JOC The Journal of Organic Chemistry

Article

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

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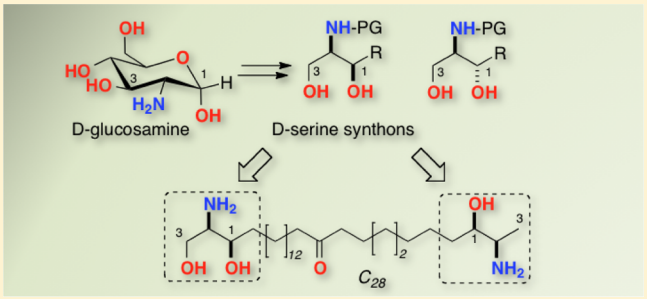
Supporting Information

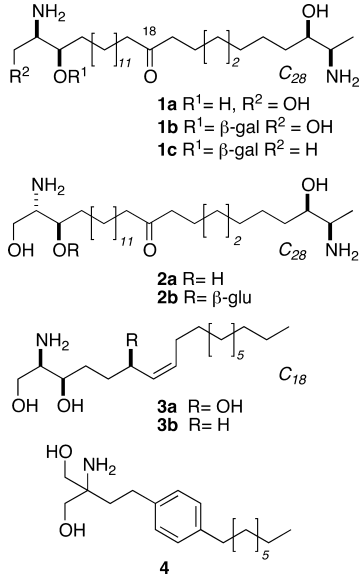
ABSTRACT: A five-step transformation of D-glucosamine, commencing with indium-mediated Barbier reaction without isolation of intermediates, into (*R*,*R*)-2-aminohex-5-ene-1,3-diol in 45−51% is described. The latter is a useful synthon for assembly of L-*threo*-sphingoid bases: long-chain aminoalkanols and aminoalkanediols 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 rhizochalinin C, the long-chain, "two-headed" sphingoid base aglycon of the natural product rhizochalin C from the marine sponge *Rhizochalina incrustata*.



INTRODUCTION

Sphingosine (2-aminooctadec-4-ene-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 composed of C_{28}−C_{30} chains functionalized at each terminus as aminoalkanols or aminoalkanediols[3] span almost the complete set of permutations (n = 16) of the four stereocenters. For example, the Madagascan sponge *Rhizochalina incrustata* contains C_{28} α,ω-bifunctionalized sphingoid bases (2*R*,3*R*,26*R*,27*R*)-rhizochalin C (**1b**)[3f] (the 3-β-galactoside of rhizochalinin C, **1a**) and the pseudo-C_2 symmetric rhizochalin (**1c**).[3a] The head groups of the latter compounds are both L-*threo*, but oceanapiside (**2b**) has a hetergeneous configuration: the 2-amino-1,3-diol headgroup is D-*erythro* while the "deoxy" headgroup is L-*threo*. Monofunctionalized L-*threo* sphingoid bases 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 aglycon oceanin (**2a**), exhibit significant antifungal activity against the pathogenic species *Candida albicans*, fluconazole-resistant *C. albicans*, C. *glabrata*, and other species.[7] Selective inhibitors of D-sphingosine kinase isoforms, SK1 and SK2, are attractive targets as anticancer and anti-inflammatory agents.[8] Fingolimod (FTY720, **4**), an analogue of 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]



Synthesis of sphinganine and related sphingoid bases has been extensively reviewed.[11] Approaches to D-*erythro*-2-amino-

Received: October 26, 2012
Published: December 10, 2012

alkanols 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, one-pot conversion of *unprotected* D-glucosamine into useful D-serine synthons based on In^0-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 refunctionalizes C-3 to a carboxaldehyde (Figure 1).[12] Conceptually, inverting the orientation of

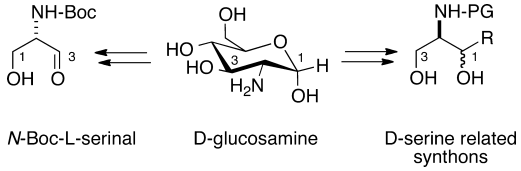


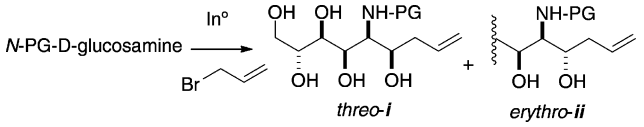
Figure 1. Conversion of D-glucosamine by oxidative remodeling to *N*-Boc-L-serinal (see ref 12) and D-serine synthons by Barbier allylation–oxidation (this work). Locant numbering is based on D-glucosamine.

