A New Synthesis of Valienamine[1]

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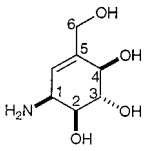
Introduction

Valienamine (Figure 1)[2] [(1*S*,2*S*,3*S*,4*R*)-1-amino-5-hydroxymethylcyclohex-5-en-2,3,4-triol] is an α-glucosidase inhibitor[3] that was isolated from the microbial degradation of validoxylamine A[4] with *Pseudomonas denitrificans*[5] or *Flavobacterium saccharophilum*[6] or from the NBS cleavage of validoxylamine A.[7,8] Since the isolation of valienamine in 1972, twelve enantiospecific syntheses have been described.[1a,9−19] The first synthesis was reported by Paulsen et al.[9] using the cyclitol quebrachitol as the chiral starting material. Seven syntheses constructed the carbocyclic framework from D-glucose involving either a Ferrier rearrangement,[10−12] an aldol-type cyclization of a nitrofuranose,[13] an intramolecular Horner−Emmons reaction,[14] a ring-closing alkene metathesis,[15] or an aldol condensation of a sulfone as the key step.[16] Three other constructions employed the Diels−Alder reaction to generate the cyclohexene skeleton.[17−19] The last one was asymmetric and involved two consecutive palladium-catalyzed asymmetric alkylations as the key steps.[19] In our previous endeavor,[1a] we described the synthesis of valienamine (**1**) on the basis of a regio- and stereospecific opening of a cyclic sulfite as the key step to generate a 2-*epi*-valienamine derivative that was followed by inversion at C_2 to provide the target molecule. In this note, valienamine was produced directly from a cyclohexene precursor bearing an allylic acetate moiety. A regio- and stereospecific palladium-catalyzed reaction was proven to effectively install the amino function.



valienamine (**1**)

Figure 1.

Results and Discussion

Synthesis of a dibenzyl ether with a cyclohexylidene blocking group similar to **8** from (−)-quinic acid (**2**) was known, and the procedure was developed by one of us.[20] We were tempted to employ the ethylpropylidene protecting group instead because it would provide simpler ^{1}H NMR spectra and would not, in particular, obscure the high-field methylene protons of the cyclohexane skeleton. Thus, the modified Stoodley[21] procedure was applied to the construction of ethylpropylidene quinic acid lactone **3**. In this method, (−)-quinic acid **2** was heated in boiling 3-pentanone with a catalytic amount of H_3PO_4 and with azeotropic removal of water, affording the crystalline lactone **3** in a 94% yield (Scheme 1). Using a Dean and Stark apparatus provided better yields because the continuous removal of water forced the equilibrium toward the target lactone **3**. It is noteworthy that 3-pentanone seems to be a better azeotropic agent than cyclohexanone; hence, the removal of water was speedy. In the presence of sodium methoxide in methanol, the lactone ring was opened to give a 98% yield of the diol **4**. The secondary alcohol in **4** was oxidized into the corresponding ketone **5** as white needles in an 86% yield and was followed by elimination of the tertiary alcohol with phosphorus oxychloride in pyridine, giving an excellent yield of enone **6**. Due to the presence of the bulky ethylpropylidene ring at the α-face of enone **6**, DIBALH attacked the ketone exclusively from the *β*-face. The diol **7** was isolated as the sole product in a 93% yield. Since both hydroxy groups remain untouched most of time during the route, a protecting group that is stable in different manipulation conditions is required and would be deprotected easily. Silyl ether had been used but was prone to migration under basic conditions in the presence of an adjacent free hydroxy group.[22] The benzyl group was thus chosen for this task and could be removed readily via hydrogenolysis or dissolving-metal reduction. Therefore, the diol **7** was treated with sodium hydride and benzyl bromide in the presence of a catalytic amount of tetra-*n*-butylammonium iodide in THF to give dibenzyl

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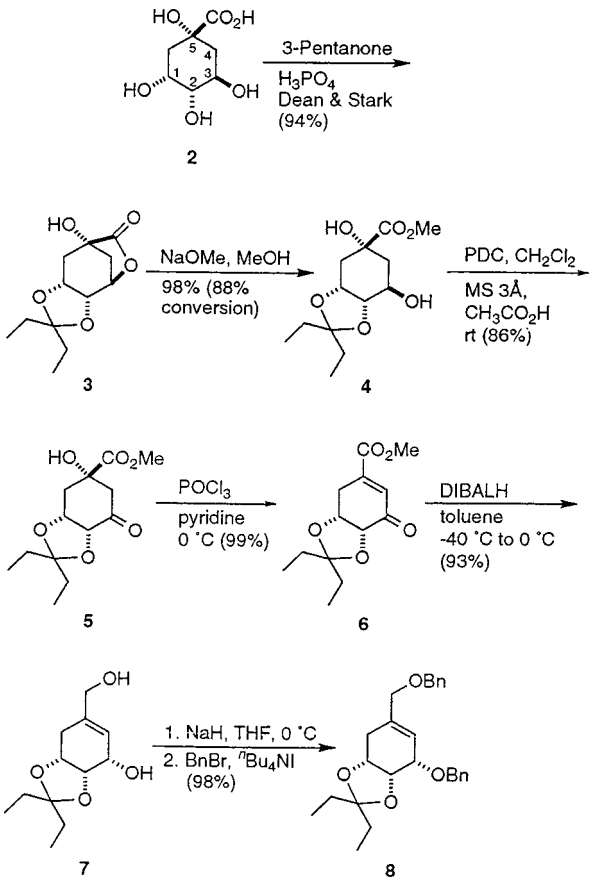
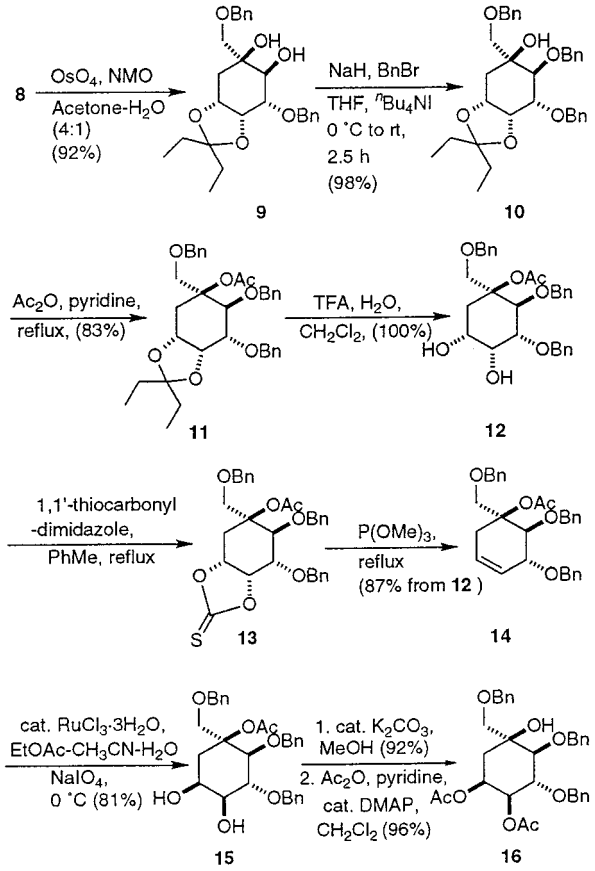
Scheme 1



Scheme 2



ether **8** in six steps with an overall yield of 63% from (−)-quinic acid.

