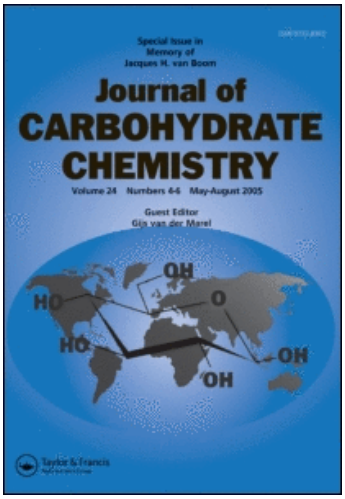

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An Asymmetric Total Synthesis of Broussonetine C

Patrick Perlmutter[a]; Filisaty Vounatsos[a]
[a] School of Chemistry, Monash University, Victoria, Australia

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An Asymmetric Total Synthesis of Broussonetine C[†]

Patrick Perlmutter[*] and Filisaty Vounatsos

School of Chemistry, Monash University, Victoria, Australia

ABSTRACT

A total synthesis of (+) Broussonetine C in 16 steps is described from D-arabinose.

Key Words: Broussonetine; Grignard; Azide; Staudinger; Mitsunobu; Cyclisation.

INTRODUCTION

Broussonetine C, a member of the Broussonetia class, was first isolated from the branches of *Broussonetia Kazinoki* (a deciduous tree distributed throughout Japan, China and Taiwan) in 1997 by Kusano *et al*.[1,2] and was assigned structure **1**. All of the Broussonetines incorporate a 2,3,4,5-tetrasubstituted pyrrolidine unit as a key motif, probably the most synthetically challenging substructure associated with this class of natural product. Significantly, Broussonetine C was found to exhibit unique β-galactosidase and β-mannosidase activities.[1,2] Such properties, coupled with the unique structure assigned to the alkaloid encouraged us to choose **1** as a novel synthetic target. Thus far, only one asymmetric total synthesis of this pyrrolidine alkaloid has been reported.[3] In this report we describe a synthesis of **1**, starting from D-arabinose.

[†]This paper is dedicated to Professor Gérard Descotes on the occasion of his 70th birthday.

[*]Correspondence: Patrick Perlmutter, School of Chemistry, Monash University, P.O. Box 23, Victoria 3800, Australia; Fax: (+613) 9905-4597; E-mail: Patrick.Perlmutter @sci.monash.edu.au.

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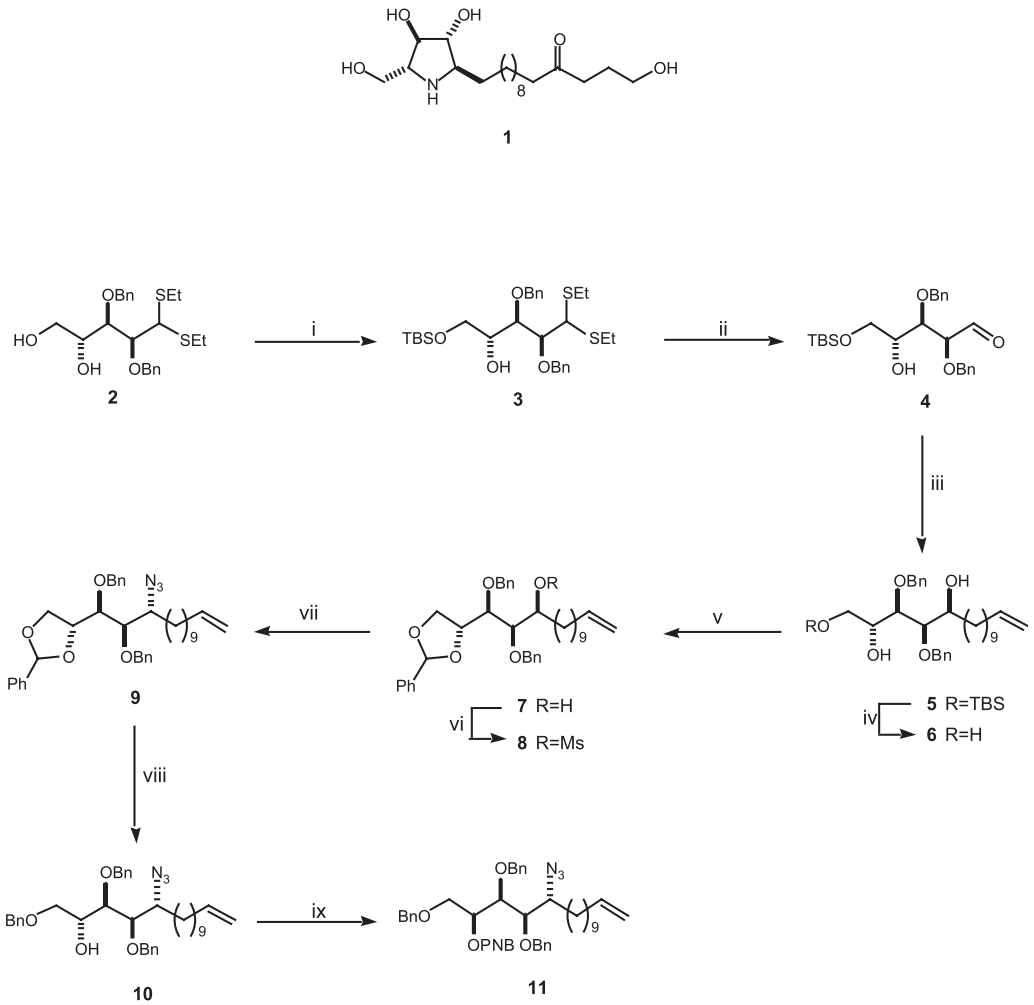
DISCUSSION

Initial studies focused on the construction of the intermediate **5**, as it was anticipated that **5** could be assembled via addition of undecenylmagnesium bromide[4] to **4**. The latter was prepared from the dithioacetal intermediate **3** obtained upon silylation of the known 2,3-di-*O*-benzyl-D-arabinose diethyl dithioacetal[5] **2** (Scheme 1). Grignard[6] addition of undecenylmagnesium bromide to lactol **4** provided **5** contaminated with less than 5% of its chromatographically separable diastereomer. Purified **5** (80%) was then



Scheme 1. (i) TBSCl, Imidazole, DMF, rt, 12 h; (ii) HgO, $HgCl_2$, acetone/water (10:1), 60 °C, 3 h; (iii) undecenylmagnesium bromide, THF, rt, 3 h; (iv) HCl (2M solution in MeOH), 0 °C, 3 h; (v) benzaldehyde dimethyl acetal, *p*-TsOH (catalytic), CH_2Cl_2, −20 °C to rt, 2 h; (vi) Et_3N, MsCl, CH_2Cl_2, 0 °C to rt, 1.5 h; (vii) NaN_3, DMF, 60 °C, 18 h; (viii) $AlCl_3$, $BH_3.NMe_3$, THF, 0 °C to rt, 3 h; (ix) DEAD, PPh_3, *p*-nitrobenzoic acid, THF, 18 h, rt.

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smoothly desilylated with methanolic HCl and transformed into the corresponding benzylidene acetal **7** by reaction with benzaldehyde dimethyl acetal (BDMA) in the presence of *p*-toluenesulfonic acid (*p*-TsOH).

