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D-Glucosamine-Derived Synthons for Assembly of L-threo-Sphingoid Bases. Total Synthesis of Rhizochalalin C

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Abstract

A five-step transformation of D-glucosamine – commencing with indium-mediated Barbier reaction, without isolation of intermediates – into (R,R)-2-amino-1,3-diol is described. The latter is a useful synthon for assembly of L-threo-sphingoid bases; long-chain aminoalkanols and aminoalkane-diols with configurations antipodal to that found in mammalian D-erythro-sphingosine, but prevalent among invertebrate-derived sphingolipids. The utility of the method is demonstrated by the first total synthesis of rhizochalalin C, the long-chain, ‘two-headed’ sphingoid base aglycone of the natural product rhizochalin C from the marine sponge *Rhizochalina incrustata*.

Introduction

Sphingosine (2-amino-octadec-4-en-1,3-diol) and related mammalian sphingosines possess the (2*S*,3*R*) configuration (D-erythro), but microbe and invertebrate-derived sphingoid bases exhibit broad stereochemical heterogeneity.^{1,2} L-threo-sphingoid bases have been reported from marine sponges, algae and tunicates. ‘Two-headed’ sphingolipids comprised of C₂₈–C₃₀ chains functionalized at each terminus as aminoalkanols or aminoalkane-diols³ span almost the complete set of permutations ($n = 16$) of the four stereocenters. For example, the Madagascan sponge *Rhizochalina incrustata* contains C₂₈ α,ω-bi-functionalized sphingoid bases (2*R*,3*R*,26*R*,27*R*)-rhizochalin C (**1b**)^{3f} (the 3-β-galactoside of rhizochalalin C, **1a**) and the pseudo-C₂ symmetric rhizochalin (**1c**).^{3a} The head groups of the latter compounds are both L-threo, but oceanapiside (**2b**) has a heterogeneous configuration: the 2-amino-1,3-diol head group is D-erythro while the ‘deoxy’ head group is L-threo. Monofunctionalized L-threo sphingoid base from marine organisms include halisphingosine A (**3a**)⁴ and its corresponding 6-deoxy derivative **3b**⁵ from two different species of *Haliclona* and (2*R*,3*R*)- and (2*R*,3*S*)-aminotetradec-5,7-dien-3-ols from *Xestospongia* sp.,⁶ while crucigasterins from the tunicate, *Pseudodistoma crucigaster*, have the L-erythro-(2*R*,3*S*)-configuration.^{2h}

Modified sphingoid bases have attracted interest because of their potent biological activity. The α,ω-bifunctionalized **2a** – and to a greater extent, the aglycone oceanin (**2a**) – exhibit significant antifungal activity against the pathogenic species *Candida albicans*, Fluconazole-

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Supporting Information Available. ¹H and ¹³C NMR data for all compounds are available free of charge via Internet at <http://pubs.acs.org>.

resistant *C. albicans*, *C. glabrata* and other species.⁷ Selective inhibitors of D-sphingosine kinase isoforms, SK1 and SK2, are attractive targets as anti-cancer and anti-inflammatory agents.⁸ Fingolimod (FTY720, **4**), an analog of the myriocin from *Mycelia sterilia*⁹ and other fungal species, is an anti-inflammatory agent and potent inhibitor of SK2; in 2010 it was approved for treatment of multiple sclerosis.¹⁰

1a R¹ = H, R² = OH

1b R¹ = β-gal R² = OH

1c R¹ = β-gal R² = H

2a R = H

2b R = β-glu

3a R = OH

3b R = H

4

Synthesis of sphinganine and related sphingoid bases has been extensively reviewed.¹¹ Approaches to D-erythro-2-aminoalkanols and 2-aminoalkan-1,3-diols utilizing chiral pool starting materials commonly begin with natural L-serine and L-alanine, respectively, however, preparation of L-sphingoid bases require more expensive D-amino acids. Here, we disclose an optimized procedure for rapid diastereoselective access to L-threo-sphingoid base synthons using a remarkable five-step conversion of *unprotected* D-glucosamine into useful D-serine synthons based on In⁰-mediated allylation. The method was successfully applied to **1a**; the first synthesis of a member of the family of two-headed sphingolipids.

Inexpensive D-glucosamine has been exploited for preparation for L-serine synthons through oxidative degradation to N-Boc-L-serinal that re-functionalizes C-3 to a carboxaldehyde (Figure 1).¹² Conceptually, inverting the orientation of oxidative remodeling of D-glucosamine by alkylation at C-1 followed by periodate cleavage of the C-3–C-4 bond and reductive workup would result in D-serine synthons.¹³ Organoindium compounds have found utility in homologation of aldohexoses and ketoses, largely due to their compatibility with water.¹⁴ Carbon-carbon bond formation at C-1 of D-glucosamine is conveniently carried out by Barbier-type allylation in the aqueous solvents necessary to

solubilize D-glucosamine. Whitesides¹⁵ and Chan^{16b} had earlier shown aldoses and some ketoses underwent Barbier allylation with allyl bromide (refluxing THF) in the presence of Sn^0 , however, *N*-acetyl-D-glucosamine and *N*-acetyl-D-mannosamine were inert under these conditions.¹⁷ In contrast, *N*-acetyl-D-mannosamine was allylated in high yield (90%) with In^0 and the more reactive ethyl α -bromomethacrylate in warm acidic ethanol (HCl, 55 °C), and subsequently converted to sialic acid (Neu5Ac).¹⁸ Paquette demonstrated Barbier allylation of *N*-acetyl-D-mannosamine with allyl bromide (In^0 , 0.5 M NH_4Cl , aqu, 25 °C) with high *threo* selectivity (8.6:1), albeit in low yield (31%).¹⁹ Amino acid derived *N*-Cbz- α -aminoaldehydes undergo Barbier-type allylations under a variety of conditions in yields up to 82%,²⁰ or *N*-Boc- α -aminoaldehydes up to 90%²⁰ – again mostly with *threo* selectivity – but *erythro* selectivity with Garner's aldehyde.²¹ Critical evaluation of these reports suggest that allylations of amino sugars under aqueous conditions suffer from lower yields compared to aldohexoses, or succeed only with *N*-acyl-2-amino-2-deoxyhexoses which limits their utility for sphingoid base synthesis.

