Enantiospecific Syntheses of Valienamine and 2-*epi*-Valienamine[1]

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Cyclic sulfite **10**, readily available from (−)-quinic acid (**3**) in 10 steps, was ring opened regio- and stereospecifically with azide anion to give (1*S*,2*R*,3*R*,4*R*)-1-azido-3,4-di-*O*-benzyl-5-(benzyloxymethyl)cyclohex-5-ene-2,3,4-triol (**11**). Deprotection of **11** afforded, for the first time, 2-*epi*-valienamine (**2**), which was isolated as penta-*N*,*O*-acetyl-2-*epi*-valienamine (**14**). The configuration of the free hydroxy group in **11** was inverted by a two-step sequence to give the blocked valienamine **19** that was deprotected to give valienamine (**1**), isolated as penta-*N*,*O*-acetylvalienamine (**21**). This approach furnished (+)-valienamine (**1**) in 16 steps (7% overall yield) and recorded the first synthesis of 2-*epi*-valienamine (**2**) in 13 steps (11% overall yield).

Introduction

Valienamine[2] [(1*S*,2*S*,3*S*,4*R*)-1-amino-5-(hydroxymethyl)cyclohex-5-ene-2,3,4-triol][t] (**1**) is a carbasugar[3] produced by the microbial degradation of validoxylamine A[4] with *Pseudomonas denitrificans*[5] or *Flavobacterium saccharophilum*.[6] The structure of valienamine was deduced by spectroscopic studies.[5] Valienamine demonstrated α-glucosidase inhibitory activity, inhibiting 50% activity of maltase and sucrase at a concentration of 3.4×10^{-4} and 5.3×10^{-5} M, respectively.[7] Also, it showed antibiotic activity against *Bacillus* species.[8,9] The absolute configuration of valienamine (**1**) is similar to that of α-D-glucose. Since valienamine is an α-glucosidase inhibitor, it was expected that the unnatural diastereomer, 2-*epi*-valienamine (**2**), which is structurally related to α-D-mannose, might be an α-mannosidase inhibitor (Figure 1).

Valienamine is an essential core unit in many kinds of pseudo-oligosaccharidic α-glucosidase inhibitors, such as acarbose,[10,11] adiposin-2,[12] acarviosin,[13] and trestatin B.[14] These pseudo-oligosaccharides exhibit stronger enzyme inhibitory activities than valienamine itself. Synthesis of partially protected valienamine is warranted for the subsequent coupling reactions targeting these pseudo-aminodisaccharides or oligosaccharides. Related carbaaminosugars (pseudoaminosugars) which show potent glycosidase activity include valiolamine,[15] validamine,[16] and hydroxyvalidamine.[17]

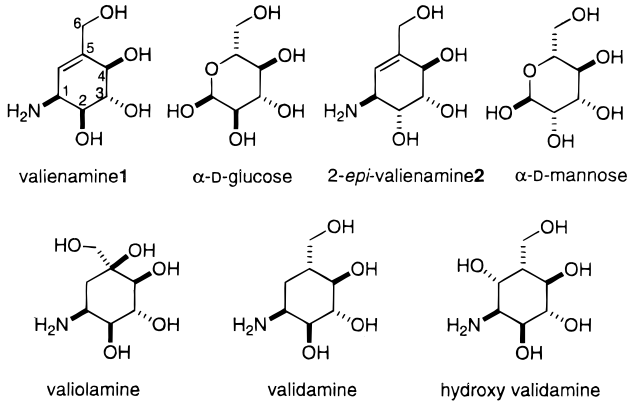

Figure 1.

