evaporated under reduced pressure and the crude residue purified by chromatography [Et_2O–EtOAc (4:1)] to give the title compound **10** (606 mg, 89%) as a colourless oil; ν_{max}/cm^{-1} 3595 and 3412; δ_H 5.10 (1 H, s, 2-H), 4.64 (2 H, s, OCH_2O), 4.29–4.20 (1 H, m, 4-H), 4.19–4.10 (1 H, m, 7-H), 3.67–3.45 (5 H, m, OCH_2CH_2O and OH), 3.40–3.30 [5 H, m, $(CH_2)_2CH_2OCH_3$], 2.27 (3 H, s, CH_3), 2.84–2.63 (2 H, m, 1-H and 5-H), 2.05–1.95 (1 H, m, 8-H) and 1.80–1.50 (7 H, m, 2 × 1'-H, 2 × 2'-H, 2 × 6-H and 8-H); δ_C 103.8 (C-2), 94.0 (OCH_2O), 79.7 and 78.8 (C-4 and C-7), 72.5, 71.7 and 66.8 (OCH_2CH_2O and C-3'), 58.9 and 58.4 (2 × OCH_3), 50.2 (C-1), 44.2 (C-5), 36.9 (C-8), 32.2 (C-6), 27.1 and 26.8 (C-1' and C-2'); *m/z* (CI) 287 (M^+ − OH, 100%) and 304 (M + NH_4 − H_2O, 9) (Found: M^+ + NH_4 − H_2O, 304.2124. $C_{15}H_{28}O_6$ requires M + NH_4 − H_2O, 304.2124).

5-N,N-*Dimethylhydrazino*-1-(1-*hydroxy*-4-*methoxybutyl*)-3-*methoxyethoxymethoxycyclopentane* **11**.—The lactol **10** (0.10 g, 0.33 mmol) was dissolved in *N,N*-dimethylhydrazine (1.2 cm^3) and a catalytic amount of toluene-*p*-sulfonic acid was added to the solution. After the reaction mixture had been refluxed for 4 h, a few drops of saturated aqueous sodium hydrogen carbonate were added to it to neutralise the acid. The mixture was then evaporated under reduced pressure, the residue diluted with dichloromethane and the solution was washed with water (5 cm^3) and brine (5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to yield the title compound (0.124 g, 0.30 mmol, 93%). This was used without any further purification.

1-(1-tert-*Butyldimethylsiloxy*-4-*methoxybutyl*)-5-N,N-*dimethylhydrazino*-3-*methoxyethoxymethoxycyclopentane* **12**.—Anhydrous triethylamine (0.130 cm^3, 0.93 mmol, 1.6 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.121 cm^3, 0.52 mmol, 1.4 equiv.) were added to a stirred solution of compound **11** (0.124 g, 0.36 mmol) in anhydrous dichloromethane (1.4 cm^3) at room temperature. The reaction mixture was stirred for 2 h and then diluted with dichloromethane (5 cm^3). After this it was washed with water (5 cm^3) and brine (5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography of the residue using petroleum (b.p. 60–80 °C)–ethyl acetate (5:1, v/v) afforded the title compound **12** (0.136 g, 0.03 mmol, 83%); δ_H(250 MHz; $CDCl_3$) 6.57 (1 H, d, *J* 6.6, N=CH), 4.70 (2 H, s, OCH_2O), 4.40–4.28 (1 H, m, 3-H), 3.74–3.62 (3 H, m, 1'-H and $OCH_2CH_2OCH_3$), 3.62–3.50 (2 H, m, $OCH_2CH_2OCH_3$), 3.38 (3 H, s, OMe), 3.38–3.31 (2 H, m, 4'-H_2), 3.30 (3 H, s, OMe), 3.00–2.86 (1 H, m, 5-H), 2.70 (6 H, s, NMe_2), 2.50–2.32 (1 H, m, 1-H), 2.12–2.00 (1 H, m, 4-H), 1.96–1.70 (3 H, m, 4-H and 2-H_2), 1.66–1.48 (4 H, m, 2'-H_2 and 3'-H_2), 0.87 (9 H, s, SiBu^t) and 0.04 (6 H, s, $SiMe_2$); δ_C(62.9 MHz; $CDCl_3$) 94.12 (CH_2, OCH_2O), 77.06 (CH, 3-C), 73.11 (CH_2, 4'-C), 73.04 (CH, 1'-C), 71.84 (CH_2, OCH_2CH_2OMe), 66.84

* 1 mm^3 = 1 μl.