Results and Discussion

In order to investigate methodology to improve the scope of the In^0 -mediated allylation reaction of aldohexoses, we further explored the Barbier allylation of D-glucosamine and its derivatives under aqueous conditions (Table 1). Various *N*-protected glucosamines (1–2 mmol) were reacted with allyl bromide in the presence of powdered In^0 (4:1 THF- H_2O , reflux) to yield mixtures of the 2-amino-1,3-hexenols diastereoisomers, *threo-i* and *erythro-ii* (Table 1) in varying diastereomeric ratios that always favored *threo-i* under chelation control, as noted earlier.^{15,20} The product yields were variable (38–78%) with the best yield obtained with *N*-Boc-D-glucosamine (entry 1, 78%). Reaction of *N*-Tosyl D-glucosamine under similar conditions, but replacement of the solvent with THF: H_2O mixtures of various ratios (1:4 to 4:1, not shown) resulted in similar or lower yields (9–40%).

We found, to our delight, that In^0 -mediated allylation of *unprotected* D-glucosamine gave the best results (Table 2) approaching quantitative yields. Optimization of conditions (Table 2, entry 4) resulted in excellent conversion of D-glucosamine (1–2 mmol) to diastereomeric allylation products (96% yield, *dr*(*threo*:*erythro*)=7.5:1) in the presence of In^0 powder (4 equiv) and excess allylbromide (6 equiv) at reflux (100 °C) in aqueous dioxane (1,4-dioxane- H_2O 2:1).

Paquette and co-workers reported higher *threo*-product in In^0 -mediated allylation of α -oxygenated-aldehydes upon addition of metal salts, $(\text{Et})_4\text{NX}$ and NH_4Cl .²² In contrast, we found higher amounts of *erythro ii* upon allylation of D-glucosamine in the presence of metal salts, particularly MgCl_2 (*i:ii dr*= 3.5:1, 94%, Entry 5), with comparable yields.

Scale-up of the 5-step conversion of D-glucosamine (0.5 – 3 g) was optimized (Scheme 1) as follows. In^0 -mediated allylation of D-glucosamine followed by sequential periodate cleavage (NaIO_4 , H_2O), reduction (NaBH_4 , MeOH), without isolation of the intermediates from the aqueous milieu, and conversion of the resulting 1,3-diols to acetonides (2,2-dimethoxypropane, CH_2Cl_2 , cat. CSA) gave *threo-5a*²³ and *erythro-5b* (*dr* = 7.5:1). Unlike allylation products *i* and *ii*, the latter compounds were sufficiently non-polar to allow recovery and separation by silica chromatography (51% total yield, *dr* 7:1 over 5 steps).²⁴ The 5-step conversion could be scaled up to 5.6 mmol of D-glucosamine (51% overall yield

of **5a**) or to 17 mmol, albeit with some loss in yield (45%) and only slight erosion of *dr* (7:1 **5a:5b**).

The products **5a** and **5b** are useful synthons for preparation of α,ω -dimeric sphingoid bases such as rhizochalalin C (**2**) according to the retrosynthetic analysis depicted in Figure 2.

The allyl groups corresponding to left-hand and right-hand halves of the target molecule can be conveniently coupled by olefin cross-metathesis with suitable differentiation by chain length and ω -functionalization for final unification of the two halves by Horner-Emmons-Wadsworth reaction and global deprotection-hydrogenation to give **1a**. A convergent advantage arises by derivation of both halves of rhizochalalin C from the allyl substituted compounds **5a** and **6a** that are procured from the same Barbier allylation of D-glucosamine followed by differential protections of NH₂ and OH groups.

The left-hand half of rhizochalalin C was elaborated as shown in Scheme 2. Compound **5a** was subject to olefin cross-metathesis with tetradec-13-enyl acetate in the presence of Grubbs II catalyst to provide, after methanolysis (NaOMe, MeOH), primary alcohol **7** (51%, 2 steps) as an inconsequential mixture of *E/Z* isomers (9.6:1) which was carried forward as such.²⁵ Oxidation of **7** (Dess-Martin periodinane) to the corresponding aldehyde **8** (80%) followed by addition of the anion derived from diethyl methylphosphonate (*n*-BuLi, -78 °C, THF)²⁶ and Dess-Martin oxidation delivered the β -ketophosphonate **9** (64%, 2 steps).

The right-hand half of **1a** was prepared as shown in Scheme 3. The multi-step Barbier allylation-oxidation sequence (Scheme 1) was repeated on D-glucosamine except for a different *N*-protecting group ((Boc)₂O, NaHCO₃, aq) and conversion of the 1,3-diol to a benzylidene acetal (benzaldehyde dimethyl acetal, CSA) to provide **6** in 35% over 5 steps. Differential C-O bond cleavage of the benzylidene group was achieved under two sets of conditions: reduction with in situ generated alane (AlCl₃, LiAlH₄, CH₂Cl₂, 0 °C, 98%)²⁷ or DIBAL-H (toluene, 0 °C, 67%) to give **10**.

The alcohol **10** was transformed into the phenylthio ether to give **11** (*n*-Bu₃P, (PhS)₂, 88%) in preparation for later reductive removal. Olefin cross-metathesis of **11** with 4-penten-1-yl acetate (Grubbs II cat.,³⁰ CH₂Cl₂, reflux) followed by methanolysis (NaOMe, MeOH) gave primary alcohol **12** as an inconsequential mixture of geometrical isomers (*E:Z* = 7:1, 85%, 2 steps) which was carried forward without separation. Reduction of **12** (Ra-Ni) delivered protected *threo*-2-amino-3-alkanol **13** (88%). Oxidation of **13** to aldehyde **14** (Dess-Martin, 85%) completed the right-hand half of **1a** and set the stage for coupling of the two segments.

Horner-Emmons-Wadsworth reaction of aldehyde **14** and phosphonate **9** (Scheme 4) under Paterson conditions²⁸ (Ba(OH)₂, THF) gave the α,β -unsaturated ketone **15** as a mixture of *E/Z* isomers (88%), but exclusively *E* at C-19, C-20. Global deprotection of compound **15** (10M HCl, MeOH, H₂ 2 atm, Pd-C) gave **1a**•2HCl. Purification of the latter salt under basic conditions (silica, flash chromatography, 9:4:1 CHCl₃, MeOH, NH₄OH aqu.) afforded the free base rhizochalalin C (**1a**) as a *single stereoisomer* (87%). The ¹H NMR, ¹³C NMR, [α]_D, HRMS data of the synthetic **1a** matched those of the algycone derived from natural rhizochalalin C (**1b**). Finally, the CD spectrum of the tetra-benzoyl derivative **16** (Figure 3) prepared from synthetic **1a** (BzCl, pyridine) was identical in sign and magnitude to that prepared in two steps from naturally-derived **1b**,^{3b} confirming the original assignment by deconvolution of CD exciton coupling^{3c} and demonstrating stereochemical integrity (>95% ee) of the final synthetic product.