Since the isolation of valienamine **1** in 1972, eight enantiospecific[18−25] syntheses have appeared. The first

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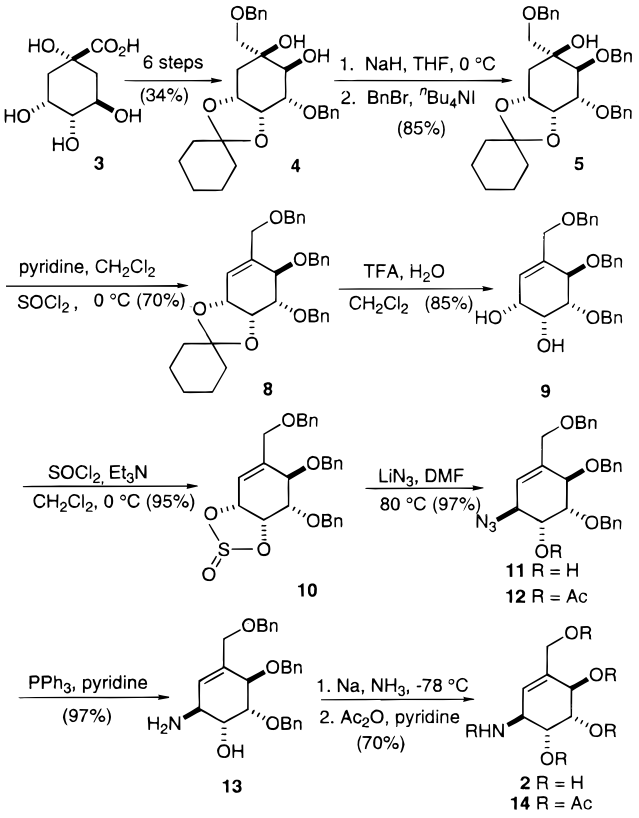
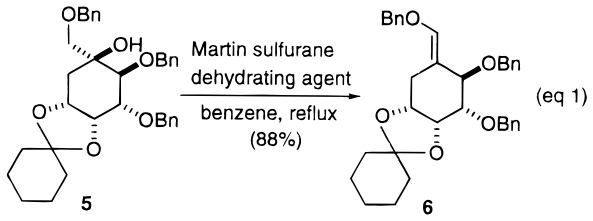
Scheme 1



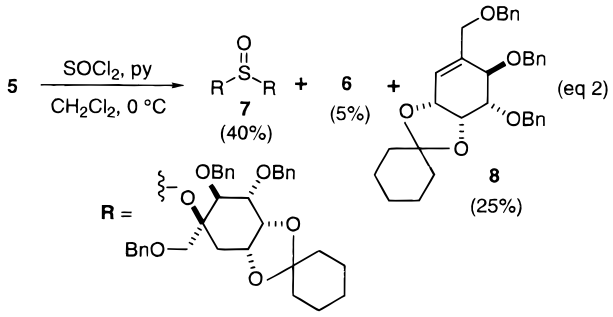
synthesis was reported by Paulsen et al.,[18] on the basis of transformations from the cyclitol quebrachitol. Four other syntheses were based on conversions from D-glucose in which three[19−21] involved a Ferrier rearrangement and one[22] employed cyclization of a nitrofuranose as the key step for the formation of the cyclohexane framework. The three[23−25] remaining constructions took advantage of the Diels−Alder reaction to fabricate the cyclohexane skeleton, which then was functionalized to give the target molecule. The most recent synthesis was asymmetric and was achieved via two consecutive palladium-catalyzed asymmetric alkylations as the key steps.[25] However, the construction of 2-*epi*-valienamine (**2**) has not been reported in the literature. In our own quest for a general and efficient entry to pseudoaminosugars, we previously described the preparations of validamine and 2-*epi*-validamine,[26] valiolamine, 1-*epi*-valiolamine, 2-*epi*-valiolamine, and (1*R*,2*R*)-valiolamine using the (−)-quinic acid approach.[1b] We herein report the versatility of this approach for the facile and enantiospecific syntheses of valienamine (**1**) and its 2-epimer **2**, involving a regioselective cyclic sulfite opening as the key step.