(CH_2, $OCH_2CH_2OCH_3$), 58.94 and 58.36 (CH_3, OMe), 45.78 (CH, 1-C or 5-C), 43.44 (CH_3, Me-N), 43.25 (CH, 5-C or 1-C), 38.67 (CH_2, 4-C), 35.24 (CH_2, 2-C), 31.79 (CH_2, 3'-C or 2'-C), 25.98 (CH_3, SiBu^t), 24.32 (CH_2, 3'-C or 2'-C), 16.12 (C, SiBu^t), −3.68 and −4.30 (CH_3, $SiMe_2$) (Found: [M + H^+], 461.3411. $C_{23}H_{49}N_2O_5Si$ requires 461.3411).

1-(1-tert-*Butyldimethylsiloxy*-4-*methoxybutyl*)-3-*methoxyethoxymethoxycyclopentane*-5-*carbaldehyde* **13**.—A solution of cupric acetate (0.112 g, 0.56 mmol, 4.6 equiv.) in water (6 cm^3) was added to a stirred solution of compound **12** (0.123 g, 0.12 mmol) in tetrahydrofuran (5.6 cm^3) at room temperature. After being stirred for 24 h, the mixture was evaporated under reduced pressure and a solution of saturated aqueous ammonium chloride and ammonium hydroxide (pH = 8) was added to the residue until a blue colour was observed; the reaction mixture was then diluted with diethyl ether (5 cm^3). The layers were separated and the aqueous phase was washed with diethyl ether (3 × 5 cm^3). The combined organic phases were washed with brine (5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography using petroleum (b.p. 60–80 °C)–ethyl acetate (1:1, v/v) afforded the *cis* formyl compound (0.05 g, 0.12 mmol, 46%); δ_H(250 MHz; $CDCl_3$) 9.78 (1 H, d, *J* 3, HC=O), 4.70 (2 H, s, OCH_2O), 4.40–4.28 (1 H, m, 3-H), 4.00–3.88 (1 H, m, 1'-H), 3.72–3.62 (2 H, m, $OCH_2CH_2OCH_3$), 3.60–3.50 (2 H, m, $OCH_2CH_2OCH_3$), 3.39 (3 H, s, OMe), 3.37–3.32 (2 H, m, 4'-H), 3.31 (3 H, s, OMe), 3.04–2.86 (1 H, m, 5-H), 2.79–2.62 (1 H, m, 1-H), 2.30–2.14 (1 H, m, 4-H), 1.98–1.82 (2 H, m, 4-H and 2-H), 1.81–1.50 (1 H, m, 2-H), 1.50–1.28 (4 H, m, 2'-H_2 and 3'-H_2), 0.90 (9 H, s, SiBu^t) and 0.10 (6 H, $SiMe_2$); δ_C(62.9 MHz; $CDCl_3$) 204.14 (C=O), 94.06 (CH_2, OCH_2O), 76.97 (CH, 3-C), 72.72 (CH_2, 4'-C), 71.79 (CH_2, $OCH_2CH_2OCH_3$), 71.73 (CH, 1'-C), 66.96 (CH_2, $OCH_2CH_2OCH_3$), 58.94 and 58.36 (CH_3, 2 × OMe), 51.70 and 45.90 (CH, 1-C and 5-C), 34.10 and 33.62 (CH_2, 2-C and 4-C), 32.24 (CH_2, 3'-C), 25.98 (CH_3, SiBu^t), 25.17 (CH_2, 2'-C), 16.12 (C, SiBu^t), −3.66 and −4.34 (CH_3, $SiMe_2$).

A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (35 mm^3, 0.23 mmol, 1.9 equiv.) in anhydrous dimethylformamide (1 cm^3) was added to a stirred solution of the above compound (0.05 g, 0.12 mmol) in anhydrous dimethylformamide (1.2 cm^3) under an atmosphere of nitrogen. After 2 h, phosphoric acid (1 cm^3) and aqueous ammonium chloride (10%; 2 cm^3) were added to the reaction mixture which was then diluted with ether (5 cm^3). The layers were separated and the aqueous phase was extracted with ether (3 × 5 cm^3). The combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure.

Flash chromatography using petroleum (b.p. 60–80 °C)–ethyl acetate (1:1, v/v) afforded the target compound **13** (0.043 g, 0.10 mmol, 84%); δ_H(250 MHz; $CDCl_3$) 9.63 (1 H, d, *J* 2, HC=O), 4.30 (2 H, s, OCH_2O), 4.80 (1 H, m, 3-H), 3.73–3.66 (1 H, m, 1'-H), 3.58–3.52 (2 H, m, $OCH_2CH_2OCH_3$), 3.40–3.32 (2 H, m, $OCH_2CH_2OCH_3$), 3.24–3.08 (8 H, m, 4'-H_2 and 2 × Me), 2.76–2.62 (1 H, m, 1-H), 2.55–2.42 (1 H, m, 5-H), 2.00 (1 H, dp, *J* 14 and *J* 2.5, 4-H_β), 1.92–1.80 (1 H, m, 2-H_α), 1.80–1.50 (2 H, m, 4-H_α and 2-H_β), 1.40–1.20 (4 H, m, 2'-H_2 and 3'-H_2), 0.90 (9 H, s, SiBu^t) and 0.10 (6 H, $SiMe_2$) (Found: [M + NH_4]$^+$, 436.3094. $C_{21}H_{46}NO_6Si$ requires 436.3136).