cis-Dihydroxylation of alkene **8** was performed using a catalytic amount of osmium tetraoxide to diastereoselectively give diol **9** (Scheme 2). Since the α-face was more sterically hindered as a result of the bulky ethylpropylidene group, dihydroxylation occurred preferentially at the *β*-face (see Figure 2). The inferior reactivity of the tertiary hydroxyl group allowed success in the regioselective benzylation of the secondary hydroxyl group. Thus, tribenzyl ether **10** was obtained in an overall yield of 90% from alkene **8**. The tertiary hydroxy group in tribenzyl ether **10** was acylated as acetate **11**. Then, hydrolysis of the acetal group in **11** with aqueous TFA in CH_2Cl_2 gave the α-diol **12**. The configuration of the diol moiety in **12** had to be inverted into the corresponding *β*-diol. The α-diol was first deoxygenated via the Corey−Winter reaction.[23] Reaction of the diol **12** with 1,1′-thiocarbonyldiimidazole in toluene afforded the intermediate thiocarbonate **13**. This intermediate was then treated with trimethyl phosphite under reflux to give the alkene **14** in an 87% overall yield from the diol **12**. Dihydroxylation of the alkene **14** could be realized using the new ruthenium-catalyzed dihydroxylation protocol developed by our group.[24] This dihydroxylation gave exclusively the *β*-diol product **15**. The stereoselectivity of the ruthenium tetraoxide attack was apparently controlled by the benzyl ether adjacent to the alkene moiety. Deacetylation of acetate **15** was accomplished using a catalytic amount of K_2CO_3 in methanol to give a triol that was converted into the diacetate **16** with acetic anhydride and pyridine in CH_2Cl_2. The ^1H NMR data of diacetate **16** clearly indicate the stereochemistries at C_1 and C_2. The coupling constants of 10.2 Hz between H_2 and H_3 and 9.3 Hz between H_3 and H_4 show that H_2, H_3, and H_4 are axial protons. Furthermore, the coupling constant of 3.4 Hz between H_1 and H_2 shows that H_1 and H_2 are *syn*-disposed (see Figure 3). These data supported the assignment of *β*-OH groups at C_1 and C_2 in diol **15**.

Attempts to convert alcohol **16** into alkene **17** were carried out with thionyl chloride and pyridine in CH_2Cl_2. It was found that the elimination reaction was very

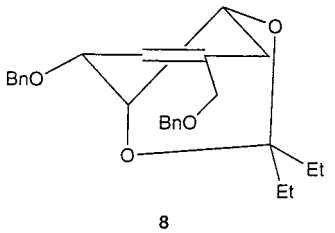


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Figure 2.

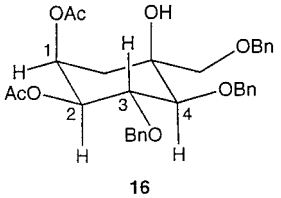

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Figure 3.

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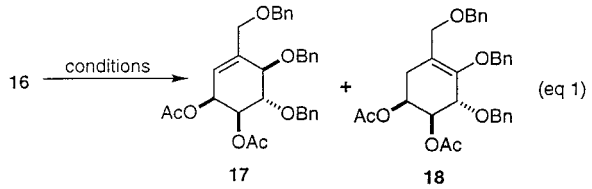
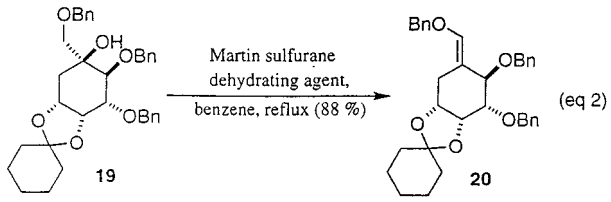
slow and that the selectivity of the elimination was poor, giving two alkene products **17** and **18** in a 1:1 ratio (eq 1).



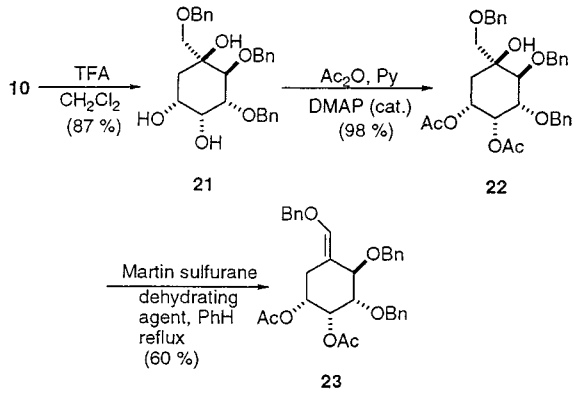
entry		yield of **17** (%)	yield of **18** (%)
1	$SOCl_2$	40	42
2	Martin sulfurane dehydrating agent	90	0

There was no improvement in selectivity when triethylamine was used instead of pyridine. In contrast to our previous findings,[1a] no dimer was found when the thionyl chloride was added dropwise to the solution of **16**. Due to the nonselectivity of the elimination of **16**, Martin sulfurane dehydrating agent was employed in dry benzene[25] under reflux to give the single product **17** in a 90% yield. According to our previous work,[1a] elimination of the tertiary hydroxy group in acetal **19** furnished the undesired exocyclic enol ether **20** (eq 2).



This elimination preference might be attributable to the bulky cyclohexylidene ring blocking the α-face. To examine if the steric effect was the dominant effect for the undesired reaction, we decided to make α-diacetate **22** for use in a direct comparison. Thus, hydrolysis of the ethylpropylidene blocking group in **10** using aqueous trifluoroacetic acid in CH_2Cl_2 gave the triol **21** in an 87% yield (Scheme 3). The secondary hydroxy groups in **21** were acetylated to give the α-diacetate **22** in a 98% yield. The elimination reaction of **22** with Martin sulfurane dehydrating agent afforded the undesired enol ether **23** as the sole product in a moderate yield of 60%. These findings supported the assignment of the E2 mechanism[26] to the elimination pathway via Martin sulfurane. The axial α-proton *trans*-periplanar to the tertiary alcohol was

Scheme 3



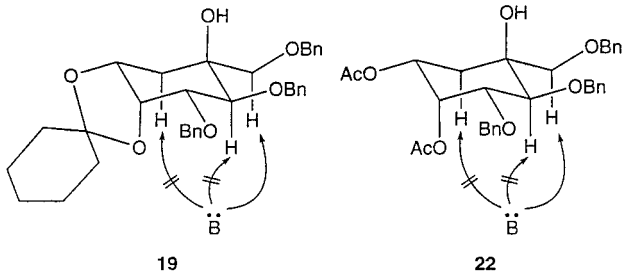


Figure 4.

apparently hindered by the juxtaposed α-substituent in acetal **19** and in diacetate **22** (see Figure 4). Proton abstraction therefore occurred at the less hindered exocyclic methylene to give *exo*-alkenes **20** and **23** from **19** and **22**, respectively. For the dehydration of tertiary alcohol **16**, the ring methylene proton is more acidic than the exocyclic methylene proton (attached to a carbon bearing an oxygen functionality) and therefore underwent elimination preferentially to give the desired alkene **17**.

The diacetate **17** obtained would act as a precursor for the syntheses of various kinds of *N*-alkylated valienamine derivatives via palladium-catalyzed allylic amination.[27] Initially, diacetate **17** was allowed to react with benzylamine in the presence of a catalytic amount of tetrakis(triphenylphosphine) palladium [$Pd(PPh_3)_4$] and with triphenylphosphine (PPh_3) in THF under reflux but failed to give any product. Conducting the reaction in a sealed tube at 140 °C caused the decomposition of $Pd(PPh_3)_4$, and metallic palladium was deposited on the wall of the tube. When acetonitrile was used as the solvent instead of THF,[28] the amination took place with benzylamine to yield the desired amine **24**. The palladium-catalyzed allylic amination of diacetate **17** with propylamine was also successful, affording the allylic amine **25**. Allylic amines **24** and **25** could not be fractionated to purity by chromatography. Fortunately, their deacetylated products could be isolated cleanly and characterized. Thus, treatment of acetate **24** or **25** with a catalytic amount of NaOMe in MeOH provided the valienamine derivative **26** or **27** in a 60 or 58% overall yield, respectively, from allylic acetate **17** (Scheme 4). The catalytic cycle of the Pd(0)-mediated allylic amination is shown in Figure 1. The stereochemistry at C_1 in **26** and in **27** was confirmed by proton NMR two-dimensional (NOESY and COSY) experiments, indicating that H_1 and H_2 were *syn*-disposed.