Synthesis of 2-*epi*-Valienamine

Our previous work has shown that the diol **4** could be obtained from (−)-quinic acid (**3**) in six steps with 34% overall yield (Scheme 1).[1b] Then, selective benzylation of the secondary alcohol in diol **4** with benzyl bromide in the presence of sodium hydride afforded the tribenzyl ether **5**. Regioselectivity could be achieved because the secondary hydroxyl group is less hindered than the tertiary one. Elimination of the tertiary hydroxyl group in **5** to furnish the double bond in valiename was our next objective. Initially, the tribenzyl ether **5** was treated with $POCl_3$ in pyridine,[27] but there was no observable reaction. The reaction of **5** with Martin sulfurane dehydrating agent,[28] however, gave the undesired enol ether **6** as the sole product in excellent yield (eq 1). It was speculated



that this pathway was preferred because the cyclohexylidene ring in **5** might block the α-face, thereby preventing *anti*-elimination from proceeding at the endocyclic methylene. The tribenzyl ether **5** was also allowed to react with thionyl chloride and pyridine in CH_2Cl_2 at 0 °C,[29] but a low yield of the desired alkene **8** was obtained. The major product was the dimer **7** together with a small amount of the enol ether **6** (eq 2). Dimer formation was



probably due to the tribenzyl ether **5** being in excess when thionyl chloride was added dropwise to the reaction mixture. The tribenzyl ether **5** could be regenerated from the dimer **7** in 90% yield upon solvolysis with sodium hydroxide in methanol. We therefore modified the elimination procedure in order to prevent the formation of dimer **7**. This was realized by ensuring that thionyl chloride was in excess throughout the reaction (reversed quenching). A solution of **5** in pyridine was therefore added dropwise to the thionyl chloride solution in CH_2Cl_2 at 0 °C. In this manner, the desired alkene **8** was obtained in 70% yield and only a small amount of the dimer **7** (15%) was produced.

Hydrolysis of the cyclohexylidene blocking group in **8** was carried out using aqueous trifluoroacetic acid (TFA) in CH_2Cl_2 to give the diol **9** in 85% yield (Scheme 1). A second reaction with thionyl chloride in the conventional way provided the cyclic sulfite[30] **10** in excellent yield. The cyclic sulfite proved to be unstable and was used in the following ring-opening reaction without characterization. To synthesize valienamine and its 2-epimer, an amino group must be installed at the allylic position. An azido group was chosen as the amine precursor, and the

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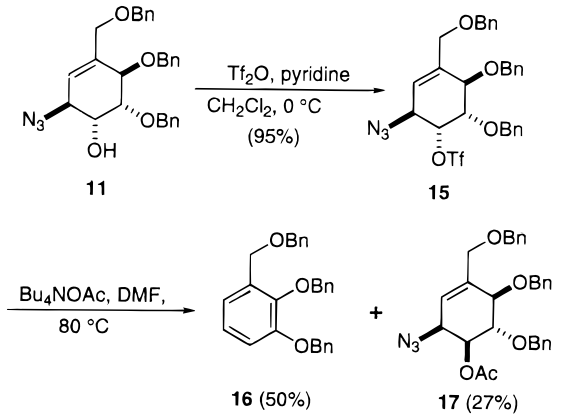
Scheme 2



