A Chemoenzymatic Total Synthesis of *ent*-Bengamide E

Martin G. Banwell* and Kenneth J. McRae

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia

mgb@rsc.anu.edu.au

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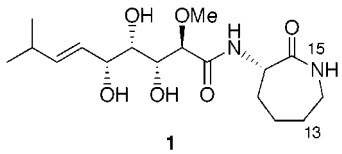
The *cis*-1,2-dihydrocatechol **3**, which can be obtained in enantiomerically pure form by microbial dihydroxylation of bromobenzene, has been converted into the enantiomer, *ent*-**1**, of the cyclolysine-based marine natural product bengamide E (**1**).

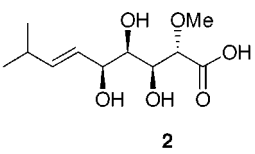
Introduction

The bengamides, which constitute one of the most prominent classes of natural product isolated from sponges of the genus *Japus* (family Jaspidae), display a useful range of biological activities including often striking differential cytotoxicity patterns as well as antihelminthic properties.[1] Furthermore, a very recent reevaluation of the bengamides, carried out by Crews and his collaborators at the Novartis Institute for Biochemical Research (NJ),[1h] has revealed that some are exceptionally potent, in vitro, against the MDA-MB-435 human breast carcinoma cell line and several of them (bengamides B, E, and Z)[2] exhibit significant anti-proliferative effects against xenografts of this same cell line in nude mice. These workers have also suggested that the cytotoxicity of the bengamides may be due to inhibition of a novel target. As such, and because of their highly restricted supply from natural sources, these compounds would appear to represent very worthy targets for synthesis.

Bengamide E (**1**) is a representative member of the class, and this amide is comprised of a 10-carbon carboxylic acid and an α-amino-ϵ-caprolactam residue. The remaining bengamides vary in the nature of the latter residue with some of the more active members carrying acylated hydroxyl groups at C-13 and/or a methyl group at *N*-15. The carboxylic acid residue, which is common to all of the bengamides, is probably the most synthetically challenging substructure associated with those compounds and has been synthesized by a number of methods starting from cyclitol, glucose, α-D-glucoheptonic-γ-lactone, tartaric acid, and glyceraldehyde-type chirons.[2] We now wish to report a concise and chemoenzymatic total synthesis of *ent*-bengamide E (*ent*-**1**) wherein the relevant acid fragment **2** has been prepared, in suitably protected form, from the *cis*-1,2-dihydrocatechol **3**, a compound available in large quantity and enantiomerically pure form by microbial oxidation of bromobenzene.[3] Since the enantiomer of diol **3** is also available,[4] the work described herein constitutes a formal total synthesis of bengamide E itself. Furthermore, since appropriate derivatives of acid **2**, and by implication *ent*-**2**, are readily available by the means described herein, both enantiomeric forms of all the bengamides should now be accessible for further biological study.



1



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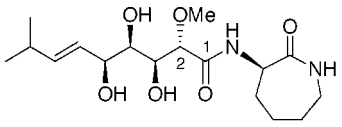
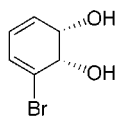


ent-**1**



3

Discussion

The early stages of our synthetic approach to the tris-TBS-ether of carboxylic acid **2** involved formation of bromoconduritol **7** by the route shown in Scheme 1. Thus, epoxidation of the well-known[5] and readily available acetonide derivative, **4**, of diol **3** with *m*-chloroperbenzoic acid afforded the previously reported[5,6] epoxide **5** (95%) in a fully regio- and diastereoselective manner. Treat-

(1) (a) Quinoa, E.; Adamczeski, M.; Crews, P.; Bakus, G. J. *J. Org. Chem.* **1986**, *51*, 4494. (b) Adamczeski, M.; Quinoa, E.; Crews, P. *J. Am. Chem. Soc.* **1989**, *111*, 647. (c) Adamczeski, M.; Quinoa, E.; Crews, P. *J. Org. Chem.* **1990**, *55*, 240. (d) Rudi, A.; Kashman, Y.; Benayahu, Y.; Schleyer, M. *J. Nat. Prod.* **1994**, *57*, 829. (e) D'Auria, M. V.; Giannini, C.; Minale, L.; Zampella, A.; Debitus, C.; Frostin, M. *J. Nat. Prod.* **1997**, *60*, 814. (f) Fernandez, R.; Dherbomez, M.; Letourneux, Y.; Nabil, M.; Verbist, J. F.; Biard, J. F. *J. Nat. Prod.* **1999**, *62*, 678. (g) Groweiss, A.; Newcomer, J. J.; O'Keefe, B. R.; Blackman, A.; Boyd, M. R. *J. Nat. Prod.* **1999**, *62*, 1691. (h) Thale, Z.; Kinder, F. R.; Bair, K. W.; Bontempo, J.; Czuchta, A. M.; Versace, R. W.; Phillips, P. E.; Sanders, M. L.; Wattanasin, S.; Crews, P. *J. Org. Chem.* **2001**, *66*, 1733.

(2) (a) Chida, N.; Tobe, T.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 1063. (b) Gurjar, M. K.; Srinivas, N. R. *Tetrahedron Lett.* **1991**, *32*, 3409. (c) Broka, C. A.; Ehrler, J. *Tetrahedron Lett.* **1991**, *32*, 5907. (d) Kishimoto, H.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1992**, *57*, 5042. (e) Chida, N.; Tobe, T.; Okada, S.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1064. (f) Marshall, J. A.; Luke, G. P. *J. Org. Chem.* **1993**, *58*, 6229. (g) Mukai, C.; Kataoka, O.; Hanaoka, M. *Tetrahedron Lett.* **1994**, *35*, 6899. (h) Chida, N.; Tobe, T.; Murai, K.; Yamazaki, K.; Ogawa, S. *Heterocycles* **1994**, *38*, 2383. (i) Mukai, C.; Kataoka, O.; Hanaoka, M. *J. Org. Chem.* **1995**, *60*, 5910. (j) Mukai, C.; Moharram, S. M.; Kataoka, O.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2849. (k) Mukai, C.; Hanaoka, M. *Synlett* **1996**, 11. (l) Chida, N.; Ogawa, S. *Chem. Commun.* **1997**, 807. (m) Kinder, F. R., Jr.; Wattanasin, S.; Versace, R. W.; Bair, K. W.; Bontempo, J.; Green, M. A.; Lu, Y. J.; Marepalli, H. R.; Phillips, P. E.; Roche, D.; Tran, L. D.; Wang, R.; Waykole, L.; Xu, D. D.; Zabludoff, S. *J. Org. Chem.* **2001**, *66*, 2118.

(3) For a very useful review on the preparation and utilization of this and related *cis*-1,2-dihydrocatechols, see: Hudlicky, T.; Gonzales, D.; Gibson, D. T. *Aldrichim. Acta* **1999**, *32*, 35.

(4) Hudlicky, T.; Claeboe, C. D.; Brammer, L. E., Jr.; Koroniak, L.; Butora, G.; Ghiviriga, I. *J. Org. Chem.* **1999**, *64*, 4909.

(5) Hudlicky, T.; Abboud, K. A.; Bolonick, J.; Maurya, R.; Stanton, M. L.; Thorpe, A. J. *Chem. Commun.* **1996**, 1717.