(S)-*Hept*-6-*yn*-2-*ol* **16**.—A solution of hept-6-yn-2-one **15** (2.10 g, 19 mmol) in Tris buffer (50 mmol dm^{-3}, pH 8.0; 80 cm^3) and propan-2-ol (20 cm^3) was flushed with argon for 0.5 h. 2-Mercaptoethanol (28 mm^3, 0.4 mmol), β-NADP$^+$ (4 mg, 0.005 mmol) and *Thermoanaerobium brockii* alcohol dehydrogenase (8.5 mg, 50 U) were added rapidly in one portion to the mixture. The resulting clear colourless liquid was stirred under argon at 35 °C for 80 h. The propan-2-ol was removed under reduced pressure and the mixture was extracted with diethyl ether; the extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash column chromatography eluting with diethyl ether–hexane (1:2), afforded (S)-hept-6-yn-2-ol (1.4 g, 66%) as a colourless oil, $[\alpha]_D^{20}$ +16.0 (*c* 7.2, C_6H_6) [lit.,[12] +14.7 (*c* 10, C_6H_6; 20 °C)]; ν_{max}(film)/cm^{-1} 3400, 3308, 1377, 1131 and 758; δ_H 3.86–3.76 (1 H, m, C*H*OH), 2.23–2.18 (2 H, m, CCH_2), 1.94 (1 H, t, *J* 2.6, HC), 1.72 (1 H, s, OH), 1.68–1.50 (4 H, m, 2 × CH_2) and 1.18 (3 H, d, *J* 6.2, CH_3).

Preparation of the Stannane **23**.—To a solution of (*S*)-hept-6-yn-2-ol **16** (1.38 g, 6.1 mmol) and imidazole (1.0 g, 14 mmol) in *N*,*N*-dimethylformamide (10 cm^3) was added *tert*-butyldimethylsilyl chloride (2.1 g, 14 mmol). The resulting mixture was stirred under argon for 12 h after which it was diluted with water (100 cm^3) and diethyl ether (100 cm^3). The organic layer was separated, washed with water (100 cm^3), dried, filtered and evaporated under reduced pressure to afford a yellow oil. Purification of this by flash column chromatography eluting with ethyl acetate–hexane (1:9), afforded the *tert*-butyldimethylsilyl ether (2.1 g, 86%) as a colourless oil, ν_{max}(film)/cm^{-1} 2950, 2100 and 1255; δ_H 3.86–3.76 (1 H, m, C*H*OTBS), 2.23–2.18 (2 H, m, $C{\equiv}CCH_2$), 1.94 (1 H, t, *J* 2.6, *H*C≡CCH$_2$), 1.68–1.50 (4 H, m, 2 × CH_2), 1.18 (3 H, d, *J* 6.2, CH_3), 0.90 (9 H, s, Bu^t), 0.10 [6 H, s, (Me_2Si)] (Found: M^+, 226.1747. $C_{13}H_{26}OSi$ requires M^+, 226.1752).

AIBN (10 mg) was added to a mixture of the alkyne (1.0 g, 4.42 mmol) and tributyltin hydride (1.35 g, 4.65 mmol) and the resulting mixture was stirred under argon at 95 °C for 12 h. The product was distilled under reduced pressure to afford the stannane **23** as a colourless oil, b.p. (195 °C, 0.2 Torr); ν_{max}(film)/cm^{-1} 2957, 1606 and 1134; δ_H 5.90 (2 H, m, HC=CH), 3.86–3.76 (1 H, m, C*H*OTBS), 2.20–2.10 (2 H, m, $C{\equiv}CCH_2$) and 1.50–0.00 (49 H, m); δ_C($CDCl_3$) 149.5, 127.2, 68.5, 39.1, 37.7, 29.2, 27.3, 27.2, 26.1, 25.0, 23.7, 18.1, 13.6, 10.2, 9.4, −4.4 and −4.7 (Found: M^+, 518.2942. $C_{25}H_{54}OSiSn$ requires M^+, 518.2966).