The presence of the alkene moiety in **26** precluded the use of catalytic hydrogenolysis; therefore, debenzylation of benzyl ether **26** was carried out using sodium in liquid ammonia at −78 °C to give valienamine **1**. Acetylation of **1** then afforded pentaacetate **28** for isolation and characterization.

The spectral and physical data of the pentaacetate **28** derived from **26** were completely identical to the data of

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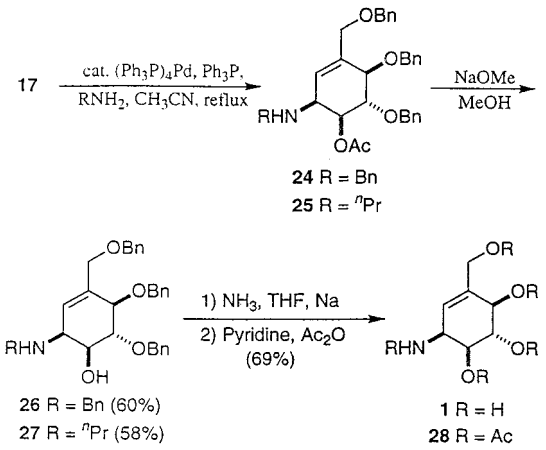
Scheme 4



an authentic sample from our previous work.[1a] The palladium-catalyzed allylic amination was therefore proved to occur with an overall retention of configuration. The synthesis of *N*,*O*,*O*,*O*,*O*-pentacetylvalienamine **28** from (−)-quinic acid was achieved in 20 steps with an overall yield of 11%.

In summary, the present studies demonstrate the high efficiency of the palladium-catalyzed coupling strategy for the synthesis of valienamine **1**. Application of this new strategy to the synthesis of pseudoaminodisaccharides or oligosaccharides is in progress.

Experimental Section

For general experimental procedures, see ref 1a. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, and in $CDCl_3$ unless otherwise stated.

3,4-*O*-Ethylpropylidenequinic Acid-1,5-lactone (3). A mixture of (−)-quinic acid (**2**) (100 g, 0.52 mol), pentan-3-one (550 mL, 1.54 mol), and concentrated phosphoric acid (1 mL) was refluxed with a Dean and Stark apparatus for 12 h at 180 °C. The excess of pentan-3-one was recovered by simple distillation. The mixture was cooled to room temperature, and ethyl acetate (200 mL), potassium hydrogen carbonate (ca. 10 g), and anhydrous sodium sulfate (ca. 10 g) were added. The mixture was stirred until neutralization was completed, and the mixture was then filtered. The filtrate was concentrated to give lactone **3** (118 g, 94%) as a solid residue that was recrystallized from ethyl acetate/hexane as colorless needles: mp 68 °C; R_f = 0.41 (1:2 hexane/diethyl ether); $[\alpha]^{21}_D$ −25.6 (c = 0.6, $CHCl_3$); IR (KBr) 2971, 2941, 2880, 1783, 1460, 1166, 1077 cm^{-1}; ^{1}H NMR δ 0.86 (3H, t, J = 7.5 Hz), 0.93 (3H, t, J = 7.5 Hz), 1.55 (2H, q, J = 7.5 Hz), 1.72 (2H, q, J = 7.5 Hz), 2.12 (1H, dd, J = 14.4 and 3.3 Hz), 2.28−2.42 (2H, m), 2.56 (1H, d, J = 11.7 Hz), 3.72 (1H, brs), 4.27 (1H, ddd, J = 6.9, 2.7, and 1.2 Hz), 4.42−4.48 (1H, m), 4.74 (1H, dd, J = 6.3 and 2.7 Hz); ^{13}C NMR δ 7.9, 8.5, 27.5, 28.6, 34.5, 38.5, 71.0, 71.4, 71.7, 75.7, 77.2, 113.8, 179.0; MS (FAB) m/z (relative intensity) 243 ([M + H]$^+$, 4); HRMS [M + H]$^+$ calcd for $C_{12}H_{19}O_5$ 243.1227, found 243.1229. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.21; H, 7.52.

Methyl 3,4-*O*-Ethylpropylidenequinate (4). To a solution of lactone **3** (2.0 g, 8.3 mmol) in methanol (30 mL) was added dropwise a solution of sodium methoxide (580 mg, 10.7 mmol) in methanol (60 mL) over 30 min at 0 °C. The mixture was stirred for 2 h, and then the pH of the solution was adjusted to 4 with glacial acetic acid. The mixture was diluted with CH_2Cl_2 (60 mL), washed with water (2 × 20 mL) and brine (2 × 20 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (2:1 hexanes/ethyl acetate) gave the tertiary alcohol **4** [1.96 g, 98% (based on recovery of 12% lactone)] as a clear yellowish oil: R_f = 0.16 (1:4 hexane/diethyl ether); $[\alpha]^{21}_D$ −37.5 (c = 0.8, $CHCl_3$); IR (film) 3418, 2972, 2943, 2883, 1732 cm^{-1}; ^{1}H NMR δ 0.85 (3H, t, J = 7.5 Hz), 0.92 (3H, t, J = 7.5 Hz), 1.60 (2H, brq, J = 7.8 Hz), 1.72 (2H, ddd, J = 14.4, 7.2, and 3.0 Hz), 1.80 (1H, dd, J = 13.5 and 11.1 Hz), 2.01 (1H, ddd, J = 13.8, 4.2, and 1.2 Hz), 2.12−2.24 (2H, m), 3.11 (1H, brd, J = 3.0 Hz), 3.49 (3H, brs), 3.77 (3H, s), 3.97 (1H, t, J = 6.6 Hz), 4.07−4.14 (1H, m), 4.43 (1H, m); ^{13}C NMR δ 8.2, 8.6, 28.3, 29.7, 34.9, 38.9, 53.0, 68.2, 72.9, 79.6, 113.2, 175.6; MS (FAB) m/z (relative intensity) 275 ([M + H]$^+$, 59); HRMS [M + H]$^+$ calcd for $C_{13}H_{23}O_6$ 275.1489, found 275.1491. Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.61; H, 8.39.

Methyl 3,4-*O*-Ethylpropylidene-5-dehydroquinate (5). To a mixture of 3 Å molecular sieves (ca. 25 g) and pyridium dichromate (19.6 g, 52 mmol) in dry CH_2Cl_2 (150 mL) was added a solution of alcohol **4** (9.5 g, 35 mmol) in CH_2Cl_2 (70 mL) in one portion under a N_2 atmosphere, followed by an addition of glacial acetic acid (0.5 mL). The mixture was stirred for 24 h at room temperature. The mixture was then filtered through a pad of silica gel, and the residue was washed with ethyl acetate. Concentration of the filtrate followed by flash chromatography (4:1 hexanes/ethyl acetate) produced the ketone **5** (8.18 g, 86%) as a white solid: mp 92 °C; R_f = 0.44 (2:1 hexanes/ethyl acetate); $[\alpha]^{21}_D$ −7.6 (c = 0.5, $CHCl_3$); IR (KBr) 3338, 2973, 2964, 2937, 2881, 1726, 1127, 1068 cm^{-1}; ^{1}H NMR δ 0.92 (3H, t, J = 7.5 Hz), 0.93 (3H, t, J = 7.5 Hz), 1.63−1.76 (4H, m), 2.56 (2H, brd, J = 3.6 Hz), 2.78 and 2.90 (2H, ABq, J = 14.7 Hz), 3.64 (1H, s), 3.84 (3H, s), 4.42 (1H, d, J = 6 Hz), 4.77 (1H, dt, J = 6.0 and 3.6 Hz); ^{13}C NMR δ 8.1, 8.3, 28.4, 29.3, 34.8, 48.6, 53.1, 75.6, 76.2, 77.9, 114.7, 173.0, 204.2; MS (FAB) m/z (relative intensity) 273 ([M + H]$^+$, 100). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.18; H, 7.48.