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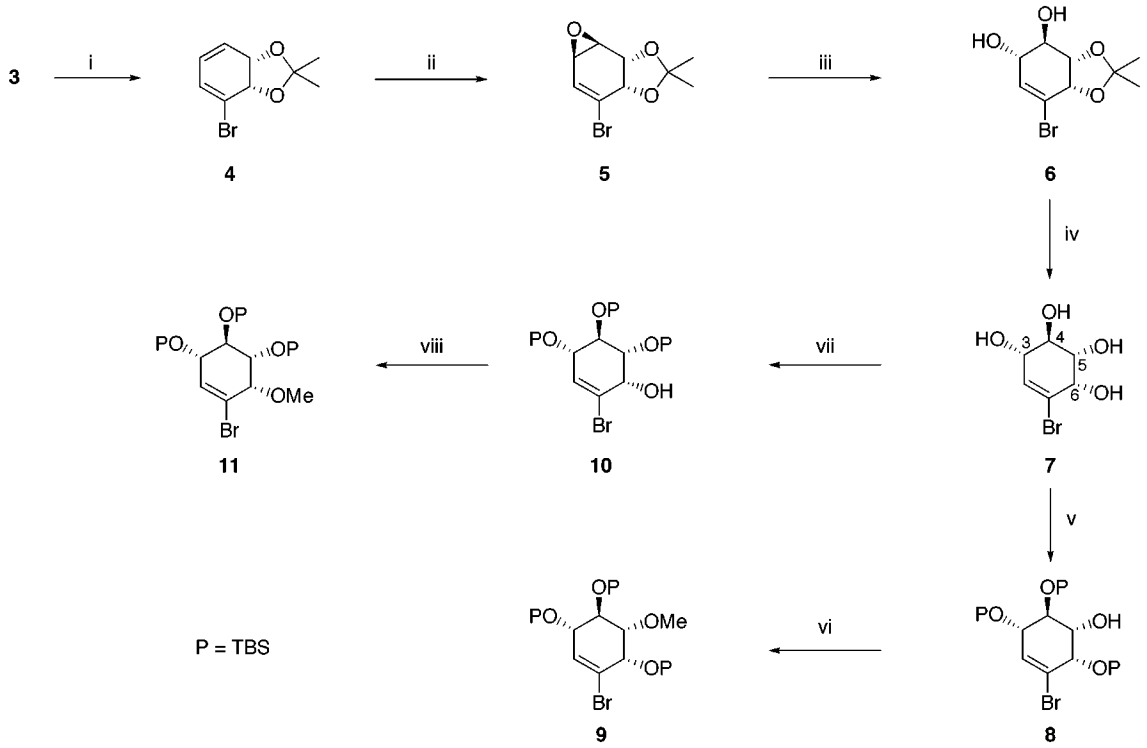
Scheme 1[a]



[a] Reagents and conditions: (i) $Me_2C(OMe)_2$ (neat), *p*-TsOH (catalyst), 18 °C, 1 h; (ii) *m*-CPBA (1.0 molar equiv), CH_2Cl_2, 0−18 °C, 15 h; (iii) HCl (catalyst), THF−H_2O (2:1), 18 °C, 24 h; (iv) AcOH-THF−H_2O (2:1:1), 60 °C, 15 h; (v) TBSCl (4.0 molar equiv), imidazole (8.0 molar equiv), DMF, 50 °C, 24 h; (vi) MeOTf (6.0 molar equiv), 2,6-di-*tert*-butyl-4-methylpyridine (7.0 molar equiv), CH_2Cl_2, 90 °C, 4 h; (vii) TBSOTf (4.0 molar equiv), 2,6-lutidine (10.0 molar equiv), CH_2Cl_2, −40 °C, 3.5 h; (viii) Ag_2O (9.0 molar equiv), MeI (neat), 110 °C, 24 h.

ment of the last compound with 1% HCl in 2:1 (v/v) THF−water resulted in smooth and completely regioselective epoxide ring opening[6] so as to deliver *trans*-diol **6** (92%),[7] which was immediately subjected to acetonide hydrolysis using aqueous acetic acid. In this manner, the bromo derivative **7** of (−)-conduritol F was obtained as a crystalline solid in 90% yield. We reasoned that it should be possible to effect selective silylation of the C-3, C-4 and C-5 hydroxyl groups within conduritol **7** because their C-6 counterpart is sterically shielded by the flanking bromine and cis-related C-5 hydroxyl group.

This selective protection would afford a tris-silyl ether that could be O-methylated (at C-6) and thereby allowing for regiocontrolled introduction of the C-2 (bengamide numbering) methoxy group as required in target **2**. In the event, treatment of tetra-ol **7** with *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole in DMF at 50 °C for 24 h resulted in the formation of the undesired tris-silyl ether derivative **8** (70%), the structure of which follows from extensive NMR spectroscopic analysis[8] of the derived *O*-methyl ether **9** (87%) which is readily prepared using methyl triflate. In contrast, when tetra-ol **7** was reacted with TBSOTf and 2,6-lutidine in DCM at −40 °C for 3.5 h then the required tris-ether **10** (70%) was obtained as the major product of reaction. O-Methylation of compound **10** under Irvine-Purdie conditions[9] then afforded the required ether **11** (95%).[10] The reaction sequence (Scheme 1) leading from diol **3** to ether **11**, which embodies C-1 to C-6 of target *ent*-**1**, is a rather efficient process that allows for the generation of substantial quantities of the latter compound.

The completion of the synthesis of *ent*-bengamide E (*ent*-**1**) is outlined in Scheme 2 and involves initial treatment of a methanolic solution of bromoalkene **11** with ozone followed by a reductive workup using dimethyl sulfide. The resulting aldehyde ester **12** was immediately subjected to a Julia olefination reaction[11] using the anion derived from 2-[(2-methylpropyl)sulfonyl]benzothiazole,[12] and in this manner, alkene **13** (62% ex bromoalkene **11**) contaminated with less than 2% of the corresponding *Z*-isomer was obtained. LiOH-promoted

(6) Banwell, M. G.; Haddad, N.; Hudlicky, T.; Nugent, T. C.; Mackay, M. F.; Richards, S. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1779.

(7) Banwell, M. G.; De Savi, C.; Hockless, D. C. R.; Pallich, S.; Watson, K. G. *Synlett* **1999**, 885.

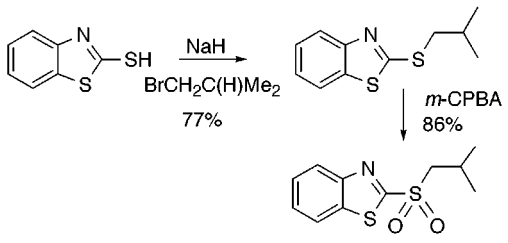
(8) In particular, a series of 1D nOe, HMBC and HMQC experiments was carried out to establish the structures of compounds **9** and **11**.

(9) Purdie, T.; Irvine, J. C. *J. Chem. Soc.* **1903**, *83*, 1021.

