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A First Generation Chemoenzymatic Synthesis of (+)-Galanthamine

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A total synthesis of (+)-galanthamine [(+)-**1**] has been achieved using the readily available and enantiomerically pure metabolite **2** as starting material. The quaternary carbon centre (C8a) associated with target **1** was constructed using the Eschenmoser–Claisen rearrangement reaction.

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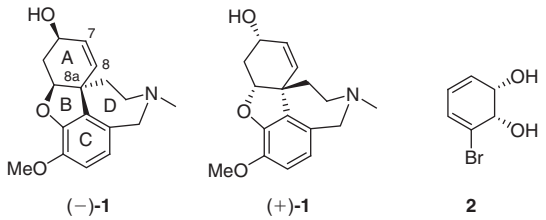
Introduction

The alkaloid (–)-galanthamine [(–)-**1**, Fig. 1] has been obtained from various *Amaryllidaceae* species including daffodils, the Red Spider Lily (*Lycoris radiata*), and the Caucasian snowdrop (*Galanthus woronowii*).[1,2] Its effectiveness as a centrally acting, selective, reversible, and competitive inhibitor of acetylcholinesterase has resulted in galanthamine being introduced into the clinic in both the USA and Europe for the symptomatic treatment of mild to moderate forms of Alzheimer's disease.[1,2] While the compound produces beneficial effects even after treatment is terminated there are no indications that it can arrest the course of the process of dementia.[2] The 2.3 Å resolution X-ray crystal structure of acetylcholinesterase complexed with (–)-**1** was reported in 1991[3] and in the intervening period this has provided a rational basis for the development of superior analogues.[2] These continue to be sought.[4] Interestingly, a recent report[5] suggests that (–)-**1** could serve as an antidote to poisoning by the nerve agent sarin and other toxic organophosphorous compounds.

The intriguing structure and biological properties of (–)-**1** have prompted extensive synthetic studies, the majority of which have provided the alkaloid in racemic form.[2] Barton and Kirby carried out the initial and most significant early studies. They employed a biomimetic and intramolecular phenolic coupling reaction to simultaneously establish the quaternary carbon centre and the tetracyclic framework of galanthamine.[6] Various refinements of this basic approach have since been introduced including ones that lead to enantiomerically enriched (–)-**1**.[6b,7] A particularly notable variant has recently been reported by Magnus and coworkers.[8] Several syntheses of (−)- or (+)-**1** have been achieved using chiral pool-derived starting materials[2,9] but Trost and Toste were the first to devise a catalytic asymmetric synthesis of the natural product.[10] A notable additional feature of their work was the use of an intramolecular Heck reaction to establish the quaternary carbon centre (C8a) of target (−)-**1**. Others have also followed this approach.[11] In 2006, Tu and coworkers described[12] the use of a semi-pinacolic rearrangement to construct the quaternary carbon centre of (±)-**1** while Cho et al. have used an intramolecular Diels–Alder reaction for the same purpose.[13]



(−)-**1** (+)-**1** **2**

Fig. 1. Structures of (−)-galanthamine [(−)-**1**], (+)-galanthamine [(+)-**1**], and (1*S*-*cis*)-3-bromo-3,5-cyclohexadiene-1,2-diol (**2**).

Herein we report a total synthesis of (+)-**1** from the enantiomerically pure *cis*-1,2-dihydrocatechol **2**. Compound **2** is readily obtained through the whole-cell biotransformation of bromobenzene using a genetically engineered microorganism that over-expresses the responsible enzyme, namely toluene dioxygenase.[14] The synthesis exploits an Eschenmoser–Claisen rearrangement[15] to establish the quaternary carbon of the target, a bromonium ion-mediated cyclization to form the benzofuran subunit,[16] and a Pictet–Spengler reaction[17] to complete the formation of the seven-membered and nitrogen-containing D-ring.

Results and Discussion

The synthesis of the substrate required for the Eschenmoser–Claisen rearrangement is outlined in Scheme 1 and starts with the conversion of the dihydrocatechol **2** into the corresponding and well known acetonide **3**[14a] that is, without purification, immediately subjected to epoxidation with *m*-chloroperbenzoic acid (*m*-CPBA) to give the previously reported oxirane **4**[14a] (90% over two steps). Regioselective nucleophilic ring-opening of compound **4** with acetic acid and using phosphoric acid as catalyst[18] afforded the hydroxy-ester **5** (81%) that was treated

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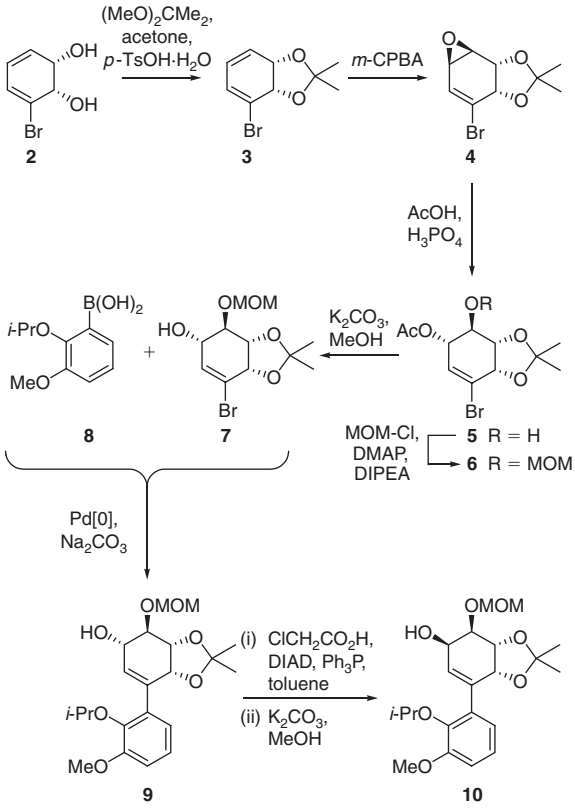
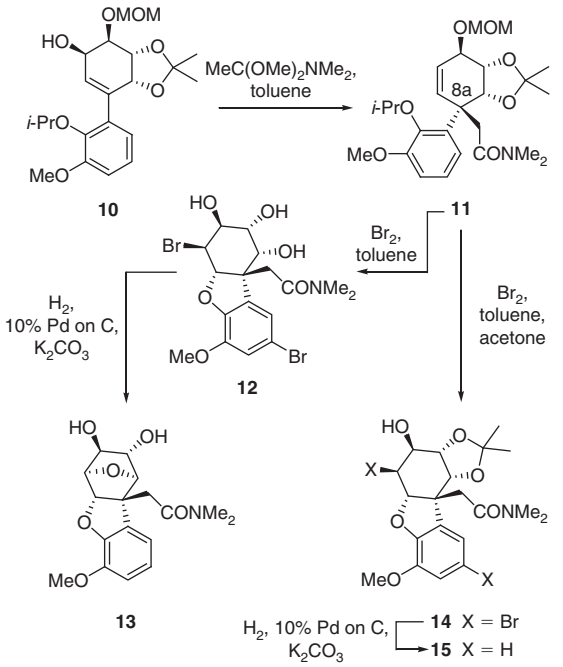


Scheme 1.



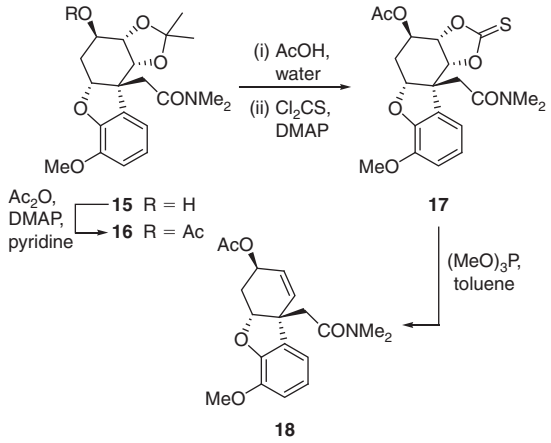
Scheme 2.

with methoxymethyl chloride (MOM-Cl) in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP)/diisopropylethylamine (DIPEA) to give the ester-ether **6** in 91% yield. Cleavage of the acetate residue within compound **6** was effected with potassium carbonate in methanol and the resulting alcohol **7** (95%) subjected to Suzuki–Miyaura cross-coupling[19] with the boronic acid **8**[20] to give the arylated cyclohexene **9** in 98% yield. Reaction of compound **9** under Mitsunobu conditions[21] using chloroacetic acid as the nucleophile followed by treatment of the crude product with potassium carbonate in methanol afforded the epimeric alcohol **10** in 93% yield.

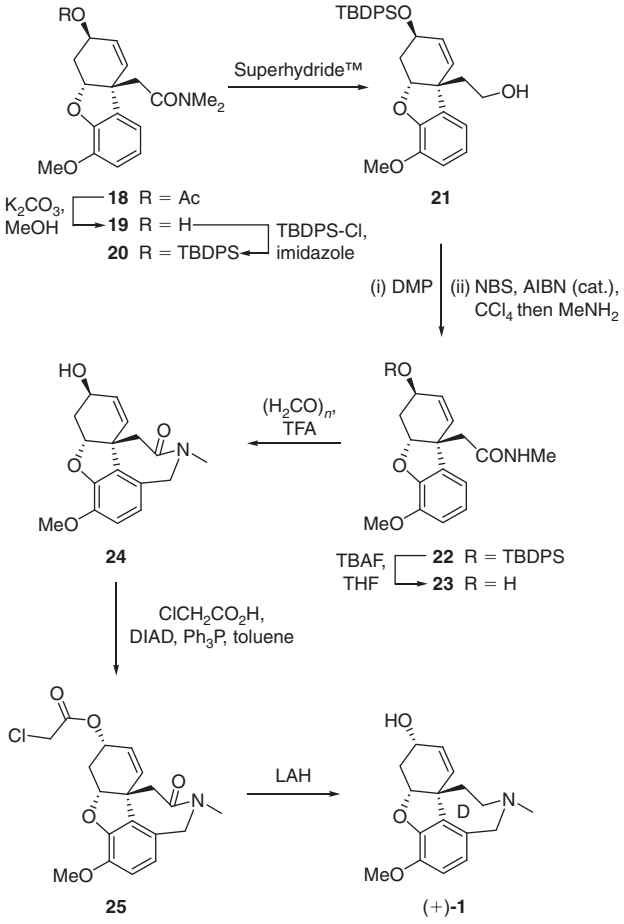
The acquisition of compound **10** allowed for an investigation of the pivotal Ecshenmoser–Claisen rearrangement as well as the construction of the benzofuran moiety associated with the galanthamine. In the event (Scheme 2), treatment of allylic alcohol **10** with the dimethylacetal of *N*,*N*-dimethylacetamide in refluxing toluene for 7 days resulted in the smooth conversion of the substrate into the acetamide **11** (89%). Compound **11** was immediately subjected to reaction with molecular bromine under conditions originally defined by Mulzer et al.[16] and used by Chida and coworkers[19] in their recently reported synthesis of (+)-**1**. When this reaction was run in toluene then the dibrominated triol **12** was obtained in 69% yield and its structure was confirmed by single-crystal X-ray analysis.[22] Clearly, the HBr generated in this reaction serves to catalyze acetonide group hydrolysis by adventitious water. In an effort to hydrogenolytically remove the bromines in product **12** it was treated with a combination of dihydrogen, 10% Pd on C, and potassium carbonate. However, rather than obtaining the desired outcome, the 7-oxanorbornene **13** (67%) was the only isolable product of the reaction. Its structure was also confirmed by X-ray crystallographic methods.[22] This unanticipated product must arise from a transannular nucleophilic displacement reaction involving one of the hydroxy groups unmasked in the preceding step. To circumvent such difficulties, the bromination step was carried out in toluene and the reaction mixture then treated with acetone. In this manner the dibromoacetonide **14** was now obtained in 93% yield and when this was subjected to hydrogenolysis under the previously described conditions then the required benzofuran derivative **15** was obtained in 68% yield.