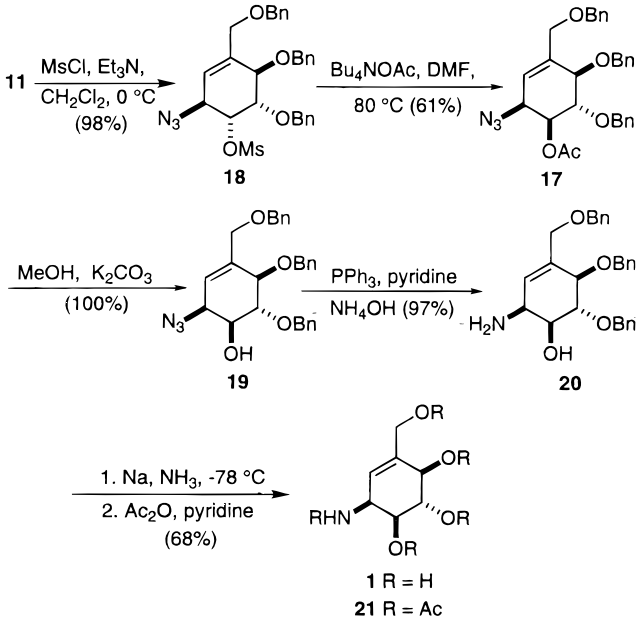
introduction of the azido group at the allylic position proceeded via a regiospecific S_N2 reaction[30] of lithium azide on the cyclic sulfite **10**, affording a single adduct **11** in 97% yield. The regio- and stereochemical assignments were based on ^1H NMR spectral analysis of the azido acetate **12** formed from **11**. The coupling constants of 1.3 Hz between H_2-H_3 and 7.8 Hz between H_1-H_2 show that H_1 and H_2 are *anti*-disposed and H_2 and H_3 are *syn*-disposed. These assignments were confirmed by spin-decoupling experiments, thus providing evidence that the nucleophilic opening reactions of the cyclic sulfite **10** by the azido group were stereospecific and occurred via the β-face.

It has been reported that reduction of an allylic azide with $NaBH_4$ would cause the azide group to migrate through a boron-assisted allylic rearrangement.[31] Thus, the reduction of the azido group in **11** was effected with triphenylphosphine (PPh_3), aqueous ammonia, and pyridine,[32] furnishing amine **13** in excellent yield. In this reaction, PPh_3 reacts with the azide group to give a triphenylphosphinimine, which is then hydrolyzed cleanly to the amine on treatment with aqueous ammonia. Because the presence of a double bond in **13** precludes the use of hydrogenolysis, debenzylation of **13** was carried out using sodium in liquid ammonia at −78 °C to give 2-*epi*-valienamine (**2**). This constitutes the first chemical synthesis of this compound. Peracetylation of **2** to the corresponding pentaacetyl derivative **14** allowed facile isolation and characterization. The overall yield of **14** from (−)-quinic acid (**3**) was 11% in 14 steps.

Synthesis of Valienamine

For the synthesis of valienamine **1**, the configuration at C-2 of **11** needs to be inverted. Activation of the free alcohol at this site as a sulfonate ester was investigated, and the preparation of a triflate ester was attempted first. Thus the hydroxy group in **11** was esterified with trifluoromethanesulfonic anhydride and pyridine in dichloromethane to yield the triflate **15** in excellent yield (Scheme 2). The triflate **15** was then reacted with *N*-hydroxysuccinimide in an attempt to invert the configuration at C-2.[33] However, no reaction occurred, probably due to the weak nucleophilicity of *N*-hydroxysuccinimide. A stronger nucleophile, tetrabutylammonium acetate, was then employed. Unfortunately, whether because the basicity of tetrabutylammonium acetate is too strong or the triflate group is too reactive, elimination rather than S_N2 substitution predominated, and the aromatic compound **16** was obtained in 50% yield together with only 27% of the desired azidoacetate **17**. When the triflate group was replaced by the less nucleofugal mesylate group via standard esterification of **11** with mesyl chloride, the elimination reaction of the resultant mesylate **18** in the presence of tetrabutylammonium acetate was minimized to 10%, and the yield of the desired azidoacetate **17** was greatly improved to 61% (Scheme 3).

Scheme 3



Since the current chirality of all the functional groups was now established, the next step was to deacetylate **17** to afford **19** using a catalytic amount of potassium carbonate in methanol. The azido group in **19** was then reduced readily to the amine **20** using PPh_3 and NH_4OH in pyridine. Finally, debenzylation of **20** with sodium in liquid ammonia at −78 °C afforded valienamine **1**. Acetylation of **1** afforded peracetate **20** for isolation and characterization. The overall yield of *N*,*O*,*O*,*O*,*O*-pentacetylvalienamine **20** from (−)-quinic acid was 7% in 17 steps. The spectral data and physical constants, of our synthetic compound **20**, mp 92−94 °C, $[\alpha]^{20}_D$ +20.1 (c = 0.8, $CHCl_3$), are in close agreement with those reported in the literature (lit.[5] mp 95 °C; lit.[23] mp 92.5−95 °C) {lit.[5] $[\alpha]^{23}_D$ +32.2 ($CHCl_3$); lit.[23] $[\alpha]^{21}_D$ +20 (c = 1.04, $CHCl_3$)}.