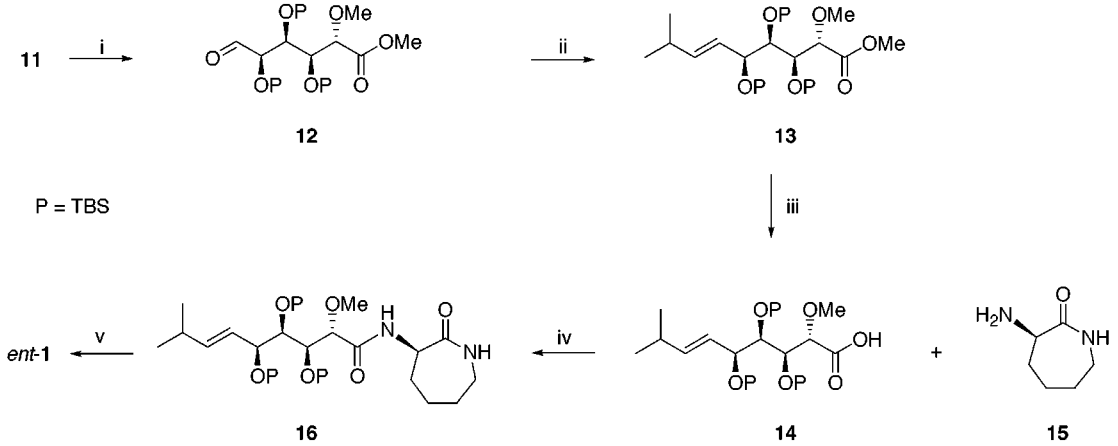
(10) It is assumed that compound **8** is the thermodynamic product of tris-silylation of tetra-ol **7** while isomer **10** is the kinetic product of the same process.

(11) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856.

(12) Gayral, P.; Bourdais, J.; Lorre, A.; Abenhaim, D.; Dusset, F.; Pommies, M.; Fouret, G. *Eur. J. Med. Chem.-Chim. Ther.* **1978**, *13*, 171 (*Chem. Abstr.* **1978**, *89*, 109204). For the purposes of the present work this sulfone was made by the following two-step sequence:



Scheme 2[a]



[a] Reagents and conditions: (i) ozone (excess), pyridine (20.0 molar equiv), MeOH−CH_2Cl_2 (1:1), −78 °C, 0.33 h then DMS (excess), 18 °C, 12 h; (ii) Compound **12** (1.0 molar equiv), 2-[(2-methylpropyl)sulfonyl]benzothiazole (1.3 molar equiv), LiHMDS (1.1 molar equiv of a 1 M solution in THF), DME, −78 to +18 °C, 1.5 h; (iii) LiOH (4.0 molar equiv), THF−MeOH (4:1), reflux, 4 h; (iv) HOBt (1.2 molar equiv), EDCI (1.2 molar equiv), compound **14** (1.0 molar equiv), DMF, 18 °C, 0.33 h then compound **15** (1.5 molar equiv), DMF, 0−18 °C, 16 h; (v) TBAF (6.5 molar equiv of a 1 M solution in THF), THF, 18 °C, 1.5 h.

saponification of this material gave, after acidic workup, the corresponding acid **14** (63% at 53% conversion). The derived NMR spectral data matched those reported for its well-characterized enantiomer, which represents a late-stage intermediate in Broka's synthesis[2c] of bengamide E.

Coupling of acid **14** with readily available D-(+)-α-amino-ϵ-caprolactam (**15**)[13] was achieved using HOBt−EDCI[14] and the amide **16** thereby obtained in 72% yield. Treatment of this amide with TBAF in THF resulted in smooth and complete desilylation and formation of *ent*-bengamide E (*ent*-**1**), which was obtained in 86% yield. The ^{1}H and ^{13}C NMR data derived from compound *ent*-**1** matched those reported[1b] for the natural product while the specific rotation {$[\alpha]_D$ −32 (*c* 0.2, MeOH)} was of the opposite sign but of essentially the same magnitude as observed[1b] for bengamide E.

ent-Bengamide E was tested in a monolayer cell proliferation assay using A549 nonsmall cell lung cancer cells, HCT116 colon cancer cells, and primary human umbilical vein endothelial cells.[1h] For all three cell types, there was no growth inhibition observed at concentrations up to 50 μM. For comparison purposes, the IC_{50} values for bengamide E in this format are 1.9, 0.6, and 0.3 μM, respectively.

Experimental Section

General Procedures. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300 or Varian Mercury 300 spectrometer operating at 300 MHz for proton and 75.4 MHz for carbon nuclei. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in deuteriochloroform ($CDCl_3$) at 20 °C unless otherwise stated. For ^{1}H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ 7.26) was used as the internal reference. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J = (Hz), relative integral, assignment (where possible)] where multiplicity is defined as follows: s = singlet; d = doublet; t = triplet; q = quartet; quintet; septet; m = multiplet or combinations of the above. The central peak (δ 77.0) of the $CDCl_3$ triplet was used as the reference for proton-decoupled ^{13}C NMR spectra. For ^{13}C NMR spectra the data are given as: chemical shift (δ) (protonicity), where protonicity is defined as follows: C = quaternary; CH = methine; CH_2 = methylene; CH_3 = methyl; C or CH_2 = quaternary or methylene; CH or CH_3 = methine or methyl. The assignments of signals observed in various NMR spectra were often assisted by conducting attached proton test (APT), homonuclear (^{1}H/^{1}H) correlation spectroscopy (COSY), nuclear Overhauser effect (NOE), and/or heteronuclear (^{1}H/^{13}C) correlation spectroscopy (HETCOR) experiments.

Infrared spectra (ν_{max}) were recorded on either a Perkin-Elmer 1800 Fourier transform infrared spectrophotometer or a Perkin-Elmer Spectrum *One* instrument. Samples were analyzed as KBr disks (for solids) or as thin films on KBr plates (for liquids/oils).

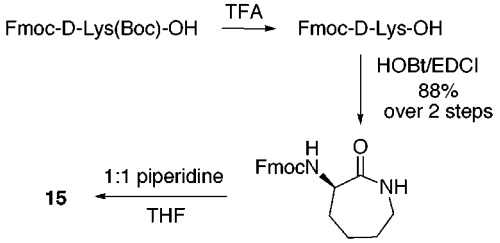
Optical rotations were measured with a Perkin-Elmer 241 polarimeter at the sodium D line (589 nm) using the spectroscopic grade solvents specified at 20 °C and at the concentrations (*c*) (g/100 mL) indicated. The measurements were carried out in a cell with a path length of 1 dm. Specific rotations ($[\alpha]^{20}_D$) were calculated using the equation $[\alpha]_D = (100\alpha)/(c1)$ and are given in 10^{-1} deg·cm^2·g^{-1}.

Melting points were recorded on a Reichert hot-stage apparatus and are uncorrected except where otherwise stated.

Elemental analyses were performed by the Australian National University Microanalytical Services Unit based in the Research School of Chemistry, The Australian National University, Canberra, Australia.

Analytical thin-layer chromatography (TLC) was conducted on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates (Merck) and the chromatograms were visualized under a 254 nm UV lamp and/or by treatment with an anisaldehyde-sulfuric acid-ethanol (3 mL: 4.5 mL: 200 mL) dip or, occasionally, with a phosphomolybdic acid−ceric sulfate−sulfuric acid−water (37.5 g: 7.5 g: 37.5 mL: 720 mL) dip, followed by heating. The retention factor (R_f) quoted is rounded to the nearest 0.1. Flash chromatography was conducted according to the method

(13) Boyle, W. J., Jr.; Sifniades, S.; Van Peppen, J. F. *J. Org. Chem.* **1979**, *44*, 4841. For the purposes of the present work this α-amino-caprolactam was made by the following three-step sequence. The starting material was purchased from Auspep (Melbourne, Australia; www.auspep.com.au).