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. Whitesides[15] and Chan[16b] had previously shown that aldoses and some ketoses undero 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, aq, 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%, or *N*-Boc-α-aminoaldehydes up to 90%, again mostly with *threo* selectivity, but *erythro* selectivity with Garner's aldehyde.[21] Critical evaluation of these reports suggests 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-hexenol diastereomers *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 with 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%).

Table 1. Barbier Reaction of *N*-Protected D-Glucosamine with In^0 and Allyl Bromide[a]



entry	*N*-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 of D-glucosamine, 4:1 THF/H_2O, reflux, In^0 powder (99.99%, 230–400 mesh, 4 equiv), 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.

We found, to our delight, that In^0-mediated allylation of *unprotected* D-glucosamine gave the best results (Table 2)

Table 2. Barbier Reaction of D-Glucosamine with In^0 and Allyl Bromide in Aqueous 1,4-Dioxane[a]

entry	1,4-dioxane/H_2O	*threo*/*erythro*	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 the reaction equation and footnote in Table 1.

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 allyl bromide (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, $(Et)_4NX$ 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%, Table 3, entry 5), with comparable yields.

Scale-up of the five-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

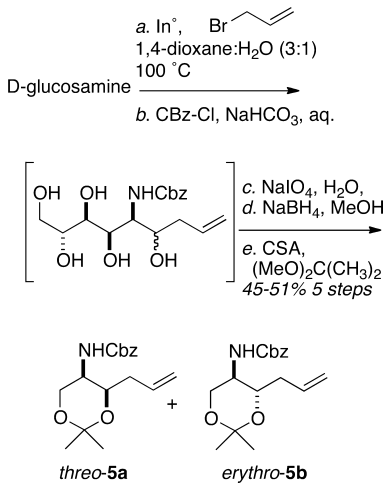
dx.doi.org/10.1021/jo302355t | J. Org. Chem. 2013, 78, 498–505

Table 3. Effect of Added Salt on Barbier Reaction of D-Glucosamine with In^0 and Allyl Bromide in Aqueous 1,4-Dioxane[a]

entry	additive	equiv	*threo*/	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	$(n\text{-Bu})_4NCl$	5.0	5.1:1	90
7	$(n\text{-Bu})_4NI$	5.0	4.7:1	98
8	NaCl	satd	3.2:1	80
9	NH_4Cl	satd	2.0:1	90
10	$LiClO_4$	5.0	2.8:1	84

[a]Conditions: solvent ratio, 2:1 dioxane/H_2O, 100 °C. PG = H. For other conditions, see the reaction equation and footnote in Table 1.

Scheme 1



sufficiently nonpolar to allow recovery and separation by silica chromatography (51% total yield, dr 7:1 over five steps).[24] The five-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 rhizochalinin C (**1a**) 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 rhizochalinin 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 NH_2 and OH groups.

The left-hand half of rhizochalinin C was elaborated as shown in Scheme 2. Compound **5a** was subjected 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%, two 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%, two steps).