Conclusions

We have described facile, practical, and enantiospecific syntheses of (+)-valienamine (**1**) and (+)-2-*epi*-valienamine (**2**) in 16 steps (7% overall yield) and 13 steps (11% overall yield), respectively, from quinic acid (**3**). The preparation of (+)-2-*epi*-valienamine (**2**) has not been previously reported. Synthetic intermediates such as amino alcohols **13** and **20** are possibly valuable substrates for the coupling reactions that lead to pseudoaminodisaccharides or oligosaccharides. Research along this line is under way.

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Experimental Section

Melting points are reported in degrees Celsius and are uncorrected. Optical rotations were measured at 589 nm. IR spectra were recorded on a FT-IR spectrometer as thin films on KBr disks. Unless otherwise stated, NMR spectra were measured in solutions of $CDCl_3$ at 250 MHz (^1H) or at 62.9 MHz (^{13}C). Spin−spin coupling constants (J) were measured directly from the spectra. Carbon and hydrogen elemental analyses were carried out at either the Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, China, or the MEDAC Ltd, Department of Chemistry, Brunel University, Uxbridge, U.K. All reactions were monitored by analytical TLC on aluminum precoated with silica gel $60F_{254}$ (E. Merck), and compounds were visualized with a spray of either 5% w/v dodecamolybdophosphoric acid in ethanol or 5% v/v concentrated sulfuric acid in ethanol and subsequent heating. All columns were packed wet using E. Merck silica gel 60 (230−400 mesh) as the stationary phase and eluted using flash column chromatographic technique.

(1*R*,2*R*,3*R*,4*S*,5*S*)-3,4-Di-*O*-benzyl-5-(benzyloxymethyl)-1,2-*O*-cyclohexylidene-1,2,3,4,5-cyclohexanepentol (5). Sodium hydride (80%, 0.10 g, 3.33 mmol) was washed with dry *n*-hexane and suspended in dry THF (5 mL) under nitrogen at 0 °C. A solution of the diol **4**[1b] (0.96 g, 2.11 mmol) in THF (8 mL) was added dropwise over 30 min at 0 °C, and then the mixture was stirred for 1 h at 0 °C. Benzyl bromide (0.5 mL, 4.21 mmol) was added dropwise over 30 min at 0 °C followed by the addition of a catalytic amount of $^nBu_4NI$. The mixture was stirred overnight at room temperature. Methanol (3 mL) was then added slowly to destroy the excess of hydride, and this was followed by the addition of water (5 mL). Concentration of the mixture gave a residue that was partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (hexane−diethyl ether, 2:1) gave the tribenzyl ether **5** (0.98 g, 85%) as a colorless oil: R_f = 0.25 (hexane−diethyl ether, 2:1); $[\alpha]^{20}_D$ +1.5 (c = 1.3, $CHCl_3$); IR (film) 3450 cm^{-1}; ^1H NMR δ 1.40−2.03 (12H, m), 2.30 (1H, s), 3.21 and 3.42 (2H, ABq, J = 8.6 Hz), 3.97 (2H, m), 4.25−4.33 (2H, m), 4.44 and 4.50 (2H, ABq, J = 12.0 Hz), 4.54 and 4.93 (2H, ABq, J = 10.8 Hz), 4.73 and 4.79 (2H, ABq, J = 12.1 Hz), 7.22−7.42 (15H, m); MS (FAB) m/z (relative intensity) 545 (MH^+, 6). Anal. Calcd for $C_{34}H_{40}O_6$: C, 74.97; H, 7.40. Found: C, 74.55; H, 7.47.