(14) Fields, G. B.; Noble, R. L. *Int. J. Pept. Protein Res.* **1990**, *35*, 161.

of Still and co-workers (Still, W. C. et al. *J. Org. Chem*. **1978**, *43*, 2923) using silica gel 60 (mesh size 0.040−0.063 mm) as the stationary phase and the analytical reagent (AR) grade solvents indicated.

Many starting materials and reagents were available from the Aldrich Chemical Co. or EGA-Chemie and were used as supplied or simply distilled. Drying agents and other inorganic salts were purchased from AJAX or BDH Chemicals. Reactions employing air- and/or moisture-sensitive reagents and intermediates were carried out under an atmosphere of dry, oxygen-free nitrogen in flame-dried apparatus.

Room temperature is assumed to be ca. 18 °C.

Tetrahydrofuran and diethyl ether were dried using sodium metal and then distilled, as required, from sodium benzophenone ketyl. Methanol was distilled from magnesium methoxide. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Ethylene glycol dimethyl ether (DME) was refluxed over calcium hydride then distilled, as required, from sodium benzophenone ketyl. *N*,*N*-dimethylformamide (DMF) was heated at reflux over calcium hydride for 16 h then distilled and stored over 3 Å molecular sieves.

Organic solutions obtained from workup of reaction mixtures were dried with magnesium sulfate ($MgSO_4$). Petrol refers to petroleum spirits boiling in the range 40−60 °C unless otherwise specified. Organic solutions were concentrated under reduced pressure on a rotary evaporator with the water bath generally not exceeding 40 °C.

(3a*S*,4*R*,5*S*,7a*S*)-7-Bromo-3a,4,5,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxole-4,5-diol (6). HCl (1.5 mL of a 1% v/v solution of concd HCl in THF) was added to a magnetically stirred solution of epoxide **5** (7.80 g, 31.5 mmol) in THF−water (90 mL of a 2:1 v/v mixture). The resulting solution was stirred at 18 °C for 24 h then concentrated under reduced pressure. The residue thus obtained was partitioned between ethyl acetate (200 mL) and NaCl (200 mL of a 50% w/v aqueous solution). The separated aqueous phase was extracted with ethyl acetate (3 × 200 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a white solid. Recrystallization (dichloromethane−hexane) of this material gave the title compound **6** (7.80 g, 92%) as fine white needles: mp 146−147 °C (lit.[7] mp 147 °C); $[\alpha]_D$ −1.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz) δ 6.26 (d, J = 2.7 Hz, 1H), 4.68 (d, J = 6.1 Hz, 1H), 4.20 (dd, J = 7.6 and 6.1 Hz, 1H), 4.09 (m, 1H), 3.77 (td, J = 7.6 and 3.2 Hz, 1H), 2.73 (d, J = 6.1 Hz, 1H), 2.71 (d, J = 3.4 Hz, 1H), 1.54 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz) δ 134.5 (CH), 119.2 (C), 111.1 (C), 77.5 (CH), 77.1 (CH), 73.3 (CH), 70.9 (CH), 28.0 (CH_3), 25.9 (CH_3); IR ν_{max} 3501, 3363, 2984, 1645, 1257, 1082, 1050, 871 cm^{-1}; MS (70 eV) *m*/*z* 251 and 249 [$(M - H_3C^{\bullet})^+$, 96 and 100], 110 (63), 101 (58); HRMS calcd for $C_9H_{13}{}^{79}BrO_4$ $(M - H_3C^{\bullet})^+$ 248.9762, found 248.9764. Anal. Calcd for $C_9H_{13}BrO_4$: C, 40.78; H, 4.94; Br, 30.14. Found: C, 40.80; H, 4.71; Br, 30.18.

(1*S*,2*R*,3*S*,4*S*)-5-Bromo-5-cyclohexene-1,2,3,4-tetrol (7). A solution of compound **6** (1.00 g, 3.77 mmol) in AcOH−THF−water (25 mL of a 2:1:1 v/v/v mixture) was stirred at 60 °C for 15 h, and then the cooled reaction mixture was concentrated under reduced pressure to give a white solid (this material could be used, without further purification, in the next step of the reaction sequence). Recrystallization (MeOH−diethyl ether) of this material provided an analytically pure sample of compound **7** (763 mg, 90%) as a white powder: mp 164−166 °C; $[\alpha]_D$ −44 (*c* 1.1, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 6.05 (d, J = 2.6 Hz, 1H), 4.21 (d, J = 4.2 Hz, 1H), 3.89 (dd, J = 7.4, 2.6 Hz, 1H), 3.60 (dd, J = 10.5, 7.4 Hz, 1H), 3.50 (dd, J = 10.5, 4.2 Hz, 1H) (resonances due to OHs not observed); ^{13}C NMR (75 MHz, CD_3OD) δ 135.2 (CH), 124.4 (C), 74.7 (CH), 74.1 (CH), 73.0 (CH), 72.4 (CH); IR ν_{max} 3350, 2914, 1640, 1412, 1262, 1103, 1066 cm^{-1}; MS (70 eV) *m*/*z* 208 and 206 [$(M - H_2O)^{\bullet+}$, 1 and 1], 190 and 188 [$(M - 2H_2O)^{\bullet+}$, 2 and 2], 179 and 177 (12 and 13), 166 and 164 [$(C_4H_5O_2Br)^{\bullet+}$, 94 and 100]; HRMS calcd for $C_6H_9{}^{79}BrO_4$ $(M-H_2O)^{\bullet+}$ 205.9579, found 205.9581. Anal. Calcd for $C_6H_9BrO_4$: C, 32.02; H, 4.03; Br, 35.51. Found: C, 32.20; H, 4.14; Br, 35.43.