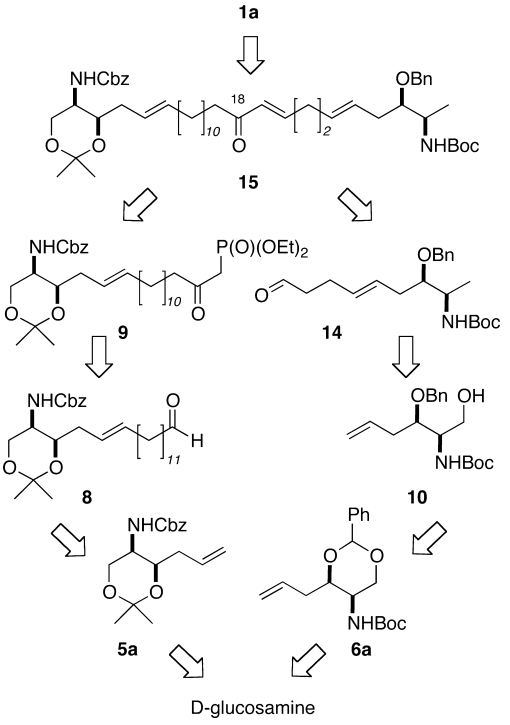
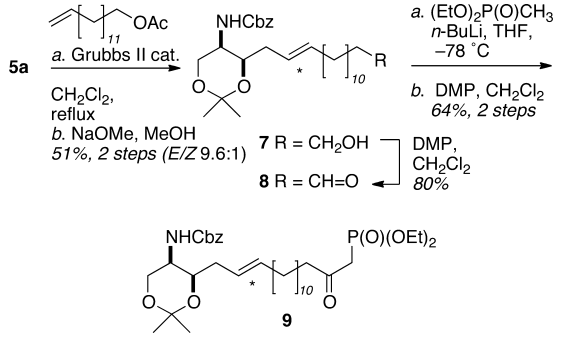


Figure 2. Retrosynthesis of rhizochalinin C (**1a**).

Scheme 2. Elaboration of the Left-Hand Half of Rhizochalinin C (1a)*



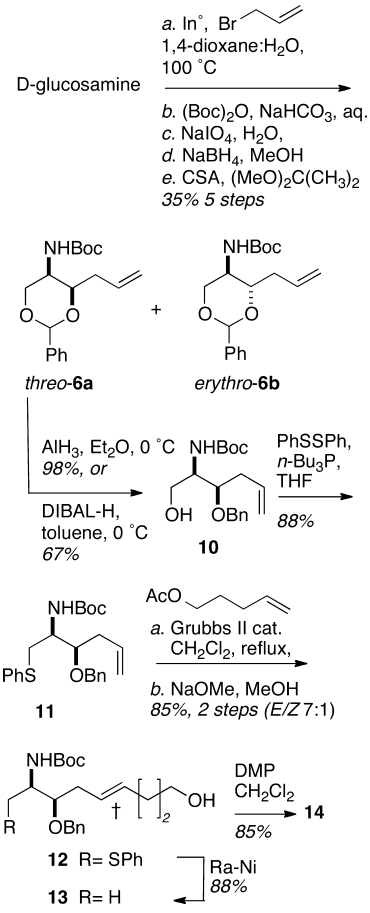
*Major geometrical isomer is depicted (*E*/Z = 9.6:1).

The right-hand half of **1a** was prepared as shown in Scheme 3. The multistep Barbier allylation–oxidation sequence (Scheme 1) was repeated on D-glucosamine except for a different *N*-protecting group ($(Boc)_2O$, $NaHCO_3$, aq) and conversion of the 1,3-diol to a benzylidene acetal (benzaldehyde dimethyl acetal, CSA) to provide **6** in 35% yield over five steps. Differential C–O bond cleavage of the benzylidene group was achieved under two sets of conditions: reduction with in situ generated alane ($AlCl_3$, $LiAlH_4$, CH_2Cl_2, 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** ($n\text{-Bu}_3P$, $(PhS)_2$, 88%) in preparation for later reductive removal. Olefin cross-metathesis of **11** with 4-penten-1-yl acetate (Grubbs II cat.,[30] CH_2Cl_2, reflux) followed by methanolysis (NaOMe, MeOH) gave primary alcohol **12** as

dx.doi.org/10.1021/jo302355t | J. Org. Chem. 2013, 78, 498–505

Scheme 3. Elaboration of the Right-Hand Half of Rhizochalinin C (1a)[†]



[†]Major geometrical isomer is depicted (E/Z = 7:1).

an inconsequential mixture of geometrical isomers (E/Z = 7:1, 85%, two 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 conditions[28] ($Ba(OH)_2$, 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** (10 M HCl, MeOH, H_2 2 atm, Pd–C) gave **1a**·2HCl. Purification of the latter salt under ammoniacal solvent (silica, flash chromatography, 9:4:1 $CHCl_3$, MeOH, NH_4OH aq) afforded the free base rhizochalinin C (**1a**) as a *single stereoisomer* (87%). The ^1H NMR, ^{13}C NMR, $[\alpha]_D$, and HRMS data of the synthetic **1a** matched those of the aglycon derived from natural rhizochalin C (**1b**). Finally, the CD spectrum of the tetrabenzoyl derivative **16** (Figure 3)