(1*R*,2*R*,3*S*,4*R*)-3,4-Di-*O*-benzyl-5-(benzyloxymethylene)-1,2-*O*-cyclohexylidenecyclohex-5-ene-1,2,3,4-tetraol (6). To a solution of the tertiary alcohol **5** (123 mg, 0.22 mmol) in dry benzene (15 mL) was added Martin sulfurane dehydrating agent[28] (230 mg, 0.34 mmol) at room temperature. The reaction mixture was heated under reflux for 3 h under nitrogen, then concentrated, diluted with CH_2Cl_2 (20 mL), and washed with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were dried over $MgSO_4$ and filtered. Concentration of the filtrate followed by flash chromatography (hexane−diethyl ether, 3:2) gave the exocyclic alkene **6** (104 mg, 88%) as a colorless oil.

6: R_f = 0.54 (hexane−diethyl ether, 4:1); $[\alpha]^{20}_D$ = +54.2 (c = 2.0, $CHCl_3$); IR (film) 1682 cm^{-1}; ^1H NMR δ 1.33−1.64 (10H, m), 2.22 (1H, dd, J = 14.5, 4.6 Hz), 2.58 (1H, dd, J = 14.5, 3.6 Hz), 3.64 (1H, dd, J = 6.9, 3.2 Hz), 4.08 (1H, d, J = 6.9 Hz), 4.24−4.30 (1H, m), 4.38−4.42 (2H, m), 4.52 (1H, d, J = 11.6 Hz), 4.76−4.87 (4H, m), 6.25 (1H, s), 7.24−7.39 (15H, m); HRMS (EI) calcd for $C_{34}H_{28}O_5$ 526.2719 (M^+), found 526.2713.

Dimer 7 and (1*R*,2*R*,3*S*,4*R*)-3,4-Di-*O*-benzyl-5-(benzyloxymethyl)-1,2-*O*-cyclohexylidenecyclohex-5-ene-1,2,3,4-tetraol (8). (a) To a solution of the tertiary alcohol **5** (185 mg, 0.34 mmol) in dry CH_2Cl_2 (20 mL) and pyridine (0.25 mL, 3.10 mmol) was added dropwise a solution of thionyl chloride (0.04 mL, 0.55 mmol) in dry CH_2Cl_2 (8 mL) for 30 min at 0 °C, and the mixture was stirred for 5 h at 0 °C. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ (12 mL). The aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (hexane−diethyl ether, 5:1) gave the endocyclic alkene **8** (45 mg, 25%) as a white solid and the exo enol ether **6** (9 mg, 5%) and the sulfite dimer **7** (77 mg, 40%) as colorless oils.

Alkene **8**: mp 65−68 °C; R_f = 0.3 (hexane−diethyl ether, 4:1); $[\alpha]^{20}_D$ −25.8 (c = 1.0, $CHCl_3$); IR (film) 2933, 2859 cm^{-1}; ^1H NMR δ 1.55−1.63 (10H, m), 3.76 (1H, dd, J = 7.9, 2.5 Hz), 3.96 and 4.26 (2H, ABq, J = 12.9 Hz), 4.39 (1H, br d, J = 7.9 Hz), 4.44 and 4.52 (2H, ABq, J = 11.8 Hz), 4.50−4.55 (2H, m), 4.69 and 4.88 (2H, ABq, J = 10.8 Hz), 4.79 (2H, s), 5.71 (1H, br s), 7.25−7.41 (15H, m); MS (FAB) m/z (relative intensity) 526 (MH^+, 7). Anal. Calcd for $C_{34}H_{38}O_5$: C, 77.54; H, 7.27. Found: C, 77.52; H, 7.24.