The introduction of the Δ^7-double bond into the A-ring of the developing galanthamine framework was readily achieved using the Corey–Winter olefination reaction[23] (Scheme 3). As a prelude to carrying out such a reaction, the free hydroxy group within compound **15** was protected as the corresponding acetate **16** (90%) using standard conditions and the latter compound then subjected to acetonide hydrolysis using acetic acid in water. The diol (94%) so-formed was immediately treated with thiophosgene and the cyclic thiocarbonate **17** thereby obtained in 99% yield. Reaction of compound **17** with trimethylphosphite resulted in the desired conversion and thus produced allylic acetate **18** in 72% yield.

The completion of the synthesis of (+)-**1** from precursor **18** requires construction of the seven-membered D-ring. This was ultimately carried out using a Pictet–Spengler reaction as shown in Scheme 4. Prior to manipulation of the amide unit within compound **18**, the acetate moiety was removed with potassium carbonate in methanol and the resulting alcohol **19** (95%) reprotected as the corresponding *tert*-butyldiphenylsilyl (TBDPS) ether[24] **20** (95%) under standard conditions. The structure of compound **19** was also confirmed by single-crystal X-ray analysis. The derived *ORTEP* diagram is shown in Fig. 2. Reaction of amide **20** with Superhydride (lithium triethylborohydride)[25] resulted in reduction of the amide residue and production of the primary alcohol **21** (95%) that was oxidized to the corresponding aldehyde in 98% yield using the Dess–Martin periodinane (DMP).[26] Reaction of this aldehyde with *N*-bromosuccinimide (NBS) in the presence of catalytic amounts of α,α′-azobisisobutyronitrile (AIBN) followed by methylamine



Scheme 3.



Scheme 4.

(to intercept the intermediate acyl halide)[12] resulted in the formation of the amide **22** (80%). Treatment of compound **22** with tetra-*n*-butylammonium fluoride (TBAF) resulted in removal of the TBDPS group and the rather insoluble alcohol **23** (85%) so-formed was then treated with a mixture of paraformaldehyde and trifluoroacetic acid (TFA) so as to effect the pivotal Pictet–Spengler reaction and thereby generate the hydroxy-lactam **24**, which was obtained in 88% yield as a white crystalline solid, mp 232–235°C. Subjection of compound **24** to a Mitsunobu reaction under the same conditions as used for the conversion

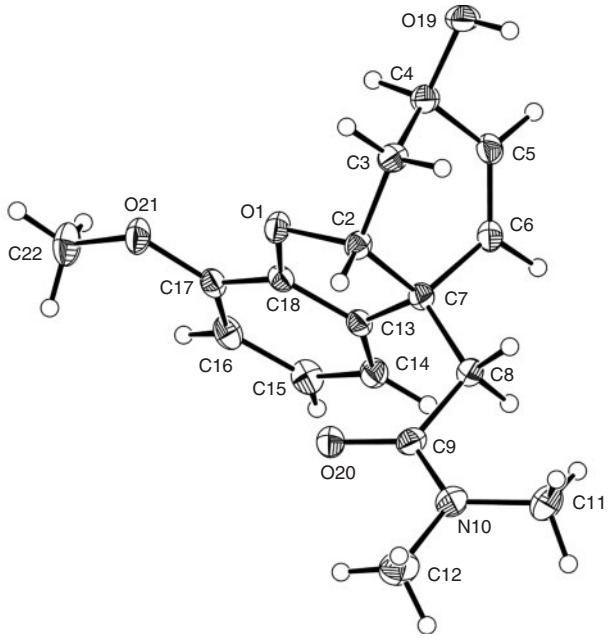


Fig. 2. View of compound **19** (CCDC 739080) with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

of **9** into **10** afforded the ester **25** (93%) that upon reaction with lithium aluminum hydride (LAH) gave (+)-**1** in 85% yield and as a white crystalline solid, mp 121–124°C (lit.[9b] mp 124–125°C), $[\alpha]_D$ +108.8 (*c* 0.4, chloroform) {lit.[9b] $[\alpha]_D$ +115.5 (*c* 0.5, ethanol)}. The ^{1}H NMR, ^{13}C NMR, and IR spectroscopic and mass spectrometry data derived from this material were in full accord with the assigned structure and matched those reported[9b] for (±)-, (−)-, and (+)-**1** as well as those derived from an authentic sample of the natural product (see Fig. 3 for a comparison of the 800 MHz ^{1}H NMR spectra of the two samples).

The first generation synthesis of (+)-**1** described here should be capable of considerable refinement, especially in regards to the use of protecting groups and the sequence of reactions used to construct the D-ring from the product of the Eschenmoser–Claisen rearrangement. Furthermore, since the enantiomer of compound **2** is also available,[27] the present work represents a formal total synthesis of the natural product itself, that is (−)-**1**. In this context it is worth noting that the allylic alcohol **9** reacts with the dimethylacetal of *N*,*N*-dimethylacetamide in refluxing toluene and thereby affords (in 37% yield) the C8a-epimer (galanthamine numbering) of compound **11** and thus possesses the same configuration at this quaternary carbon as seen in (−)-**1**. In principle, then, the chemistry described herein could be used to make both the natural and the non-natural enantiomeric forms of galanthamine from the same enantiomeric form of the starting material **2**. Work aimed at developing such possibilities is now underway in these laboratories.

Experimental

General Experimental Procedures

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Mercury machine operating at 300 MHz. 800 MHz ^{1}H NMR spectra were recorded on a Bruker AV800 machine. Unless otherwise specified, spectra were acquired at 20°C in deuterochloroform ($CDCl_3$) that had been filtered through

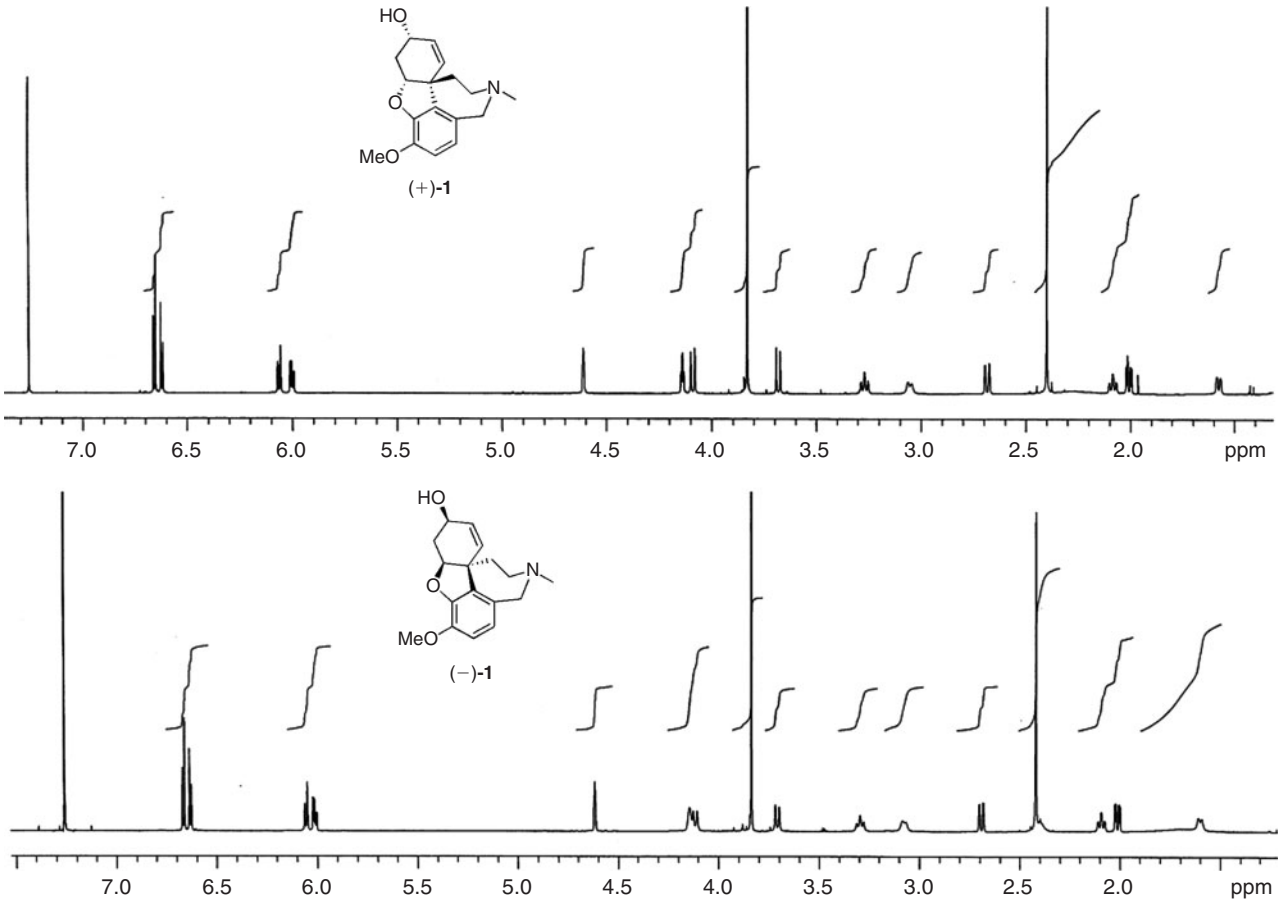


Fig. 3. The 800 MHz ^{1}H NMR spectra of synthetically derived (+)-galanthamine (top) and naturally derived (−)-galanthamine (bottom) (both spectra recorded in $CDCl_3$).

basic alumina immediately before use. Chemical shifts are recorded as δ values in parts per million [ppm]. Infrared spectra (ν_{max}) were normally recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analyzed as thin films on KBr plates (for liquids) or as a KBr disc (for solids). Low-resolution electrospray ionization (ESI) mass spectra were recorded on a Micromass–Waters LC-ZMD single quadrupole liquid chromatograph-mass spectrometer while low- and high-resolution electron impact (EI) mass spectra were recorded on a VG Fisons AUTOSPEC three-sector double-focusing instrument. Melting points were measured on Reichert hot-stage microscope or a Stanford Research Systems Optimelt–Automated Melting Point System and were uncorrected. Analytical TLC was performed on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included a mixture of phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g/7.5 g/37.5 g/720 mL). The retardation factor (R_F) values cited here have been rounded at the first decimal point. Flash chromatographic separations were carried out following protocols defined by Still et al.[28] with silica gel 60 (0.040–0.0063 mm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem, or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH, or Unilab Chemical Companies. Tetrahydrofuran (THF), dichloromethane, and benzene were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[29] Spectroscopic grade solvents were used for all analyses. Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Synthetic Procedures and Product Characterization