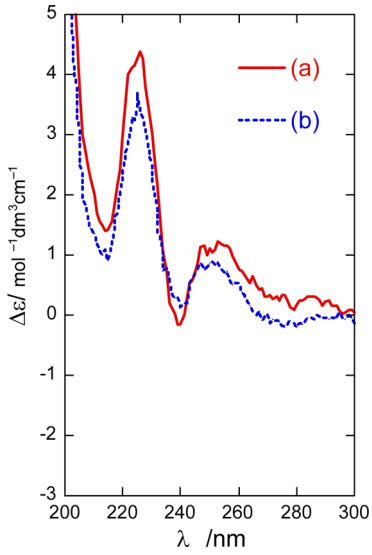


Figure 3. CD spectra (CH_3OH, 24 °C) of (a) naturally derived **16** and (b) synthetic **16**.

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.

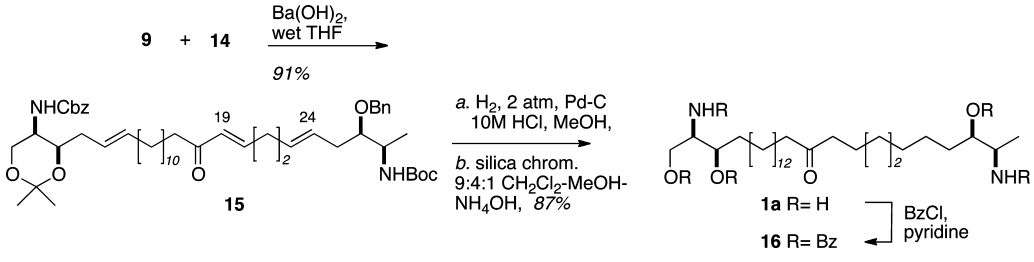
In conclusion, we have demonstrated a practical and versatile preparation of D-*threo*-serine-related synthons in good yield by a five-step conversion of D-glucosamine. The latter was exploited for a bidirectional bond construction and convergent assembly of rhizochalinin C (**1a**),[3] the first total 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; a subject of ongoing research in our laboratories that will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. General experimental procedures are described in the Supporting Information and elsewhere.[29] ^{13}C NMR signal multiplicities (CH_3, CH_2, CH, Cq) 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 In^0 powder (4 equiv) was suspended in solvent (15

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].

dx.doi.org/10.1021/jo302355t | J. Org. Chem. 2013, 78, 498–505

mL, freshly purified THF, 1,4-dioxane, H_2O, or mixtures thereof; see Tables 1−3) at rt. Allyl bromide (6 equiv) was added, and the mixture was heated to reflux and allowed to react until no starting material was evident (TLC) or no change of product to starting material ratio could be detected (^{1}H 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 $NaHCO_3$. Excess $(Boc)_2O$ was added, and the mixture subsequently stirred at room temperature for 2 h, diluted with methanol, and filtered with microfilter (0.45 μm). The filtrate was analyzed by HPLC (reversed-phase C_{18}, 22.5:77.5 CH_3CN/H_2O, ELSD detector).

*Benzyl (4R,5R)-4-Allyl-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (**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 In^0 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 1 M NaOH solution prior to addition of $NaHCO_3$ (1.7 g, 21 mmol) and benzyl chloroformate (3 mL, 20.8 mmol) with continued stirring at room temperature for 24 h. After the mixture was recooled to 5 °C, sodium periodate (8.9 g, 41.7 mmol) was added slowly portionwise and the mixture stirred vigorously for 3 h at room temperature before removal of volatiles 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 $MgSO_4$ and concentrated under reduced pressure. The oily residue was dissolved in acetone (50 mL) treated with excess 2,2-dimethoxypropane (24 mL) and a catalytic amount of camphorsulfonic acid (60 mg), and then stirred at room temperature for 5 h. After completion of the reaction was confirmed 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% Et_2O 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).