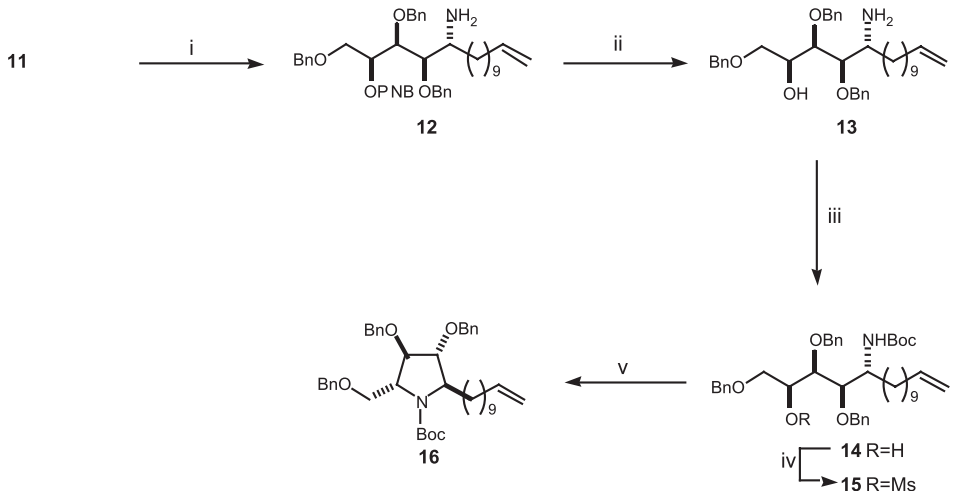
Introduction of nitrogen at C5 required activation and inversion of the hydroxyl group in the precursor **7**. This was effected by treatment of **7** with methanesulfonyl chloride (MsCl) in the presence of Et_3N. The resulting product **8** was immediately treated with NaN_3 in DMF providing azide **9** as a single isomer in 82% yield.[7] Regioselective opening[8] of the benzylidene acetal **9** using $AlCl_3$, $BH_3.NMe_3$ in THF delivered **10** in 67% yield.

Mitsunobu inversion[9] of the free hydroxyl group in **10** with *p*-nitrobenzoic acid as the nucleophilic species afforded **11**. Subsequent Staudinger reduction[10] of the azide moiety under neutral conditions [using PPh_3:H_2O (1:1) in THF at reflux] gave **12** in quantitative yield. Methanolysis followed by treatment of **13** with Et_3N, $(Boc)_2O$ in THF (Scheme 2) provided the pivotal cyclisation precursor **14** (61% over two steps).

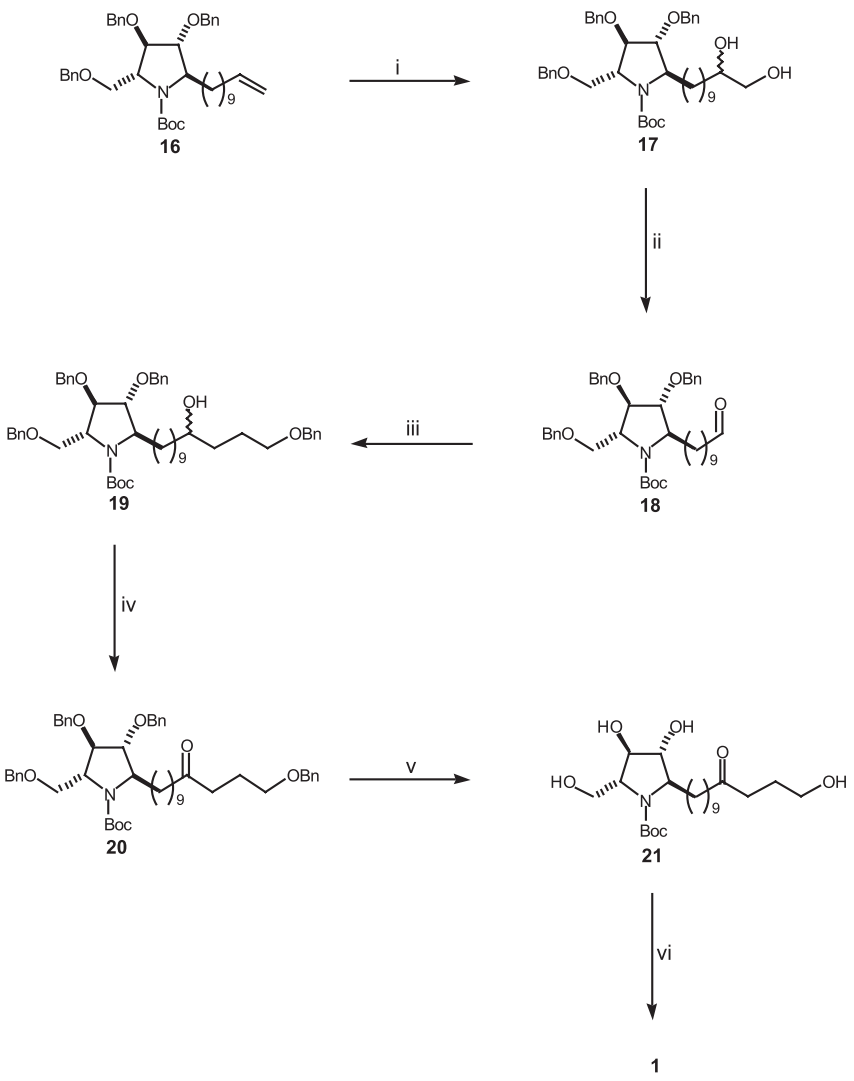
Mesylation of **14** was achieved under standard conditions and the product **15** was immediately treated with potassium *tert*-butoxide (*t*-BuOK).[11] In this way mesylate **15** underwent intramolecular cyclisation with the secondary amide and concomitant inversion at C2 to give **16**, in which all the stereocenters have the correct configuration for the natural product (90% over two steps).

Dihydroxylation[12] of **16** followed by oxidative cleavage of the diol in **17** yielded aldehyde **18** (Scheme 3). Aldehyde **18** was immediately treated with benzyloxypropylmagnesium bromide[13] and the resulting mixture of diastereomeric alcohols **19** (70%) was oxidized to the corresponding ketone **20** (98%) using Dess-Martin periodinane.[14]

Completion of the synthesis of Broussonetine C (**1**) (Scheme 3) was achieved by hydrogenolysis of the benzyl ethers using palladium on carbon under an atmosphere of hydrogen, followed by hydrolysis with TFA in THF. The ^1H and ^{13}C NMR spectroscopic data for synthetic **1** were identical to those of the natural product and



Scheme 2. (i) PPh_3:H_2O (1:1), THF, 60 °C, 4 h; (ii) NaOH, methanol, rt, 1 h; (iii) Et_3N, $(Boc)_2O$, THF, rt, 3 h; (iv) Et_3N, MsCl, CH_2Cl_2, 0 °C to rt, 1.5 h; (v) *t*-BuOK, THF, 8 h.