*Compound **5***

A magnetically stirred solution of epoxide **4**[30] (5.6 g, 22.7 mmol) in acetic acid (30 mL) was treated with phosphoric acid (0.1 mL). After stirring at 18°C for 1 h the reaction mixture was quenched with NH_4Cl (150 mL of a saturated aqueous solution) and ethyl acetate (50 mL). The separated aqueous phase was extracted with ethyl acetate (4 × 50 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1.5:1 v/v ethyl acetate/hexane elution) to provide, after concentration of the appropriate fractions (R_F 0.4 in 8:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane), *acetate* ***5*** (5.7 g, 81%) as a white, crystalline solid, mp 107–108°C, $[\alpha]_D$ +68.5 (*c* 0.8, $CHCl_3$) [Found: $M^{+\bullet}$, 306.0104. $C_{11}H_{15}{}^{79}BrO_5$ requires $M^{+\bullet}$, 306.0103]. δ_H (300 MHz) 6.05 (d, *J* 2.3, 1H), 5.13 (m, *J* 8.0, 1H), 4.64 (d, *J* 6.3, 1H), 4.17 (dd, *J* 8.2 and 6.3, 1H), 3.76 (td, *J* 10.7 and 2.6, 1H), 3.33 (br s, 1H), 2.06 (s, 3H), 1.48 (s, 3H),

1.36 (s, 3H). δ_C (75 MHz) 170.6 (C), 131.2 (CH), 120.7 (C), 111.1 (C), 77.4 (CH), 76.9 (CH), 72.6 (CH), 70.6 (CH), 28.0 (CH_3), 26.0 (CH_3), 21.0 (CH_3). ν_{max} (KBr)/cm^{-1} 3467, 2989, 2936, 1748, 1649, 1373, 1234, 1081, 1050, 1021, 978, 869. *m/z* (EI, 70 eV) 308 and 306 ($M^{+\bullet}$, both 11%), 293 and 291 (96 and 100), 248 and 246 (both 35), 191 and 189 (75 and 76), 110 (76), 109 (73), 101 (85), 81 (65), 59 (78).

Compound **6**

Chloromethyl methyl ether (42 mL, technical grade) was added to a magnetically stirred solution of compound **5** (6.9 g, 22.5 mmol), DMAP (13.7 g, 112.1 mmol), and DIPEA (117 mL, 672.2 mmol) in dichloromethane (80 mL) maintained under a nitrogen atmosphere. After stirring at 18°C for 18 h the reaction mixture was treated with NH_4Cl (100 mL of a saturated aqueous solution) and the separated aqueous phase was extracted with dichloromethane (1 × 50 mL). The combined organic layers were washed with NH_4Cl (1 × 150 mL of a saturated aqueous solution) and $NaHCO_3$ (1 × 150 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_F 0.4 in 2:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane), *MOM-ether* **6** (7.2 g, 91%) as a white, crystalline solid, mp 64.5–66.0°C, $[\alpha]_D$ +83.0 (*c* 0.9, $CHCl_3$) [Found: $M^{+\bullet}$, 350.0369. $C_{13}H_{19}{}^{79}BrO_6$ requires $M^{+\bullet}$, 350.0365]. δ_H (300 MHz) 6.10 (d, *J* 2.8, 1H), 5.21 (dddd, *J* 7.3, 2.7, 1.8, and 1.0, 1H), 4.82 (d, *J* 6.6, 1H), 4.72 (d, *J* 6.6, 1H), 4.65 (dd, *J* 6.0 and 0.7, 1H), 4.27 (dd, *J* 7.3 and 6.0, 1H), 3.90 (t, *J* 7.5, 1H), 3.37 (s, 3H), 2.07 (s, 3H), 1.52 (s, 3H), 1.39 (s, 3H). δ_C (75 MHz) 170.3 (C), 130.8 (CH), 121.9 (C), 111.0 (C), 96.6 (CH_2), 77.0 (2 × CH), 74.0 (CH), 71.6 (CH), 55.8 (CH_3), 27.8 (CH_3), 26.3 (CH_3), 21.0 (CH_3). ν_{max} (KBr)/cm^{-1} 2988, 2936, 2825, 1749, 1651, 1454, 1440, 1374, 1232, 1084, 1047, 921, 869, 794. *m/z* (EI, 70 eV) 352 and 350 ($M^{+\bullet}$, both 10%), 337 and 335 (both 31), 290 and 288 (17 and 16), 203 (24), 189 (32), 145 (100), 59 (36).

Compound **7**

Potassium carbonate (4.3 g, 31.1 mmol) was added to a magnetically stirred solution of MOM-ether **6** (7.2 g, 20.5 mmol) in methanol (40 mL) and after being maintained at 18°C for 1 h the reaction mixture was concentrated under reduced pressure. The solid mass thus obtained was treated with NH_4Cl (100 mL of a saturated aqueous solution) and ethyl acetate (100 mL) and the separated aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the ensuing residue subjected to flash chromatography (silica, 1:8:16 v/v/v methanol/ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions (R_F 0.3 in 4:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane), *alcohol* **7** (6.0 g, 95%) as a clear, light-yellow oil, $[\alpha]_D$ +45.8 (*c* 0.6, $CHCl_3$) [Found: $M^{+\bullet}$, 308.0264. $C_{11}H_{17}{}^{79}BrO_5$ requires $M^{+\bullet}$, 308.0259]. δ_H (300 MHz) 6.27 (d, *J* 3.3, 1H), 4.78 (dd, *J* 16.6 and 6.9, 2H), 4.66 (d, *J* 5.9, 1H), 4.31 (t, *J* 6.5, 1H), 4.08 (br s, 1H), 3.78 (br s, 1H), 3.72 (t, *J* 6.5, 1H), 3.43 (s, 3H), 1.53 (s, 3H), 1.41 (s, 3H). δ_C (75 MHz) 133.3 (CH), 121.2 (C), 111.1 (C), 97.8 (CH_2), 80.2 (CH), 77.0 (CH), 76.6 (CH), 69.6 (CH), 56.1 (CH_3), 28.1 (CH_3), 26.2 (CH_3). ν_{max} (KBr)/cm^{-1} 3420, 2987, 2933, 1645, 1382, 1218, 1153, 1107, 1067, 1036, 988, 915, 868. *m/z* (EI, 70 eV) 310 and 308 ($M^{+\bullet}$, 55 and 54%), 295 and 293 (41 and 43), 191 and 189 (25 and 34), 161 (25), 145 (100), 110 (42), 109 (40), 58 (75).

Compound **8**

Step i: A magnetically stirred solution of *tert*-butylamine (6 mL, 56.8 mmol) in toluene (100 mL) was cooled to between −50 and −40°C then treated with molecular bromine (1.4 mL, 27.3 mmol). The resulting mixture was stirred at this temperature for 1 h and then treated with guaiacol (3.00 g, 24.2 mmol) and allowed to warm to −10°C over ~4 h. The ensuing mixture was quenched with $Na_2S_2O_3$ (100 mL of a 10% w/v aqueous solution) and then stirred for a further 1 h while being allowed to warm to room temperature. The separated aqueous phase was extracted with ethyl acetate (4 × 50 mL) and the combined organic phases were washed with NH_4Cl (1 × 100 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The light-yellow oil thus obtained was dissolved in *N*,*N*-dimethylformamide (50 mL) and the resulting solution treated with 2-bromopropane (4.5 mL, 47.9 mmol) and potassium carbonate (8.0 g, 57.9 mmol). After stirring the ensuing mixture at 18°C for 18 h it was treated with water (100 mL) and diethyl ether (100 mL). The separated aqueous phase was extracted with diethyl ether (2 × 50 mL) and the combined organic phases were then washed with NH_4Cl (2 × 100 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the ensuing residue to flash chromatography (silica, 1:20 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.5 in 0.5:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane) afforded the bromide precursor[31] to compound **8** (5.5 g, 93% over two steps) as a clear, light-yellow syrup [Found: $M^{+\bullet}$, 244.0116. $C_{10}H_{13}{}^{79}BrO_2$ requires $M^{+\bullet}$, 244.0099]. δ_H (300 MHz) 7.09 (dd, *J* 7.7 and 1.2, 1H), 6.87–6.77 (complex m, 2H), 4.54 (sept, *J* 6.2, 1H), 3.77 (s, 3H), 1.31 (d, *J* 6.2, 6H). δ_C (75 MHz) 154.0 (C), 144.6 (C), 124.8 (CH), 124.3 (CH), 118.6 (C), 111.5 (CH), 75.7 (CH), 55.8 (CH_3), 22.4 (2 × CH_3). ν_{max} (KBr)/cm^{-1} 2977, 2936, 2837, 1582, 1572, 1474, 1451, 1435, 1261, 1233, 1105, 1037, 931, 833, 761. *m/z* (EI, 70 eV) 246 and 244 ($M^{+\bullet}$, 2 and 3%), 204 and 202 (37 and 38), 167 (24), 149 (77), 83 (31), 57 (86), 43 (100).

Step ii: *n*-Butyllithium (11.4 mL of a 2.5 M solution in hexanes, 28.5 mmol) was added, dropwise, to a magnetically stirred solution of the above-mentioned bromide (4.35 g, 17.76 mmol) and triisopropyl borate (6.1 mL, 26.4 mmol) in dry THF (60 mL) maintained at −78°C under a nitrogen atmosphere. Stirring was continued for 3 h and then the reaction mixture was warmed to 0°C and treated with NH_4Cl (100 mL of a saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (3 × 30 mL) and the combined organic phases were then washed with brine (1 × 200 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:5 v/v ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions (R_F 0.4 in 2:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane), boronic acid **8**[31] (3.06 g, 82%) as a white, crystalline solid, mp 77–79°C [Found: $M^{+\bullet}$, 210.1064. $C_{10}H_{15}{}^{11}BO_4$ requires $M^{+\bullet}$, 210.1063]. δ_H (300 MHz) 7.42 (dd, *J* 7.3 and 1.3, 1H), 7.10 (t, *J* 8.1, 1H), 7.02 (dd, *J* 8.1 and 1.3, 1H), 6.89 (s, 2H), 4.77 (sept, *J* 6.2, 1H), 3.85 (s, 3H), 1.31 (d, *J* 6.2, 6H). δ_C (75 MHz) 151.8 (3 × C), 127.4 (CH), 124.2 (CH), 115.8 (CH), 75.4 (CH), 55.9 (CH_3), 22.5 (2 × CH_3). ν_{max} (KBr)/cm^{-1} 3365, 2983, 2838, 1594,

1575, 1473, 1343, 1264, 1085, 1031, 773, 739, 692. *m/z* (EI, 70 eV) 210 ($M^{+\bullet}$, 4%), 196 (94), 195 (47), 178 (53), 150 (100), 149 (56), 135 (37), 107 (36), 77 (22), 59 (6), 53 (16).