In conclusion, we have demonstrated a practical and versatile preparation of *D-threo* serine-related synthons in good yield by a five-step conversion of D-glucosamine. The latter was

exploited for a bidirectional bond construction and convergent assembly of rhizochalinin C (**1a**),³ the first total synthesis of a member of the marine-derived ‘two-headed’ sphingolipids.^{3f} The method should find utility in the synthesis of other *L-threo* sphingoid bases that is the subject of ongoing research in our laboratories to be reported in due course.

Experimental Section

General Experimental Procedures

General experimental procedures are described in the Supporting Information and elsewhere.²⁹ ¹³C NMR signal multiplicities (CH₃, CH₂, CH, C_q) were determined from DEPT 90 and DEPT 135 experiments.

General procedure for Indium-mediated allylation (Barbier reaction)

A mixture of D-glucosamine or *N*-protected D-glucosamine (1.16 mmol) and In⁰ powder (4 equiv) was suspended in solvent (15 mL, freshly purified THF, 1,4-dioxane, H₂O or mixtures thereof; see Tables 1–3) at rt. Allyl bromide (6 equiv) was added and the mixture was heated to reflux (100 °C) and allowed to react until no starting material was evident (TLC) or no change of product to starting material ratio could be detected (¹H NMR, internal calibration with added caffeine) (See Tables 1–3). The heterogeneous mixture was cooled to room temperature, the insoluble solid was removed by centrifugation and the supernatant was neutralized (pH 7~8) by addition of saturated NaHCO₃. Excess (Boc)₂O was added, and the mixture subsequently stirred at room temperature for 2 hours, diluted with methanol and filtered with micro filter (0.45 μm). The filtrate was analyzed by HPLC (reversed phase C₁₈, 22.5:77.5 CH₃CN: H₂O, ELSD detector).

Benzyl (4*R*,5*R*)-4-allyl-2,2-dimethyl-1,3-dioxan-5-yl-carbamate (5a and 5b)—D-Glucosamine (3.00 g, 13.9 mmol) was suspended in 1,4-dioxane (135 mL) and distilled water (45 mL). Allyl bromide (4.8 mL, 56 mmol) and In⁰ powder (3.2 g, 28 mmol) were added, and the mixture was heated at reflux for 20 h. The reaction mixture was cooled to 10 °C and neutralized to pH 7~8 with 1M NaOH solution prior to addition of NaHCO₃ (1.7 g, 21 mmol) and benzyl chloroformate (3 mL, 20.8 mmol) with continued stirring at room temperature for 24 h. After recooling to 5 °C, sodium periodate (8.9 g, 41.7 mmol) was slowly portionwise and the mixture stirred vigorously for 3 h at room temperature before removal of volatiles was removed under reduced pressure. The residue was suspended in methanol (200 mL) and insoluble material was removed by filtration. The filtrate was cooled to 5 °C and sodium borohydride (1.6 g, 41.7 mmol) was slowly added, followed by stirring for 3 h before quenching by addition of water (50 mL). Volatiles were removed under reduced pressure and the mixture was diluted with brine (200 mL) and extracted with ethyl acetate (200 mL × 2). The combined organic extracts were dried with MgSO₄ and concentrated under reduced pressure. The oily residue was dissolved in acetone (50 mL) and treated with excess 2,2-dimethoxypropane (24 mL) and a catalytic amount of camphorsulfonic acid (60 mg), then stirred at room temperature for 5 h. After confirming the completion of reaction by TLC, the reaction was quenched with triethylamine (9 mL) and the mixture concentrated under reduced pressure. Purification of the residue by flash chromatography (silica, 10% Et₂O in hexanes) gave the two diastereomers (4*R*,5*R*)-**5a** and (4*S*,5*R*)-**5b** (total 1.9 g, 45 %, *dr* = 7:1).

(4*R*,5*R*)-**5a**: FTIR (ATR, neat) ν 1715, 1504, 1214, 1085 cm⁻¹; [α]_D -23 (*c* 0.083, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.30–7.41 (m, 5H), 5.74–5.83 (m, 1H), 5.57 (dd, *J* = 9.7 Hz, 1H), 5.05–5.15 (m, 4H), 4.06 (dd, *J* = 12.0, 1.7 Hz, 1H), 3.98 (dt, *J* = 6.9, 1.7 Hz, 1H), 3.77 (dd, *J* = 12.0, 1.7 Hz, 1H), 3.61 (m, 1H), 2.21 (m, 2H), 1.46 (s, 3H), 1.39 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.2 (C_q), 136.5 (C_q), 133.4 (CH), 128.6 (CH), 128.2

(CH), 128.1 (CH), 117.8 (CH₂), 99.2 (C_q), 72.0 (CH), 66.9 (CH₂), 65.2 (CH₂), 47.2 (CH), 36.3 (CH₂), 29.7 (CH₃), 18.6 (CH₃); HR-ESI-FT-MS m/z [M+Na]⁺ 328.1516 calcd for C₁₇H₂₃NO₄Na 328.1519.

(4*S*,5*R*)-**5b**: FTIR (ATR, neat) ν 1691, 1536, 1225, 1023 cm⁻¹; [α]_D -21 (*c* 0.076, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.30–7.38 (m, 5H), 5.77–5.88 (m, 1H), 5.03–5.13 (m, 4H), 4.66 (br, 1H), 3.91–3.94 (m, 1H), 3.55–3.67 (m, 3H), 2.38–2.42 (m, 1H), 2.25–2.29 (m, 1H), 1.42 (s, 3H), 1.39 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 155.8 (C_q), 136.3 (C_q), 133.1 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 117.1 (CH₂), 98.9 (C_q), 72.2 (CH), 67.0 (CH₂), 63.1 (CH₂), 49.6 (CH), 37.1 (CH₂), 28.1 (CH₃), 19.9 (CH₃); HR-ESI-FT-MS m/z [M+Na]⁺ 328.1517 calcd for C₁₇H₂₃NO₄Na 328.1519.