Scheme 3. (i) $K_2OsO_4.2H_2O$, NMO, acetone:H_2O (1:1), rt, 3 h; (ii) $NaIO_4$, Et_2O:H_2O (1:1), rt, 2 h; (iii) benzyloxypropylmagnesium bromide, THF, 0 °C to rt, 3 h; (iv) Dess-Martin reagent, CH_2Cl_2, 0 °C to rt, 2 h; (v) Pd/C, 5% AcOH in MeOH, H_2, 18 h; (vi) Trifluroacetic acid in THF,

the specific rotation {$[\alpha]_D$ + 32 (*c* 0.40, MeOH) } was comparable to that of the natural product.[1,2]

EXPERIMENTAL

General Procedures. Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian Mercury 300 spectrometer operating at 300

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MHz for proton and 75 MHz for carbon nuclei. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in deuterochloroform ($CDCl_3$) at 20°C unless otherwise stated. For ^1H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ 7.26) was used as the internal reference. ^1H 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: s = singlet; d = doublet; t = triplet; q = quartet; 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: 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) and homonuclear ($^1H/^1H$) correlation spectroscopy (COSY) experiments. Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer 1600 Fourier Transform Infrared Spectrophotometer. Samples were analysed as thin films on NaCl plates (for liquids/oils). High resolution mass spectra (HRMS) for accurate mass determinations were recorded on a Bruker BioApex 47e FTMS fitted with an analytical electrospray source using NaI for accurate mass calibration. The principal ion peaks (*m*/*z*) are reported along with their intensities, expressed as a percentage of the base peak (100%). M^+ refers to the molecular ion. Optical rotations were measured with a PolAAr 2001 automatic 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 $\{[\alpha]_D^{20}\}$ were calculated using the equation $[\alpha]_D = (100.\alpha)/(c.l)$ and are given in 10^{-1}.deg.cm^2.g^{-1}. Analytical thin-layer chromatography (TLC) was conducted on Polygram Sil G/UV_{254} and the chromatograms were visualised under a 254 nm UV lamp and/or by treatment with an ammonium molybdate/ cerium sulfate solution followed by heating. Flash chromatography was conducted 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 Company 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. Tetrahydrofuran (THF) and diethyl ether were dried using sodium metal and then distilled, as required, from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. *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 work-up of reaction mixtures were dried with magnesium sulfate ($MgSO_4$). Hexane refers to the hydrocarbon fraction 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.

2,3-Bis-phenylmethyloxy-5-[(1,1-dimethylethyl)dimethylsilyloxy]-D-arabinose (3). *tert*-Butyldimethylsilyl chloride (8.42 g, 54.50 mmol) was added to a magnetically stirred solution of 2,3-di-*O*-benzyl-D-arabinose diethyl dithioacetal (**2**), (20 g,

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45.42 mmol) and imidazole (4.02 g, 59.05 mmol) in anhydrous DMF (100 mL) maintained at rt under an atmosphere of nitrogen. After 12 h the reaction mixture was poured into water (500 mL) and extracted with CH_2Cl_2 (3 × 250 mL). The combined organic phases were washed with water (500 mL) and brine (400 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light yellow oil. Flash chromatography (5%–25% v/v ethyl acetate/hexane elution) gave compound **3** (21.9 g, 87%) as a yellow oil: $[\alpha]_D$ + 17.7 (*c* 0.72, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.38–7.25 (m, 10H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.77 (d, *J* = 11.4 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.18 (d, *J* = 6.3 Hz, 1H), 4.00 (m, 2H), 3.80 (m, 2H), 3.67 (m, 1H), 2.67 (m, 4H), 1.24 (m, 6H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz) δ 138.3 (C), 138.2 (C), 128.5 (2 × CH, coincident), 128.4 (2 × CH, coincident), 128.2 (2 × CH, coincident), 128.1 (2 × CH, coincident), 127.8 (CH), 127.7 (CH), 82.8 (CH), 79.3 (CH), 75.3 (CH_2), 74.5 (CH_2), 71.9 (CH_2), 64.3 (CH_2), 53.7 (CH), 26.2 (3 × CH_3, coincident), 26.1 (2 × CH_2, coincident), 25.2 (C), 14.8 (2 × CH_3, coincident), −4.9 (2 × CH_3, coincident); IR ν_{max} 3540, 3031, 2928, 2856, 1497, 1454, 1255, 1097, 1028, 836 cm^{-1}; HRMS Calcd for $C_{29}H_{46}O_4S_2Si$: $[M + Na]^+$ *m/z* 573.2504. Found 573.2495.

(2*R*,3*R*,4*R*,5*S*)-1-[(1,1-Dimethylethyl)dimethylsilyloxy]-3,4-bis(phenylmethyloxy)hexadec-15-ene-2,5-diol (5). Compound **3** (21 g, 36 mmol) was dissolved in acetone/water (60 mL of a 10:1 solution) and HgO (19.4 g, 88.36 mmol) was added in one portion, followed by $HgCl_2$ (10.95 g, 40.34 mmol). The reaction mixture was heated to 60°C for 3 h, then filtered through a bed of Celite™. The solvent was concentrated under reduced pressure and the residue was diluted with CH_2Cl_2 (150 mL), then washed with potassium iodide (3 × 100 mL of a 1M aq solution) and brine (1 × 200 mL), before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 2,3-di-*O*-benzyl-5-*O*-*tert*-butyldimethylsilyl-D-arabinose (4) as a pale yellow oil. This material was used, without purification, in the next step of the reaction sequence. Undecenylmagnesium bromide (364 mL of a 0.1 M solution in THF, 0.36 mol) was added, dropwise, to neat lactol **4** (18 g, 40.38 mmol) maintained at 20°C under a nitrogen atmosphere. The reaction mixture was stirred at rt for 3 h, then treated with NH_4Cl (500 mL of a saturated aq solution). The mixture thus obtained was partitioned between diethyl ether (3 × 500 mL) and the combined organic phases were washed with brine (1 × 500 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Flash chromatography (0%–25% v/v ethyl acetate-hexane elution) gave **5** (19.3 g, 80%) as a clear colourless oil: $[\alpha]_D$ + 7 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.38–7.25 (m, 10H), 5.80 (m, 1H), 5.03–4.90 (complex m, 2H), 4.79 (d, *J* = 11.2 Hz, 1H), 4.62 (d, *J* = 7 Hz, 2H), 4.58 (d, *J* = 11.3 Hz, 1H), 3.87 (m, 1H), 3.81 (d, *J* = 3.7 Hz, 1H), 3.78 (d, *J* = 3.3 Hz, IH), 3.72 (m, 2H), 3.56 (t, *J* = 4.1 Hz, 1H), 2.93 (br s, 1H), 2.65 (br s, 1H), 2.02 (app. q, *J* = 6.8 Hz, 2H), 1.30 (m, 18H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz) δ 139.4 (CH), 138.3 (C), 138.2 (C), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (2 × CH, coincident), 128.1 (CH), 128.0 (2 × CH, coincident), 127.9 (CH), 114.3 (CH_2), 81.9 (CH), 78.5 (CH), 74.8 (CH_2), 74.0 (CH_2), 72.2 (CH), 71.2 (CH), 64.3 (CH_2), 34.6 (CH_2), 34.1 (CH_2), 30.0 (CH_2), 29.9 (2 × CH_2, coincident), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 26.2 (3 × CH_3, coincident), 18.6 (C), −4.8 (CH_3), −4.9 (CH_3); IR ν_{max} 3442, 2926, 1640, 1455, 1252, 1090, 836, 778, 698 cm^{-1}; HRMS Calcd for $C_{36}H_{58}O_5Si$: $[M + Na]^+$ *m/z* 621.3951. Found 621.3938.