4-exo-*Hydroxy*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*one* **18**.—Triphenylphosphine (9.54 g, 36.4 mmol) and chloroacetic acid (6.1 g, 64.3 mmol) were added to a solution of *endo*-hydroxy lactone **17** (3 g, 21.4 mmol) in tetrahydrofuran (215 cm^3) followed by diethyl azodicarboxylate (6.34 g, 36.4 mmol) in tetrahydrofuran (35 cm^3) added slowly. The resulting solution was stirred under argon at room temperature for 20 h after which it was evaporated under reduced pressure. The residue was dissolved in dichloromethane (150 cm^3) and the solution was washed with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), filtered and evaporated. The resulting slurry was purified by flash column chromatography eluting with ethyl acetate–hexane (3:7), to yield the *exo*-chloroacetyl ester (4.9 g, 100%) as a colourless oil, $[\alpha]_D$ +49 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3017, 1796 and 1614; δ_H 6.13 (1 H, m, 8-H), 5.92 (1 H, m, 7-H), 5.61 (1 H, m, 1-H), 5.16 (1 H, d, *J* 7.0, 4-H), 4.21 (1 H, d, *J* 14.5, CH_2Cl), 4.14 (1 H, d, *J* 14.5, CH_2Cl), 3.11 (1 H, ddd, *J* 14.5, 7.0, 2.5, 5-H) and 2.88–2.64 (2 H, m, 6-H_2); δ_C($CDCl_3$) 172.0, 166.7, 137.0, 129.1, 87.7, 76.3, 42.5, 40.5 and 36.8 (Found: M^+ + H, 217.026. $C_9H_9ClO_4$ requires *M* + H, 217.026).

Thiourea (2.4 g, 32.1 mmol) was added to a solution of the *exo*-chloroacetyl ester (4.6 g, 21.4 mmol) in ethanol (210 cm^3) followed by sodium hydrogen carbonate (2.7 g, 32.1 mmol). The resulting mixture was heated to 95 °C for 2 h and then evaporated under reduced pressure. A mixture of brine and water (150 cm^3; 2:1) was added to the residue and the product was extracted into ethyl acetate. The extract was dried ($MgSO_4$), filtered and evaporated to give a yellow oil which was purified by flash column chromatography eluting with ethyl

acetate–hexane (1 : 1), to yield the *exo*-hydroxy lactone **18** (2.7 g, 87%) as a colourless oil; $[\alpha]_D$ +79 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3427, 1764, 1615, 1184, 1116 and 986; δ_H 6.1 (1 H, m, 7-H or 8-H), 5.9 (1 H, m, 8-H or 7-H), 5.55 (1 H, m, 1-H), 4.15 (1 H, d, *J* 7.0, 4-H), 3.5 (1 H, br s, OH) and 3.05–2.55 (3 H, m, 5-H and 2 × 6-H); δ_C($CDCl_3$) 178.2, 136.9, 129.2, 87.5, 74.3, 44.3 and 36.6 (Found: C, 59.9; H, 5.7. $C_7H_8O_3$ requires C, 60.0; H, 5.75%).

4-exo-*Methoxyethoxymethoxy*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*one* **19**.—Diisopropylethylamine (3.4 cm^3, 19.3 mmol) was added to a solution of the *exo*-hydroxy lactone **18** (1.4 g, 10.2 mmol) in dichloromethane (12 cm^3) followed by methoxyethoxymethyl chloride (1.7 cm^3, 15.3 mmol). The reaction mixture was stirred under argon for 24 h after which it was washed with water, dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield the ether **19** (2.1 g, 91%) as a colourless oil; $[\alpha]_D$ −35 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3072, 2927, 1792, 1131 and 1041; δ_H 6.04 (1 H, m, 8-H), 5.85 (1 H, m, 7-H), 5.46 (1 H, m, 1-H), 4.97 (1 H, d, *J* 7.5, OCH_2O), 4.59 (1 H, d, *J* 7.5, OCH_2O), 4.11 (1 H, d, *J* 7.5, 4-H), 3.72 (2 H, m, OCH_2CH_2O), 3.53 (2 H, m, OCH_2CH_2O), 3.32 (3 H, s, OCH_3), 3.0 (1 H, m, 5-H), 2.71 (1 H, m, 6-H) and 2.53 (1 H, m, 6-H); δ_C($CDCl_3$) 36.5, 43.0, 58.8, 67.3, 71.5, 77.2, 88.8, 94.8, 129.4, 136.5 and 174.7 (Found: M^+, 228.099. $C_{11}H_{16}O_5$ requires *M*, 228.099).