tert-Butyl (5*R*)-4-allyl-2-phenyl-1,3-dioxan-5-ylcarbamate (6a, 6b)—D-glucosamine (3g, 13.9 mmol) was suspended in 1,4-dioxane (135 mL) and distilled water (45 mL). Allyl bromide (4.8 mL, 56 mmol) and In^o powder (3.2 g, 28 mmol) were added and the mixture heated at reflux for 20 h. The reaction solution was cool to 10 °C and adjusted to pH 7~8 with 1M NaOH solution. NaHCO₃ (1.7 g, 20.8 mmol) and di-*tert*-butyl bicarbonate (4.5 g, 21 mmol) were added to neutralized solution of allylated D-glucosamine at 5 °C. The solution was stirred at room temperature for 24 h then cooled to 5 °C prior to slow, portion-wise addition of sodium periodate (8.9 g, 42 mmol). The mixture was stirred vigorously for 3 h at room temperature and, after completion of reaction, the volatiles were removed under reduced pressure, the residue resuspended in methanol (200 mL) and the insoluble solid removed by filtration. The filtrate was cool to 5 °C and sodium borohydride (1.6 g, 42 mmol) was added slowly, and the solution stirred for 3 h. After quenching the mixture by addition of H₂O (50 mL), the volatiles were removed under reduced pressure. Brine (200 mL) was added to the mixture followed by extraction with EtOAc (200 mL $\times$ 2). The combined organic extracts were dried with MgSO₄ and concentrated under reduced pressure, and the oily residue dissolved in dry CH₂Cl₂ (50 mL). Benzaldehyde dimethyl acetal (2.7 mL, 19 mmol) and a catalytic amount of camphorsulfonic acid (10 mg) were added to the solution, and the mixture stirred at room temperature for 5 h. After the completion of the reaction (TLC), the reaction mixture was quenched by addition of triethylamine (4 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, elution with 10% ether in hexanes) gave the pure compounds (4*R*,5*R*)-**6a** and (4*S*,5*R*)-**6b** (total 1.5 g, 35 %, 5 steps, *dr* = 7:1).

(4*R*, 5*R*)-**6a**: FTIR (ATR, neat) ν 1711, 1499, 1365, 1168 cm⁻¹; [α]_D +3.2 (*c* 0.11, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.45–7.52 (m, 2H), 7.32–7.42 (m, 3H), 5.88 (m, 1H), 5.57 (s, 1H), 5.38 (d, *J* = 10.3 Hz, 1H), 5.10 – 5.18 (m, 2H), 4.17 (dd, *J* = 11.5, 1.7 Hz, 1H), 4.06 (dd, *J* = 11.5, 1.7 Hz, 1H), 3.98 (m, 1H), 3.70 (m, 1H), 2.41 (m, 1H), 2.32 (m, 1H), 1.46(s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 155.8 (C_q), 138.1 (C_q), 133.4 (CH), 129.1 (CH), 128.4 (CH), 126.0 (CH), 118.1 (CH₂), 101.6 (CH), 79.7 (C_q), 79.5 (CH), 72.2 (CH₂), 46.9 (CH), 36.3 (CH₂), 28.5 (CH₃) HR-ESI-FT-MS m/z [M+Na]⁺ 342.1674 calcd for C₁₈H₂₅NO₄Na 342.1681

(4*S*, 5*R*)-**6b**: [α]_D -22.3 (*c* 0.16, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.45–7.52 (m, 2H), 7.30–7.40 (m, 3H), 5.95 (m, 1H), 5.43 (s, 1H), 5.10 – 5.17 (m, 2H), 4.29 (dd, *J* = 10.8, 4.3 Hz, 1H), 4.27 (br, 1H), 3.75 (m, 1H), 3.59 (m, 1H), 3.50 (dd, *J* = 10.8, 10.8 Hz, 1H), 2.53 (m, 1H), 2.42 (m, 1H), 1.47(s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 155.1 (C_q), 137.9 (C_q), 134.1 (CH), 129.0 (CH), 128.4 (CH), 126.2 (CH), 117.5 (CH₂), 101.1 (CH), 80.6 (CH), 80.1 (C_q), 70.0 (CH₂), 47.4 (CH), 36.7 (CH₂), 28.5 (CH₃); HR-ESI-FT-MS m/z [M+Na]⁺ 342.1674 calcd for C₁₈H₂₅NO₄Na 342.1681

Benzyl (4*R*,5*R*)-4-((*E*)-15-hydroxypentadec-2-enyl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (7)—To a solution of **5a** (709 mg, 2.32 mmol) in dry CH₂Cl₂ (20 mL) was added tetradec-13-enyl acetate (3.6 g, 14 mmol) and Grubbs 2nd generation catalyst (90 mg, 0.10 mmol)³⁰ under N₂ at room temperature. After reaction mixture was stirred for 2h under reflux, solvent was removed *in vacuo* to give a dark-brown oil. To the stirred solution of dark brown oil in MeOH (20 mL) at room temperature was added 1M CH₃ONa in methanol (3.5 mL, 3.5 mmol) and after 2h, methanol was removed under reduced pressure. Water (20 mL) was added and the reaction mixture was extracted with ethyl acetate (30 mL × 2) and combined organic extracts were dried with MgSO₄ and concentrated under reduced pressure. Flash chromatography of the residue (silica gel, 15% EtOAc-hexane) gave alcohol **7** (580 mg, 51% for 2 steps) as a colorless oil (*E/Z* = 9.6:1).

FTIR (ATR, neat) ν 1715, 1506, 1215, 1083 cm⁻¹; *E*-isomer: ¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.40 (m, 5H), 5.55 (d, *J* = 9.9 Hz, 1H), 5.47 (dt, *J* = 15.4, 6.6 Hz, 1H), 5.34 (dt, *J* = 15.4, 6.9 Hz, 1H), 5.11 (m, 2H), 4.03 (dd, *J* = 11.7, 1.5 Hz, 1H), 3.90 (td, *J* = 6.9, 1.5 Hz, 1H), 3.72 (dd, *J* = 12.1, 1.5 Hz, 1H), 3.63 (t, *J* = 6.6 Hz, 2H), 3.58 (m, 1H), 2.13 (m, 2H), 1.96 (m, 2H), 1.72 (brs, 1H), 1.55 (m, 2H), 1.45 (s, 3H), 1.38 (s, 3H), 1.20 – 1.36 (m, 18H); ¹³C NMR (100 MHz, CDCl₃) δ 156.2 (C_q), 136.6 (C_q), 134.4 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 124.2 (CH), 99.3 (C_q), 71.7 (CH), 66.9 (CH₂), 65.3 (CH₂), 63.2 (CH₂), 47.1 (CH), 35.2 (CH₂), 33.0 (CH₂), 32.8 (CH₂), 29.8 (CH₃), 29.7₅ (CH₂), 29.7₃ (CH₂), 29.7₀ (CH₂), 29.6 (CH₂), 29.5₆ (CH₂), 29.5₂ (CH₂), 29.3 (CH₂), 25.9 (CH₂), 18.7 (CH₃); HR-ESI-FT-MS *m/z* [M+Na]⁺ 512.3344 calcd for C₂₉H₄₇NO₅Na 512.3351

Benzyl (4*R*,5*R*)-2,2-dimethyl-4-((*E*)-15-oxopentadec-2-enyl)-1,3-dioxan-5-ylcarbamate (8)—Dess-Martin periodinane (390 mg, 0.92 mmol) was added portionwise to a stirred, cooled (5 °C) solution of compound **7** (300 mg, 0.61 mmol) in dry CH₂Cl₂ (10 mL) and, after 2h at 0 °C, the reaction was quenched by the addition of satd. aqueous NaHCO₃ (10 mL). The reaction mixture was extracted with CH₂Cl₂ (15 mL × 2) and the combined organic extracts were dried with MgSO₄ and concentrated under reduced pressure. Flash chromatography of the residue (silic, 12% EtOAc-hexane) gave aldehyde **8** (238 mg, 80 %) as colorless oil (*E/Z* = 9.6:1).