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(2*R*,3*R*,4*R*,5*S*)-3,4-Bis(phenylmethyloxy)hexadec-15-ene-1,2,5-triol (6). A solution of compound **5** (15 g, 25.08 mmol) in 2M methanolic HCl (100 mL) was stirred at 0°C under an atmosphere of nitrogen. After 3 h, the reaction mixture was concentrated under reduced pressure to afford a yellow oil. Flash chromatography (0%–15% v/v ethyl acetate-hexane elution) gave **6** (10.5 g, 86%) as a clear colourless oil: $[\alpha]_D$ + 7 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.38–7.25 (m, 10H), 5.80 (m, 1H), 5.03–4.90 (complex m, 2H), 4.70 (d, *J* = 11.3 Hz, 1H), 4.60 (d, *J* = 4.1 Hz, 2H), 4.51 (d, *J* = 11.3 Hz, 1H), 3.90 (m, 1H), 3.80 (m, 1H), 3.74 (dd, *J* = 4.6 and 2.5 Hz, 2H), 3.46 (m, 2H), 2.04 (app q. *J* = 6.7 Hz, 2H), 1.50–1.20 (m, 18H); ^{13}C NMR (75 MHz) δ 139.3 (CH), 138.0 (C), 137.6 (C), 128.7 (CH), 128.6 (2 × CH, coincident), 128.5 (CH), 128.4 (2 × CH, coincident), 128.3 (CH), 128.2 (2 × CH, coincident), 128.1 (CH), 114.3 (CH_2), 80.9 (CH), 77.6 (CH), 74.3 (CH_2), 73.9 (CH_2), 72.3 (CH), 70.3 (CH), 68.8 (CH_2), 35.0 (CH_2), 34.1 (CH_2), 30.0 (CH_2), 29.9 (2 × CH_2, coincident), 29.8 (CH_2), 29.5 (CH_2), 29.3 (2 × CH_2, coincident); IR ν_{max} 3405, 2923, 2247, 1640, 1455, 1065, 909, 734, 698 cm^{-1}; HRMS Calcd for $C_{30}H_{44}O_5$: $[M + Na]^+$ *m/z* 507.3086. Found 507.3076.

(4*R*)-4-[1*R*,2*R*,3*S*-1,2-Bis(phenylmethyloxy)-3-hydroxy-13-tetradecen-1-yl]-2-phenyl-1,3-dioxolane (7). Benzaldehyde dimethyl acetal (BDMA) (1.67 mL, 11.15 mmol) was added dropwise to a solution of compound **6** (4.5 g, 9.30 mmol) and *p*-TsOH (catalytic) in CH_2Cl_2 (90 mL) maintained at −20°C under a nitrogen atmosphere. The reaction mixture was allowed to warm to 10°C over 1 h, then treated with 1M aq NaOH (90 mL). The separated aq layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were washed with brine (1 × 250 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Flash chromatography (0%–20% v/v ethyl acetate-hexane elution) gave **7** (3.7 g, 70%) as a clear colourless oil: $[\alpha]_D$ + 9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.38–7.25 (m, 15H), 5.80 (m, 1H), 5.70 (s, 1H), 5.08–4.96 (complex m, 2H), 4.82 (d, *J* = 11.5 Hz, 1H), 4.80 (d, *J* = 11.2 Hz, 1H), 4.75 (d, *J* = 11.4 Hz, 1H), 4.60 (d, *J* = 11.3 Hz, 1H), 4.30 (dd, *J* = 8.2 and 2.4 Hz, 1H), 4.14 (t, *J* = 7.8 Hz, 1H), 4.03 (t, *J* = 4.4 Hz, 1H), 3.78 (br m, 1H), 3.47 (dd, *J* = 3.3 and 1.1 Hz, 1H), 2.23 (br s, 1H), 2.09 (app q, *J* = 6.9 Hz, 2H), 1.55–1.30 (m, 18H); ^{13}C NMR (75 MHz) δ 139.4 (CH), 138.4 (C), 138.1 (C), 137.4 (C), 129.5 (CH), 129.3 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (2 × CH, coincident), 128.1 (CH), 128.0 (CH), 127.9 (2 × CH, coincident), 126.9 (CH), 126.8 (CH), 126.6 (CH), 126.5 (CH), 114.4 (CH_2), 103.7 (CH), 81.4 (CH), 78.8 (CH), 77.5 (CH), 74.7 (CH_2), 71.0 (CH), 67.1 (CH_2), 34.9 (CH_2), 34.2 (CH_2), 30.0 (2 × CH_2, coincident), 29.9 (2 × CH_2, coincident), 29.5 (CH_2), 29.3 (CH_2, coincident); IR ν_{max} 3483, 2925, 2247, 1639, 1455, 1091, 910, 732, 697 cm^{-1}; HRMS Calcd for $C_{37}H_{48}O_5$: $[M + Na]^+$ *m/z* 595.3399. Found 595.3399.

(4*R*)-4-[1*R*,2*R*,3*S*-1,2-Bis(phenylmethyloxy)-3-azido-13-tetradecen-1-yl]-2-phenyl-1,3-dioxolane (9). Et_3N (1.87 mL, 13.45 mmol) was added, dropwise, to a stirred solution of compound **7** (3.5 g, 6.11 mmol) in CH_2Cl_2 (60 mL), maintained at 0°C under an atmosphere of nitrogen. After 10 min, MsCl (1.05 mL, 13.45 mmol) was added dropwise over 5 min. The reaction mixture thus obtained was allowed to warm to room temperature over 1.5 h, then treated with saturated aq NH_4Cl (60 mL). The separated aq layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with brine (1 × 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford (4*R*)-4-[1*R*,2*R*,3*S*-1,2-bis-(phenylmethy-

loxy)-3-methanesulfonyloxy-13-tetradecen-1-yl]-2-phenyl-1,3-dioxolane (8) as a pale yellow oil (3.7 g). Sodium azide (1.25 g, 19.37 mmol) was added, in portions, to a solution of the crude mesylate **8** (3.7 g) in DMF (20 mL) and heated to 60°C under an atmosphere of nitrogen. After 18 h, the reaction mixture was treated with saturated aq NH_4Cl (50 mL) and CH_2Cl_2 (100 mL). The separated aq layer was extracted with CH_2Cl_2 (3 × 80 mL), and the combined organic phases were washed with water (3 × 350 mL), and brine (1 × 350 mL), before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Flash chromatography (0%–15% v/v ethyl acetate-hexane elution) gave **9** (2.8 g, 80%) as a clear yellow oil: $[\alpha]_D$ + 8 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.38–7.25 (m, 15H), 5.80 (m, 1H), 5.02–4.90 (complex m, 2H), 4.56 (d, *J* = 1.7 Hz, 2H), 4.53 (s, 1H), 4.50 (d, *J* = 1.9 Hz, 2H), 4.20 (m, 1H), 4.00 (t, *J* = 3.4 Hz, 1H), 3.95 (m, 1H), 3.79 (dd, *J* = 2.8 and 1.8 Hz, 1H), 3.56 (m, 2H), 2.03 (app q, *J* = 6.9 Hz, 2H), 1.40–1.20 (m, 18H); ^{13}C NMR (75 MHz) δ 139.4 (CH), 138.3 (C), 138.1 (C), 137.2 (C), 129.5 (CH), 129.4 (CH), 128.7 (CH), 128.5 (CH), 128.3 (2 × CH, coincident), 128.2 (CH), 128.1 (2 × CH, coincident), 128.0 (CH), 127.9 (CH), 126.9 (CH), 126.8 (2 × CH, coincident), 126.6 (CH), 114.3 (CH_2), 103.7 (CH), 88.2 (CH), 85.7 (CH), 82.7 (CH), 81.4 (CH), 73.6 (CH_2), 72.0 (CH_2), 70.5 (CH_2), 34.1 (CH_2), 33.7 (CH_2), 29.8 (CH_2), 29.5 (2 × CH_2, coincident), 29.3 (2 × CH_2, coincident), 29.2 (2 × CH_2, coincident); IR ν_{max} 2925, 2099, 1731, 1496, 1364, 1098, 909, 734, 897 cm^{-1}; HRMS Calcd for $C_{37}H_{47}N_3O_4$: $[M + Na]^+$ *m/z* 620.3464. Found 620.3456.