Methyl 4,5-*O*-Ethylpropylidene-3-dehydro-4-*epi*-shikimate (6). Phosphorus oxychloride (3.0 mL, 32.2 mmol) was slowly added to a solution of tertiary alcohol **5** (4.25 g, 15.6 mmol) in pyridine (30 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 12 h. The solution was washed successively with saturated NH_4Cl (20 mL), extracted with CH_2Cl_2 (2 × 30 mL), dried with $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (5:1 hexanes/ethyl acetate) gave the enone **6** (3.92 g, 99%) as a yellow solid: mp 63 °C; R_f = 0.41 (2:1 hexanes/ethyl acetate); $[\alpha]^{21}_D$ −41.3 (c = 0.6, $CHCl_3$); IR (KBr) 2948, 1723 cm^{-1}; ^{1}H NMR δ 0.79 (3H, t, J = 7.4 Hz), 0.91 (3H, t, J = 7.4 Hz), 1.52 (2H, dq, J = 7.5 and 2.2 Hz), 1.66 (2H, q, J = 7.6 Hz), 2.82 (1H, ddd, J = 20.2, 5.0, and 2.8 Hz), 3.24 (1H, d, J = 20 Hz), 3.85 (3H, s), 4.30 (1H, d, J = 5.4 Hz), 4.73 (1H, dt, J = 5.2 and 1.7 Hz), 6.84 (1H, dd, J = 3.0 and 0.8 Hz); ^{13}C NMR δ 7.8, 8.3, 26.6, 29.0, 29.7, 52.7, 72.3, 74.7, 113.4, 131.3, 144.3, 166.1, 196.0; MS (FAB) m/z (relative intensity) 255 ([M + H]$^+$, 83); HRMS [M + H]$^+$ calcd for $C_{13}H_{19}O_5$ 255.1227, found 255.1232.

(1*R*,2*S*,3*S*)-1,2-*O*-Ethylpropylidene-5-(hydroxymethyl)-4-cyclohexene-1,2,3-triol (7). To a solution of the enone **6** (267 mg, 1.1 mmol) in dry toluene (5 mL) was added dropwise a solution of DIBALH (4 mL, 4.0 mmol) over 30 min at −40 °C. The mixture was stirred for 30 min at 0 °C, quenched with saturated NH_4Cl, and filtered through a pad of Celite. The filtrate was extracted with ethyl acetate (3 × 15 mL). The combined extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (1:2 hexanes/ethyl acetate) gave the diol **7** (233 mg, 93%) as a yellowish syrup: R_f = 0.12 (1:1 hexanes/ethyl acetate); $[\alpha]^{21}_D$ −4.8 (c = 0.6, $CHCl_3$); IR (film) 3393, 2972, 2935, 1075, 985 cm^{-1}; ^{1}H NMR δ 0.80−0.91 (6H, m), 1.54−1.67 (5H, m), 1.98 (1H, d, J = 15.9 Hz), 2.42 (1H, dd, J = 16.2 and 2.4 Hz), 2.62 (1H, s), 4.07 (3H, brd, J = 3.9 Hz), 4.50 (1H, ddd, J = 7.8, 4.5, and 1.2 Hz), 4.57 (1H, ddd, J = 7.5, 3.9, and 2.7 Hz); ^{13}C NMR δ 7.3, 8.3, 27.8, 28.3, 28.4, 65.3, 67.1, 72.3, 76.2, 77.0, 112.1, 124.8, 136.8; MS (FAB) m/z (relative intensity) 229 ([M + H]$^+$, 4); HRMS [M + H]$^+$ calcd for $C_{12}H_{21}O_4$ 229.1434, found 229.1433.

(1*R*,2*S*,3*S*)-3-*O*-Benzyl-5-(benzyloxymethyl)-1,2-*O*-ethylpropylidene-4-cyclohexene-1,2,3-triol (8). Sodium hydride (60%, 945 mg, 23.6 mmol) was washed with dry hexane (3 × 5 mL) and suspended in dry THF (20 mL) under nitrogen at 0 °C. A solution of the diol **7** (1.29 g, 5.66 mmol) in THF (30 mL) was added dropwise over 20 min, and the mixture was stirred for 0.5 h at 0 °C. Benzyl bromide (2.7 mL, 22.6 mmol) was added dropwise over 20 min at 0 °C followed by the addition of a catalytic amount of tetra-*n*-butylammonium iodide. The mixture was refluxed for 12 h. Methanol (3 mL) was added slowly

followed by the addition of water (10 mL). Concentration of the mixture was followed by dilution with ethyl acetate (30 mL), and the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (8:1 hexane/diethyl ether) gave dibenzyl ether **8** (2.26 g, 98%) as a colorless oil: $R_f = 0.27$ (8:1 hexane/diethyl ether); $[\alpha]^{21}_D$ +33.9 (c = 0.8, $CHCl_3$); IR (film) 3086, 3062, 3028, 2970, 2934, 2879, 1071, 736, 697 cm^{-1}; ^1H NMR δ 0.81 (3H, t, J = 7.4 Hz), 0.89 (3H, t, J = 7.4 Hz), 1.55−1.70 (4H, m), 1.85 (1H, d, J = 16.0 Hz), 2.22 (1H, d, J = 17 Hz), 3.81 (1H, t, J = 1.7 Hz), 3.97 (2H, brs), 4.46−4.59 (4H, m), 4.69 and 4.81 (2H, ABq, J = 12.8 Hz), 5.90 (1H, brs), 7.25−7.41 (10H, m); ^{13}C NMR δ 7.5, 8.8, 28.1, 28.6, 29.7, 70.9, 72.3, 73.1, 73.5, 74.1, 75.4, 112.4, 125.1, 127.5, 127.7, 127.9, 128.3, 134.7, 138.1, 138.2; MS (FAB) m/z (relative intensity) 408 ($[M]^+$, 4); HRMS $[M + H]^+$ calcd for $C_{26}H_{33}O_4$ 409.2373, found 409.2370.