FTIR (ATR, neat) ν 1724, 1505, 1214, 1085 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) *E*-isomer: δ 9.75 (t, *J* = 1.8 Hz, 1H), 7.29 – 7.39 (m, 5H), 5.54 (d, *J* = 9.9 Hz, 1H), 5.45 (dt, *J* = 15.5, 6.9 Hz, 1H), 5.36 (dt, *J* = 15.5, 6.9 Hz, 1H), 5.10 (m, 2H), 4.03 (dd, *J* = 12.0, 1.7 Hz, 1H), 3.90 (td, *J* = 6.9, 1.7 Hz, 1H), 3.77 (dd, *J* = 12.0, 1.7 Hz, 1H), 3.59 (m, 1H), 2.40 (dt, *J* = 7.5, 1.7 Hz, 2H), 2.14 (dd, *J* = 6.9, 6.9 Hz, 2H), 1.96 (m, 2H), 1.60 (m, 2H), 1.44 (s, 3H), 1.37 (s, 3H), 1.23 – 1.37 (m, 16H). ¹³C NMR (100 MHz, CDCl₃) δ 203.1 (CH), 156.2 (C_q), 136.6 (C_q), 134.4 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 124.2 (CH), 99.3 (C_q), 71.7 (CH), 66.9 (CH₂), 65.3 (CH₂), 47.1 (CH), 44.1 (CH₂), 35.2 (CH₂), 32.8 (CH₂), 29.8 (CH₃), 29.7₅ (CH₂), 29.7₃ (CH₂), 29.6 (CH₂), 29.5₇ (CH₂), 29.5₅ (CH₂), 29.5₁ (CH₂), 29.3 (CH₂), 22.2 (CH₂), 18.7 (CH₃); HR-ESI-FT-MS *m/z* [M+Na]⁺ 510.3191 calcd for C₂₉H₄₅NO₅Na 510.3190

Benzyl (4*R*,5*R*)-4-((*E*)-16-(diethoxyphosphoryl)-15-oxohexadec-2-enyl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (9)—To a cooled solution of diethyl methylphosphonate (242 mg, 1.54 mmol) in THF (10 mL) was added *n*-butyllithium (2.21 M in hexane, 698 μ L, 1.54 mmol) over 10 min at –78 °C followed, after 15 min, by a solution of aldehyde **8** (251 mg, 0.51 mmol) in THF (10 mL). After 60 min at –78 °C, saturated aqueous NH₄Cl was added, and mixture was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Flash chromatography of the residue (silica, 35% EtOAc-hexane) gave the secondary alcohol (262 mg) as colorless oil and starting material (38 mg, 15 %). The

secondary alcohol (262 mg, 0.41 mmol) was dissolved in dry CH₂Cl₂ (15 mL), cooled to 0 °C and treated portionwise with Dess-Martin periodinane (261 mg, 0.62 mmol) followed by stirring for 2 h at 0 °C. The reaction was quenched by the addition of sat. NaHCO₃ solution (10 mL), the mixture extracted with CH₂Cl₂ (15 mL × 2) and the combined organic extracts were dried with MgSO₄ and concentrated under reduced pressure. Flash chromatography of the residue (silica gel, 50% EtOAc-hexane) gave phosphonate **9** (210 mg, 64% for 2 steps) as colorless oil (*E/Z* = 9.6:1).

FTIR (ATR, neat) ν 1714, 1505, 1242, 1023, 970 cm⁻¹; *E*-isomer ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.40 (m, 5H), 5.52 (d, *J* = 9.7 Hz, 1H), 5.45 (dt, *J* = 14.9, 6.9 Hz, 1H), 5.35 (dt, *J* = 14.9, 6.9 Hz, 1H), 5.11 (m, 2H), 4.14 (m, 4H), 4.04 (dd, *J* = 12.0, 1.7 Hz, 1H), 3.90 (td, *J* = 6.9, 1.7 Hz, 1H), 3.77 (dd, *J* = 12.0, 1.7 Hz, 1H), 3.59 (m, 1H), 3.06 (d, *J* = 22.9 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 2H), 2.13 (m, 2H), 1.96 (m, 2H), 1.56 (m, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 1.33 (t, *J* = 6.9 Hz, 6H), 1.21–1.30 (m, 16H); ¹³C NMR (100 MHz, CDCl₃) δ 202.3 (d, *J*_{CP} = 6.1 Hz, C_q), 156.2 (C_q), 136.5 (C_q), 134.3 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 124.1 (CH), 99.1 (C_q), 71.6 (CH), 66.8 (CH₂), 65.2 (CH₂), 62.5 (d, *J*_{CP} = 6.1 Hz, CH₂), 47.0 (CH), 44.1 (CH₂), 41.7 (d, *J*_{CP} = 127.4 Hz, CH₂), 35.1 (CH₂), 32.7 (CH₂), 29.7 (CH₃), 29.6₄ (CH₂), 29.6₀ (CH₂), 29.5₂ (CH₂), 29.5₀ (CH₂), 29.4 (CH₂), 29.2 (CH₂), 29.0 (CH₂), 23.5 (CH₂), 18.6 (CH₃), 16.3 (d, *J*_{CP} = 6.1 Hz, CH₃); HR-ESI-FTMS *m/z* [M+H]⁺ 638.3815 calcd for C₃₄H₅₇NO₈P 638.3816

***tert*-Butyl (2*R*,3*R*)-3-(benzyloxy)-1-hydroxyhex-5-en-2-ylcarbamate (10)**

(alane method): To a cool suspension of LiAlH₄ (90 mg, 2.3 mmol) and **6a** (163 mg, 0.51 mmol) in CH₂Cl₂-diethyl ether (1:1, 5 mL) at 0 °C was added, dropwise, an ethereal solution of AlCl₃ (182 μ L, 4.1 M diethyl ether solution, 0.76 mmol) and the mixture stirred at 25 °C for 2 h before quenching at 0 °C by dropwise addition of EtOAc (2 mL), followed by H₂O (10 mL). The resulting mixture was extracted with EtOAc (10 mL × 3) and the combined organic extracts were washed with brine (5 mL), dried with MgSO₄ and concentrated under reduced pressure. Flash chromatography of the residue (silica, 17% EtOAc-hexane) gave the alcohol **10** (160 mg, 98 %) as a colorless oil.