(2*R*,3*R*,4*R*,5*R*)-1,3,4-Tris(phenylmethyloxy)-5-azidohexadec-15-en-2-ol (10). $AlCl_3$ (2.1 g, 15.8 mmol) was added, in portions, to a solution of compound **9** (2.7 g, 4.51 mmol) and $BH_3.NMe_3$ (1.15 g, 15.8 mmol) in THF (45 mL) maintained at 0°C under an atmosphere of nitrogen. After 3 h, the reaction mixture was treated with water (50 mL) and extracted with diethyl ether (3 × 60 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ (150 mL) and brine (1 × 150 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Flash chromatography (0%–15% v/v ethyl acetate-hexane elution) gave **10** (2.4 g, 89%) as a yellow oil: $[\alpha]_D$ + 17 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.30–7.22 (m, 15H), 5.80 (m, 1H), 5.03–4.92 (complex m, 2H), 4.73 (d, *J* = 11.2 Hz, 1H), 4.66 (d, *J* = 11.2 Hz, 1H), 4.64 (d, *J* = 11.3 Hz, 1H), 4.55 (d, *J* = 11.1 Hz, 1H), 4.53 (s, 2H), 3.97 (m, 1H), 3.74 (d, *J* = 6.5 Hz, 2H), 3.67 (complex m, 2H), 3.54 (m, 1H), 2.56 (d, *J* = 5.9 Hz, 1H), 2.05 (app q, *J* = 6.7 Hz, 2H), 1.40–1.27 (m, 18H); ^{13}C NMR (75 MHz) δ 139.3 (CH), 138.2 (C), 138.1 (C), 138.0 (C), 128.8 (CH), 128.7 (2 × CH, coincident), 128.6 (CH), 128.5 (2 × CH, coincident), 128.3 (CH), 128.2 (2 × CH, coincident), 128.1 (CH), 127.8 (2 × CH, coincident), 126.9 (CH), 126.8 (2 × CH, coincident), 114.3 (CH_2), 81.0 (CH), 79.2 (CH), 74.8 (CH_2), 74.5 (CH_2), 73.7 (CH_2), 71.2 (CH_2), 70.3 (CH), 62.8 (CH), 34.1 (CH_2), 32.2 (CH_2), 30.5 (2 × CH_2, coincident), 30.0 (CH_2), 29.8 (2 × CH_2, coincident), 29.4 (CH_2), 29.3 (CH_2); IR ν_{max} 3465, 2923, 2100, 1640, 1454, 1069, 909, 733, 697 cm^{-1}; HRMS Calcd for $C_{37}H_{49}N_3O_4$: $[M + Na]^+$ *m/z* 622.3620. Found 622.3609.

(2*S*,3*R*,4*R*,5*R*)-1,3,4-Tris(phenylmethyloxy)-2-p-nitrobenzoyloxy-5-azidohexadec-15-enyl (11). DEAD (1.78 mL, 11.3 mmol) was added dropwise at rt to a solution of compound **10** (2.4 g, 5.7 mmol) containing PPh_3 (2.9 g, 11.3 mmol) and

p-nitrobenzoic acid (1.9 g, 11.3 mmol) in THF (57 mL) under a nitrogen atmosphere. After 18 h at rt, the reaction mixture was diluted with water (80 mL), and the resulting solution was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ (250 mL) and brine (1 × 250 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Flash chromatography (0%–20% v/v ethyl acetate-hexane elution) gave **11** (2.6 g, 88%) as a pale yellow oil: $[\alpha]_D$ + 10 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.26 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.30–7.22 (m, 15H), 5.80 (m, 1H), 5.00 (q, *J* = 5.1 and 4.8 Hz, 1H), 5.02–4.91 (complex m, 2H), 4.78 (d, *J* = 11.4 Hz, 1H), 4.68 (d, *J* = 11.3 Hz, 1H), 4.63 (d, *J* = 11.3 Hz, 1H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.58 (d, *J* = 12.1 Hz, 1H), 4.41 (d, *J* = 12.2 Hz, 1H), 4.06 (t, *J* = 5.2 Hz, 1H), 3.70–3.60 (complex m, 3H), 3.53 (m, 1H), 2.04 (app q, *J* = 6.7 Hz, 2H), 1.37–1.26 (m, 18H); ^{13}C NMR (75 MHz) δ 139.4 (CH), 138.0 (C), 137.8 (C), 137.0 (C), 135.4 (C), 131.0 (2 × CH, coincident), 128.7 (2 × CH, coincident), 128.6 (2 × CH, coincident), 128.5 (2 × CH, coincident), 128.3 (CH), 128.0 (2 × CH, coincident), 127.9 (2 × CH, coincident), 127.5 (2 × CH, coincident), 127.3 (2 × CH, coincident), 123.7 (2 × CH, coincident), 114.3 (CH_2), 80.8 (CH), 78.1 (CH), 75.4 (CH_2), 74.3 (CH), 74.1 (CH_2), 73.5 (CH_2), 68.2 (CH_2), 63.0 (CH), 34.1 (2 × CH_2, coincident), 30.0 (CH_2), 29.9 (2 × CH_2, coincident), 29.8 (2 × CH_2, coincident), 29.5 (CH_2), 29.2 (CH_2); IR ν_{max} 2923, 2100, 1728, 1530, 1270, 910, 783, 696 cm^{-1}; HRMS Calcd for $C_{44}H_{52}N_4O_7$: $[M + Na]^+$ *m/z* 771.3733. Found 771.3742.

(2*S*,3*R*,4*R*,5*R*)-1,3,4-Tris(phenylmethyloxy)-2-p-nitrobenzoyloxy-5-aminohexadec-15-enyl (12). PPh_3 (3.4 g, 13.0 mmol) was added to a solution of compound **11** (2.6 g, 4.3 mmol) in THF:H_2O (4.5 mL of a 10:1 v/v mixture), and heated to reflux (*ca.* 60°C). After 4 h, the reaction mixture was cooled to rt and partitioned between diethyl ether (20 mL) and saturated aq NH_4Cl (30 mL). The separated aqueous layer was extracted with diethyl ether (3 × 25 mL) and washed with brine (1 × 80 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Flash chromatography (0%–25% v/v ethyl acetate-hexane elution) gave **12** (2.12 g, 85%) as a pale yellow oil: $[\alpha]_D$ + 9 (*c* 3.3, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.33–7.25 (m, 15H), 5.82 (m, 1H), 5.04–4.92 (complex m, 2H), 4.06 (m, 1H), 3.80 (m, 1H), 3.67–3.60 (complex m, 2H), 3.51 (m, 1H), 3.22 (broad s, 1H), 3.09 (m, 1H), 2.05 (app q, *J* = 6.8 Hz, 2H), 1.50–1.24 (m, 18H); ^{13}C NMR (75 MHz) δ 139.4 (CH), 138.6 (C), 138.4 (C), 138.3 (C), 128.7 (2 × CH, coincident), 128.6 (2 × CH, coincident), 128.5 (3 × CH, coincident), 128.4 (CH), 128.3 (2 × CH, coincident), 128.0 (2 × CH, coincident), 127.9 (2 × CH, coincident), 127.7 (CH), 114.3 (CH), 80.8 (CH), 78.5 (CH), 74.1 (CH_2), 73.3 (CH_2), 73.0 (CH_2), 71.3 (CH_2), 67.4 (CH), 53.3 (CH), 34.1 (CH_2), 33.5 (CH_2), 30.0 (2 × CH_2, coincident), 29.9 (2 × CH_2, coincident), 29.5 (CH_2), 29.3 (CH_2); IR ν_{max} 3372, 2924, 2854, 1730, 1640, 1454, 1070, 909, 807, 733 cm^{-1}; HRMS Calcd for $C_{37}H_{51}NO_4$: $[M + Na]^+$ *m/z* 596.3715. Found 596.3712.