Compound ***9***

$Pd(Ph_3P)_4$ (836 mg) was added to a magnetically stirred mixture of alcohol **7** (4.47 g, 14.46 mmol), boronic acid **8** (3.46 g, 16.47 mmol), Na_2CO_3 (20 mL of a 2.0 M aqueous solution), and benzene (80 mL) maintained under a nitrogen atmosphere. The ensuing mixture was heated at reflux for 18 h and then cooled to 18°C and treated with NH_4Cl (100 mL of a saturated aqueous solution). The separated aqueous phase was extracted with ethyl acetate (2 × 40 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the ensuing residue to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (R_F 0.3 in 4:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane), *alcohol* ***9*** (5.62 g, 98%) as a clear, light-yellow oil, $[\alpha]_D$ −19.7 (*c* 0.9, $CHCl_3$) [Found: $M^{+\bullet}$, 394.1994. $C_{21}H_{30}O_7$ requires $M^{+\bullet}$, 394.1992]. δ_H (300 MHz) 7.03 (t, *J* 7.8, 1H), 6.91–6.85 (complex m, 2H), 5.94 (d, *J* 2.3, 1H), 5.30 (d, *J* 6.3, 1H), 4.87 (dd, *J* 15.1 and 6.9, 2H), 4.36 (sept, *J* 6.2, 1H), 4.29 (dd, *J* 8.2 and 6.2, 1H), 4.20 (m, 1H), 4.07 (d, *J* 3.4, 1H), 3.83 (s, 3H), 3.63 (t, *J* 7.9, 1H), 3.48 (d, *J* 0.5, 3H), 1.45 (s, 3H), 1.33 (s, 3H), 1.26 (d, *J* 6.2, 3H), 1.15 (d, *J* 6.2, 3H). δ_C (75 MHz) 153.1 (C), 144.6 (C), 134.8 (C), 134.2 (C), 131.8 (CH), 123.8 (CH), 122.3 (CH), 111.9 (CH), 110.2 (C), 98.1 (CH_2), 83.3 (CH), 76.5 (CH), 75.5 (CH), 74.4 (CH), 69.4 (CH), 55.9 (CH_3), 55.8 (CH_3), 28.3 (CH_3), 26.1 (CH_3), 22.7 (CH_3), 22.6 (CH_3). ν_{max} (KBr)/cm^{-1} 3438, 2979, 2933, 1576, 1460, 1380, 1371, 1259, 1219, 1108, 1059, 867, 785. *m/z* (EI, 70 eV) 394 ($M^{+\bullet}$, 56%), 336 (14), 294 (13), 244 (31), 232 (71), 231 (65), 215 (64), 214 (60), 204 (61), 203 (100), 190 (81), 161 (46), 145 (33).

Compound ***10***

A solution of compound **9** (5.62 g, 14.25 mmol) in toluene (150 mL) maintained at 18°C was treated with α-chloroacetic acid (5.4 g, 57.1 mmol), triphenylphosphine (16.8 g, 64.0 mmol), and diisopropyl azodicarboxylate (9.8 mL, 49.8 mmol). After 18 h the reaction mixture was treated with $NaHCO_3$ (100 mL of a saturated aqueous solution) and the separated aqueous phase was extracted with ethyl acetate (2 × 25 mL). The combined organic phases were then washed with NH_4Cl (100 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing viscous mixture was dissolved in methanol (50 mL) and the resulting solution treated with anhydrous potassium carbonate (2.2 g, 15.9 mmol). After stirring at 18°C for 1 h, the reaction mixture was concentrated under reduced pressure and the residue thus obtained was treated with water (50 mL), NH_4Cl (150 mL of a saturated aqueous solution), and ethyl acetate (100 mL). The separated aqueous phase was extracted with ethyl acetate (3 × 40 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions (R_F 0.3 in 4:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane), *alcohol* ***10*** (5.22 g, 93% over two steps from **9**) as a clear, light-yellow oil, $[\alpha]_D$ −68.0 (*c* 0.6, $CHCl_3$) [Found: $M^{+\bullet}$, 394.1993. $C_{21}H_{30}O_7$ requires $M^{+\bullet}$, 394.1992]. δ_H (300 MHz) 7.02 (t, *J* 8.2, 1H), 6.88–6.81 (complex m, 2H), 5.90 (d, *J* 3.2, 1H), 5.34 (d, *J* 5.8, 1H), 4.83 (dd, *J* 8.2 and 6.6, 2H), 4.55 (t, *J* 5.6, 1H), 4.49 (t, *J* 3.4, 1H), 4.40 (sept, *J* 6.1, 1H), 4.08 (dd, *J* 5.6 and 3.7, 1H), 3.83 (s, 3H), 3.45 (s, 3H), 2.40 (br s, 1H), 1.38 (s, 3H), 1.32 (s, 3H), 1.25 (d, *J* 6.1, 3H), 1.16 (d, *J* 6.1, 3H). δ_C (75 MHz) 153.3 (C), 144.6 (C), 138.2 (C), 135.0 (C), 130.4 (CH), 123.8 (CH), 122.6 (CH), 112.0 (CH), 109.4 (C), 97.6 (CH_2), 78.8 (CH), 75.3 (CH), 74.9 (CH), 73.9 (CH), 65.9 (CH), 56.1 (CH_3), 55.9 (CH_3), 27.8 (CH_3), 26.2 (CH_3), 22.6 (CH_3), 22.5 (CH_3). ν_{max} (KBr)/cm^{-1} 3452, 2927, 2854, 1576, 1459, 1371, 1260, 1219, 1112, 1069, 1035, 918, 735. *m/z* (EI, 70 eV) 394 ($M^{+\bullet}$, 63%), 336 (10), 320 (8), 244 (21), 232 (81), 215 (57), 204 (60), 203 (100), 190 (85), 161 (48), 145 (54), 115 (28).

Compound ***11***

A magnetically stirred solution of compound **10** (3.18 g, 8.06 mmol) in toluene (50 mL) was treated with *N*,*N*-dimethylacetamide dimethyl acetal (13 mL, 80.0 mmol) and the ensuing mixture heated (oil bath) at reflux. When TLC analysis indicated that no starting material remained (~7 days), the reaction mixture was cooled and then concentrated under reduced pressure. Subjection of the ensuing residue to flash chromatography (silica, 1:10:40 v/v/v methanol/hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_F 0.3 in 8:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane) afforded *amide* ***11*** (3.33 g, 89%) as a clear, colourless oil, $[\alpha]_D$ +58.0 (*c* 1.0, $CHCl_3$) [Found: $M^{+\bullet}$, 463.2569. $C_{25}H_{37}NO_7$ requires $M^{+\bullet}$, 463.2570]. δ_H (300 MHz) 6.97–6.86 (complex m, 2H), 6.77 (dd, *J* 7.9 and 1.6, 1H), 6.53 (d, *J* 10.5, 1H), 5.82 (dd, *J* 10.5 and 3.9, 1H), 5.08 (sept, *J* 6.2, 1H), 4.92 (dd, *J* 5.4 and 1.2, 1H), 4.77 (dd, *J* 18.4 and 6.7, 2H), 4.47 (dd, *J* 5.4 and 3.7, 1H), 4.17 (m, 1H), 3.77 (s, 3H), 3.58 (d, *J* 15.6, 1H), 3.39 (s, 3H), 3.11 (d, *J* 15.6, 1H), 2.88 (s, 3H), 2.76 (s, 3H), 1.27 (s, 6H), 1.26 (d, *J* 6.2, 3H), 1.23 (d, *J* 6.2, 3H). δ_C (75 MHz) 170.2 (C), 151.9 (C), 144.4 (C), 137.2 (CH), 135.4 (C), 123.7 (CH), 122.9 (CH), 121.4 (CH), 111.2 (CH), 107.8 (C), 95.5 (CH_2), 79.5 (CH), 78.2 (CH), 73.7 (CH), 72.9 (CH), 55.7 (CH_3), 55.4 (CH_3), 45.8 (C), 43.0 (CH_2), 37.6 (NCH_3), 35.3 (NCH_3), 27.6 (CH_3), 26.0 (CH_3), 22.7 (CH_3), 22.4 (CH_3). ν_{max} (KBr)/cm^{-1} 2983, 2938, 2836, 1657, 1580, 1455, 1380, 1263, 1214, 1150, 1106, 1039, 918, 737. *m/z* (EI, 70 eV) 463 ($M^{+\bullet}$, 41%), 402 (62), 376 (84), 302 (38), 244 (53), 229 (52), 215 (57), 162 (63), 87 (96), 72 (96), 46 (78), 45 (100), 43 (85).

Compound ***12***

Molecular bromine (0.6 mL, 11.71 mmol) was added to a magnetically stirred solution of compound **11** (1.83 g, 3.95 mmol) in toluene (60 mL) maintained at 18°C. After 18 h the reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 1:3:6 v/v/v methanol/hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_F 0.5 in 1:3 v/v methanol/ethyl acetate) then gave *dibromotriol* ***12*** (1.35 g, 69%) as a white, crystalline solid, mp 192–196°C, $[\alpha]_D$ +114.0 (*c* 0.5, CH_3OH) [Found: $(M + Na)^+$, 515.9640. $C_{17}H_{21}{}^{79}Br_2NO_6$ requires $(M + Na)^+$, 515.9633]. δ_H (300 MHz) 7.42 (d, *J* 2.0, 1H), 6.95 (d, *J* 2.0, 1H), 5.10 (d, *J* 9.0, 1H), 4.46 (d, *J* 3.4, 1H), 4.36 (dd, *J* 9.0 and 2.6, 1H), 4.01 (dd, *J* 4.4 and 3.4, 1H), 3.97 (dd, *J* 4.4 and 2.6, 1H), 3.84 (s, 3H), 3.05 (d, *J* 14.6, 1H), 2.85 (s, 3H), 2.77 (s, 3H), 2.56 (d, *J* 14.6, 1H). δ_C (75 MHz) 172.8 (C), 147.3 (C), 147.0 (C), 136.8 (C), 123.5 (CH), 117.3 (CH), 113.9 (C), 91.2 (CH), 75.0 (CH), 74.7 (CH), 71.8 (CH), 57.3 (CH_3), 54.8 (CH_3), 54.3 (C), 42.1 (CH_2), 38.3 (CH_3), 36.0 (CH_3). ν_{max} (KBr)/cm^{-1} 3511, 3391, 2910, 2889, 1608, 1581, 1479, 1408,

1297, 1198, 1180, 1132, 1088, 1020, 986, 938, 894, 840, 815, 739. *m/z* (ESI, +ve ion) 520 [$(M + Na)^+$, 52%], 518 (100), 516 (50), 496 (11).