(1*R*,2*S*,3*S*,4*R*,5*S*)-3-*O*-Benzyl-5-(benzyloxymethyl)-1,2-*O*-ethylpropylidene-cyclohexane-1,2,3,4,5-pentol (9). To a solution of dibenzyl ether **8** (3.0 g, 7.4 mmol) in acetone/water (20 mL:5 mL) was added NMO (1.72 g, 14.7 mmol) with a catalytic amount of osmium tetraoxide (ca. 5 mg) at room temperature. The mixture was stirred for 48 h and quenched with saturated $Na_2S_2O_3$ (30 mL). The solution was washed with brine (2 × 20 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (2:1 hexanes/ethyl acetate) gave diol **9** (3.0 g, 92%) as a white solid: mp 77−78 °C; $R_f = 0.21$ (2:1 hexanes/ethyl acetate); $[\alpha]^{21}_D$ −29.5 (c = 0.6, $CHCl_3$); IR (KBr) 3331, 2969, 2939, 2854, 1098, 1077, 743, 696 cm^{-1}; ^1H NMR δ 0.87−0.96 (6H, m), 1.54−1.87 (4H, m), 2.02 (1H, dd, J = 14.5 and 6.6 Hz), 2.63 (1H, brs), 2.75 (1H, s), 3.34 (1H, brs), 3.79 (1H, dd, J = 9.5 and 3.9 Hz), 4.00 (1H, dd, J = 9.5 and 1.6 Hz), 4.28−4.39 (2H, m), 4.53 (2H, s), 4.68 and 4.77 (2H, ABq, J = 12 Hz), 7.24−7.41 (10H, m); ^{13}C NMR δ 8.7, 8.8, 28.1, 30.3, 35.3, 70.7, 72.1, 72.2, 73.3, 73.4, 73.6, 75.6, 113.3, 127.5, 127.7, 127.9, 128.1, 128.4, 128.5, 137.8, 137.8, 138.2; MS (FAB) m/z (relative intensity) 443 ($[M + H]^+$, 100). Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.37; H, 7.45.

(1*R*,2*R*,3*R*,4*S*,5*S*)-3,4-Di-*O*-benzyl-5-(benzyloxymethyl)-1,2-*O*-ethylpropylidene-cyclohexane-1,2,3,4,5-pentol (10). Sodium hydride (60%, 118 mg, 3.1 mmol) was washed with dry hexane (2 × 5 mL) and suspended in dry THF (50 mL) under nitrogen at 0 °C. A solution of the diol **9** (791 mg, 1.8 mmol) in THF (10 mL) was added dropwise for 15 min at 0 °C, and the mixture was stirred for 45 min at 0 °C. Benzyl bromide (0.35 mL, 2.9 mmol) was added dropwise for 20 min at 0 °C followed by the addition of a catalytic amount of tetra-*n*-butylammonium iodide. The mixture was stirred for 3 h at room temperature. Methanol (5 mL) was added slowly and followed by the addition of water (20 mL). Concentration of the mixture was followed by dilution with ethyl acetate (20 mL), and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (5:1 hexane/diethyl ether) afforded the tribenzyl ether **10** (785 mg, 98%) as a yellowish clear oil: $R_f = 0.58$ (4:1 hexanes/ethyl acetate); $[\alpha]^{21}_D$ +6.7 (c = 0.6, $CHCl_3$); IR (film) 3440, 2971, 2938, 2876, 1353, 1172 cm^{-1}; ^1H NMR δ 0.91−0.99 (6H, m), 1.57−1.99 (5H, m), 3.97 (2H, brd, J = 1.2 Hz), 4.28−4.34 (2H, m), 4.51 and 4.46 (2H, ABq, J = 12.0 Hz), 4.79 and 4.74 (2H, ABq, J = 12.3 Hz), 4.93 and 4.54 (2H, ABq, J = 10.8 Hz), 7.23−7.42 (15H, m); ^{13}C NMR δ 8.6, 8.7, 28.2, 30.2, 35.6, 72.0, 72.6, 73.1, 74.3, 74.5, 75.3, 77.6, 77.8, 113.0, 127.4, 127.5, 127.7, 128.0, 128.2, 137.9, 138.3; MS (FAB) m/z (relative intensity) 532 ($[M]^+$, 9); HRMS $[M + H]^+$ calcd for $C_{33}H_{41}O_6$ 533.2897, found 533.2877.

(1*R*,2*S*,3*S*,4*S*,5*S*)-5-*O*-Acetyl-3,4-di-*O*-benzyl-5-(benzyloxymethyl)-1,2-*O*-ethylpropylidene-cyclohexane-1,2,3,4,5-pentol (11). To a solution of the tertiary alcohol **10** (467 mg, 0.88 mmol) in dry pyridine (5 mL) were added acetic anhydride (6 mL, 64 mmol) and a catalytic amount of DMAP (ca. 5 mg) at room temperature. The reaction mixture was stirred for 24 h. The mixture was diluted with CH_2Cl_2 (30 mL) and washed with saturated $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (6:1 hexane/diethyl ether) gave acetate **11** (419 mg, 83%) as a colorless oil: $R_f = 0.45$ (3:1 hexanes/ethyl acetate); $[\alpha]^{21}_D$ −1.3 (c = 0.36, $CHCl_3$); IR (film) 3088, 3064, 3030, 2974, 2936, 1738, 1094, 735, 697 cm^{-1}; ^1H NMR δ 0.88−0.99 (6H, m), 1.61−1.71 (3H, m), 1.87−2.04 (2H, m), 1.97 (3H, s), 1.99−2.04 (1H, m), 2.88 (1H, dd, J = 14.1 and 6.3 Hz), 3.84 (1H, d, J = 7.1 Hz), 4.02−4.15 (4H, m), 4.37 (1H, t, J = 4.5 Hz), 4.65 and 4.49 (2H, ABq, J = 11.8 Hz), 4.65 and 4.94 (2H, ABq, J = 10.8 Hz), 4.74 and 4.83 (2H, ABq, J = 11.7 Hz), 7.22−7.42 (15H, m); ^{13}C NMR δ 8.7, 8.8, 21.8, 28.4, 30.4, 32.4, 69.7, 72.0, 73.0, 73.3, 74.3, 75.7, 77.7, 78.0, 84.5, 113.3, 127.3, 127.4, 127.5, 127.7, 127.9, 128.0, 128.2, 128.3, 137.9, 138.5, 138.9, 170.0; HRMS (L-SIMS) $[M + H]^+$ calcd for $C_{35}H_{42}O_7$ 575.3003, found 575.3006.

(1*R*,2*S*,3*S*,4*S*,5*S*)-5-*O*-Acetyl-3,4-di-*O*-benzyl-5-(benzyloxymethyl)cyclohexane-1,2,3,4,5-pentol (12). To a solution of the acetate **11** (266 mg, 0.46 mmol) in CH_2Cl_2 (10 mL) were added TFA (5 drops) and water (2 drops) at room temperature. The mixture was stirred for 24 h and poured into saturated $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (3:2 hexanes/ethyl acetate) gave the diol **12** (233 mg, 100%) as a colorless oil: R_f = 0.22 (1:1 hexanes/ethyl acetate); $[\alpha]^{21}_D$ −0.5 (c = 0.9, $CHCl_3$); IR (film) 3441, 1732 cm^{-1}; ^1H NMR δ 2.0 (3H, s), 2.19 (1H, dd, J = 13.7 and 12.5 Hz), 2.45 (1H, brd, J = 8.2 Hz), 2.75−2.82 (2H, m), 3.67 (1H, m), 3.82 (1H, dd, J = 9.7 and 2.9 Hz), 3.84 (1H, d, J = 8.2 Hz), 4.07 (1H, d, J = 9.8 Hz), 4.18−4.21 (2H, m), 4.42 and 4.51 (2H, ABq, J = 11.8 Hz), 4.63 and 4.86 (2H, ABq, J = 11 Hz), 4.67 and 4.73 (2H, ABq, J = 11.3 Hz), 7.18−7.35 (15H, m); MS (L-SIMS) m/z (relative intensity) 507 ($[M + H]^+$, 0.35); HRMS (EI) $[M]^+$ calcd for $C_{30}H_{34}O_7$ 506.2305, found 506.2349.