(2*S*,3*R*,4*R*,5*R*)-1,3,4-Tris(phenylmethyloxy)-5-aminohexadec-15-en-2-ol (13). Sodium hydroxide (2.26 g, 56.5 mmol) was added to a solution of **12** (4.24 g, 5.6 mmol) in MeOH (56 mL) at 0°C. After 1 h, the reaction mixture was warmed to rt and partitioned between diethyl ether (200 mL) and 5% aq HCl (100 mL). The separated aq

layer was extracted with diethyl ether (3 × 150 mL) and washed with brine (1 × 250 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford an orange oil. Flash chromatography (0%–30% v/v ethyl acetate-hexane elution) gave **13** (2.6 g, 76%) as a clear colourless oil: $[\alpha]_D$ + 21 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.30–7.22 (m, 15H), 5.80 (m, 1H), 5.04–4.92 (complex m, 2H), 4.78 (d, *J* = 11.3 Hz, 1H), 4.70 (s, 2H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.50 (d, *J* = 11.3 Hz, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 3.90–3.73 (complex m, 3H), 3.49 (m, 3H), 2.50 (d, *J* = 7.1 Hz, 1H), 2.05 (app q, *J* = 6.8 Hz, 2H), 1.50–127 (m, 18H); ^{13}C NMR (75 MHz) δ 139.3 (CH), 138.2 (C), 138.1 (C), 138.0 (C), 128.6 (2 × CH, coincident), 128.5 (2 × CH, coincident), 128.3 (2 × CH, coincident), 128.0 (2 × CH, coincident), 127.9 (CH), 127.8 (CH), 127.5 (CH), 126.8 (2 × CH, coincident), 126.5 (CH), 126.4 (CH), 114.3 (CH_2), 81.8 (CH), 78.6 (CH), 75.2 (CH_2), 74.7 (CH_2), 73.6 (CH_2), 71.4 (CH_2), 70.1 (CH), 63.6 (CH), 34.1 (2 × CH_2, coincident), 30.0 (2 × CH_2, coincident), 29.8 (CH_2), 29.7 (CH_2), 29.4 (2 × CH_2, coincident), 29.3 (CH_2); IR ν_{max} 3450, 2925, 2101, 1731, 1640, 1454, 1111, 909, 755, 697 cm^{-1}; HRMS Calcd for $C_{37}H_{49}N_3O_4$: $[M + Na]^+$ *m/z* 622.3620. Found 622.3620.

(2*S*,3*R*,4*R*,5*R*)-1,3,4-Tris(phenylmethyloxy)-5-{[(1,1-dimethylethoxy)carbonyl] amino}-hexadec-15-en-2-ol (14). Et_3N (0.56 mL, 4.0 mmol) was added, dropwise, to a solution of compound **13** (1.92 g, 3.3 mmol) in THF (33 mL), maintained at 0°C under a nitrogen atmosphere. After 10 min, $(Boc)_2O$ (876 mg, 4.0 mmol) was added, and the reaction mixture was allowed to warm to rt over 2 h before being treated with saturated aq NH_4Cl (25 mL) and water (25 mL). The separated aq layer was extracted with diethyl ether (3 × 50 mL) and washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Flash chromatography (0%–30% v/v ethyl acetate-hexane elution) gave **14** (1.8 g, 80%) as a clear colourless oil: $[\alpha]_D$ + 26 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.33–7.25 (m, 15H), 5.81 (m, 1H), 5.03–4.90 (complex m, 2H), 4.73 (d, *J* = 11.2 Hz, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.47 (s, 2H), 4.03 (m, 1H), 3.89 (m, 1H), 3.75–3.66 (complex m, 2H), 3.49 (d, *J* = 6 Hz, 2H), 2.92 (d, *J* = 5.3 Hz, 1H), 2.04 (app q, *J* = 6.8 Hz, 2H), 1.4 (s, 9H), 1.35–1.26 (m, 18H); ^{13}C NMR (75 MHz) δ 139.4 (CH), 138.4 (C), 138.3 (2 × C), 128.6 (3 × CH, coincident), 128.5 (3 × CH, coincident), 128.3 (3 × CH, coincident), 128.0 (3 × CH, coincident), 127.9 (3 × CH, coincident), 114.3 (CH_2), 80.8 (CH), 79.3 (CH), 74.8 (CH_2), 73.6 (CH_2), 71.3 (CH_2), 70.9 (CH), 50.9 (CH), 34.1 (2 × CH_2, coincident), 29.9 (2 × CH_2, coincident), 29.8 (2 × CH_2, coincident), 29.5 (2 × CH_2, coincident), 29.3 (CH_2), 28.7 (3 × CH_3, coincident); IR ν_{max} 3429, 3064, 3061, 2925, 2855, 1713, 1497, 1454, 1365, 1173, 909, 733, 697 cm^{-1}; HRMS Calcd for $C_{42}H_{59}NO_6$: $[M + Na]^+$ *m/z* 696.4239. Found 696.4227.

(2*R*,3*R*,4*R*,5*R*)-N-{[(1,1-Dimethylethoxy)carbonyl]amino}-2-[(phenylmethoxy)-methyl]-3,4-bis-(phenylmethyloxy)-5-(undec-1-en-11-yl)pyrrolidine (16). Et_3N (0.8 mL, 5.7 mmol) was added, dropwise, to a stirred solution of compound **14** (1.75 g, 2.6 mmol) in CH_2Cl_2 (26 mL), maintained at 0°C under an atmosphere of nitrogen. After 10 min, MsCl (0.44 mL, 5.7 mmol) was added, dropwise, over 5 min. The reaction mixture thus obtained was allowed to warm to rt 1.5 h, then treated with saturated aq NH_4Cl (30 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic phases were washed with brine (1 × 120 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford (2*S*,3*R*,4*R*,