Compound ***13***

A magnetically stirred mixture of compound **12** (722 mg, 1.458 mmol), 10% Pd/C (90 mg), anhydrous potassium carbonate (1.0 g, 7.2 mmol), and methanol (5 mL) was exposed to a balloon of hydrogen gas. After stirring at 18°C for 18 h, the reaction mixture was purged with nitrogen and then filtered through a short pad of Celite. The filtrate was concentrated under reduced pressure and the residue so obtained was subjected to flash chromatography (silica, 1:3 v/v methanol/ethyl acetate elution). Concentration of the relevant fractions (R_F 0.5 in 1:3 v/v methanol/ethyl acetate) then gave *7-oxanorbornene* ***13*** (329 mg, 67%) as a white, crystalline solid, mp 214–217°C, $[\alpha]_D$ +155.0 (*c* 0.4, CH_3OH) [Found: $(M + Na)^+$, 358.1272. $C_{17}H_{21}NO_6$ requires $(M + Na)^+$, 358.1267]. δ_H (300 MHz, CD_3OD) 6.93 (dd, *J* 6.8 and 1.7, 1H), 6.76 (dd, *J* 8.1 and 1.7, 1H), 6.74 (dd, *J* 8.1 and 6.8, 1H), 5.10 (s, 1H), 4.61 (t, *J* 1.2, 1H), 5.21 (dd, *J* 5.6 and 1.2, 1H), 4.02 (dt, *J* 5.6 and 1.0, 1H), 3.90 (d, *J* 1.0, 1H), 3.80 (s, 3H), 3.06 (d, *J* 5.6, 2H), 2.98 (s, 3H), 2.93 (s, 3H). δ_C (75 MHz, CD_3OD) 172.4 (C), 151.3 (C), 145.3 (C), 133.9 (C), 122.2 (CH), 117.5 (CH), 113.5 (CH), 92.9 (CH), 90.5 (CH), 85.0 (CH), 80.4 (CH), 78.3 (CH), 58.2 (C), 56.5 (CH_3), 38.8 (CH_2), 38.0 (CH_3), 35.8 (CH_3). ν_{max} (KBr)/cm^{-1} 3385, 2929, 2840, 1625, 1491, 1460, 1272, 1200, 1133, 1099, 1063, 1036, 980, 739. *m/z* (ESI, +ve ion) 358 [$(M + Na)^+$, 100%], 336 (3).

Compound ***14***

Molecular bromine (2.2 mL, 43.0 mmol) was added to a magnetically stirred solution of compound **11** (4.0 g, 8.6 mmol) in toluene (150 mL) maintained at 18°C. After 18 h the reaction mixture was treated with acetone (100 mL) and stirring continued for a further 2 h. The reaction mixture was then concentrated under reduced pressure and the ensuing residue subjected to flash chromatography (silica, 1:8:12 v/v/v methanol/hexane/ethyl acetate elution). Concentration of the relevant fractions (R_F 0.4 in 1:5:6 v/v/v methanol/hexane/ethyl acetate) provided the *dibromoacetonide* ***14*** (4.3 g, 93%) as a white, crystalline solid, mp 145–149°C, $[\alpha]_D$ +79.0 (*c* 0.5, $CHCl_3$) [Found: $(M - CH_3\bullet)^+$, 521.9780. $C_{19}H_{22}{}^{81}Br_2NO_6$ requires $(M - CH_3\bullet)^+$, 521.9773]. δ_H (300 MHz) 7.03 (d, *J* 1.7, 1H), 6.87 (d, *J* 1.7, 1H), 5.21 (d, *J* 7.8, 1H), 4.92 (d, *J* 6.6, 1H), 4.56 (m, 2H), 3.98 (br s, 1H), 3.86 (s, 3H), 2.93 (s, 3H), 2.89 (s, 3H), 2.85 (d, *J* 5.6, 2H), 1.57 (br s, 1H), 1.34 (s, 3H), 1.31 (s, 3H). δ_C (75 MHz) 169.4 (C), 146.2 (C), 145.0 (C), 132.7 (C), 121.0 (CH), 115.2 (CH), 112.3 (C), 108.9 (C), 89.8 (CH), 77.8 (CH), 76.5 (CH), 56.3 (CH), 53.7 (CH_3), 51.3 (C), 42.3 (CH_2), 37.7 (CH_3), 35.8 (CH_3), 26.6 (CH), 24.4 ($2 \times CH_3$). ν_{max} (KBr)/cm^{-1} 3368, 2988, 2936, 1622, 1487, 1263, 1209, 1052, 995, 909, 730. *m/z* (EI, 70 eV) 522, 520, and 518 [$(M - CH_3\bullet)^+$, 12, 7, and 7%], 438 and 436 (31 and 29), 380 and 378 (both 60), 307 and 305 (29 and 27), 227 (12), 115 (11), 87 (72), 72 (100), 49 (65).

Compound ***15***

A magnetically stirred mixture of compound **14** (1.87 g, 3.49 mmol), 10% Pd/C (318 mg), potassium carbonate (434 mg, 3.14 mmol), and methanol (6 mL) was exposed to a balloon of hydrogen gas. After stirring at 18°C for 18 h, the reaction mixture was purged with nitrogen and then filtered through a short pad of Celite. The filtrate was concentrated under reduced pressure and the residue so obtained subjected to flash chromatography (silica, 1:1:8 v/v/v methanol/hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_F 0.4 in 1:1:8 v/v/v methanol/hexane/ethyl acetate) then gave *benzofuran* ***15*** (896 mg, 68%) as a white, crystalline solid, mp 76–79°C, $[\alpha]_D$ +25.0 (*c* 0.5, $CHCl_3$) [Found: $M^{+\bullet}$, 377.1835. $C_{20}H_{27}NO_6$ requires $M^{+\bullet}$, 377.1838]. δ_H (300 MHz) 7.06 (dd, *J* 6.8 and 1.8, 1H), 6.76 (m, 2H), 5.13 (t, *J* 3.8, 1H), 4.90 (d, *J* 8.3, 1H), 4.24 (t, *J* 6.8, 1H), 3.83 (s, 3H), 3.79 (m, 1H), 3.00 (d, *J* 7.1, 1H), 2.91 (s, 3H), 2.90 (s, 3H), 2.67 (br s, 1H), 2.52 (d, *J* 7.1, 1H), 2.20–2.03 (complex m, 2H), 1.38 (s, 3H), 1.31 (s, 3H). δ_C (75 MHz) 170.2 (C), 147.7 (C), 143.9 (C), 131.7 (C), 120.3 (CH), 120.1 (CH), 111.4 (CH), 108.8 (C), 85.9 (CH), 80.8 (CH), 76.8 (CH), 67.2 (CH), 55.9 (CH_3), 49.6 (C), 43.3 (CH_2), 37.3 (CH_3), 35.4 (CH_3), 35.0 (CH_2), 25.7 (CH_3), 24.3 (CH_3). ν_{max} (KBr)/cm^{-1} 3428, 2984, 2938, 1637, 1491 1460, 1401, 1381, 1272, 1208, 1074, 996, 868, 735. *m/z* (EI, 70 eV) 377 ($M^{+\bullet}$, 30%), 362 (39), 319 (12), 301 (21), 290 (45), 272 (25), 233 (67), 215 (84), 204 (63), 175 (100), 161 (65), 115 (25).

Compound ***16***

DMAP (18 mg, 0.147 mmol) was added to a magnetically stirred solution of compound **15** (961 mg, 2.55 mmol) and acetic anhydride (0.8 mL, 8.46 mmol) in pyridine (20 mL). After stirring at 18°C for 2 h, the reaction mixture was concentrated under reduced pressure and the residue so obtained was subjected to flash chromatography (silica, 1:1:8 v/v/v methanol/hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_F 0.4 in 1:5:6 v/v/v methanol/hexane/ethyl acetate) then gave the *acetate* ***16*** (961 mg, 90%) as a white, crystalline solid, mp 75–78°C, $[\alpha]_D$ +41.2 (*c* 0.5, $CHCl_3$) [Found: $M^{+\bullet}$, 419.1939. $C_{22}H_{29}NO_7$ requires $M^{+\bullet}$, 419.1944]. δ_H (300 MHz) 7.06 (t, *J* 4.6, 1H), 6.76 (m, 2H), 5.12 (t, *J* 3.7, 1H), 5.01 (d, *J* 8.1, 1H), 4.91 (ddd, *J* 12.0, 7.1, and 3.2, 1H), 4.39 (dd, *J* 8.1 and 7.1, 1H), 3.88 (s, 3H), 3.05 (d, *J* 16.8, 1H), 2.98 (s, 3H), 2.90 (s, 3H), 2.54 (d, *J* 16.8, 1H), 2.32 (dt, *J* 13.9 and 3.2, 1H), 2.09 (m, 1H), 2.02 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H). δ_C (75 MHz) 170.2 (C), 169.8 (C), 148.2 (C), 144.2 (C), 131.2 (C), 120.3 (CH), 120.2 (CH), 112.8 (CH), 109.2 (C), 85.7 (CH), 77.7 (CH), 76.5 (CH), 70.0 (CH), 56.8 (CH_3), 49.5 (C), 42.9 (CH_2), 37.4 (CH_3), 35.4 (CH_3), 32.6 (CH_2), 25.8 (CH_3), 24.4 (CH_3), 21.4 (CH_3). ν_{max} (KBr)/cm^{-1} 2982, 2938, 1743, 1642, 1491, 1460, 1380, 1273, 1237, 1209, 1078, 1047, 735. *m/z* (EI, 70 eV) 419 ($M^{+\bullet}$, 14%), 404 (12), 302 (13), 272 (16), 215 (38), 214 (23), 175 (15), 87 (100), 72 (41), 57 (5), 43 (35).

Compound ***17***

Step i: Acetate **16** (734 mg, 1.750 mmol) was dissolved in acetic acid/water (30 mL of a ~2:1 v/v mixture) and the resulting solution stirred at 18°C for 20 h and then concentrated under reduced pressure. Subjection of the ensuing residue to flash chromatography (silica, 1:1:8 v/v/v methanol/hexane/ethyl acetate elution) afforded, after concentration of the appropriate fractions (R_F 0.4 in 1:1:8 v/v/v methanol/hexane/ethyl acetate), the *diol precursor to compound* ***17*** (628 mg, 94%) as a white, crystalline solid, mp 129–131°C, $[\alpha]_D$ +86.0 (*c* 0.5, $CHCl_3$) [Found: $M^{+\bullet}$, 379.1630. $C_{19}H_{25}NO_7$ requires $M^{+\bullet}$, 379.1631]. δ_H (300 MHz) 7.08 (dd, *J* 7.3 and 1.2, 1H), 6.80 (m, 2H), 4.95 (m, 2H), 4.45 (d, *J* 4.6, 1H), 4.00 (t, *J* 4.0, 1H), 3.86 (s, 3H), 3.33 (d, *J* 15.3, 1H), 2.93 (d, *J* 5.6, 1H), 2.88 (s, 3H), 2.71 (s, 3H), 2.45 (d, *J* 15.3, 1H), 2.28–2.18 (complex m, 2H), 2.08 (s, 3H), 1.60 (br s, 1H). δ_C (75 MHz) 171.6 (C), 171.4 (C), 146.7 (C), 145.0 (C), 132.0 (C),

121.6 (CH), 118.4 (CH), 111.8 (CH), 86.2 (CH), 73.6 (CH), 71.7 (CH), 71.5 (CH), 56.0 (CH_3), 50.1 (C), 42.2 (CH_2), 37.8 (CH_3), 35.8 (CH_3), 28.3 (CH_2), 21.2 (CH_3). ν_{max} (KBr)/cm^{-1} 3393, 2938, 2837, 1732, 1620, 1491, 1458, 1247, 1044, 740. *m/z* (EI, 70 eV) 379 ($M^{+\bullet}$, 24%), 361 (2), 292 (4), 232 (22), 215 (36), 175 (14), 161 (16), 87 (100), 72 (47), 57 (11), 45 (37), 43 (33).