Sulfite dimer **7**: R_f = 0.33 (hexane−diethyl ether, 4:1); $[\alpha]^{20}_D$ +4.5 (c = 1.3, $CHCl_3$); IR (film) 2934, 2859 cm^{-1}; ^1H NMR δ 1.43−1.73 (20H, m), 1.83−1.94 (2H, m), 2.27−2.40 (2H, m), 3.57 and 3.73 (2H, ABq, J = 8.9 Hz), 3.62 and 3.78 (2H, ABq, J = 9 Hz), 4.00−4.18 (6H, m), 4.23−4.36 (6H, m), 4.58 (2H, d, J = 11.3 Hz), 4.63−4.66 (2H, m), 4.74 (2H, d, J = 11.8 Hz), 4.97 (2H, d, J = 11.4 Hz), 7.11−7.32 (30H, m); MS (FAB) m/z (relative intensity) 545 ($M^+ - C_{34}H_{37}O_7S$, 27%). Anal. Calcd for $C_{68}H_{78}O_{13}S$: C, 71.93; H, 6.92; S, 2.82. Found: C, 71.78; H, 6.81; S, 2.83.

(b) To a solution of thionyl chloride (0.015 mL, 0.21 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added dropwise a solution of the tertiary alcohol **5** (60 mg, 0.11 mmol) in dry CH_2Cl_2 (5 mL) and pyridine (0.1 mL, 1.24 mmol) within 30 min, and the mixture was stirred for 5 h 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 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (hexane−diethyl ether, 5:1) gave the alkene **8** (41 mg, 70%) as a white solid and the dimer **7** (15%).

(1*R*,2*R*,3*R*,4*R*)-3,4-Di-*O*-benzyl-5-(benzyloxymethyl)cyclohex-5-ene-1,2,3,4-tetraol (9). To a solution of the alkene **8** (115 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) was added TFA (0.5 mL) and water (0.1 mL) at room temperature. The mixture was stirred for 24 h at room temperature and poured into saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (hexane−diethyl ether, 1:2) gave the diol **9** (83 mg, 85%) as a white solid.

Diol **9**: mp 79−85 °C; R_f = 0.16 (hexane−diethyl ether, 1:2); $[\alpha]^{20}_D$ −75.7 (c = 1.0, $CHCl_3$); IR (film) 3422 cm^{-1}; ^1H NMR δ 2.83 (1H, br d, J = 10.6 Hz), 3.33 (1H, br d, J = 7.6 Hz), 3.85−3.89 (2H, m), 4.05−4.18 (4H, m), 4.34 and 4.47 (2H, ABq, J = 11.8 Hz), 4.43 and 4.59 (2H, ABq, J = 11.3 Hz), 4.52 and 4.58 (2H, d, J = 11.7 Hz), 5.95 (1H, d, J = 3.5 Hz), 7.21−7.37 (15H, m); MS (FAB) m/z (relative intensity) 447 (MH^+, 2). Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77. Found: C, 75.57; H, 7.01.

(1*R*,2*S*,3*S*,4*R*)-3,4-Di-*O*-benzyl-5-(benzyloxymethyl)-1,2-*O*,*O*-sulfonylcyclohex-5-ene-1,2,3,4-tetraol (10). To a solution of the diol **9** (455 mg, 1.02 mmol) in CH_2Cl_2 (10 mL) and Et_3N (0.7 mL) was added a solution of thionyl chloride (0.22 mL, 3.02 mmol) in CH_2Cl_2 (10 mL) at 0 °C, and the mixture was stirred for 1 h at 0 °C. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford the crude cyclic sulfite **10**, which was used directly in the following ring-opening experiment.

(1*S*,2*R*,3*R*,4*R*)-1-Azido-3,4-di-*O*-benzyl-5-(benzyloxymethyl)cyclohex-5-en-2,3,4-triol (11). The above cyclic sulfite **10** was dissolved in DMF (10 mL), and LiN_3[34] (130 mg) was added. The reaction mixture was stirred for 3 h at 80 °C. The

(34) Hofmann-Bang, N. *Acta Chem. Scand.* **1957**, *11*, 581.

cooled mixture was then diluted with EtOAc (15 mL), washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatgraphy (hexane−diethyl ether, 3:1) gave the azide **11** (433 mg, 90%) as a colorless oil.