5*R*)-1,3,4-tris-(phenylmethyloxy)-2-methanesulfonyloxy-5-{[(1,1-dimethylethoxy)carbonyl]amino}-hexadec-15-enyl (15) as a pale yellow oil (1.95 g). Potassium *tert*-butoxide (7.8 mL of 1M solution in THF, 7.8 mmol) was added dropwise to a solution of crude **15** (1.95 g) in CH_2Cl_2 (26 mL) maintained at 0°C under an atmosphere of nitrogen. After 18 h at rt, the reaction mixture was treated with saturated aq NH_4Cl (30 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic phases were washed with brine (1 × 120 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Flash chromatography (0%–15% v/v ethyl acetate-hexane elution) gave **16** (1.6 g, 93%) as a clear colourless oil: $[\alpha]_D$−30 (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.30–7.22 (m, 15H), 5.80 (m, 1H), 5.04–4.92 (complex m, 2H), 4.64 (m, 2H), 4.44 (complex m, 5H), 4.15 (d, *J* = 6.2 Hz, 1H), 4.02 (m, 1H), 3.76 (m, 2H), 3.51 (d, *J* = 9.0 Hz, 1H), 3.44 (d, *J* = 9.0 Hz, 1H), 2.04 (app q, *J* = 6.7 Hz, 2H), 1.43 (d, *J* = 14.5 Hz, 9H), 1.37–1.26 (m, 18H); ^{13}C NMR (75 MHz) δ 139.4 (CH), 138.4 (C), 138.2 (2 × C), 128.6 (3 × CH, coincident), 128.5 (3 × CH, coincident), 128.4 (3 × CH, coincident), 127.8 (3 × CH, coincident), 127.7 (3 × CH, coincident), 114.3 (CH_2), 84.8 (CH), 83.6 (CH), 73.2 (CH_2), 71.0 (CH_2), 69.0 (CH_2), 64.9 (CH), 62.7 (CH), 34.1 (CH_2), 32.3 (CH_2), 31.8 (CH_2), 30.6 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 28.8 (3 × CH_3, coincident); IR 3063, 2927, 1682, 1496, 1455, 1265, 1174, 1097, 912, 738, 699 ν_{max} cm^{-1}; HRMS Calcd for $C_{42}H_{57}NO_5$: $[M + Na]^+$ *m/z* 678.4134. Found 678.4129.

(2*R*,3*R*,4*R*,5*R*)-N-{[(1,1-dimethylethoxy)carbonyl]amino}-2-[(phenylmethoxy)-methyl]-3,4-bis-(phenylmethyloxy)-5-(1-oxodecan-11-yl)-pyrrolidine (18). $K_2OsO_4.2H_2O$ (112 mg, 3.0 mmol) was added, in one portion, to a solution of compound **16** (1.6 g, 2.4 mmol) in acetone:H_2O (24 mL of a 1:1 v/v mixture), maintained at 0°C. After 10 min, *N*-methylmorpholine oxide (1.4 g, 4.9 mmol) was added, dropwise, to the reaction mixture. After 3 h at rt, the reaction mixture was diluted with water (30 mL) and the resulting solution was extracted with ethyl acetate (3 × 40 mL). The combined organic phases were washed with brine (120 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford (2*R*,3*R*,4*R*,5*R*)-*N*-{[(1,1-dimethylethoxy)carbonyl]amino}-2-[(phenylmethoxy)methyl]-3,4-bis-(phenylmethyloxy)-5-(1,2-dihydroxyundecan-11-yl)-pyrrolidine (**17**) as a pale yellow oil (1.5 g). Sodium periodate (745 mg, 3.5 mmol) was added in one portion to a solution of crude **17** (800 mg, 1.2 mmol) in diethyl ether:H_2O (10 mL of a 1:1 v/v mixture), maintained at 0°C. After 2 h at room temperature the reaction mixture was diluted with water (20 mL) and the resulting solution was extracted with diethyl ether (3 × 30 mL). The combined organic phases were washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford **18** as a pale yellow oil. Flash chromatography (0%–15% v/v ethyl acetate-hexane elution) gave **18** (740 mg, 88%) as a clear colourless oil: $[\alpha]_D$−30 (*c* 2.7, $CHCl_3$); ^{1}H NMR (300 MHz) δ 9.75 (s, 1H), 7.31–7.23 (m, 15H), 4.62 (m, 2H), 4.51–4.34 (complex m, 5H), 4.15 (d, *J* = 6.2 Hz, 1H), 4.02 (m, 1H), 3.80–3.72 (m, 2H), 3.46 (m, 1H), 2.41 (app t, *J* = 7.4 Hz, 2H), 1.43 (d, *J* = 14.5 Hz, 9H), 1.37–1.18 (m, 18H); ^{13}C NMR (75 MHz) δ 202.2 (CO), ester, 138.4 (C), 138.1 (C), 138.0 (C), 129.9 (3 × CH, coincident), 129.1 (3 × CH, coincident), 128.5 (3 × CH, coincident), 128.4 (3 × CH, coincident), 127.8 (3 × CH, coincident), 84.8 (CH), 83.6 (CH), 73.2 (CH_2), 71.4 (CH_2), 71.0 (CH_2), 68.2 (CH_2), 64.9 (CH), 62.6 (CH), 44.2 (CH_2), 34.0 (CH_2), 31.7 (CH_2), 30.6 (CH_2), 29.9 (CH_2), 29.8 (2 × CH_2, coincident), 29.7 (2 × CH_2, coincident), 28.8 (3 × CH_3, coincident); IR

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3014, 2930, 1722, 1684, 1454, 1395, 1217, 1097, 758 ν_{max} cm^{-1}; HRMS Calcd for $C_{41}H_{55}NO_6$: $[M + Na]^+$ *m/z* 680.3926. Found 680.3899.

(2*R*,3*R*,4*R*,5*R*)-N-{[(1,1-dimethylethoxy)carbonyl]amino}2-[(phenylmethoxy)-methyl]-3,4-bis-(phenylmethyloxy)-5-(1-phenylmethyloxy-4-hydroxytridecan-13-yl)pyrrolidine (19). Benzyloxypropylmagnesium bromide (1.5 mL of a 1 M solution in THF, 1.5 mmol) was added dropwise to neat aldehyde **18** (760 mg, 1.15 mmol) maintained at 0°C under a nitrogen atmosphere. The reaction mixture was stirred at rt for 3 h, then treated with saturated aq NH_4Cl (10 mL). The mixture thus obtained was partitioned between diethyl ether (3 × 15 mL) and the combined organic phases were washed with brine (1 × 40 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Flash chromatography (0%−15% v/v ethyl acetate-hexane elution) gave **19** (650 mg, 70%) as a clear colourless oil: $[\alpha]_D$ −18.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.33−7.25 (m, 20H), 4.62 (m, 2H), 4.53 (d, *J* = 2.9 Hz, 2H), 4.51−4.34 (complex m, 5H), 4.15 (d, *J* = 6.2 Hz, 1H), 4.02 (m, 1H), 3.82−3.75 (m, 2H), 3.67 (t, *J* = 5.7 Hz, 2H), 3.53−3.44 (m, 2H), 3.32−2.2 (m, 4H), 1.88 (quintet, *J* = 5.6 Hz, 2H), 1.43 (d, *J* = 14.5 Hz, 9H), 1.7−1.2 (m, 18H); ^{13}C NMR (75 MHz) δ 154.2 (CO), 138.8 (C), 138.5 (C), 138.2 (C), 137.9 (C), 128.6 (3 × CH, coincident), 128.5 (3 × CH, coincident), 128.4 (3 × CH, coincident), 127.9 (3 × CH, coincident), 127.8 (3 × CH, coincident), 127.7 (3 × CH, coincident), 127.6 (2 × CH, coincident), 84.9 (CH), 83.5 (CH), 73.2 (CH_2), 71.4 (CH_2), 71.9 (CH), 71.1 (CH_2), 70.8 (CH_2), 69.0 (CH_2), 64.9 (CH), 62.8 (CH), 62.3 (CH_2), 37.9 (CH_2), 35.1 (CH_2), 32.4 (CH_2), 32.3 (CH_2), 31.8 (CH_2), 30.6 (2 × CH_2, coincident), 30.0 (2 × CH_2, coincident), 29.8 (CH_2), 29.7 (2 × CH_2, coincident), 28.8 (3 × CH_3, coincident); IR ν_{max} 3463, 3018, 2928, 1683, 1454, 1394, 1173, 1096, 928, 751, 688 cm^{-1}; HRMS Calcd for $C_{51}H_{69}NO_7$: $[M + Na]^+$ *m/z* 830.4971. Found 830.4945.