(1*S*,2*S*,5*S*,6*R*)-3-Bromo-2,5,6-*tris*-[(1,1-dimethylethyl)-dimethylsiloxy)-3-cyclohexen-1-ol (8). *tert*-Butyldimethylsilyl chloride (984 mg, 6.51 mmol) was added to a magnetically stirred solution of compound **7** (366 mg, 1.63 mmol) and imidazole (886 mg, 13.04 mmol) in anhydrous DMF (3.5 mL) maintained at room temperature under an atmosphere of nitrogen. After 24 h at 50 °C, the reaction mixture was diluted with water (20 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with HCl (1 × 50 mL of a 5% v/v aqueous solution), water (1 × 50 mL), and brine (1 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale yellow oil. Subjection of this material to flash chromatography (silica, 10 → 50% v/v toluene−petrol elution) provided, after concentration of the appropriate fractions (R_f 0.2 in 2% v/v ethyl acetate−petrol), compound **8** (648 mg, 70%) as a clear, colorless oil: $[\alpha]_D$ +10 (*c* 1.9, $CHCl_3$); ^{1}H NMR (300 MHz) δ 6.04 (m, 1H), 4.42 (d, J = 4.1 Hz, 1H), 3.95 (m, 2H), 3.74 (m, 1H), 2.91 (br d, J = 7.1 Hz, 1H), 0.95 (s, 9H), 0.89(3) (s, 9H), 0.89 (s, 9H), 0.21 (s, 3H), 0.15 (s, 3H), 0.11 (s, 3H), 0.10 (s, 9H); ^{13}C NMR (75 MHz) δ 130.7 (CH), 127.1 (C), 72.9 (CH), 72.6 (2 × CH, overlapping), 72.1 (CH), 25.9 (CH_3), 25.8(5) (CH_3), 25.7(8) (CH_3), 18.5 (C), 18.1 (C), 18.0 (C), −4.2(7) (CH_3), −4.3(7) (CH_3), −4.4(5) (CH_3), −4.5 (CH_3), −4.6 (2 × CH_3 overlapping); IR ν_{max} 3582, 2930, 2858, 1641, 1472, 1362, 1254, 1100, 837, 778 cm^{-1}; MS (70 eV) *m*/*z* 553 and 551 [$(M - H_3C^{\bullet})^+$, <1 and <1], 511 and 509 {[$M - (CH_3)_3C^{\bullet}]^+$, 5 and 4}, 73 (100); HRMS calcd for $C_{24}H_{51}{}^{79}BrO_4Si_3$ [M-$(CH_3)_3C^{\bullet}]^+$ 509.1574, found 509.1583. Anal. Calcd for $C_{24}H_{51}BrO_4Si_3$: C, 50.77; H, 9.05; Br, 14.07. Found: C, 50.70; H, 9.10; Br, 14.07.

(3*S*,4*R*,5*S*,6*S*)-1-Bromo-3,4,6-*tris*-[(1,1-dimethylethyl)-dimethylsiloxy)-5-methoxycyclohexene (9). A solution of compound **8** (84 mg, 0.15 mmol) in dichloromethane (0.5 mL) was treated with 2,6-di-*tert*-butyl-4-methylpyridine (210 mg, 1.05 mmol) and methyl trifluoromethanesulfonate (101 μL, 0.90 mmol) and heated to 90 °C in a sealed tube. After 4 h, the reaction mixture was to cooled to 18 °C, poured into water (5 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with HCl (1 × 10 mL of a 5% v/v aqueous solution), water (1 × 10 mL), and brine (1 × 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale yellow oil. Subjection of this material to flash chromatography (silica, 10→25% v/v toluene-petrol elution) provided, after concentration of the appropriate fractions (R_f 0.6 in 25% v/v toluene−petrol), compound **9** (76 mg, 87%) as a clear, colorless oil: $[\alpha]_D$ −20 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz) δ 5.92 (d, J = 2.8 Hz, 1H), 4.36 (d, J = 3.3 Hz, 1H), 4.00 (dd, J = 6.5, 2.8 Hz, 1H), 3.91 (dd, J = 9.5, 6.5 Hz, 1H), 3.35 (s, 3H), 3.00 (dd, J = 9.5, 3.3 Hz, 1H), 0.92 (s, 9H), 0.90 (s, 18H), 0.13 (s, 3H), 0.10 (s, 6H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz) δ 133.8 (CH), 123.5 (C), 82.1 (CH), 75.5 (CH), 72.3 (CH), 72.2 (CH), 57.9 (CH_3), 26.2 (CH_3), 26.1 (CH_3), 25.9 (CH_3), 18.4 (C), 18.2 (C), 18.1(8) (C), −3.7 (CH_3), −3.8 (CH_3), −4.0 (CH_3), −4.2 (CH_3), −4.4 (2 × CH_3 overlapping); IR ν_{max} 2954, 1646, 1472, 1463, 1361, 1253, 1114, 956, 836, 778 cm^{-1}; MS (70 eV) *m*/*z* 567 and 565 [$(M - H_3C^{\bullet})^+$, <1 and <1], 525 and 523 {[$M - (CH_3)_3C^{\bullet}]^+$, 28 and 25}, 73 (100); HRMS calcd for $C_{25}H_{53}{}^{79}BrO_4Si_3$ $(M - H_3C^{\bullet})^+$ 565.2200, found 565.2202.

(1*S*,4*S*,5*R*,6*S*)-2-Bromo-4,5,6-*tris*-[(1,1-dimethylethyl)-dimethylsiloxy)-2-cyclohexen-1-ol (10). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (8.16 mL, 35.2 mmol) was added to a magnetically stirred solution of compound **7** (2.0 g, 8.9 mmol) and 2,6-lutidine (10.2 mL, 88.0 mmol) in anhydrous dichloromethane (88 mL) maintained at −40 °C under an atmosphere of nitrogen. After 3.5 h, the reaction mixture was poured into HCl (50 mL of a 5% v/v aqueous solution) and then extracted with diethyl ether (3 × 200 mL). The combined organic phases were washed with water (1 × 300 mL) and brine (1 × 300 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale yellow oil. Subjection of this material to flash chromatography (silica, 25% v/v toluene−petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.2 in 2% v/v ethyl acetate−petrol), compound **10** (3.50 g, 70%) as crystalline masses: mp

60−62 °C; $[\alpha]_D$ +35 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz) δ 6.03 (dm, J = 4.2 Hz, 1H), 4.22 (dm, J = 9.8 Hz, 1H), 3.96 (m, 1H), 3.94−3.86 (complex m, 2H), 2.47 (d, J = 9.8 Hz, 1H), 0.92 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.09 (m, 9H), 0.08 (s, 3H); ^{13}C NMR (75 MHz) δ 131.0 (CH), 126.2 (C), 73.3 (CH), 73.1 (CH), 72.0 (CH), 69.0 (CH), 26.1 (CH_3), 26.0 (CH_3), 25.8 (CH_3), 18.3(3) (C), 18.2(5) (C), 17.9 (C), −3.8 (CH_3), −4.3 (CH_3), −4.4 (CH_3), −4.5 (2 × CH_3 overlapping), −4.9 (CH_3); IR ν_{max} 3564, 2930, 1644, 1472, 1255, 1086, 836 cm^{-1}; MS (70 eV) *m*/*z* 553 and 551 [(M−$H_3C^•$)$^+$, <1 and <1], 511 and 509 {[M − $(CH_3)_3C^•$]$^+$, 10 and 8}, 288 (40), 73 (100); HRMS calcd for $C_{24}H_{51}{}^{79}BrO_4Si_3$: (M − H_2O)$^{•+}$ 548.2173, found 548.2176. Anal. Calcd for $C_{24}H_{51}BrO_4Si_3$: C, 50.77; H, 9.05; Br, 14.07. Found: C, 50.65; H, 8.92; Br, 14.27.