(DIBAL-H method): To a cooled solution of **6a** (92 mg, 0.29 mmol) in dry CH₂Cl₂ (3 mL) was added DIBAL-H (575 μ L, 1.5 M toluene solution, 0.86 mmol) at 0 °C and the reaction mixture was stirred for 2 h. A solution of Rochelle's salt (3 mL, satd) was added and the mixture was stirred for 1 h then extracted with CH₂Cl₂ (5 mL × 3). The combined organic extracts were washed with brine (5 mL), dried with MgSO₄ and concentrated under reduced pressure. Purification, as described above, gave **10** (62 mg, 67 %) as a colorless oil.

FTIR (ATR, neat) ν 3441, 1692, 1496, 1164 cm⁻¹; [α]_D -4.1 (c 0.066, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.39 (m, 5H), 5.82 (m, 1H), 5.09–5.17 (m, 2H), 5.03 (d, *J* = 8.6 Hz, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 3.76 (m, 1H), 3.70 (m, 2H), 3.62 (m, 1H), 2.46 (m, 1H), 2.35 (m, 1H), 1.67 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 156.5 (C_q), 138.0 (C_q), 134.0 (CH), 128.6 (CH), 128.1 (CH), 128.0 (CH), 118.2 (CH₂), 79.7 (C_q), 78.1 (CH), 72.4 (CH₂), 64.0 (CH₂), 54.0 (CH), 35.6 (CH₂), 28.5 (CH₃).

***tert*-Butyl (2*S*,3*R*)-3-(benzyloxy)-1-(phenylthio)hex-5-en-2-ylcarbamate (11)—**

Compound **10** (406 mg, 1.26 mmol) in THF (10 mL) was added to a solution of tri-*n*-butylphosphine (786 μ L, 3.16 mmol) and phenyl disulfide (190 mg, 3.16 mmol) in THF (10 mL) at 0 °C. After stirring at room temperature for 18 h, the solvent was removed under reduced pressure to give the crude product which was purified by flash chromatography (silica gel, 5% EtOAc-hexane) to provide phenylthioether **11** (462 mg, 88%) as a colorless oil.

FTIR (ATR, neat) ν 1712, 1494, 1166 cm^{-1} ; $[\alpha]_{\text{D}} -3.5$ (c 0.14, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.23–7.42 (m, 9H), 7.13–7.21 (m, 1H), 5.76 (m, 1H), 5.02–5.15 (m, 2H), 4.96 (d, $J = 9.2$ Hz, 1H), 4.64 (d, $J = 11.5$ Hz, 1H), 4.37 (d, $J = 11.5$ Hz, 1H), 3.87 (m, 2H), 3.16 (dd, $J = 13.8, 5.7$ Hz, 1H), 2.99 (dd, $J = 13.2, 9.2$ Hz, 1H), 2.46 (m, 1H), 2.28 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.5 (C_q), 138.2 (C_q), 136.1 (C_q), 134.0 (CH), 129.3 (CH), 129.1 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 126.2 (CH), 118.1 (CH_2), 79.5 (C_q), 77.5 (CH), 72.5 (CH_2), 52.1 (CH), 35.8 (CH_2), 35.7 (CH_2), 28.5 (CH_3); HR-ESI-FT-MS m/z $[\text{M}+\text{Na}]^+$ 436.1919 calcd for $\text{C}_{24}\text{H}_{31}\text{NO}_3\text{Na}$ 436.1917

***tert*-Butyl (2*S*,3*R*,*E*)-3-(benzyloxy)-9-hydroxy-1-(phenylthio)non-5-en-2-ylcarbamate (12)**—Grubbs 2nd Generation catalyst (45 mg, 0.05 mmol) was added to a solution of compound **11** (437 mg, 1.06 mmol) and 4-penten-1-yl acetate (1.50 mL, 10.6 mmol) in dry CH_2Cl_2 (20 mL) under N_2 at room temperature, and the mixture stirred for 4h under reflux. Removal of the volatiles under reduced pressure gave a dark brown oil which was taken up in MeOH (20 mL) was treated with 1M $\text{CH}_3\text{O}^-\text{Na}^+$ in methanol (12.7 mL, 12.7 mmol). After stirring the reaction mixture for 2h at room temperature, methanol was removed under reduced pressure and the residue purified by flash chromatography (silica gel, 20% EtOAc-hexane) to afford compound **12** as colorless oil (*E*:*Z* = 7:1) (423 mg, 85 % for 2 steps).

FTIR (ATR, neat) ν 3443, 1695, 1494, 1162 cm^{-1} ; $[\alpha]_{\text{D}} -3.1$ (c 0.093, CHCl_3); *E*-isomer ^1H NMR (500 MHz, CDCl_3) δ 7.25–7.41 (m, 9H), 7.13–7.91 (m, 1H), 5.40 (dt, $J = 14.9, 6.9$ Hz, 1H), 5.23 (dt, $J = 14.9, 7.5$ Hz, 1H), 4.99 (d, $J = 9.2$ Hz, 1H), 4.63 (d, $J = 11.5$ Hz, 1H), 4.36 (d, $J = 11.5$ Hz, 1H), 3.85 (m, 2H), 3.47 (t, $J = 6.3$ Hz, 2H), 3.07 (dd, $J = 13.2, 5.2$ Hz, 1H), 2.88 (dd, $J = 13.2, 9.2$ Hz, 1H), 2.33 (m, 1H), 2.09 (m, 1H), 1.93 (m, 2H), 1.70 (br, 1H), 1.46 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.6 (C_q), 138.2 (C_q), 136.1 (C_q), 133.7 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.1 (CH), 127.9 (CH), 126.1 (CH), 125.6 (CH), 79.5 (C_q), 77.6 (CH), 72.3 (CH_2), 62.3 (CH_2), 52.5 (CH), 35.5 (CH_2), 34.1 (CH_2), 32.1 (CH_2), 28.9 (CH_2), 28.5 (CH_3); HR-ESI-FT-MS m/z $[\text{M}+\text{Na}]^+$ 494.2337 calcd for $\text{C}_{27}\text{H}_{37}\text{NO}_4\text{Na}$ 494.2336

***tert*-Butyl (2*R*,3*R*,*E*)-3-(benzyloxy)-9-hydroxynon-5-en-2-ylcarbamate (13)**—To a solution of compound **12** (200 mg, 0.42 mmol) in methanol (3 mL) was added an excess of Raney 2800 nickel (washed with methanol three times *just prior to use*). The reaction mixture was stirred vigorously at room temperature for 2h at which point TLC analysis indicated completion of the reaction. The mixture was filtered through Celite and the filtrate concentrated under reduced pressure to a residue that was purified by flash chromatography (silica, 20% EtOAc-hexane) to provide primary alcohol **13** as a colorless oil (135 mg, 88%, *E*/*Z* = 7:1).