*(4R,5R)-**5a**:* FTIR (ATR, neat) ν 1715, 1504, 1214, 1085 cm^{-1}; $[\alpha]_D$ −23 (*c* 0.083, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2 (C_q), 136.5 (C_q), 133.4 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 117.8 (CH_2), 99.2 (C_q), 72.0 (CH), 66.9 (CH_2), 65.2 (CH_2), 47.2 (CH), 36.3 (CH_2), 29.7 (CH_3), 18.6 (CH_3); HR-ESI-FT-MS *m*/*z* $[M + Na]^+$ 328.1516, calcd for $C_{17}H_{23}NO_4Na$ 328.1519.

*(4S,5R)-**5b**:* FTIR (ATR, neat) ν 1691, 1536, 1225, 1023 cm^{-1}; $[\alpha]_D$ −21 (*c* 0.076, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 (C_q), 136.3 (C_q), 133.1 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 117.1 (CH_2), 98.9 (C_q), 72.2 (CH), 67.0 (CH_2), 63.1 (CH_2), 49.6 (CH), 37.1 (CH_2), 28.1 (CH_3), 19.9 (CH_3); HR-ESI-FT-MS *m*/*z* $[M + Na]^+$ 328.1517 calcd for $C_{17}H_{23}NO_4Na$ 328.1519.

*tert-Butyl (5R)-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^0 powder (3.2 g, 28 mmol) were added, and the mixture was heated at reflux for 20 h. The reaction solution was cool to 10 °C and adjusted to pH 7−8 with 1 M NaOH solution. $NaHCO_3$ (1.7 g, 20.8 mmol) and di-*tert*-butyl bicarbonate (4.5 g, 21 mmol) were added to the neutralized solution of allylated D-glucosamine at 5 °C. The solution was stirred at room temperature for 24 h and then cooled to 5 °C prior to slow, portionwise 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 cooled to 5 °C, sodium borohydride (1.6 g, 42 mmol) was added slowly, and the solution was stirred for 3 h. After the mixture was quenched by addition of H_2O (50 mL), the volatiles were removed under reduced pressure. Brine (200 mL) was added to the mixture followed by extraction with EtOAc (200 mL × 2). The combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure, and the oily residue dissolved in dry CH_2Cl_2 (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 was 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) togive the pure compounds (4*R*,5*R*)-**6a** and (4*S*,5*R*)-**6b** (total 1.5 g, 35%, five steps, dr = 7:1).

*(4R,5R)-**6a**:* FTIR (ATR, neat) ν 1711, 1499, 1365, 1168 cm^{-1}; $[\alpha]_D$ +3.2 (c 0.11, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 (C_q), 138.1 (C_q), 133.4 (CH), 129.1 (CH), 128.4 (CH), 126.0 (CH), 118.1 (CH_2), 101.6 (CH), 79.7 (C_q), 79.5 (CH), 72.2 (CH_2), 46.9 (CH), 36.3 (CH_2), 28.5 (CH_3); HR-ESI-FT-MS *m*/*z* $[M + Na]^+$ 342.1674, calcd for $C_{18}H_{25}NO_4Na$ 342.1681.

*(4S, 5R)-**6b**:* $[\alpha]_D$ −22.3 (c 0.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1 (C_q), 137.9 (C_q), 134.1 (CH), 129.0 (CH), 128.4 (CH), 126.2 (CH), 117.5 (CH_2), 101.1 (CH), 80.6 (CH), 80.1 (C_q), 70.0 (CH_2), 47.4 (CH), 36.7 (CH_2), 28.5 (CH_3); HR-ESI-FT-MS *m*/*z* $[M + Na]^+$ 342.1674, calcd for $C_{18}H_{25}NO_4Na$ 342.1681.