(3*R*,4*R*,5*S*)-5-*O*-Acetyl-3,4-di-*O*-benzyl-5-(benzyloxymethyl)-1-cyclohexene-3,4,5-triol (14). To a solution of the diol **12** (1.82 g, 3.6 mmol) in toluene (100 mL) was added 1,1′-thiocarbonyldiimidazole (0.96 g, 5.4 mmol) at room temperature. The reaction mixture was refluxed for 4 h. Concentration of the cooled mixture followed by flash chromatography (4:1 hexanes/ethyl acetate) gave the thiocarbonate **13** as a colorless oil. The thiocarbonate was then dissolved in trimethyl phosphite (50 mL) at room temperature, and the mixture was gently refluxed for 24 h. The excess of trimethyl phosphite was removed under reduced pressure. The residue was purified by flash chromatography (8:1 hexane/diethyl ether) to give alkene **14** (1.48 g, 87%) as a colorless oil: $R_f = 0.80$ (1:1 hexanes/ethyl acetate); $[\alpha]^{21}_D$ −39.0 (c = 0.5, $CHCl_3$); IR (film) 3030, 1731 cm^{-1}; ^1H NMR δ 1.99 (3H, s), 2.67 (1H, dd, J = 18.7 and 2.6 Hz), 2.98 (1H, dd, J = 15.0 and 3.8 Hz), 3.73 (1H, d, J = 13.4 Hz), 3.99 and 4.17 (2H, ABq, J = 8.9 Hz), 4.14 (1H, d, J = 6.3 Hz), 4.25−4.33 (1H, m), 4.44 and 4.50 (2H, ABq, J = 11.9 Hz), 4.58 and 4.65 (2H, ABq, J = 11.5 Hz), 4.71 and 4.83 (2H, ABq, J = 11.3 Hz), 5.63 (1H, brd, J = 10.3 Hz), 5.75 (1H, brd, J = 10.2 Hz), 7.19−7.31 (15H, m); ^{13}C NMR δ 22.1, 30.0, 68.9, 71.7, 73.2, 74.7, 78.2, 78.8, 84.5, 125.6, 125.6, 127.4, 127.6, 127.8, 128.2, 138.0, 138.5, 138.7, 170.5; MS (FAB) m/z (relative intensity) 472 ($[M]^+$, 2); HRMS (EI) $[M]^+$ calcd for $C_{30}H_{32}O_5$ 472.2249, found 472.2251.

(1*S*,2*S*,3*R*,4*S*,5*S*)-5-*O*-Acetyl-3,4-di-*O*-benzyl-5-(benzyloxymethyl)cyclohexane-1,2,3,4,5-pentol (15). To a solution of the alkene **14** (288 mg, 0.61 mmol) in ethyl acetate (6 mL) and CH_3CN (6 mL) was added a solution of $NaIO_4$ (200 mg, 0.94 mmol) and ruthenium trichloride (9 mg, 0.04 mmol) in H_2O (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3 min and quenched with a saturated, aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (1:1 hexanes/ethyl acetate) gave the diol **15** (245 mg, 81%) as a colorless oil: $R_f = 0.33$ (1:1 hexanes/ethyl acetate); $[\alpha]^{21}_D$ +34.9 (c = 2.3, $CHCl_3$); IR (film) 3452, 1730 cm^{-1}; ^1H NMR δ 1.80 (1H, dd, J = 15.5 and 3.1 Hz), 1.95 (3H, s), 2.14 (1H, brs), 2.20 (1H, brs), 2.93 (1H, brd, J = 10.6 Hz), 3.50−3.53 (1H, m), 3.74 (2H, d, J = 8.4 Hz), 3.93−4.03 (2H, m), 4.10 (1H, d, J = 8.6 Hz), 4.34 and 4.43 (2H, ABq, J = 11.7 Hz), 4.68 and 4.63 (2H, ABq, J = 4 Hz), 4.76 (1H, d, J = 11.2 Hz), 4.86 (1H, d, J = 11.4 Hz), 7.18−

7.31 (15H, m); MS (FAB) *m*/*z* (relative intensity) 507 ([M + H]$^+$, 1). Anal. Calcd for $C_{30}H_{34}O_7$: C, 71.13; H, 6.76. Found: C, 71.20; H, 6.68.

(1*S*,2*S*,3*R*,4*S*,5*S*)-1,2-Di-*O*-acetyl-3,4-di-*O*-benzyl-5-(benzyloxymethyl)cyclohexane-1,2,3,4,5-pentol (16). To a solution of the diol **15** (31 mg, 0.061 mmol) in MeOH (2 mL) was added a catalytic amount of potassium carbonate at room temperature, and the mixture was stirred for 3 h at room temperature. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with a saturated, aqueous ammonium chloride solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (1:1 hexanes/ethyl acetate) gave a triol (26 mg, 92%) as a white solid: mp 81−83 °C; R_f = 0.36 (1:1 hexanes/ethyl acetate); $[\alpha]^{20}_D$ +34.3 (*c* = 1.1, $CHCl_3$); IR (film) 3418 cm^{-1}; ^{1}H NMR δ 1.91 (1H, dd, *J* = 15.3 and 2.7 Hz), 2.06 (1H, dd, *J* = 15.3 and 3.1 Hz), 2.68 (1H, d, *J* = 6.4 Hz), 3.20 and 3.47 (2H, ABq, *J* = 8.7 Hz), 3.27 (1H, brs), 3.53−3.56 (2H, m), 3.90 (1H, t, *J* = 9.4 Hz), 4.02−4.06 (1H, m), 4.41 and 4.48 (2H, ABq, *J* = 11.8 Hz), 4.54 (1H, d, *J* = 10.8 Hz), 4.84−4.93 (3H, m), 7.19−7.39 (15H, m); ^{13}C NMR δ 34.2, 70.2, 72.9, 73.1, 75.1, 75.4, 76.2, 80.8, 81.4, 127.5, 127.6, 127.7, 128.0, 128.3, 137.6, 138.0, 138.6; MS (FAB) *m*/*z* (relative intensity) 465 ([M + H]$^+$, 100); HRMS (L-SIMS) [M + H]$^+$ calcd for $C_{28}H_{33}O_6$ 465.2277, found 465.2256.

To a solution of the triol (26 mg, 0.056 mmol) in CH_2Cl_2 (10 mL) were added acetic anhydride (1 mL, 10.6 mmol), pyridine (1 mL, 11 mmol), and a catalytic amount DMAP at room temperature. The reaction mixture was stirred for 12 h at room temperature. The mixture was diluted with CH_2Cl_2 (15 mL) and washed with aqueous, saturated Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (1:1 hexane/diethyl ether) afforded the tertiary alcohol **16** (30 mg, 96%) as a white solid: mp 62−65 °C; R_f = 0.65 (1:1 hexanes/ethyl acetate); $[\alpha]^{21}_D$ +23 (*c* = 0.9, $CHCl_3$); IR (film) 3478, 1738 cm^{-1}; ^{1}H NMR δ 1.97 (3H, s), 2.04 (2H, dd, *J* = 5.7 and 3.5 Hz), 2.09 (3H, s), 2.68 (1H, brs), 3.14 and 3.45 (2H, ABq, *J* = 8.7 Hz), 3.78 (1H, d, *J* = 9.4 Hz), 4.19 (1H, t, *J* = 9.9 Hz), 4.39 and 4.45 (2H, ABq, *J* = 11.9 Hz), 4.52 and 4.90 (2H, ABq, *J* = 10.9 Hz), 4.75 and 4.83 (2H, ABq, *J* = 11.2 Hz), 4.96 (1H, dd, *J* = 10.2 and 3.3 Hz), 5.37 (1H, q, *J* = 3.2 Hz), 7.19−7.38 (15H, m); ^{13}C NMR δ 20.8, 21.2, 32.9, 69.4, 73.0, 73.2, 73.6, 74.3, 75.6, 75.7, 78.2, 80.5, 127.5, 127.6, 127.8, 128.0, 128.3, 128.4, 137.6, 138.1, 138.5, 170.2, 170.3; HRMS (EI) [M − H]$^+$ calcd for $C_{32}H_{36}O_8$ 547.2332, found 547.2359.