(3*S*,4*R*,5*S*,6*S*)-1-Bromo-3,4,5-*tris*-[(1,1-dimethylethyl)-dimethylsiloxy)-6-methoxycyclohexene (11). A solution of compound **10** (300 mg, 0.53 mmol) in iodomethane (4 mL) was treated with Ag_2O (367 mg, 1.58 mmol) and heated to 110 °C in a sealed tube. After 8 h, the reaction mixture was allowed to cool to 18 °C and then treated with extra Ag_2O (367 mg, 1.58 mmol). The reaction mixture was again heated at 110 °C for 8 h. This procedure was repeated for a third time, and 8 h after the final addition of Ag_2O the reaction mixture was cooled to 18 °C and the solid material removed by filtration. The filtrate thus obtained was concentrated under reduced pressure to afford a pale yellow oil that was subjected to flash chromatography (silica, 2% v/v ethyl acetate-petrol elution). Concentration of the appropriate fractions (R_f 0.4) then provided compound **11** (292 mg, 95%) as a clear, colorless oil: $[\alpha]_D$ +16 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz) δ 5.97 (m, 1H), 3.92 (m, 1H), 3.86 (m, 2H), 3.81 (m, 1H), 3.52 (s, 3H), 0.89(3) (s, 18H), 0.88(7) (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (75 MHz) δ 131.4 (CH), 123.5 (C), 79.6 (CH), 74.4 (CH), 74.2 (CH), 70.7 (CH), 59.5 (CH_3), 26.1 (CH_3), 26.0 (CH_3), 18.4 (C), 18.3 (C), 18.0 (C), −4.2 (2 × CH_3 overlapping), −4.3 (CH_3), −4.3(9) (CH_3), −4.4(3) (CH_3), −4.5 (CH_3) (one signal obscured or overlapping); IR ν_{max} 2930, 1642, 1472, 1463, 1254, 1152, 1116, 1087, 836 cm^{-1}; MS (70 eV) *m*/*z* 567 and 565 [(M − $H_3C^•$)$^+$, <1 and <1], 525 and 523 {[M − $(CH_3)_3C^•$]$^+$, 28 and 25}, 288 (42), 73 (100); HRMS calcd for $C_{25}H_{53}{}^{81}BrO_4Si_3$ (M − $H_3C^•$)$^+$ 567.2180, found 567.2186.

Methyl 2-*O*-Methyl-3,4,5-tris-*O*-[(1,1-dimethylethyl)-dimethylsilyl]-L-guloronate (12). A magnetically stirred solution of compound **11** (115 mg, 0.20 mmol) in MeOH (2 mL) containing dichloromethane (2 mL) and pyridine (320 μL, 3.95 mmol) was cooled to −78 °C and treated with a stream of ozone (ca. 40% ozone in oxygen). When the green/blue color of ozone persisted and TLC analysis indicated that no starting material remained (ca. 0.33 h), the reaction mixture was purged with nitrogen (20 min), treated with dimethyl sulfide (1 mL), and allowed to warm to 18 °C. After 12 h, the reaction mixture was concentrated under reduced pressure, and the residue thus obtained was treated with water (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with HCl (1 × 10 mL of a 5% v/v aqueous solution), water (2 × 10 mL), and brine (1 × 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford compound **12** (107 mg, 95%) as a light yellow oil: $[\alpha]_D$ +2 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz) δ 9.70 (s, 1H), 4.38 (br d, J = 6.1 Hz, 1H), 4.26 (d, J = 3.7 Hz, 1H), 4.02 (dd, J = 4.4, 3.7 Hz, 1H), 3.92 (dd, J = 6.1, 4.4 Hz, 1H), 3.73 (s, 3H), 3.32 (s, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.84 (s, 9H), 0.11 (s, 3H), 0.08 (s, 6H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz) δ 201.7 (CH), 170.7 (C), 82.3 (CH), 78.0 (CH), 74.9 (CH), 74.3 (CH), 58.1 (CH_3), 51.6 (CH_3), 25.9 (CH_3), 25.8 (CH_3), 18.3 (C), 18.1 (C), 18.0 (C), −4.4 (4 × CH_3 overlapping), −4.6 (2 × CH_3 overlapping) (one signal obscured or overlapping); IR ν_{max} 2930, 1755, 1737, 1472, 1463, 1255, 1197, 1114 cm^{-1}; MS (70 eV) *m*/*z* 549 [(M − $H_3C^•$)$^+$, <1], 533 [(M − $CH_3O^•$)$^+$, 1], 507 {[M − $(CH_3)_3C^•$]$^+$, 7}, 73 (100); HRMS calcd for $C_{26}H_{56}O_7Si_3$: [M − $(CH_3)_3C^•$]$^+$ 507.2630, found 507.2647. Anal. Calcd for $C_{26}H_{56}O_7Si_3$: C, 55.27; H, 9.99. Found: C, 55.35; H, 9.87.

In general, this somewhat unstable material was immediately subjected to the next step of the reaction sequence.

2-[(2-Methylpropyl)sulfonyl]benzothiazole. A magnetically stirred solution of 2-mercaptobenzothiazole (5.00 g, 29.9 mmol) in THF−DMF (80 mL of a 3:1 v/v mixture) and maintained at 0 °C under an atmosphere of nitrogen was treated, portionwise, with sodium hydride (1.55 g of a 60% dispersion in mineral oil, 38.9 mmol). After 0.5 h, the reaction mixture was treated, dropwise, with 1-bromo-2-methylpropane (6.5 mL, 59.8 mmol), and the resulting mixture was allowed to warm to room temperature over 0.5 h before being heated to 50 °C. After 1 h at this temperature, the reaction mixture was cooled and then poured into water (200 mL) and extracted with diethyl ether (3 × 200 mL). The combined organic phases were washed with NaOH (1 × 200 mL of a 1 M aqueous solution), water (2 × 200 mL), and brine (1 × 200 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale yellow oil. Subjection of this material to flash chromatography (silica, 10% v/v ethyl acetate−petrol elution) provided, after concentration of the appropriate fractions (R_f 0.5), 2-[(2-methylpropyl)sulfanyl]benzothiazole (5.1 g, 77%) as a pale yellow oil.

A magnetically stirred solution of 2-[(2-methylpropyl)sulfanyl]benzothiazole (3.00 g, 13.4 mmol), prepared as described above, in dichloromethane (200 mL) maintained at 0 °C was treated, portionwise, with *m*-chloroperbenzoic acid [8.20 g (80% technical grade), 33.6 mmol]. After 14 h at 18 °C, the reaction mixture was treated with sodium sulfite (100 mL of a 15% w/v aqueous solution) and stirred vigorously for 15 min. The resulting solution was extracted with diethyl ether (3 × 200 mL) and the combined organic phases were washed with $NaHCO_3$ (1 × 200 mL of a saturated aqueous solution), water (1 × 200 mL), and brine (1 × 200 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale yellow oil. Subjection of this material to flash chromatography (silica, 10% v/v ethyl acetate-petrol elution) provided, after concentration of the appropriate fractions (R_f 0.2), the title compound (2.94 g, 86%) as a clear, colorless oil that crystallized upon standing. Recrystallization (diethyl ether−hexane) of a portion of this material afforded an analytically pure sample of 2-[(2-methylpropyl)sulfonyl]benzothiazole as white crystals: mp 42−43 °C; ^{1}H NMR (300 MHz) δ 8.22 (m, 1H), 8.02 (m, 1H), 7.62 (m, 2H), 3.44 (d, J = 6.7 Hz, 2H), 2.43 (nonatet, J = 6.7 Hz, 1H), 1.13 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz) δ 166.5 (C), 152.5 (C), 136.5 (C), 127.9 (CH), 127.5 (CH), 125.2 (CH), 122.3 (CH), 61.9 (CH_2), 24.0 (CH), 22.5 (CH_3); IR ν_{max} 2964, 1554, 1470, 1322, 1148, 855, 762, 628 cm^{-1}; MS (70 eV) *m*/*z* 255 (M$^{•+}$, 8), 240 [(M − $H_3C^•$)$^+$, 2], 198 (10), 135 (100); HRMS calcd for $C_{11}H_{13}NO_2{}^{32}S_2$ (M − $H_3C^•$)$^+$ 240.0153, found 240.0156. Anal. Calcd for $C_{11}H_{13}NO_2S_2$: C, 51.74; H, 5.13; N, 5.49. Found: C, 51.62; H, 5.23; N, 5.50.