FTIR (ATR, neat) ν 3444, 1713, 1519, 1206, 1059 cm^{-1} ; *E*-isomer ^1H NMR (500 MHz, CDCl_3) δ 7.28–7.38 (m, 5H), 5.53 (dt, $J = 15.3, 6.6$ Hz, 1H), 5.44 (dt, $J = 15.5, 6.8$ Hz, 1H), 4.79 (br, 1H), 4.64 (d, $J = 11.5$ Hz, 1H), 4.49 (d, $J = 11.5$ Hz, 1H), 3.83 (m, 1H), 3.64 (t, $J = 6.4$ Hz, 2H), 3.32 (m, 1H), 2.34 (m, 1H), 2.21 (m, 1H), 2.10 (m, 2H), 1.81 (br, 1H), 1.64 (m, 2H), 1.44 (s, 9H), 1.16 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.6 (C_q), 138.4 (C_q), 133.1 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 126.2 (CH), 81.7 (CH), 78.9 (C_q), 72.4 (CH_2), 62.3 (CH_2), 47.8 (CH), 34.2 (CH_2), 32.2 (CH_2), 28.9 (CH_2), 28.4 (CH_3), 18.6 (CH_3); HR-FAB-MS m/z $[\text{M}+\text{H}]^+$ 364.2491 calcd for $\text{C}_{21}\text{H}_{34}\text{NO}_4$ 364.2488

***tert*-Butyl-(2*R*,3*R*,*E*)-3-(benzyloxy)-9-oxonon-5-en-2-ylcarbamate (14)**—To a cool solution of compound **13** (103 mg, 0.283 mmol) in dry CH_2Cl_2 (mL) was added Dess-Martin periodinane (178 mg, 0.420 mmol) at 0 °C and the reaction mixture was stirred for 2h at 0 °C. Saturated aqueous NaHCO_3 (5 mL) was added to reaction mixture and the

reaction mixture was extracted with CH_2Cl_2 (5 mL $\times$ 2) and combined organic extracts were dried with MgSO_4 and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 35 % EtOAc-hexanes) gave the aldehyde **14** as a colorless oil (87 mg, 85%, *E/Z*=7:1).

FTIR (ATR, neat) ν 1713, 1505, 1169, 1060 cm^{-1} ; *E*-isomer ^1H NMR (700 MHz, CDCl_3) δ 9.76 (s, 1H), 7.28–7.38 (m, 5H), 5.49 (m, 2H), 4.76 (br, 1H), 4.62 (d, J = 11.4 Hz, 1H), 4.49 (d, J = 11.4 Hz, 1H), 3.81 (m, 1H), 3.31 (m, 1H), 2.50 (t, J = 7.0 Hz, 2H), 2.34 (m, 3H), 2.19 (m, 1H), 1.44 (s, 9H), 1.16 (d, J = 6.6 Hz, 3H); ^{13}C NMR (175 MHz, CDCl_3) δ 202.2 (CH), 155.5 (C_q), 138.3 (C_q), 131.1 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.1 (CH), 81.5 (CH), 78.9 (C_q), 72.4 (CH_2), 47.8 (CH), 43.2 (CH_2), 34.2 (CH_2), 28.4 (CH_3), 25.1 (CH_2), 18.6 (CH_3); HR-FAB-MS m/z $[\text{M}+\text{H}]^+$ 362.2337 calcd for $\text{C}_{21}\text{H}_{32}\text{NO}_4$ 362.2331

Compound 15

$\text{Ba}(\text{OH})_2$ monohydrate (20 mg, 0.11 mmol; activated by heating under low pressure, 0.5 mm Hg) was added to a solution of phosphonate **9** (85 mg, 0.13 mmol) in THF (2 mL) with stirring. After 30 min, aldehyde **14** (48 mg, 0.13 mmol) in wet THF (4 mL, THF- H_2O 40:1) was added and the mixture stirred at room temperature for an additional 2 h. The mixture was diluted with H_2O , and the aqueous mixture was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried with MgSO_4 , concentrated, and the residue purified by flash chromatography (silica, 35 % EtOAc-hexane) to provide enone **15** as a colorless oil (mixture of *E/Z* isomers, 99 mg, 91%); FTIR (ATR, neat) ν 1714, 1505, 1169, 1085 cm^{-1} ; *E/Z*-isomers ^1H NMR (700 MHz, CDCl_3) δ 7.24 – 7.42 (m, 10H), 6.81 (dt, J = 15.8, 6.6 Hz, 1H), 6.09 (d, J = 15.8 Hz, 1H), 5.53 (d, J = 9.7 Hz, 1H), 5.50 (m, 1H), 5.46 (m, 2H), 5.35 (dt, J = 15.4, 6.6 Hz, 1H), 5.12 (m, 2H), 4.77 (d, J = 7.9 Hz, 1H), 4.62 (d, J = 11.4 Hz, 1H), 4.47 (d, J = 11.4 Hz, 1H), 4.02 (d, J = 11.9 Hz, 1H), 3.91 (m, 1H), 3.82 (m, 1H), 3.76 (d, J = 11.9 Hz, 1H), 3.59 (m, 1H), 3.30 (m, 1H), 2.51 (t, J = 7.0 Hz, 2H), 2.33 (m, 1H), 2.27 (m, 2H), 2.20 (m, 1H), 2.18 (m, 2H), 2.14 (m, 2H), 1.97 (m, 2H), 1.58 (m, 2H), 1.45 (s, 3H), 1.42 (s, 9H), 1.38 (s, 3H), 1.21–1.35 (m, 16H), 1.16 (d, J = 6.6 Hz, 3H); ^{13}C NMR (175 MHz, CDCl_3) δ 200.8 (C_q), 155.9 (C_q), 155.4 (C_q), 146.3 (CH), 138.2 (C_q), 136.3 (C_q), 134.2 (CH), 131.8 (CH), 130.5 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 127.6 (CH), 126.9 (CH), 123.9 (CH), 99.0 (C_q), 81.6 (CH), 78.8 (C_q), 72.3 (CH_2), 71.5 (CH), 66.7 (CH_2), 65.1 (CH_2), 47.7 (CH), 46.8 (CH), 39.9 (CH_2), 34.9 (CH_2), 34.1 (CH_2), 32.5 (CH_2), 32.1 (CH_2), 31.0 (CH_2), 29.5 (CH_3), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 24.2 (CH_2), 18.5 (CH_3), 18.4 (CH_3). HR-FAB-MS m/z $[\text{M}+\text{H}]^+$ 845.5685 calcd for $\text{C}_{51}\text{H}_{76}\text{N}_2\text{O}_8$ 845.5680