4-exo-*Methoxyethoxymethoxy*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*ol* **20**.—The lactone **18** (1.5 g, 6.6 mmol) in tetrahydrofuran (50 cm^3) was cooled to −78 °C and diisobutylaluminium hydride (8.8 cm^3, 13.1 mmol) was added over 0.5 h to the solution. The resulting mixture was stirred under argon for 2 h after which methanol (5 cm^3) was added to it and the whole allowed to warm to room temperature. Saturated aqueous potassium sodium tartrate (50 cm^3) and ethyl acetate (50 cm^3) was added to the mixture which was then stirred vigorously until a clear separation of two phases occurred. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the lactol **20** (1.5 g, 100%) as a colourless oil; $[\alpha]_D$ −56 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3414, 3059, 2921, 1117 and 1038; δ_H 5.75 (1 H, m, 8-H), 5.20 (1 H, m, 7-H), 4.70 (2 H, s, OCH_2O), 4.00–3.50 (7 H, m, OCH_2CH_2O, 3-H, 4-H, 1-H), 3.32 (3 H, s, OCH_3) and 2.90–2.20 (3 H, m, 6-H_2, 5-H); δ_C($CDCl_3$) 36.2, 42.21, 58.7, 67.2, 71.47, 85.8, 86.1, 95.6, 96.1, 131.1 and 133.1 (Found: M^+, 230.115. $C_{11}H_{18}O_5$ requires *M*, 230.115).

Methyl 4-(2-*Hydroxycyclopent*-3-*enyl*)-4-*methoxyethoxymethoxybut*-2-*enoate* **21**.—The Wittig reagent (3.5 g, 9.7 mmol) was added to the lactol **20** (1.5 g, 6.5 mmol) in dry toluene (50 cm^3) and the resulting mixture was stirred under argon at 95 °C for 6 h. After cooling to room temperature the mixture was evaporated under reduced pressure and the resulting yellow slurry was subjected to flash column chromatography eluting with ethyl acetate–hexane (7 : 3), to yield the allylic alcohol **21** (1.4 g, 80%) as a colourless oil; $[\alpha]_D$ −60.6 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3473, 3019, 2954, 1723, 1275 and 1031; δ_H 6.68 (1 H, dd, *J* 15.5, 6.0, 3-H), 6.04 (1 H, dd, *J* 15.5, 1.2, 2-H), 5.98 (1 H, dt, *J* 5.5, 2.0, 8-H), 5.86 (1 H, m, 7-H), 4.69 (2 H, s, OCH_2O), 4.63 (1 H, m, 9-H), 4.54 (1 H, m, 4-H), 3.78 (1 H, m, OCH_2CH_2O), 3.72 (3 H, s, OCH_3), 3.60 (1 H, m, OCH_2CH_2O), 3.51 (2 H, m, OCH_2CH_2O), 3.35 (3 H, s, OCH_3), 2.42 (2 H, m, 6-H), 2.28 (1 H, m, 5-H) and 2.10 (1 H, s, OH); δ_C($CDCl_3$) 33.5, 46.3, 51.6, 59.0, 67.6, 71.7, 76.2, 76.3, 94.3, 121.9, 133.1, 134.9, 147.7 and 166.7 (Found: M^+, 286.142. $C_{14}H_{22}O_6$ requires *M*, 286.142).

Methyl 4-(4-*Oxocyclopent*-2-*enyl*)-4-*methoxyethoxymethoxybut*-2-*enoate* **22**.—Pyridinium chlorochromate (1.96 g, 9.1 mmol) was added to toluene-*p*-sulfonic acid (2.59 g, 13.6 mmol) and the cyclopentenol **21** (1.3 g, 4.54 mmol) in dry dichloromethane (450 cm^3). The reaction mixture was stirred under argon at room temperature for 12 h after which water and saturated brine (1 : 2; 150 cm^3) were added to it. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer and extract were dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford a black slurry. Purification of this by flash column chromatography eluting with ethyl acetate–hexane (7 : 3) afforded the cyclopentenone **22** (0.78 g, 60%) as a colourless oil; $[\alpha]_D$ +30.6 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3026, 2894, 1717, 1172 and 1032; δ_H 7.54 (1 H, dd, *J* 5.7, 2.5, 9-H), 6.73 (1 H, dd, *J* 15.7, 6.6, 3-H), 6.20 (1 H, dd, *J* 5.7, 2.1, 8-H), 6.00 (1 H, dd, *J* 15.7, 1.3, 2-H), 4.65 (1 H, d, *J* 7.1, OCH_2O), 4.61 (1 H, d, *J* 7.1, OCH_2O), 4.35 (1 H, tdd, *J* 5.1, 6.6, 1.3, 4-H), 3.71 (4 H, m, OCH_3 ester, OCH_2CH_2O), 3.58–3.46 (3 H, m, OCH_2CH_2O), 3.33 (3 H, s, OCH_3), 3.18 (1 H, m, 5-H), 2.37 (1 H, dd, *J* 18.8, 6.4, 6-H), 2.23 (1 H, dd, *J* 18.8, 2.7, 6-H); δ_C($CDCl_3$) 36.3, 45.8, 51.7, 58.9, 67.5, 71.6, 75.9, 93.7, 123.8, 135.9, 144.6, 163.2, 165.9 and 206.22 (Found: M^+, 284.125. $C_{14}H_{20}O_6$ requires *M*, 284.126).