(1*S*,2*S*,3*S*,4*R*)-1,2-Di-*O*-acetyl-3,4-di-*O*-benzyl-5-(benzyloxymethyl)-5-cyclohexene-1,2,3,4-tetraol (17). Method A. To a solution of thionyl chloride (0.01 mL, 0.14 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added dropwise a solution of the tertiary alcohol **16** (50 mg, 0.09 mmol) in dry CH_2Cl_2 (5 mL) and pyridine (0.08 mL, 0.99 mmol) for 30 min at 0 °C, and the resultant mixture was stirred overnight at 0 °C. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (2:1 hexane/diethyl ether) gave alkene **17** (20 mg, 40%) and alkene **18** (21 mg, 42%) as colorless oils. Compound **17**: R_f = 0.34 (2:1 hexane/diethyl ether); $[\alpha]^{21}_D$ +48.5 (*c* = 0.9, $CHCl_3$); IR (film) 1746 cm^{-1}; ^{1}H NMR δ 1.97 (3H, s), 2.07 (3H, s), 3.98 (1H, d, *J* = 6.4 Hz), 4.13−4.54 (3H, m), 4.44 and 4.52 (2H, ABq, *J* = 11.8 Hz), 4.68 (1H, d, *J* = 10.9 Hz), 4.74−4.84 (3H, m), 5.13 (1H, dd, *J* = 9.6 and 3.8 Hz), 5.58 (1H, t, *J* = 4.5 Hz), 5.85 (1H, d, *J* = 5.3 Hz), 7.24−7.37 (15H, m); HRMS (L-SIMS) [M]$^+$ calcd for $C_{32}H_{34}O_7$ 530.2304, found 530.2306. Compound **18**: R_f = 0.37 (2:1 hexane/diethyl ether); $[\alpha]^{21}_D$ +23.1 (*c* = 0.8, $CHCl_3$); IR (film) 1744 cm^{-1}; ^{1}H NMR δ 2.04 (3H, s), 2.06 (3H, s), 2.40−2.62 (2H, m), 4.08 (1H, d, *J* = 11.5 Hz), 4.16−4.22 (2H, m), 4.35 and 4.40 (2H, ABq, *J* = 11.9 Hz), 4.63 (3H, d, *J* = 11.4 Hz), 4.82 (1H, d, *J* = 11.4 Hz), 5.34−5.41 (1H, m), 5.46 (1H, dd, *J* = 3.6 and 2.3 Hz), 7.25−7.41 (15H, m); HRMS (L-SIMS) [M]$^+$ calcd for $C_{32}H_{34}O_7$ 530.2304, found 530.2309.

Method B. To a solution of the tertiary alcohol **16** (30 mg, 0.05 mmol) in dry benzene (4 mL) was added Martin sulfurane dehydrating agent[25] (60 mg, 0.09 mmol) at room temperature. The reaction mixture was refluxed for 1 h under nitrogen. Concentration of the mixture was followed by dilution with CH_2Cl_2 (15 mL) and washing with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. Concentration of the filtrate followed by flash chromatography (1:1 hexane/diethyl ether) gave the alkene **17** (24 mg, 90%).

(1*R*,2*R*,3*R*,4*S*,5*S*)-3,4-Di-*O*-benzyl-5-(benzyloxymethyl)-cyclohexane-1,2,3,4,5-pentol (21). To a solution of the acetal **10** (169 mg, 0.32 mmol) in CH_2Cl_2 (15 mL) were added TFA (0.25 mL) and water (5 drops) at room temperature. The mixture was stirred for 3 h. Concentration of the mixture followed by flash chromatography (1:1 hexanes/ethyl acetate) gave the triol **21** (129 mg, 87%) as a colorless oil: R_f = 0.16 (2:1 hexanes/ethyl acetate); $[\alpha]^{21}_D$ −1.2 (*c* = 1.5, $CHCl_3$); IR (film) 3428, 3087, 3062, 3029, 2918, 2864, 1027 cm^{-1}; ^{1}H NMR δ 1.86 (1H, dd, *J* = 13.2 and 4.8 Hz), 1.89−2.15 (4H, m), 3.20 and 3.41 (2H, ABq, *J* = 8.7 Hz), 3.77 (1H, dd, *J* = 9.3 and 2.7 Hz), 3.90 (1H, d, *J* = 9.3 Hz), 3.99 (1H, ddd, *J* = 11.7, 4.8, and 2.7 Hz), 4.19 (1H, brs), 4.44 and 4.52 (2H, ABq, *J* = 12.0 Hz), 4.51 and 4.88 (2H, ABq, *J* = 10.8 Hz), 4.69 (2H, brs), 7.19−7.35 (15H, m); ^{13}C NMR δ 35.1, 66.5, 70.5, 72.3, 73.2, 73.4, 74.0, 75.5, 77.6, 80.3, 127.7, 127.8, 128.1, 128.3, 128.3, 128.4, 137.8, 138.0, 138.2; MS (EI) *m*/*z* (relative intensity) 466 ([M + 2H]$^+$, 9); HRMS (L-SIMS) [M + H]$^+$ calcd for $C_{28}H_{32}O_6$ 465.2272, found 465.2251.

(1*R*,2*R*,3*R*,4*S*,5*S*)-1,2-Di-*O*-acetyl-3,4-di-*O*-benzyl-5-(benzyloxymethyl)cyclohexane-1,2,3,4,5-pentol (22). To a solution of the diol **21** (69 mg, 0.15 mmol) in dry pyridine (10 mL) were added acetic anhydride (1 mL, 11 mmol) and a catalytic amount of DMAP (ca. 3 mg) at room temperature. The reaction mixture was stirred for 2 h. Concentration of the reaction mixture followed by flash chromatography (1:1 hexanes/ethyl acetate) gave diacetate **22** (81 mg, 98%) as a white solid: mp 100−101 °C; R_f = 0.16 (2:1 hexanes/ethyl acetate); $[\alpha]^{21}_D$ −8.7 (*c* = 0.8, $CHCl_3$); IR (film) 3463, 3092, 3064, 3031, 2937, 2865, 1744, 1243, 1228, 1047, 1029, 739, 698 cm^{-1}; ^{1}H NMR δ 1.86 (1H, dd, *J* = 13.5 and 4.8 Hz), 2.01 (3H, s), 2.17 (3H, s), 2.26 (1H, t, *J* = 13.2 Hz), 2.49 (1H, brs), 3.21 and 3.47 (2H, ABq, *J* = 8.7 Hz), 3.85−3.94 (2H, m), 4.42−4.55 (4H, m), 4.72 (1H, d, *J* = 11.7 Hz), 4.90 (1H, d, *J* = 11.4 Hz), 5.20 (1H, ddd, *J* = 12.3, 4.8, and 2.4 Hz), 5.80 (1H, brs), 7.17−7.36 (15H, m); ^{13}C NMR δ 20.9, 21.0, 32.4, 67.5, 68.8, 72.0, 73.2, 73.2, 73.8, 75.6, 77.4, 78.1, 127.5, 127.7, 127.7, 127.8, 128.0, 128.1, 128.3, 128.3, 128.3, 128.4, 137.7, 138.0, 138.2, 170.1, 170.5; MS (EI) *m*/*z* (relative intensity) 549 ([M + H]$^+$, 4); HRMS (L-SIMS) [M + H]$^+$ calcd for $C_{35}H_{42}O_7$ 549.2483, found 549.2448.