Step ii: A solution of the diol (628 mg, 1.655 mmol), prepared as described immediately above, and DMAP (910 mg, 7.449 mmol) in dry dichloromethane (20 mL) maintained at 0°C (ice-bath) under a nitrogen atmosphere was treated, dropwise, with thiophosgene (189 μL, 2.479 mmol). After stirring at 0°C for 1 h, the reaction mixture was treated with methanol (2 mL) and then concentrated under reduced pressure. Subjection of the ensuing residue to flash chromatography (silica, 1:4:6 v/v/v methanol/hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_F 0.5 in 1:3:6 v/v/v methanol/hexane/ethyl acetate) afforded *compound **17*** (691 mg, 99%) as a white, crystalline solid, mp 122–124°C, $[\alpha]_D$ −25.0 (*c* 0.5, $CHCl_3$) [Found: $M^{+\bullet}$, 421.1198. $C_{20}H_{23}NO_7S$ requires $M^{+\bullet}$, 421.1195]. δ_H (300 MHz) 7.06 (dd, *J* 6.7 and 2.1, 1H), 6.83 (m, 2H), 5.95 (d, *J* 8.9, 1H), 5.15–5.02 (complex m, 3H), 3.87 (s, 3H), 3.13 (d, *J* 17.6, 1H), 2.93(4) (s, 3H), 2.93(0) (s, 3H), 2.62 (d, *J* 17.6, 1H), 2.38 (dt, *J* 14.0 and 2.8, 1H), 2.11 (m, 1H), 2.01 (s, 3H). δ_C (75 MHz) 190.7 (C), 169.4 (C), 169.2 (C), 148.2 (C), 144.5 (C), 127.4 (C), 122.4 (CH), 118.4 (CH), 114.0 (CH), 84.7 (CH), 84.1 (CH), 82.1 (CH), 66.9 (CH), 56.5 (CH_3), 48.8 (C), 41.7 (CH_2), 37.2 (CH_3), 35.4 (CH_3), 32.1 (CH_2), 21.0 (CH_3). ν_{max} (KBr)/cm^{-1} 2937, 2838, 1749, 1639, 1492, 1286, 1230, 1049, 982, 734. *m/z* (EI, 70 eV) 421 ($M^{+\bullet}$, 6%), 408 (10), 365 (5), 361 (4), 229 (10), 215 (50), 149 (24), 105 (33), 87 (100), 84 (38), 72 (37), 57 (60), 43 (77).

*Compound **18***

A magnetically stirred solution of thiocarbonate **17** (691 mg, 1.640 mmol) in trimethylphosphite/toluene (40 mL of a 1:1 v/v mixture) was heated at reflux for 18 h and then cooled and concentrated under reduced pressure. Subjection of the ensuing residue to flash chromatography (silica, 1:4:5 v/v/v methanol/hexane/ethyl acetate elution) afforded, after concentration of the appropriate fractions (R_F 0.4 in 1:4:6 v/v/v methanol/hexane/ethyl acetate), *compound **18*** (407 mg, 72%) as a clear, colourless oil, $[\alpha]_D$ +131.0 (*c* 0.5, $CHCl_3$) [Found: $M^{+\bullet}$, 345.1577. $C_{19}H_{23}NO_5$ requires $M^{+\bullet}$, 345.1576]. δ_H (300 MHz) 6.85–6.72 (complex m, 3H), 5.92 (d, *J* 10.0, 1H), 5.78 (d, *J* 10.0, 1H), 5.42 (m, 1H), 5.04 (t, *J* 4.1, 1H), 3.86 (s, 3H), 3.02 (d, *J* 15.8, 1H), 2.95 (s, 3H), 2.92 (s, 3H), 2.71 (d, *J* 15.8, 1H), 2.55 (m, 1H), 2.25 (m, 1H), 2.05 (s, 3H). δ_C (75 MHz) 170.6 (C), 169.5 (C), 146.7 (C), 144.9 (C), 134.0 (C), 132.1 (CH), 127.4 (CH), 121.6 (CH), 115.7 (CH), 111.7 (CH), 85.6 (CH), 66.0 (CH), 56.0 (CH_3), 47.5 (C), 41.7 (CH_2), 38.0 (CH_3), 35.6 (CH_3), 30.1 (CH_2), 21.3 (CH_3). ν_{max} (KBr)/cm^{-1} 2938, 2836, 1732, 1648, 1492, 1459, 1278, 1242, 1204, 1031, 732. *m/z* (EI, 70 eV) 345 ($M^{+\bullet}$, 6%), 244 (3), 199 (24), 198 (21), 128 (4), 87 (100), 72 (26), 45 (26), 43 (27).

*Compound **19***

Potassium carbonate (244 mg, 1.765 mmol) was added to a magnetically stirred solution of allylic acetate **18** (407 mg, 1.178 mmol) in methanol (8 mL) maintained at 18°C. After 1 h the reaction mixture was concentrated under reduced pressure and the residue so-obtained was treated with ethyl acetate (40 mL) and $NaHCO_3$ (60 mL of a saturated aqueous solution). The separated aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 1:1:8 v/v/v methanol/hexane/ethyl acetate elution) and gave, after concentration of the appropriate fractions (R_F 0.4 in 1:1:8 v/v/v methanol/hexane/ethyl acetate), the *allylic alcohol **19*** (338 mg, 95%) as a white, crystalline solid, mp 163–166°C, $[\alpha]_D$ +10.0 (*c* 0.5, $CHCl_3$) [Found: $(M + Na)^+$, 326.1365. $C_{17}H_{21}NO_4$ requires $(M + Na)^+$, 326.1368]. δ_H (300 MHz) 6.89–6.82 (complex m, 1H), 6.80–6.73 (complex m, 2H), 6.12 (dd, *J* 9.8 and 5.5, 1H), 5.86 (d, *J* 9.8, 1H), 5.42 (dd, *J* 10.3 and 5.5, 1H), 4.19 (m, 1H), 3.87 (s, 3H), 3.28 (br s, 1H), 2.93 (s, 6H), 2.70 (s, 2H), 2.42 (m, 1H), 1.84 (m, 1H). δ_C (75 MHz) 170.0 (C), 146.3 (C), 145.6 (C), 133.8 (C), 130.2 (CH), 129.8 (CH), 121.6 (CH), 115.2 (CH), 111.8 (CH), 84.1 (CH), 63.2 (CH), 56.1 (CH_3), 47.8 (C), 42.6 (CH_2), 37.3 (CH_3), 35.6 (CH_3), 35.2 (CH_2). ν_{max} (KBr)/cm^{-1} 3391, 2937, 2838, 1623, 1592, 1491, 1458, 1400, 1278, 1201, 1046. *m/z* (ESI) 326 [$(M + Na)^+$, 100%], 286 (10).

*Compound **20***

tert-Butylchlorodiphenylsilane (184 μL, 0.72 mmol) was added to a magnetically stirred solution of allylic alcohol **19** (136 mg, 0.45 mmol) and imidazole (155 mg, 2.28 mmol) in dry dichloromethane (15 mL) maintained at 18°C under a nitrogen atmosphere. After 18 h the reaction mixture was poured into brine (50 mL of a saturated aqueous solution) and the separated aqueous phase was extracted with dichloromethane (1 × 25 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the ensuing crude material to flash chromatography (silica, 1:1 v/v hexane/ethyl acetate elution) afforded, after concentration of the appropriate fractions (R_F 0.5 in 8:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane), the *TBDPS-ether **20*** (231 mg, 95%) as a clear, colourless oil, $[\alpha]_D$ +107.2 (*c* 0.5, $CHCl_3$) [Found: $(M - C_4H_9\bullet)^+$, 484.1943. $C_{33}H_{39}NO_4Si$ requires $(M - C_4H_9\bullet)^+$, 484.1944]. δ_H (300 MHz) 7.69–7.60 (complex m, 4H), 7.44–7.31 (complex m, 6H), 6.82 (dd, *J* 7.6 and 1.7, 1H), 6.77 (t, *J* 7.6, 1H), 6.69 (dd, *J* 7.6 and 1.7, 1H), 5.81 (dd, *J* 10.2 and 1.0, 1H), 5.73 (dd, *J* 10.2 and 2.7, 1H), 4.99 (t, *J* 4.2, 1H), 4.48 (m, 1H), 3.79 (s, 3H), 2.97 (d, *J* 14.6, 1H), 2.94 (s, 3H), 2.92 (s, 3H), 2.68 (d, *J* 14.6, 1H), 2.42 (dt, *J* 13.7 and 5.4, 1H), 2.09 (m, 1H), 1.05 (s, 9H). δ_C (75 MHz) 169.7 (C), 147.0 (C), 144.8 (C), 135.9(4) (2 × CH), 135.9(1) (2 × CH), 134.3 (C), 134.2(5) (C), 134.1(9) (C), 131.6 (CH), 129.8 (CH), 129.7 (2 × CH), 127.7(4) (2 × CH), 127.7(1) (2 × CH), 121.4 (CH), 116.1 (CH), 111.7 (CH), 86.2 (CH), 64.3 (CH), 56.1 (CH_3), 47.4 (C), 41.4 (CH_2), 38.2 (CH_3), 35.6 (CH_3), 33.6 (CH_2), 27.1 (3 × CH_3), 19.3 (C). ν_{max} (KBr)/cm^{-1} 3070, 2932, 2857, 1650, 1590, 1490, 1460, 1390, 1284, 1203, 1100, 1090. *m/z* (EI, 70 eV) 541 ($M^{+\bullet}$, 3%), 484 [$(M - C_4H_9\bullet)^+$, 17], 397 (4), 286 (40), 199 (100), 135 (8), 87 (88), 57 (16).