Conjugate Addition to the Ketone **22**.—Methyllithium (2.91 cm^3, 4.1 mmol) was added to a suspension of copper cyanide (160 mg, 1.78 mmol) in tetrahydrofuran (2 cm^3) under argon at 0 °C after which the mixture was allowed to warm to room temperature. The stannane **23** (1.1 g, 2.1 mmol) in tetrahydrofuran (1 cm^3) was added to the mixture which was then stirred for 1.5 h. The resulting cloudy solution was cooled to −78 °C and the ketone **22** (364.3 mg, 1.28 mmol) in tetrahydrofuran (1 cm^3) was added to it. After the reaction mixture had been stirred for 0.5 h it was quenched at −78 °C with ammonium chloride–ammonium hydroxide (9 : 1; 2 cm^3) and poured in diethyl ether (50 cm^3) and water (50 cm^3). The organic layer was separated, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a yellow oil. Purification of this by flash chromatography eluting with ethyl acetate–hexane (3 : 7) afforded the cyclopentanone **24** (0.56 g, 87%) as a colourless oil; $[\alpha]_D$ −69.3 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2930, 1746, 1728, 1664, 1262, 1170 and 1031; δ_H 6.80 (1 H, dd, *J* 15.6, 6.2, 3-H), 5.98 (1 H, dd, *J* 15.6, 1.2, 2-H), 5.55 (1 H, m, 11-H), 5.34 (1 H, m, 10-H), 4.70 (2 H, m, OCH_2O), 4.40 (1 H, m, 15-H), 3.8–3.2 (11 H, m, OCH_2CH_2O, 4-H, 2 × OCH_3), 2.80–2.00 (8 H, m, 6-H_2, 8-H_2, 9-H, 5-H, 12-H_2), 1.45 (4 H, m, 13-H_2, 14-H_2), 1.12 (3 H, d, *J* 6.0, CH_3), 0.90 (9 H, s, TBDMS) and 0.04 (6 H, s, TBDMS); δ_C($CDCl_3$) −4.70, −4.38, 15.24, 18.13, 23.79, 25.45, 25.89, 32.50, 41.39, 45.52, 47.26, 51.64, 59.03, 67.77, 68.40, 71.66, 74.09, 76.57, 94.39, 94.62, 121.96, 130.76, 133.14, 147.09, 166.30 and 216.19 (Found: M^+, 500.318. $C_{26}H_{48}O_7Si$ requires *M*, 500.317).

Preparation of the Alcohol **25** *using* DIBAL-H.—To a solution of the cyclopentanone **24** (658 mg, 1.38 mmol) in diethyl ether (25 cm^3) at −78 °C was slowly added diisobutylaluminium hydride (9.6 cm^3, 1.52 mmol). The resulting mixture was stirred under argon for 1 h after which methanol (5 cm^3) was added to it followed, after the whole had been allowed to warm to room temperature, by saturated aqueous sodium potassium tartrate (75 cm^3) and diethyl ether (50 cm^3). The mixture was vigorously stirred for 3 h after which the ether layer was separated, dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification of the residue by flash chromatography eluting with ethyl acetate–hexane (1 : 2) afforded the cyclopentanol **25** (200 mg) as a colourless oil; $[\alpha]_D$ −31.8 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3455, 2930, 1727, 1658, 1255 and 1035; δ_H 6.82 (1 H, dd, *J* 15.6, 6.2, 3-H), 5.96 (1 H, dd, *J* 15.6, 1.2, 2-H), 5.38 (2 H, m, 10-H, 11-H), 4.70 (2 H, m, OCH_2O), 4.30 (1 H, m, 15-H), 4.22 (1 H, m, 7-H), 3.8–3.5 (8 H,

m, OCH_2CH_2O, OCH_3 ester, 4-H), 3.3 (3 H, s, OCH_3), 2.50–1.30 (13 H, m, 6-H_2, 8-H_2, 5-H, 9-H, 12-H_2, 13-H_2, 14-H_2, OH), 1.12 (3 H, d, *J* 6.0, CH_3), 0.90 (9 H, s, TBDMS) and 0.04 (6 H, s, TBDMS); $\delta_C(CDCl_3)$ −4.70, −4.38, 18.07, 23.72, 25.87, 32.41, 35.95, 39.19, 42.85, 43.26. 48.29, 51.41, 58.92, 67.49, 68.43, 71.71, 72.11, 76.52, 77.03, 77.54, 94.32, 121.30, 130.91, 133.57, 148.09 and 166.48 (Found: M^+, 502.335. $C_{26}H_{50}O_7Si$ requires *M*, 502.332).