Rhizochalinin C (1a)

A solution of compound **15** (30 mg, 0.035 mmol) in methanol (5 mL) was treated with 10M HCl (1 mL) and a catalytic amount of Pd-C (10% w/w) and the reaction mixture was shaken under an atmosphere of H_2 (2 atm) for 10 h. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure. Purification of the residue by flash chromatography (silica, 9:4:1 CHCl_3 -MeOH- NH_4OH) gave rhizochalinin C (**1a**) (14.8 mg, 87 %) as white solid, identical to **1a** derived from natural rhizochalin C (**1b**).^{3f}

^1H NMR (500 MHz, CD_3OD) δ 3.78 (1H, dd, J = 11.7, 4.1 Hz, 1-H), 3.68 (1H, m, 3-H), 3.66 (1H, dd, J = 11.7, 6.9 Hz, 1-H), 3.46 (1H, m, 26-H), 3.10 (1H, m, 27-H), 3.06 (1H, m, 2-H), 2.454 (2H, t, J = 7.3 Hz, 17-H), 2.447 (2H, t, J = 7.3 Hz, 19-H), 1.49–1.61 (m, 8H), 1.29–1.47 (m, 30H), 1.27 (3H, d, J = 6.6 Hz, 28-H); ^{13}C NMR (125 MHz, CD_3OD) δ 214.4 (C_q , C-19), 73.1 (CH, C-26), 69.1 (CH, C-3), 60.5 (CH, C-2), 59.1 (CH_2 , C-1), 53.5 (CH, C-27), 43.5 (CH_2 , C-17), 43.4 (CH_2 , C-19), 34.9 (CH_2), 34.6 (CH_2), 30.76 (CH_2), 30.72 (CH_2), 30.71 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 30.46 (CH_2), 30.43 (CH_2), 30.3 (CH_2),

30.2 (CH₂), 26.3 (CH₂), 26.2 (CH₂), 24.9 (CH₂), 24.8 (CH₂), 16.0 (CH₂, C-28); ESI HRMS *m/z* 509.4288 [M+Na]⁺ calcd for C₂₈H₅₈N₂O₄Na 509.4289.

Rhizochalinin C Perbenzoate (16)

Perbenzoate **16** was prepared from synthetic **1a** using the previously reported procedure.^{3f} The CD, ¹H NMR and HMRS data for synthetic **16** were in excellent agreement with those reported for natural-product-derived **16**.^{3f} CD, See Figure 3. ¹H NMR (500 MHz, CDCl₃) δ 7.35–8.08 (m, 25H), 6.61 (d, *J* = 9.3 Hz, 1H), 6.36 (d, *J* = 9.0 Hz, 1H), 5.54 (dt, *J* = 8.0, 5.0 Hz, 1H), 5.21 (dt, *J* = 7.9, 5.1 Hz, 1H), 4.88 (m, 1H), 4.55 (dd, *J* = 11.6, 5.9 Hz, 1H), 4.51 (m, 1H), 4.46 (dd, *J* = 11.6, 5.0 Hz, 1H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.35 (t, *J* = 7.3 Hz, 2H), 1.15–1.96 (m, 38H), 1.28 (d, *J* = 6.7 Hz, 3H). ESI HRMS *m/z* 1029.5599 [M+Na]⁺ calcd for C₆₃H₇₈N₂O₉Na 1029.5600.

Supplementary Material

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Acknowledgments

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Figure 1. Conversion of D-glucosamine by oxidative remodeling to *N*-Boc-L-serinal (see Ref. 12), and D-serine synthons by Barbier allylation-oxidation (this work). Locant numbering is based on D-glucosamine.

Figure 2.
Retrosynthesis of rhizochalalin C (**1a**).

Figure 3. CD spectra (CH₃OH, 24 °C) of (a) naturally-derived **16** and (b) synthetic **16**.

Scheme 1.

Scheme 2.

Elaboration of the left-hand half of rhizochalinin C (**1a**). *Major geometrical isomer is depicted *E:Z* = 9.6:1.

Scheme 3.

Elaboration of the right-hand half of rhizochalinin C (**1a**). †Major geometrical isomer is depicted, *E*:*Z* = 7:1.

Scheme 4.

Coupling of left-hand and right-hand halves and global deprotection to give rhizochalinin C (**1a**). Major geometrical isomer of **15** is depicted [C-5, C-6 *E:Z* = 9.6:1; C-23, C-24, *E:Z* = 7:1].

Table 1Barbier reaction of *N*-protected D-glucosamine with In⁰ and allyl bromide.^a

Entry	<i>N</i> -Protecting group, PG	Yield
1	Boc	78% ^b
2.	Cbz	55%
3.	Tosyl	40%
4.	Pht ^c	38%
5.	CF ₃ (C=O)	50%

^a Conditions: 1–2 mmol D-glucosamine, 4:1 THF:H₂O, reflux, In⁰ powder (99.99%, 230–400 mesh, 4 equiv) and allyl bromide (6 equiv). Yields were calculated by ¹H NMR integration of the allyl vinyl signals and the *N*-Me signals of caffeine added as an internal standard.

^b for *N*-Boc-mannosamine 88%, Ref. 15b

^c Pht = phthalimido.

Table 2

Barbier reaction of D-glucosamine with In^o and allyl bromide in aqueous 1,4-dioxane.

Entry	1,4-dioxane:H ₂ O	<i>threo:erythro</i>	Yield
1	0:100	1.8:1	21%
2.	25:75	2.0:1	39%
3.	50:50	4.4:1	60%
4.	67:33	7.5:1	96%
5.	83:17	7.0:1	99%
6.	94:6	5.7:1	95%

^a Conditions: 100 °C. PG = H. For other conditions, see reaction equation and footnote in Table 1.

Table 3Effect of added salt on Barbier reaction of D-glucosamine with In⁰ and allyl bromide in aqueous 1,4-dioxane.

Entry	Additive	Equiv.	<i>threo:erythro</i>	Yield
1	—	5.0	7.5:1	96%
2	LiCl	5.0	5.4:1	98%
3	LiBr	5.0	5.7:1	95%
4	KCl	5.0	4.5:1	98%
5	MgCl ₂	5.0	3.5:1	94%
6	(<i>n</i> -Bu) ₄ NCl	5.0	5.1:1	90%
7	(<i>n</i> -Bu) ₄ NI	5.0	4.7:1	98%
8	NaCl	satd.	3.2:1	80%
9	NH ₄ Cl	satd.	2.0:1	90%
10	LiClO ₄	5.0	2.8:1	84%

^aConditions: Solvent ratio, 2:1 dioxane:H₂O, 100 °C. PG = H. For other conditions, see reaction equation and footnote in Table 1.