*Compound **21***

A magnetically stirred solution of TBDPS-ether **20** (218 mg, 0.40 mmol) in dry THF (20 mL) maintained at 18°C under a nitrogen atmosphere was treated, dropwise, with Superhydride (2.0 mL of a 1.0 M solution in THF, 2.0 mmol). After 4 h the reaction mixture was quenched with methanol (1.0 mL) and then concentrated under reduced pressure. Subjection of the ensuing light-yellow oil to flash chromatography (silica, 7:10 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_F 0.3 in 2:2.5:5.5 v/v/v ethyl

acetate/dichloromethane/hexane), *compound* ***21*** (191 mg, 95%) as a white foam, $[\alpha]_D$ +101.0 (*c* 0.5, $CHCl_3$) [Found: $M^{+\bullet}$, 500.2382. $C_{31}H_{36}O_4Si$ requires $M^{+\bullet}$, 500.2383]. δ_H (300 MHz) 7.72–7.67 (complex m, 4H), 7.46–7.34 (complex m, 6H), 6.82 (dd, *J* 8.2 and 7.2, 1H), 6.70 (dm, *J* 4.2, 2H), 5.80 (dd, *J* 10.2 and 2.9, 1H), 5.60 (d, *J* 10.2, 1H), 5.02 (m, 1H), 4.50 (m, 1H), 3.82 (s, 3H), 3.78 (t, *J* 6.6, 2H), 2.33 (dt, *J* 13.8 and 5.5, 1H), 2.01 (m, 3H), 1.80 (br s, 1H), 1.09 (s, 9H). δ_C (75 MHz) 146.8 (C), 144.9 (C), 135.9 (4 × CH), 134.6 (C), 134.1 (C), 134.0 (C), 131.3 (CH), 130.8 (CH), 129.9 (CH), 129.8 (CH), 127.8 (2 × CH), 127.7 (2 × CH), 121.5 (CH), 115.2 (CH), 111.6 (CH), 85.2 (CH), 64.4 (CH), 59.6 (CH_2), 56.0 (CH_3), 47.7 (C), 41.2 (CH_2), 34.0 (CH_2), 27.0 (3 × CH_3), 19.2 (C). ν_{max} (KBr)/cm^{-1} 3436, 3070, 2931, 2893, 2857, 1618, 1590, 1492, 1459, 1427, 1280, 1203, 1111, 1083, 1029. *m/z* (EI, 70 eV) 500 ($M^{+\bullet}$, 7%), 443 (13), 365 (10), 244 (27), 227 (51), 199 (100), 139 (14).

Compound ***22***

Step i: A magnetically stirred solution of alcohol **21** (181 mg, 0.361 mmol) in dry dichloromethane (15 mL) maintained at 18°C was treated with the Dess–Martin periodinane (184 mg, 0.434 mmol). After 16 h the reaction mixture was filtered through a short pad of Celite and the filtrate concentrated under reduced pressure. Subjection of the resulting light-yellow to flash chromatography (silica, 3:5 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_F 0.5 in 1:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane), the *aldehydic precursor to compound* ***22*** (177 mg, 98%) as a clear, light-yellow oil, $[\alpha]_D$ +123.0 (*c* 0.5, $CHCl_3$) [Found: $M^{+\bullet}$, 498.2213. $C_{31}H_{34}O_4Si$ requires $M^{+\bullet}$, 498.2226]. δ_H (300 MHz) 9.79 (t, *J* 2.7, 1H), 7.70–7.65 (complex m, 4H), 7.46–7.33 (complex m, 6H), 6.84 (m, 1H), 6.72 (m, 2H), 5.79 (dd, *J* 10.2 and 2.2, 1H), 5.65 (dd, *J* 10.2 and 2.2, 1H), 4.89 (t, *J* 4.4, 1H), 4.52 (m, 1H), 3.82 (s, 3H), 2.80 (dd, *J* 2.7 and 1.7, 2H), 2.40 (dt, *J* 13.5 and 5.1, 1H), 1.99 (dddd, *J* 11.7, 8.1, 4.6, and 3.1, 1H), 1.07 (s, 9H). δ_C (75 MHz) 200.8 (CH), 146.9 (C), 145.1 (C), 135.9 (2 × CH), 135.8(8) (2 × CH), 134.0 (C), 133.9 (C), 132.9 (C), 132.2 (CH), 129.9 (CH), 129.8 (CH), 128.9 (CH), 127.8 (2 × CH), 127.7(7) (2 × CH), 122.0 (CH), 115.3 (CH), 112.0 (CH), 85.2 (CH), 64.0 (CH), 56.1 (CH_3), 51.3 (C), 46.8 (CH_2), 33.2 (CH_2), 27.0 (3 × CH_3), 19.3 (C). ν_{max} (KBr)/cm^{-1} 3069, 2931, 2857, 1722, 1617, 1590, 1492, 1458, 1286, 1203, 1111, 1086, 1035, 864, 702. *m/z* (EI, 70 eV) 498 ($M^{+\bullet}$, 3%), 441 (11), 225 (8), 199 (100), 165 (18), 139 (37), 105 (9), 84 (11), 57 (15).

Step ii: NBS (119 mg, 0.669 mmol) and AIBN (11 mg, 0.067 mmol) were added to a magnetically stirred solution of the above-mentioned aldehyde (167 mg, 0.335 mmol) in dry carbon tetrachloride (20 mL) and the ensuing mixture was placed in a pre-heated oil-bath maintained at 95°C. After 0.75 h the reaction mixture was cooled, placed in an ice-bath (0°C), and then treated with methylamine (1.0 mL of a 2.0 M solution in THF). After being stirred at 0°C for 1 h the reaction mixture was concentrated under reduced pressure and the residue so obtained was subjected to flash chromatography (silica, 1:3:7 v/v/v methanol/hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_F 0.4 in 8:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane) then gave *compound* ***22*** (141 mg, 80%) as a white, crystalline solid, mp 56–60°C, $[\alpha]_D$ +87.6 (*c* 0.5, $CHCl_3$) [Found: $M^{+\bullet}$, 527.2481. $C_{32}H_{37}NO_4Si$ requires $M^{+\bullet}$, 527.2492]. δ_H (300 MHz) 7.69–7.62 (complex m, 4H), 7.45–7.31 (complex m, 6H), 6.83–6.68 (complex m, 3H), 5.74 (dd, *J* 10.1 and 1.7, 1H), 5.62 (dd, *J* 10.1 and 1.2, 1H), 5.51 (m, 1H), 4.96 (t, *J* 3.7, 1H), 4.52 (m, 1H), 3.80 (s, 3H), 2.76 (d, *J* 4.8, 3H), 2.64 (d, *J* 4.8, 2H), 2.48 (m, 1H), 1.97 (m, 1H), 1.07 (s, 9H). δ_C (75 MHz) 170.0 (C), 146.9 (C), 144.9 (C), 135.9 (4 × CH), 134.2 (C), 134.0 (C), 133.8 (C), 132.3 (CH), 129.8 (CH), 129.7 (CH), 129.3 (CH), 127.7(6) (2 × CH), 127.7(3) (2 × CH), 121.6 (CH), 115.3 (CH), 112.0 (CH), 85.4 (CH), 64.1 (CH), 56.0 (CH_3), 47.0 (C), 45.2 (CH_2), 33.1 (CH_2), 27.0 (3 × CH_3), 26.4 (CH_3), 19.3 (C). ν_{max} (KBr)/cm^{-1} 3310, 3071, 2932, 2858, 1644, 1590, 1492, 1460, 1278, 1204, 111, 1090, 909, 864, 733, 702. *m/z* (EI, 70 eV) 527 ($M^{+\bullet}$, 3%), 470 (45), 397 (4), 272 (26), 199 (100), 135 (11), 73 (44), 57 (28), 43 (19).

Compound ***23***

A magnetically stirred solution of amide **22** (131 mg, 0.248 mmol) in THF (10 mL) was treated with TBAF (0.4 mL of 1.0 M solution in THF, 0.4 mmol) and then stirred at 18°C for 30 h. The resulting mixture was concentrated under reduced pressure and the light-yellow oil so-obtained was subjected to flash chromatography (silica, 3:20 v/v methanol/ethyl acetate elution). Concentration of the appropriate fractions (R_F 0.4 in 1:9 v/v methanol/ethyl acetate) then gave *alcohol* ***23*** (61 mg, 85%) as a white, crystalline solid, mp 233–236°C, $[\alpha]_D$ +142.0 (*c* 0.2, CH_3OH) [Found: $M^{+\bullet}$, 289.1313. $C_{16}H_{19}NO_4$ requires $M^{+\bullet}$, 289.1314]. δ_H (300 MHz) 6.85 (t, *J* 7.0, 1H), 6.76 (d, *J* 7.0, 1H), 6.73 (dd, *J* 7.0 and 1.2, 1H), 6.05 (dd, *J* 10.0 and 4.7, 1H), 5.79 (d, *J* 10.0, 1H), 5.51 (br s, 1H), 5.40 (dd, *J* 8.2 and 4.7, 1H), 4.30 (br s, 1H), 3.87 (s, 3H), 3.22 (br s, 1H), 2.78 (d, *J* 4.7, 3H), 2.71 (d, *J* 15.2, 1H), 2.50 (d, *J* 15.2, 1H), 2.24 (m, 1H), 2.12 (m, 1H). δ_C (75 MHz) 172.8, 148.1, 146.0, 135.6, 133.0, 131.4, 122.6, 116.7, 113.5, 86.6, 63.0, 56.6, 45.2, 34.1, 30.8, 26.2. ν_{max} (KBr)/cm^{-1} 3306, 2941, 2836, 1650, 1619, 1592, 1491, 1459, 1280, 1201, 1043, 742. *m/z* (EI, 70 eV) 289 ($M^{+\bullet}$, 5%), 271 (3), 240 (6), 216 (75), 199 (63), 188 (15), 115 (10), 73 (100), 57 (18), 43 (17).

Compound ***24***

A magnetically stirred solution of compound **23** (50 mg, 0.173 mmol), paraformaldehyde (30 mg, 0.990 mmol), and trifluoroacetic acid (266 μL, 3.453 mmol) in dry 1,2-dichloroethane (15 mL) was heated at 60°C for 48 h and then cooled and concentrated under reduced pressure. The residue thus obtained was dissolved in methanol (5 mL) and the resulting solution treated with triethylamine (2 mL). After 2 h the reaction mixture was concentrated under reduced pressure and the resulting light-yellow oil subjected to flash chromatography (silica, 1:10 v/v methanol/chloroform elution). Concentration of the appropriate fractions (R_F 0.4 in 1:1:9 v/v/v methanol/hexane/ethyl acetate) then gave *lactam* ***24*** (46 mg, 88%) as a white, crystalline solid, mp 232–235°C, $[\alpha]_D$ +223.0 (*c* 0.2, $CHCl_3$) [Found: $(M+H)^+$, 302.1389. $C_{17}H_{19}NO_4$ requires $(M+H)^+$, 302.1392]. δ_H (300 MHz) 6.66 (m, 2H), 5.84 (dd, *J* 10.0 and 1.8, 1H), 5.45 (dt, *J* 10.0 and 1.8, 1H), 4.69–4.60 (complex m, 2H), 4.50 (d, *J* 15.8, 1H), 4.23 (d, *J* 15.8, 1H), 3.85 (s, 3H), 2.98 (s, 3H), 2.94–2.74 (m, 3H), 2.01 (br s, 1H), 1.80 (m, 1H). δ_C (75 MHz) 171.3 (C), 147.8 (C), 144.8 (C), 131.9 (CH), 131.7 (C), 129.0 (CH), 125.5 (C), 119.6 (CH), 111.8 (CH), 87.7 (CH), 62.8 (CH), 56.2 (CH_3), 52.2 (C), 43.5 (CH_2), 42.9 (CH_2), 35.8 (CH_3), 31.2 (CH_2). ν_{max} (KBr)/cm^{-1} 3408, 2922, 1632, 1508, 1435, 1342, 1282, 1103, 1050, 1037, 802, 732. *m/z* (EI, 70 eV) 302 [$(M+H)^+$, 54%], 301 (100), 230 (35), 229 (33), 197 (26), 174 (22), 115 (16), 85 (29), 71 (37), 57 (56), 43 (42).