Preparation of the Alcohol **25** *using K-Selectride*.—To a solution of the cyclopentanone **24** (45 mg, 0.09 mmol) in tetrahydrofuran (1 cm^3) at −78 °C was slowly added K-Selectride (0.1 cm^3, 0.1 mmol) under argon. The resulting mixture was stirred for 1.5 h and then quenched with saturated aqueous ammonium chloride (5 cm^3) and extracted with diethyl ether. The extract was dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification of the residue by flash chromatography eluting with ethyl acetate–hexane (1:2) afforded the cyclopentanol **25** (29 mg) and its C-7 epimer (10 mg).

Preparation of the Fully Protected Compound **26**.—To a solution of the alcohol **25** (190 mg, 0.38 mmol) in dichloromethane (1 cm^3) was added diisopropylethylamine (0.3 cm^3) and methoxyethoxymethyl chloride (60 mm^3). The resulting mixture was stirred under argon at room temperature for 12 h. Flash chromatography of that mixture eluting with ethyl acetate–hexane (35:65) afforded the fully protected compound **26** (195 mg, 87%) as a colourless oil; $[\alpha]_D$ −34.0 (*c* 1.0, $CHCl_3$) {lit.,[3] $[\alpha]_D$ = −27.7 (*c* 1.44, $CHCl_3$)}; ν_{max}(film)/cm^{-1} 2934, 1728, 1657, 1098 and 1039; δ_H 6.79 (1 H, dd, *J* 16.8, 7.0, 3-H), 5.93 (1 H, dd, *J* 16.8, 1.2, 2-H), 5.33 (2 H, m, 10-H, 11-H), 4.67 (2 H, s, OCH_2O), 4.66 (2 H, s, OCH_2O), 4.22–4.08 (2 H, m, 15-H, 7-H), 3.8–3.7 (1 H, m, 4-H), 3.71 (3 H, s, OCH_3 ester), 3.67–3.62 (4 H, m, OCH_2CH_2O), 3.55–3.48 (4 H, m, OCH_2CH_2O), 3.36 (3 H, s, OCH_3), 3.35 (3 H, s, OCH_3), 2.50–1.30 (12 H, m, 6-H_2, 8-H_2, 5-H, 9-H, 12-H_2, 13-H_2, 14-H_2), 1.09 (3 H, d, *J* 6.0, CH_3), 0.86 (9 H, s, TBDMS) and 0.024 (6 H, s, TBDMS); $\delta_C(CDCl_3)$ −4.71, −4.42, 18.08, 23.73, 25.58, 25.87, 32.43, 32.89, 39.21, 40.21, 42.98, 48.30, 51.40, 58.88, 58.93, 66.83, 67.52, 68.44, 71.71, 71.81, 75.73, 76.81, 94.19, 94.34, 121.29, 131.05, 133.30, 148.14 and 166.50 (Found: M^+, 590.385. $C_{30}H_{58}O_9Si$ requires *M*, 590.385).

Preparation of the Hydroxy Acid **27**.—Aqueous hydrochloric acid (1 mol dm^{-3}; 1 cm^3) was added to the ester **26** (45 mg, 0.076 mmol) in tetrahydrofuran (2 cm^3). The resulting mixture was stirred at room temperature for 14 h after which an excess of solid sodium hydrogen carbonate was added to it. The mixture was partitioned between water and dichloromethane, and the organic layer separated, dried ($MgSO_4$) and concentrated under reduced pressure to afford the hydroxy ester as a colourless oil that was used in the next step without further purification.

To the crude product was added water (0.5 cm^3) and methanolic lithium hydroxide (0.5 mol dm^{-3}; 2 cm^3). The mixture was stirred at room temperature for 10 h after which it was acidified with aqueous hydrochloric acid and extracted with dichloromethane. The resulting extract was dried ($MgSO_4$) filtered and evaporated under reduced pressure. Purification of the residue by flash chromatography eluting with methanol–dichloromethane (5:95) afforded hydroxy acid **27** (32 mg, 90%) a colourless oil; $[\alpha]_D$ −9.33 (*c* 0.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 3438, 2932, 2891, 1716, 1664, 1459, 1105, 1038 and 849; $\delta_H(CDCl_3)$ 6.86 (1 H, dd, *J* 15.8, 6.3, 3-H), 5.95 (1 H, dd, *J* 15.8, 1.2, 2-H), 5.33 (2 H, m, 10-H, 11-H), 4.68 (4 H, m, 2 × OCH_2O), 4.15 (2 H, m, 15-H, 7-H), 3.78–3.55 (9 H, m, 4-H, 2 × OCH_2CH_2O), 3.38 (3 H, s, OCH_3), 3.37 (3 H, s, OCH_3), 2.50–1.30 (12 H, m, 6-H_2, 8-H_2, 5-H, 9-H, 12-H_2, 13-H_2, 14-H_2) and 1.18 (3 H, d, *J* 6.0, CH_3); $\delta_C(CDCl_3)$ 23.26, 25.57, 32.31, 33.97, 38.60, 40.41, 43.21, 48.32, 58.89, 58.93, 66.85, 67.51, 68.07, 71.70, 71.80, 76.69, 76.79, 94.16, 94.25, 121.22, 130.83, 133.77, 149.95 and 169.64 (Found: M^+, 474.2816. $C_{24}H_{42}O_9$ requires *M*, 474.2828).