(1*S*,2*S*,3*R*,4*S*)-1,2-Di-*O*-acetyl-3,4-di-*O*-benzyl-5-(benzyloxymethylene)-5-cyclohexene-1,2,3,4-tetraol (23). To a solution of the tertiary alcohol **22** (34 mg, 0.06 mmol) in dry benzene (10 mL) was added Martin sulfurane dehydrating agent (60 mg, 0.09 mmol) at room temperature. The reaction mixture was refluxed for 1 h under nitrogen. Concentration of the mixture was followed by dilution with CH_2Cl_2 (15 mL) and washing with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. Concentration of the filtrate followed by flash chromatography (1:1 hexane/diethyl ether) gave the alkene **23** (19 mg, 60%) as a colorless oil: R_f = 0.29 (2:1 hexane/diethyl ether); $[\alpha]^{21}_D$ −36.5 (*c* = 1.5, $CHCl_3$); IR (film) 1744, 1684 cm^{-1}; ^{1}H NMR δ 2.01 (3H, s), 2.12 (3H, s), 2.32 (1H, t, *J* = 10.5 Hz), 2.87 (1H, dd, *J* = 13.5 and 5.1 Hz), 3.51 (1H, dd, *J* = 8.2 and 3.0 Hz), 4.10 (1H, brd, *J* = 8.2 Hz), 4.54 and 4.68 (2H, ABq, *J* = 11.6 Hz), 4.55 and 4.65 (2H, ABq, *J* = 11.4 Hz), 4.80−4.86 (3H, m), 5.65 (1H, m), 6.37 (1H, s), 7.22−7.41 (15H, m); HRMS (EI) [M]$^+$ calcd for $C_{32}H_{34}O_7$ 530.2304, found 530.2297.

(1*S*,2*S*,3*S*,4*R*)-3,4-Di-*O*-benzyl-1-benzylamino-5-(benzyloxymethyl)-5-cyclohexene-2,3,4-triol (26). To a solution of the allylic acetate **17** (100 mg, 0.19 mmol) in CH_3CN (15 mL) were added PPh_3 (10 mg, 0.04 mmol) and $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) at room temperature. The mixture was stirred for 30 min at room temperature. Benzylamine (0.06 mL, 0.55 mmol) was added at room temperature, and the reaction mixture was then heated under reflux overnight. The solvent was removed under reduced pressure. The residue was purified by flash chroma-

tography (1:1 hexanes/EtOAc) to give the crude coupled product **24** (70 mg, 65%) as a colorless oil. To a solution of compound **24** in MeOH (10 mL) was added a catalytic amount of NaOMe, and the mixture was refluxed overnight. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (2:1 hexanes/EtOAc) to give benzylamine **26** (61 mg, 60%) as a colorless oil: $R_f = 0.37$ (2:1 hexanes/EtOAc); $[\alpha]^{21}_D$ +39.4 ($c = 1.0$, $CHCl_3$); IR (film) 3418 cm^{-1}; ^1H NMR δ 2.11 (2H, brs), 3.40 (1H, t, $J = 4.3$ Hz), 3.81 (1H, dd, $J = 7.7$ and 5.1 Hz), 3.88−3.49 (4H, m), 4.06 (1H, d, $J = 5.1$ Hz), 4.19 (1H, d, $J = 12.2$ Hz), 4.40 and 4.49 (2H, ABq, $J = 11.8$ Hz), 4.57 and 4.73 (2H, ABq, $J = 11.1$ Hz), 4.68 and 4.82 (2H, ABq, $J = 11.5$ Hz), 5.90 (1H, d, $J = 2.8$ Hz), 7.22−7.36 (20H, m); MS (EI) *m*/*z* (relative intensity) 534 ([M − H]$^+$, 0.7); HRMS (EI) [M]$^+$ calcd for $C_{35}H_{37}NO_4$ 535.2723, found 535.2722.

(1*S*,2*S*,3*S*,4*R*)-3,4-Di-*O*-benzyl-5-(benzyloxymethyl)-1-propylamino-5-cyclohexene-2,3,4-triol (27). To a solution of the allylic acetate **17** (116 mg, 0.22 mmol) in CH_3CN (15 mL) were added PPh_3 (10 mg, 0.04 mmol) and $Pd(PPh_3)_4$ (25 mg, 0.02 mmol) at room temperature. The mixture was stirred for 30 min at room temperature. Propylamine (0.07 mL, 0.85 mmol) was added, and the reaction mixture was refluxed overnight. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (1:1 hexanes/EtOAc) to give the crude compound **25** (74 mg) as a colorless oil. To a solution of amine **25** in MeOH (10 mL) was added a catalytic amount of NaOMe, and the mixture was refluxed overnight. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (EtOAc) to give the propylamine **27** (60 mg, 58%) as a colorless oil: $R_f = 0.37$ (EtOAc); $[\alpha]^{21}_D$ +31.7 ($c = 0.8$, $CHCl_3$); IR (film) 3417 cm^{-1}; ^1H NMR δ 0.92 (3H, t, $J = 7.4$ Hz), 1.53 (2H, q, $J = 7.3$ Hz), 2.19 (2H, brs), 2.57−2.82 (2H, m), 3.33 (1H, m), 3.75 (1H, dd, $J = 7.8$ and 5.3 Hz), 3.88−3.94 (2H, m), 4.07 (1H, d, $J = 5.4$ Hz), 4.20 (1H, d, $J = 12.3$ Hz), 4.41 and 4.50 (2H, ABq, $J = 11.9$ Hz), 4.57 and 4.74 (2H, ABq, $J = 11.1$ Hz), 4.70 and 4.86 (2H, ABq, $J = 11.3$ Hz), 5.96 (1H, d, $J = 3.1$ Hz), 7.22−7.35 (15H, m); MS (EI) *m*/*z* (relative intensity) 488 (MH$^+$, 7.7); HRMS (EI) [M]$^+$ calcd for $C_{31}H_{37}NO_4$ 487.2722, found 487.2694.

(1*S*,2*S*,3*S*,4*R*)-1-Acetamido-5-(acetoxymethyl)-2,3,4-tri-*O*-acetyl-5-cyclohexene-2,3,4-triol (28). To a solution of the amine **26** (78.4 mg, 0.15 mmol) in dry THF (3 mL) and liquid NH_3 (15 mL) was added sodium (76 mg, 3.3 mmol) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C. Solid NH_4Cl (100 mg) was added to the mixture at −78 °C. After the disappearance of the blue color of the mixture, NH_3 and solvent were removed under reduced pressure to give crude valienamine (**1**). The crude product **1** was dissolved in pyridine (10 mL) and acetic anhydride (3 mL) containing a catalytic amount of DMAP. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (10 mL) and washed with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (1:4 hexanes/EtOAc) gave pentaacetate **28** (38.3 mg, 69%) as a white solid, identical to an authentic sample from our previous work: mp 93−94 °C (lit.[1a] mp 92−94 °C); $R_f = 0.29$ (1:4 hexanes/EtOAc); $[\alpha]^{20}_D$ +20.1 ($c = 0.8$, $CHCl_3$); IR (film) 3366, 3281, 1746, 1658 cm^{-1}; ^1H NMR δ 2.00−2.05 (15H, m), 4.37 and 4.63 (2H, ABq, $J = 13.2$ Hz), 4.98−5.09 (2H, m), 5.36 (1H, brd, $J = 6.3$ Hz), 5.43 (1H, dd, $J = 9.3$ and 6.3 Hz), 5.80 (1H, brd, $J = 8.6$ Hz), 5.87 (1H, dd, $J = 5$ and 1.1 Hz); ^{13}C NMR δ 20.6, 23.2, 44.9, 62.9, 68.5, 69.2, 71.2, 126.2, 134.3, 169.8, 170.0, 170.1, 170.2.

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Supporting Information Available: ^1H spectra of **6**−**8**, **10**−**12**, **14**, **16**−**18**, **21**−**23**, **26**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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