Methyl (6*E*)-6,7,8,9-Tetradeoxy-3,4,5-tris-*O*-[(1,1-dimethylethyl)dimethylsilyl]-8-methyl-2-*O*-methyl-L-gulonon-6-enonoate (13). A magnetically stirred solution of aldehyde **12** (658 mg, 1.16 mmol) and 2-[(2-methylpropyl)sulfonyl]-benzothiazole (385 mg, 1.51 mmol) in DME (22 mL) maintained under an atmosphere of nitrogen was cooled to −78 °C and then treated with LiHMDS (1.28 of a 1 M solution in THF, 1.28 mmol). After being warmed to 18 °C over 1.5 h, the reaction mixture was treated with HCl (10 mL of a 5% v/v aqueous solution) and extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with NaOH (50 mL of a 1 M aqueous solution) and brine (1 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a light yellow oil. Subjection of this material to flash chromatography (silica, 2% v/v ethyl acetate−petrol elution) provided, after concentration of the appropriate fractions (R_f 0.4), compound **13** (434 mg, 62% ex bromoalkene **11**) as a clear, colorless oil: $[\alpha]_D$ −6 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz) δ 5.57 (m, 2H), 4.52 (br s, 1H), 4.35 (br s, 1H) 3.93 (br s, 2H), 3.71 (s, 3H), 3.31 (s, 3H), 2.32 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz) δ 171.1, 138.6, 126.8, 82.8, 74.8, 74.1, 73.8, 57.8, 51.2, 30.9, 26.2, 26.1, 26.0, 22.3, 22.2, 18.2(4), 18.1(9), −3.6, −3.9, −4.4(8), −4.5(0), −4.6 (two signals overlapping); IR ν_{max} 2954, 1760, 1733, 1472,

1463, 1254, 1110, 837 cm^{-1}; MS (70 eV) *m/z* 589 [$(M - H_3C^{\bullet})^+$, 3], 547 {$[M - (CH_3)_3C^{\bullet}]^+$, 32}, 359 (90), 213 (71), 73 (100); HRMS calcd for $C_{30}H_{64}O_6Si_3$ $(M - H_3C^{\bullet})^+$ 589.3776, found 589.3773.

(6*E*)-6,7,8,9-Tetradeoxy-3,4,5-tris-*O*-[(1,1-dimethylethyl)dimethylsilyl]-8-methyl-2-*O*-methyl-L-gulonon-6-enonic acid (14). A magnetically stirred solution of ester **13** (100 mg, 0.17 mmol) in THF (4 mL) containing MeOH (1 mL) was treated with LiOH (680 μL of a 1 M aqueous solution, 0.68 mmol). After 4 h at reflux, the cooled reaction mixture was treated with HCl (10 mL of a 5% v/v aqueous solution) and then extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 20 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a light yellow oil. Subjection of this material to flash chromatography (silica, 20% v/v ethyl acetate−petrol elution) then provided two fractions, A and B.

Concentration of fraction A (R_f 0.5) afforded acid **14** (33 mg, 63% at 53% conversion) as a clear, colorless oil: $[\alpha]_D$ +5 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz) δ 10.03 (br s, 1H), 5.65 (m, 2H), 4.46 (m, 1H), 4.32 (d, J = 1.7 Hz, 1H), 3.98 (dd, J = 7.5, 1.7 Hz, 1H), 3.81 (dd, J = 7.5, 3.0 Hz, 1 H), 3.38 (s, 3H), 2.33 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.93 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 2 × CH_3 overlapping, 6H), 0.06 (s, 3H); ^{13}C NMR (75 MHz) δ 170.2 (C), 140.0 (CH), 125.8 (CH), 82.2 (CH), 75.0 (CH), 73.9 (CH), 73.5 (CH), 58.0 (CH_3), 30.9 (CH), 26.1 (CH_3), 26.0 (CH_3), 22.1 (2 × CH_3), 18.4 (C), 18.1(9) (C), 18.1(7) (C), −3.7 (CH_3), −3.8 (CH_3), −3.9 (CH_3), −4.6 (3 × CH_3 overlapping) (one signal obscured); IR ν_{max} 2955, 1720, 1463, 1362, 1254, 1110, 938, 836, 776, 671 cm^{-1}; MS (70 eV) *m/z* 533 {$[M - (CH_3)_3C^{\bullet}]^+$, 2}, 213 (69), 201 (58), 73 (100); HRMS calcd for $C_{29}H_{62}O_6Si_3$: $[M - (CH_3)_3C^{\bullet}]^+$ 533.3150, found 533.3155.

Concentration of fraction B (R_f 0.4) afforded ester **13** (47 mg, 47% recovery) which proved identical with an authentic sample.

9*H*-Fluoren-9-ylmethyl (*R*)-hexahydro-2-oxo-1*H*-azepin-3-ylcarbamate. A magnetically stirred solution of Fmoc-D-Lys(Boc)-OH (700 mg, 1.49 mmol) in dichloromethane (15 mL) maintained at 0 °C under an atmosphere of nitrogen was treated with TFA (15 mL), in a dropwise manner and over a period of 5 min. After 0.5 h, the reaction mixture was diluted with toluene (20 mL) and then concentrated under reduced pressure to afford a light yellow solid. This material was dissolved in water (10 mL), cooled to −78 °C, and then freeze-dried for 12 h to afford Fmoc-D-Lys-OH·TFA (719 mg, 100%) as a white flocculent solid. This material was used, without purification, in the next step of the reaction sequence. Thus, a magnetically stirred solution of the above-mentioned TFA.salt (719 mg, 1.49 mmol) in dichloromethane (57 mL) containing DMF (14 mL) and maintained at 18 °C under an atmosphere of nitrogen was treated with Hünig's base (287 μL, 1.1 mmol). After 10 min, the resulting white suspension was cooled to 0 °C and treated with 1-hydroxybenzotriazole (HOBt) hydrate (243.6 mg, 1.79 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (343.8 mg, 1.79 mmol). After 16 h at 18 °C, the reaction mixture was diluted with tartaric acid (20 mL of a 1 M aqueous solution) then extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with $NaHCO_3$ (1 × 50 mL of a saturated aqueous solution), water (1 × 50 mL), and brine (1 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a light yellow oil. Subjection of this material to flash chromatography (silica, 1:98:1 v/v/v MeOH−chloroform−NEt_3 elution) provided, after concentration of the appropriate fractions (R_f 0.5), Fmoc-D-(+)-α-amino-ϵ-caprolactam (460 mg, 88%) as a white powder: mp 115−117 °C; ^{1}H NMR (300 MHz) δ 7.77 (d, J = 7.5 Hz, 2H), 7.64 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 6.90 (m, 1H), 6.31 (br d, J = 6.0 Hz, 1H), 4.38 (m, 3H), 4.25 (m, 1H), 3.26 (m, 2H), 2.12 (br d, J = 12.6 Hz, 1H), 2.04 (m, 1H), 1.85−1.37 (complex m, 4H); ^{13}C NMR (75 MHz) δ 175.5 (C), 155.4 (C), 143.8 (C), 141.1 (C), 127.5 (CH), 126.9 (CH), 125.1 (CH), 119.8 (CH), 66.8 (CH_2), 53.5 (CH), 47.1 (CH), 41.9 (CH_2), 31.9 (CH_2), 28.7 (CH_2), 27.9 (CH_2); IR ν_{max} 3395, 3300, 2928, 1710, 1669, 1477, 1449, 1364, 1249, 1211, 1049, 738 cm^{-1}; MS (70 eV) *m/z* 350 ($M^{\bullet+}$, 1), 178 (100); HRMS calcd for $C_{21}H_{22}N_2O_3$ $M^{\bullet+}$ 350.1630, found 350.1627.