(2*R*,3*R*,4*R*,5*R*)-N-{[(1,1-dimethylethoxy)carbonyl]amino}2-[(phenylmethoxy)-methyl]-3,4-bis-(phenylmethyloxy)-5-[1-phenylmethyloxy-4-oxy-tridecan-13-yl]pyrrolidine (20). Dess-Martin Periodinane (787 mg, 1.85 mmol) was added, in portions, to a solution of compound **19** (500 mg, 0.62 mmol) in CH_2Cl_2 (2 mL) maintained at 0°C under a nitrogen atmosphere. After 3 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) then treated with 1M aq $Na_2S_2O_3$ (5 mL) and 1M aq $NaHCO_3$ (5 mL). After being stirred vigorously for 15 min, the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL) and 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 pale yellow oil. Flash chromatography (0%−15% v/v ethyl acetate-hexane elution) gave **20** (450 mg, 90%) as a clear colourless oil: $[\alpha]_D$ + 12 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.33−7.25 (m, 20H), 4.62 (m, 2H), 4.53−4.34 (complex m, 7H), 4.15 (d, *J* = 6.2 Hz, 1H), 4.02 (m, 1H), 3.83−3.78 (m, 2H), 3.47 (m, 1H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.88 (quintet, *J* = 7.2 Hz, 2H), 1.45 (d, *J* = 14.5 Hz, 9H), 1.37−1.18 (m, 18H); ^{13}C NMR (75 MHz) δ 210.8 (C), 154.2 (CO), 138.8 (C), 138.5 (C), 138.2 (C), 137.9 (C), 128.6 (3 × CH, coincident), 128.5 (3 × CH, coincident), 128.4 (3 × CH, coincident), 127.9 (3 × CH, coincident), 127.8 (3 × CH, coincident), 127.7 (3 × CH, coincident), 127.6 (2 × CH, coincident), 84.9 (CH), 83.5 (CH), 73.2 (CH_2), 71.4 (CH_2), 71.9 (CH), 71.1 (CH_2), 70.8 (CH_2), 69.0 (CH_2), 64.9 (CH), 62.8 (CH), 62.3 (CH_2), 42.9 (CH_2), 35.7 (2 × CH_2, coincident), 32.4 (CH_2), 32.3 (CH_2), 31.8 (CH_2), 30.6 (2 × CH_2, coincident), 30.0 (2 × CH_2, coincident), 29.8 (CH_2), 29.7 (2 × CH_2, coincident), 28.8

($3 \times CH_3$, coincident); IR ν_{max} 3018, 2920, 1715, 1693, 1496, 1454, 1392, 1109, 737, 697 cm^{-1}; HRMS Calcd for $C_{51}H_{67}NO_7$: $[M + Na]^+$ *m/z* 828.4815. Found 828.4808.

***N*-Boc Broussonetine C (21).** Palladium black (10 mg) was added in one portion to a solution of compound **20** (50 mg, 0.06 mmol) in EtOH (0.6 mL) containing 3% acetic acid. The reaction mixture was stirred for 18 h at rt under an atmosphere of hydrogen. The reaction mixture was then filtered through a bed of Celite™, and the solvent was concentrated under reduced pressure to afford **21** (20 mg, 70%) as an amorphous white solid: $[\alpha]_D$ + 15 (*c* 0.1, $CHCl_3$); ^1H NMR (300 MHz) δ 4.72 (t, *J* = 6.4 Hz, 1H), 4.44 (t, *J* = 6.4 Hz, 1H), 4.28 (dd, *J* = 11.0 and 5.0 Hz, 1H), 4.22 (dd, *J* = 11.0 and 5.0 Hz, 1H), 3.92 (t, *J* = 7.3 Hz, 2H), 3.85 (m, 1H), 3.56 (m, 1H), 2.71 (t, *J* = 7.3 Hz, 2H), 2.44 (t, *J* = 7.3 Hz, 2H), 2.12 (quintet, *J* = 7.3 Hz, 2H), 2.04 (m, 2H), 1.62−1.15 (m, 16H), 1.45 (d, *J* = 14.5 Hz, 9H); ^{13}C NMR (75 MHz) δ 210.8 (C), 154.2 (CO), 84.4 (CH), 80.4 (CH), 65.3 (CH), 62.9 (CH), 61.4 ($2 \times CH_2$, coincident), 42.9 (CH_2), 35.7 ($2 \times CH_2$, coincident), 30.2 (CH_2), 29.9 (CH_2), 29.7 ($2 \times CH_2$, coincident), 29.5 (CH_2), 28.8 ($3 \times CH_3$, coincident), 27.9 (CH_2), 27.3 (CH_2), 24.2 (CH_2); IR ν_{max} 3405, 2920, 1704, 1693, 1496, 1454, 1352, 1098, cm^{-1}; HRMS Calcd for $C_{23}H_{43}NO_7$: $[M + Na]^+$ *m/z* 468.2937. Found 468.2925.

Broussonetine C (1). Trifluroacetic acid (0.2 mL) was added, dropwise, to a solution of **21** (15 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL) maintained at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 2 h after which time the solution was subsequently concentrated under reduced pressure. The residue was then stirred with diethyl ether (3 mL) whereupon the product crystallized. The solid material was collected by filtration, and washed with ether (3×2 mL) to afford Broussonetine C (8 mg, 60%): mp 146–149°C (lit.[2] mp 147–149°C); $[\alpha]_D$ + 32 (*c* 0.40, MeOH) {lit.[2] $[\alpha]_D$ + 25 (*c* 0.96, MeOH)}; ^1H NMR (300 MHz) δ 4.72 (t, *J* = 6.4 Hz, 1H), 4.44 (t, *J* = 6.4 Hz, 1H), 4.28 (dd, *J* = 11.0 and 5.0 Hz, 1H), 4.22 (dd, *J* = 11.0 and 5.0 Hz, 1H), 3.92 (t, *J* = 7.3 Hz, 2H), 3.85 (m, 1H), 3.56 (m, 1H), 2.71 (t, *J* = 7.3 Hz, 2H), 2.44 (t, *J* = 7.3 Hz, 2H), 2.12 (q, *J* = 7.3 Hz, 2H), 2.04 (m, 1H), 1.75 (m, 1H), 1.62 (m, 2H), 1.62−1.15 (m, 14H); ^{13}C NMR (75 MHz) δ 210.8 (CO), 84.4 (CH), 80.4 (CH), 65.3 (CH), 62.9 (CH), 61.41 ($2 \times CH_2$, coincident), 42.9 (CH_2), 35.7 ($2 \times CH_2$, coincident), 30.2 (CH_2), 29.9 (CH_2), 29.8 ($2 \times CH_2$, coincident), 29.5 (CH_2), 27.9 (CH_2), 27.3 (CH_2), 24.2 (CH_2).

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MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016