*Benzyl (4R,5R)-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 CH_2Cl_2 (20 mL) were added tetradec-13-enyl acetate (3.6 g, 14 mmol) and Grubbs second-generation catalyst (90 mg, 0.10 mmol)[30] under N_2 at room temperature. After the reaction mixture was stirred for 2 h 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 1 M CH_3ONa in methanol (3.5 mL, 3.5 mmol), and after 2 h, methanol was removed under reduced pressure. Water (20 mL) was added, the reaction mixture was extracted with ethyl acetate (30 mL × 2), and the combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. Flash chromatography of the residue (silica gel, 15% EtOAc−hexane) gave alcohol 7 (580 mg, 51% for two steps) as a colorless oil (*E*/*Z* = 9.6:1): FTIR (ATR, neat) ν 1715, 1506, 1215, 1083 cm^{-1}; *E*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 (CH_2), 65.3 (CH_2), 63.2 (CH_2), 47.1 (CH), 35.2 (CH_2), 33.0 (CH_2), 32.8 (CH_2), 29.8 (CH_3), 29.7$_5$ (CH_2), 29.7$_3$ (CH_2), 29.7$_0$ (CH_2), 29.6 (CH_2), 29.5$_6$ (CH_2), 29.5$_2$ (CH_2), 29.3 (CH_2), 25.9 (CH_2), 18.7 (CH_3); HR-ESI-FT-MS *m*/*z* $[M + Na]^+$ 512.3344 calcd for $C_{29}H_{47}NO_5Na$ 512.3351.

*Benzyl (4R,5R)-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 CH_2Cl_2 (10 mL), and after 2 h at 0 °C, the reaction was quenched by the addition of satd aqueous $NaHCO_3$ (10 mL). The reaction mixture was extracted with CH_2Cl_2

(15 mL × 2), and the combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. Separation of the residue by flash chromatography (silica gel, 12% EtOAc–hexane) gave aldehyde **8** (238 mg, 80%) as a colorless oil (*E*/*Z* = 9.6:1): FTIR (ATR, neat) ν 1724, 1505, 1214, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 (CH_2), 65.3 (CH_2), 47.1 (CH), 44.1 (CH_2), 35.2 (CH_2), 32.8 (CH_2), 29.8 (CH_3), 29.7$_5$ (CH_2), 29.7$_3$ (CH_2), 29.6 (CH_2), 29.5$_7$ (CH_2), 29.5$_5$ (CH_2), 29.5$_1$ (CH_2), 29.3 (CH_2), 22.2 (CH_2), 18.7 (CH_3); HR-ESI-FT-MS *m*/*z* $[M + Na]^+$ 510.3191, calcd for $C_{29}H_{45}NO_5Na$ 510.3190.

*Benzyl (4R,5R)-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 μL, 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 NH_4Cl was added, and the mixture was extracted with EtOAc (×3). The combined organic layers were washed with brine, dried over $MgSO_4$, 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 CH_2Cl_2 (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 satd $NaHCO_3$ solution (10 mL), the mixture extracted with CH_2Cl_2 (15 mL × 2), and the combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. Flash chromatography of the residue (silica gel, 50% EtOAc–hexane) gave phosphonate **9** (210 mg, 64% for two 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 (CH_2), 65.2 (CH_2), 62.5 (d, J_{CP} = 6.1 Hz, CH_2), 47.0 (CH), 44.1 (CH_2), 41.7 (d, J_{CP} = 127.4 Hz, CH_2), 35.1 (CH_2), 32.7 (CH_2), 29.7 (CH_3), 29.6$_4$ (CH_2), 29.6$_0$ (CH_2), 29.5$_2$ (CH_2), 29.5$_0$ (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 23.5 (CH_2), 18.6 (CH_3), 16.3 (d, J_{CP} = 6.1 Hz, CH_3); HR-ESI-FTMS *m*/*z* $[M + H]^+$ 638.3815, calcd for $C_{34}H_{57}NO_8P$ 638.3816.

*tert-Butyl (2R,3R)-3-(Benzyloxy)-1-hydroxyhex-5-en-2-ylcarbamate (**10**). Alane Method.* To a cooled suspension of $LiAlH_4$ (90 mg, 2.3 mmol) and **6a** (163 mg, 0.51 mmol) in CH_2Cl_2–diethyl ether (1:1, 5 mL) at 0 °C was added, dropwise, an ethereal solution of $AlCl_3$ (182 μL, 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 H_2O (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 $MgSO_4$, 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 CH_2Cl_2 (3 mL) was added DIBAL-H (575 μL, 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 CH_2Cl_2 (5 mL × 3). The combined organic extracts were washed with brine (5 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Purification of the residue, as described above, gave **10** (62 mg, 67%) as a colorless oil: FTIR (ATR, neat) ν 3441, 1692, 1496, 1164 cm^{-1}; $[\alpha]_D$ −4.1 (*c* 0.066, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5 (C_q), 138.0 (C_q), 134.0 (CH), 128.6 (CH), 128.1 (CH), 128.0 (CH), 118.2 (CH_2), 79.7 (C_q), 78.1 (CH), 72.4 (CH_2), 64.0 (CH_2), 54.0 (CH), 35.6 (CH_2), 28.5 (CH_3).