(6*E*)-6,7,8,9-Tetradeoxy-3,4,5-tris-*O*-[(1,1-dimethylethyl)dimethylsilyl]-*N*-[(3*R*)-hexahydro-2-oxo-1*H*-azepin-3-yl]-8-methyl-2-*O*-methyl-L-gulonon-6-enonamide (16). A magnetically stirred solution of the Fmoc-D-(+)-α-amino-ϵ-caprolactam (22 mg, 0.06 mmol) in THF (1 mL) maintained at 18 °C under a nitrogen atmosphere was treated with piperidine (1 mL). After 3 h, the reaction mixture was concentrated under reduced pressure to afford D-(+)-α-amino-ϵ-caprolactam (**15**)[14] as a pale yellow solid that was used, without purification, in the next step of the reaction sequence.

A magnetically stirred solution of compound **14** (25 mg, 0.04 mmol) in DMF (1 mL) maintained at room temperature under an atmosphere of nitrogen was treated with 1-hydroxybenzotriazole (HOBt) hydrate (7.0 mg, 0.05 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (9.8 mg, 0.05 mmol). After 0.33 h, the reaction mixture was cooled to 0 °C and treated, dropwise and via cannula, with a solution of D-(+)-α-amino-ϵ-caprolactam (22 mg) in DMF (1 mL). After 16 h at room temperature, the reaction mixture was diluted with HCl (2 mL of a 5% v/v aqueous solution) and extracted with diethyl ether (3 × 5 mL). The combined organic phases were washed with water (1 × 5 mL) and brine (1 × 5 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a light yellow oil. Subjection of this material to flash chromatography (silica, 1:98:1 v/v/v MeOH−chloroform−NEt_3 elution) provided, after concentration of the appropriate fractions (R_f 0.5), compound **16** (21 mg, 72%) as a clear, colorless oil: $[\alpha]_D$ −41 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.85 (d, J = 5.7 Hz, 1H), 6.05 (m, 1H), 5.61 (m, 2H), 4.47 (m, 1H), 4.26−4.17 (complex m, 3H), 4.01 (dd, J = 7.5, 1.5 Hz, 1H), 3.35 (s, 3H), 3.28−3.20 (complex m, 2H), 2.32 (m, 1H), 2.13 (m, 1H), 1.96−1.76 (complex m, 4H), 1.53−1.28 (complex m, 2H), 1.01 (d, J = 6.6 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H), 0.90 (s, 18H), 0.84 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz) δ 175.3 (C), 169.1 (C), 138.4 (CH), 126.0 (CH), 84.1 (CH), 75.2 (CH), 72.7 (CH), 72.6 (CH), 57.9 (CH_3), 51.6 (CH), 42.0 (CH_2), 31.5 (CH_2), 30.9 (CH), 29.0 (CH_2), 27.9 (CH_2), 26.3 (CH_3), 26.2 (CH_3), 26.0 (CH_3), 22.4 (CH_3), 22.3 (CH_3), 18.3 (C), 18.2(6) (C), 18.2(2) (C), −3.6 (CH_3), −3.7 (CH_3), −4.0 (CH_3), −4.4 (CH_3), −4.5 (CH_3), −4.6 (CH_3); IR ν_{max} 3394, 3233, 2929, 2862, 1666, 1471, 1361, 1254, 1099, 836, 671 cm^{-1}; MS (70 eV) *m/z* 685 [$(M - H_3C^{\bullet})^+$, 5], 643 {$[M - (CH_3)_3C^{\bullet}]^+$, 92}, 487 (80), 455 (56), 355 (58), 213 (62), 155 (72), 73 (100); HRMS calcd for $C_{35}H_{72}N_2O_6Si_3$ $(M - H_3C^{\bullet})^+$ 685.4464, found 685.4459.

(6*E*)-6,7,8,9-Tetradeoxy-*N*-[(3*R*)-hexahydro-2-oxo-1*H*-azepin-3-yl]-8-methyl-2-*O*-methyl-L-gulonon-6-enonamide (*ent*-1). A magnetically stirred solution of compound **16** (15.0 mg, 0.02 mmol) in THF (1 mL), maintained at 18 °C under a nitrogen atmosphere, was treated with TBAF (130 μL of a 1 M solution in THF, 0.13 mmol). After 1.5 h, the reaction mixture was treated with HCl (1 mL of a 5% v/v aqueous solution) and then extracted with ethyl acetate (5 × 2 mL). The combined organic phases were washed with brine (1 × 3 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a light yellow oil. Subjection of this material to flash chromatography (silica, 5% v/v MeOH−chloroform elution) provided, after concentration of the appropriate fractions (R_f 0.1), *ent*-bengamide E (*ent*-**1**) (6.5 mg, 86%) as a clear, colorless and viscous oil: $[\alpha]_D$ −32 (*c*, 0.2 $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.98 (d, J = 6.3 Hz, 1H), 6.22 (m, 1H), 5.81 (ddd, J = 15.3, 6.3, 0.6 Hz, 1H), 5.48 (ddd, J = 15.3, 7.2, 1.2 Hz, 1H), 4.54 (dd, J = 9.0, 6.0 Hz, 1H), 4.37 (br s, 1H), 4.22 (br t, J = 6.6 Hz, 1H), 3.82−3.77 (complex m, 1H), 3.60 (m, 1H), 3.53 (s, 3H), 3.48−3.20 (complex m, 5H), 2.31 (m, 1H), 2.06 (m, 1H), 2.12−1.36 (complex m, 5H), 1.00 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz) δ 174.7 (C), 172.1 (C), 141.8 (CH), 125.4 (CH), 80.9 (CH), 74.3 (CH), 72.8 (CH), 72.4 (CH), 59.9 (CH_3), 52.0 (CH), 42.1 (CH_2), 31.0 (CH_2), 30.8 (CH), 28.8 (CH_2), 27.9 (CH_2), 22.2 (CH_3), 22.1 (CH_3); IR ν_{max} 3355, 2930, 1651, 1110, 973, 911, 731 cm^{-1}; MS (70 eV) *m/z* 359

[$(M + H)^+$, 12], 57 (100); HRMS calcd for $C_{17}H_{30}N_2O_6$ 359.2182, found 359.2171.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for *ent*-bengamide E. This material is available free of charge via the Internet at http://pubs.acs.org.

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