Compound ***25***

A magnetically stirred solution of lactam **24** (46 mg, 0.153 mmol) in toluene (10 mL) maintained at 18°C was treated with chloroacetic acid (43 mg, 0.455 mmol), triphenylphosphine (140 mg, 0.554 mmol), and diisopropyl azodicarboxylate (75 μL, 0.381 mmol). After 18 h the reaction mixture was diluted with ethyl acetate (50 mL) and then treated with $NaHCO_3$ (50 mL of a saturated aqueous solution). The separated aqueous phase was extracted with ethyl acetate (2 × 15 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:4:5 v/v/v methanol/ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions (R_F 0.5 in 1:1:8 v/v/v methanol/hexane/ethyl acetate), *chloroacetate* ***25*** (54 mg, 93%) as a white, crystalline solid, mp 55–58°C, $[\alpha]_D$ +80.5 (*c* 0.2, $CHCl_3$) [Found: $M^{+\bullet}$, 377.1033. $C_{19}H_{20}{}^{35}ClNO_5$ requires $M^{+\bullet}$, 377.1030]. δ_H (300 MHz) 6.90 (ABq, *J* 13.5, 2H), 5.92 (dd, *J* 10.0 and 5.9, 1H), 5.22 (dd, *J* 10.0 and 1.2, 1H), 5.43 (t, *J* 4.7, 1H), 4.66 (s, 1H), 4.48 (d, *J* 16.4, 1H), 4.33 (d, *J* 16.4, 1H), 4.09 (ABq, *J* 8.2, 1H), 3.86 (s, 3H), 3.02 (s, 3H), 2.88–2.45 (complex m, 3H), 2.22 (dm, *J* 5.7, 1H). δ_C (75 MHz) 170.9 (C), 167.3 (C), 147.4 (C), 144.9 (C), 132.9 (CH), 131.0 (C), 125.2 (C), 122.6 (CH), 119.7 (CH), 112.5 (CH), 85.5 (CH), 65.0 (CH), 56.3 (CH_3), 52.2 (C), 43.1 (CH_2), 42.1 (CH_2), 41.4 (CH_2), 36.1 (CH_3), 26.7 (CH_2). ν_{max} (KBr)/cm^{-1} 2956, 2930, 1748, 1648, 1508, 1438, 1284, 1190, 1072, 1025, 730. *m/z* (EI, 70 eV) 379 and 377 ($M^{+\bullet}$, 34 and 100%), 308 and 306 (4 and 10), 240 (15), 211 (41), 165 (12), 115 (9), 85 (18), 71 (25), 57 (37), 43 (27).

*(+)-Galanthamine [(+)-****1****]*

A magnetically stirred solution of chloroacetate **25** (34 mg, 0.090 mmol) in dry THF (10 mL) maintained under a nitrogen atmosphere was treated with lithium aluminum hydride (0.5 mL of a 1.0 M solution in THF, 0.5 mmol). After stirring at 18°C for 4 h the reaction mixture was treated with methanol (2 mL) and then $NaHCO_3$ (40 mL of a saturated aqueous solution). The separated aqueous phase was extracted with chloroform (4 × 15 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the residue so obtained to flash chromatography (silica, 1:20 v/v triethylamine/methanol elution) provided, after concentration of the appropriate fractions (R_F 0.5 in 1:20 v/v triethylamine/methanol), the title compound (+)-**1** (22 mg, 85%) as a white, crystalline solid, mp 121–124°C (lit.[9b] mp 124–125°C), $[\alpha]_D$ +108.8 (*c* 0.4, $CHCl_3$) [Found: $M^{+\bullet}$, 287.1518. $C_{17}H_{21}NO_3$ requires $M^{+\bullet}$, 287.1521]. δ_H (800 MHz) 6.64 (d, *J* 8.2, 1H), 6.62 (d, *J* 8.2, 1H), 6.06 (d, *J* 10.3, 1H), 6.00 (ddd, *J* 10.3, 5.0, and 1.3, 1H), 4.61 (d, *J* 1.7, 1H), 4.14 (ddd, *J* 10.1, 5.1, and 1.3, 1H), 4.09 (d, *J* 5.1, 1H), 3.83 (s, 3H), 3.68 (dd, *J* 5.1 and 0.8, 1H), 3.27 (t, *J* 13.2, 1H), 3.05 (d, *J* 13.2, 1H), 2.68 (dddd, *J* 15.8, 6.5, 5.0, and 1.3, 1H), 2.40 (s, 3H), 2.28 (br s, 1H), 2.08 (dt, *J* 13.2 and 2.9, 1H), 2.00 (m, 1H), 1.58 (dd, *J* 13.2 and 2.1, 1H). δ_C (75 MHz) 145.9 (C), 144.3 (C), 133.1 (C), 129.3 (C), 127.7 (CH), 126.9 (CH), 122.2 (CH), 111.2 (CH), 88.8 (CH), 62.2 (CH), 60.7 (CH_2), 56.0 (CH_3), 53.9 (C), 48.3 (CH_2), 42.2 (CH_3), 33.9 (CH_2), 30.0 (CH_2). ν_{max} (KBr)/cm^{-1} 3563, 2919, 2849, 1625, 1592, 1507, 1438, 1280, 1047, 908, 732. *m/z* (EI, 70 eV) 287 ($M^{+\bullet}$, 94%), 286 (100), 270 (23), 244 (36), 230 (28), 216 (44), 174 (42), 115 (20), 85 (16), 71 (24), 57 (34), 43 (28).

*Compound C8a-*epi*-****11****

A magnetically stirred solution of compound **9** (541 mg, 1.37 mmol) in toluene (20 mL) was treated with *N*,*N*-dimethylacetamide dimethyl acetal (2.5 mL, 15.4 mmol) and the ensuing mixture heated (oil bath) at reflux. When TLC analysis indicated that no starting material remained (~28 days), the reaction mixture was cooled and then concentrated under reduced pressure. Subjection of the ensuing residue to flash chromatography (silica, 1:10:40 v/v/v methanol/hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_F 0.3 in 8:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane) afforded *amide C8a-*epi-***11*** (238 mg, 37%) as a clear, colourless oil, $[\alpha]_D$ −16.8 (*c* 1.0, $CHCl_3$) [Found: $M^{+\bullet}$, 463.2573. $C_{25}H_{37}NO_7$ requires $M^{+\bullet}$, 463.2570]. δ_H (300 MHz) 6.88 (t, *J* 8.0, 1H), 6.77 (dd, *J* 8.0 and 1.5, 1H), 6.71 (dd, *J* 8.0 and 1.5, 1H), 6.52 (dd, *J* 10.2 and 2.5, 1H), 5.66 (dd, *J* 10.2 and 2.2, 1H), 5.16 (sept, *J* 6.2, 1H), 4.86 (d, *J* 6.6, 1H), 4.72 (d, *J* 7.1, 2H), 4.32 (m, 1H), 4.22 (dd, *J* 7.6 and 4.8, 1H), 3.77 (s, 3H), 3.53 (d, *J* 17.3, 1H), 3.39 (s, 3H), 3.04 (s, 3H), 2.85 (s, 3H), 2.51 (d, *J* 17.3, 1H), 1.47 (s, 3H), 1.30 (s, 3H), 1.26 (d, *J* 6.2, 3H), 1.21 (d, *J* 6.2, 3H). δ_C (75 MHz) 170.7 (C), 152.3 (C), 143.7 (C), 139.4 (CH), 137.2 (C), 122.2 (CH), 121.6 (CH), 121.0 (CH), 111.5 (CH), 108.0 (C), 95.3 (CH_2), 80.0 (CH), 79.5 (CH), 74.4 (CH), 72.9 (CH), 55.7 (CH_3), 55.4 (CH_3), 45.1 (C), 37.9 (CH_2), 37.5 (NCH_3), 35.4 (NCH_3), 27.0 (CH_3), 24.9 (CH_3), 22.7 (CH_3), 22.0 (CH_3). ν_{max} (KBr)/cm^{-1} 2982, 2935, 1659, 1580, 1454, 1393, 1381, 1263, 1151, 1104, 1056, 919, 761. *m/z* (EI, 70 eV) 463 ($M^{+\bullet}$, 12%), 402 (14), 87 (59), 73 (46), 72 (63), 59 (36), 45 (100), 43 (77).

X-ray Crystallographic Studies

Crystal Data for Compound ***12***

$C_{17}H_{21}Br_2NO_6$, *M* 495.16, *T* 200 K, monoclinic, space group $P2_1$, *Z* 2, *a* 8.1312(2), *b* 7.1811(1), *c* 16.7998(4) Å, *β* 103.2724(10)°, *V* 954.75(4) $Å^3$, D_x 1.722 g cm^{-3}, 4351 unique data ($2\theta_{max}$ 55°), *R* 0.024 [for 3770 reflections with $I > 2.0\sigma(I)$]; *Rw* 0.062 (all data), *S* 0.90, Flack parameter −0.02(1).

Data for the Hemihydrate of bis-Ether ***13***

$C_{17}H_{21}NO_6 \cdot 0.5(H_2O)$, *M* 344.36, *T* 200 K, monoclinic, space group $P2_1$, *Z* 8, *a* 13.9312(2), *b* 14.5592(1), *c* 17.2168(2) Å, *β* 106.0707(6)°, *V* 3355.57(7) $Å^3$, D_x 1.363 g cm^{-3}, 10191 unique data ($2\theta_{max}$ 60.2°), *R* 0.034 [for 7031 reflections with $I > 2.0\sigma(I)$]; *Rw* 0.076 (all data), *S* 0.77.

Data for Compound ***19***

$C_{17}H_{21}NO_4$, *M* 303.36, *T* 200 K, orthorhombic, space group $P2_12_12_1$, *Z* 4, *a* 8.3701(2), *b* 10.4272(3), *c* 17.8797(5) Å, *V* 1560.48(7) $Å^3$, D_x 1.291 g cm^{-3}, 2062 unique data ($2\theta_{max}$ 55°), *R* 0.032 [for 1471 reflections with $I > 2.0\sigma(I)$]; *Rw* 0.070 (all data), *S* 0.79.

Structure Determination

Images were measured on a Nonius Kappa CCD diffractometer ($Mo_{K\alpha}$, graphite monochromator, λ = 0.71073 Å) and data extracted using the *DENZO* package.[32] Structure solution was by direct methods (SIR92).[33] The structures of the abovementioned compounds were refined using the *CRYSTALS* program package.[34] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 735777, 735778, and 739080 for compound **12**, the hemihydrate of bis-ether **13** and

compound **19**, respectively). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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