*tert-Butyl (2S,3R)-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 μL, 3.16 mmol) and phenyl disulfide (190 mg, 3.16 mmol) in THF (10 mL) at 0 °C. After the mixture was stirred 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}; $[\alpha]_D$ −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* $[M + Na]^+$ 436.1919, calcd for $C_{24}H_{31}NO_3SNa$ 436.1917.

*tert-Butyl (2S,3R,E)-3-(Benzyloxy)-9-hydroxy-1-(phenylthio)non-5-en-2-ylcarbamate (**12**).* Grubbs second-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 4 h under reflux. Removal of the volatiles under reduced pressure gave a dark brown oil which was taken up in MeOH (20 mL) and treated wtih 1 M NaOMe in methanol (12.7 mL, 12.7 mmol). After stirring the mixture for 2 h 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 a colorless oil (*E*/*Z* = 7:1) (423 mg, 85% for two steps): FTIR (ATR, neat) ν 3443, 1695, 1494, 1162 cm^{-1}; $[\alpha]_D$ −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* $[M + Na]^+$ 494.2337, calcd for $C_{27}H_{37}NO_4SNa$ 494.2336.

*tert-Butyl (2R,3R,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 2 h 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),

dx.doi.org/10.1021/jo302355t | *J. Org. Chem.* 2013, 78, 498–505

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 [M + H]$^+$ 364.2491, calcd for $C_{21}H_{34}NO_4$ 364.2488

*tert-Butyl (2R,3R,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 2 h at 0 °C. Saturated aqueous $NaHCO_3$ (5 mL) was added, the reaction mixture was extracted with CH_2Cl_2 (5 mL × 2), and the 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: ^{1}H 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 [M + H]$^+$ 362.2337, calcd for $C_{21}H_{32}NO_4$ 362.2331

*Compound **15**.* $Ba(OH)_2$ monohydrate (20 mg, 0.11 mmol; activated by heating under low pressure, 0.5 mmHg) was added to a stirred solution of phosphonate **9** (85 mg, 0.13 mmol) in THF (2 mL). 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 (×3). The combined organic extracts were dried with $MgSO_4$ and concentrated, and the residue was 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: ^{1}H 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 [M + H]$^+$ 845.5685, calcd for $C_{51}H_{76}N_2O_8$ 845.5680.

*Rhizochalinin C (**1a**).* A solution of compound **15** (30 mg, 0.035 mmol) in methanol (5 mL) was treated with 10 M 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 a white solid, identical to **1a** derived from natural rhizochalin C (**1b**):[3f] ^{1}H 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(Cq, 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 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 16.0 (CH_2, C-28); ESI HRMS m/z 509.4288 [M + Na]$^+$, calcd for $C_{28}H_{58}N_2O_4Na$ 509.4289.

*Rhizochalinin C Perbenzoate (**16**).* Perbenzoate **16** was prepared from synthetic **1a** using the previously reported procedure.[3f] The CD, ^{1}H NMR, and HMRS data for synthetic **16** were in excellent agreement with those reported for natural-product-derived **16**:[3f] CD, see Figure 3; ^{1}H NMR (500 MHz, $CDCl_3$) 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 $C_{63}H_{78}N_2O_9Na$ 1029.5600.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR NMR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Y. Su and Anthony Mrse (UCSD) for assistance with HRMS and NMR measurements, respectively, E. P. Stout for measurement of CD spectra, and J. Olejniczak for preparation of *N*-phthalimido-D-glucosamine. The purchase of the HPLC-TOF mass spectrometer and the 500 MHz NMR spectrometer was made possible with funds from the NIH Shared Instrument Grant program (S10RR025636) and the NSF Chemical Research Instrument Fund (CHE0741968), respectively. We are grateful for funding support of this work from the NIH (AI039978, AI100776).

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