Preparation of the Lactone **28**.—To a solution of the hydroxy acid **27** (30 mg, 0.063 mmol) in tetrahydrofuran (0.5 cm^3) was added triethylamine (11.5 mm^3, 0.082 mmol) and 2,4,6-trichlorobenzoyl chloride (11.0 mm^3, 0.069 mmol). The resulting mixture was stirred under argon at room temperature for 6 h after which it was diluted with dry toluene (30 cm^3) and transferred to a syringe. The content of the syringe was added over 3 h to a refluxing solution of *N*,*N*-dimethylaminopyridine (50 mg, 0.41 mmol) in toluene (5 cm^3). The resulting mixture was refluxed for an additional 14 h and then allowed to cool to room temperature; the toluene was removed under reduced pressure and diethyl ether was added to the residue. Purification of the product by flash chromatography eluting with ethyl acetate–hexane (1:1) afforded partially protected brefeldin **28** (24 mg, 80%) as a colourless oil; $\delta_H(CDCl_3)$ 7.09 (1 H, dd, *J* 15.7, 3.7, 3-H), 5.83 (1 H, dd, *J* 15.6 1.2, 2-H), 5.62 (1 H, m, 11-H), 5.20 (1 H, dd, *J* 9.60, 6.00, 10-H), 4.95–4.60 (4 H, m, 2 × OCH_2O), 4.20–4.05 (2 H, m, 15-H, 7-H), 3.83 (1 H, m, 4-H), 3.65 (4 H, m, OCH_2CH_2O), 3.55 (4 H, m, OCH_2CH_2O), 3.38 (6 H, s, 2 × OCH_3), 2.35–1.40 (12 H, m, 6-H_2, 8-H_2, 5-H, 9-H, 12-H_2, 13-H_2, 14-H_2) and 1.22 (3 H, d, *J* 6.20, CH_3); $\delta_C(CDCl_3)$ 20.76, 26.38, 31.82, 34.29, 38.58, 40.78, 44.27, 50.52, 58.94, 58.95, 66.84, 67.49, 71.53, 71.76, 71.82, 76.88, 80.20, 92.42, 94.02, 119.21, 130.17, 136.34, 149.26 and 166.07 (Found: M^+, 456.2730. $C_{24}H_{40}O_8$ requires *M*, 456.2723).

(+)-*Brefeldin A* **29**.—To a solution of compound **28** (10 mg, 0.02 mmol) in dichloromethane (2 cm^3) was added titanium tetrachloride (1.0 mol dm^{-3} solution in dichloromethane; 0.15 cm^3). The resulting mixture was stirred under argon at 0 °C for 2 h after which it was quenched with saturated aqueous sodium hydrogen carbonate and partitioned between ethyl acetate and sodium hydrogen carbonate. The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography eluting with ethyl acetate–hexane (1:1) afforded brefeldin-A **29** (5.2 mg, 85%) as a white solid which upon recrystallization from ethyl acetate gave dextrorotatory synthetic brefeldin (2.7 mg) identical with a natural sample; m.p. 204–205 °C; $\delta_H(CDCl_3)$ 7.32 (1 H, dd, *J* 15.6, 3.1, 3-H), 5.83 (1 H, dd, *J* 15.6, 1.5, 2-H), 5.62 (1 H, m, 11-H), 5.20 (1 H, dd, *J* 14.9, 9.2, 10-H), 4.76 (1 H, m, 15-H), 4.20–4.00 (2 H, m, 7-H, 4-H), 2.35–0.77 (12 H, m, 6-H_2, 8-H_2, 5-H, 9-H, 12-H_2, 13-H_2, 14-H_2) and 1.22 (3 H, d, *J* 6.2, CH_3); $\delta_C(CDCl_3)$ 20.92, 27.85, 32.84, 34.90, 41.74, 44.01, 45.37, 53.06, 72.85, 73.08, 76.52, 117.69, 131.28, 137.99, 154.95 and 168.26 (Found: M^+, 280.1683. $C_{16}H_{24}O_4$ requires *M*, 280.1674).

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