Azide **11:** $R_f = 0.52$ (hexane−diethyl ether, 1:1); $[\alpha]^{20}_D$ +36 ($c = 1.3$, $CHCl_3$); IR (film) 3502, 2099 cm^{-1}; ^1H NMR δ 2.26 (1H, d, $J = 7.8$ Hz), 3.86−3.96 (3H, m), 4.05−4.17 (3H, m), 4.36 and 4.48 (2H, ABq, $J = 11.9$ Hz), 4.46 and 4.57 (2H, ABq, $J = 11.3$ Hz), 4.54 and 4.61 (2H, ABq, $J = 11.9$ Hz), 5.74 (1H, s), 7.22−7.38 (15H, m); MS (FAB) *m*/*z* (relative intensity) 472 (MH^+, 6). Anal. Calcd for $C_{28}H_{29}N_3O_4$: C, 71.32; H, 6.20; N, 8.91. Found: C, 71.15; H, 6.26; N, 8.80.

(1*S*,2*R*,3*S*,4*R*)-2-*O*-Acetyl-1-azido-3,4-di-*O*-benzyl-5-(benzyloxymethyl)cyclohex-5-ene-2,3,4-triol (12). To a solution of the alcohol **11** (100 mg, 0.21 mmol) in CH_2Cl_2 (10 mL) was added Ac_2O (0.04 mL, 0.42 mmol), pyridine (0.07 mL, 0.84 mmol), and a catalytic amount of DMAP (1 mg) at room temperature. The reaction mixture was stirred overnight at room temperature, then diluted with CH_2Cl_2 (15 mL), and washed with saturated Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (hexane−diethyl ether, 4:1) gave the acetate **12** (100 mg, 95%) as a colorless oil.

Acetate **12**: $R_f = 0.47$ (hexane−diethyl ether, 3:1); $[\alpha]^{20}_D$ +49.7 ($c = 0.4$, $CHCl_3$); IR (film) 2098, 1743 cm^{-1}; ^1H NMR δ 2.08 (3H, s), 3.90 and 3.10 (2H, ABq, $J = 12.5$ Hz), 4.00 (2H, s), 4.34−4.44 (3H, m), 4.49 (1H, d, $J = 11.9$ Hz), 4.53 (1H, s), 4.60 (1H, d, $J = 11.4$ Hz), 5.21 (1H, d, $J = 7.7$ Hz), 5.75 (1H, s), 7.25−7.37 (15H, m).

(1*S*,2*R*,3*R*,4*R*)-1-Amino-3,4-di-*O*-benzyl-5-(benzyloxymethyl)cyclohex-5-ene-2,3,4-triol (13). To a solution of the alcohol **11** (379 mg, 0.81 mmol) in pyridine (10 mL) and aqueous NH_3 (32%, 2 mL) was added PPh_3 (317 mg, 1.21 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with brine. The aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were dried over $MgSO_4$ and filtered. Concentration of the filtrate followed by flash chromatography ($CHCl_3$−MeOH, 10:1) gave the amine **13** (349 mg, 97%) as a white solid.

Amine **13**: mp 80−82 °C; $R_f = 0.39$ ($CHCl_3$−MeOH, 10:1); $[\alpha]^{20}_D$ −9.7 ($c = 1.1$, $CHCl_3$); IR (film) 3355, 3289, 3022 cm^{-1}; ^1H NMR δ 2.27 (3H, br s), 3.47 (1H, br d, $J = 8.2$ Hz), 3.60 (1H, dd, $J = 8.4$, 2.3 Hz), 3.82 and 4.10 (2H, ABq, $J = 12.1$ Hz), 3.89 (1H, br t, $J = 2.5$ Hz), 4.02 (1H, br d, $J = 2.5$ Hz), 4.31 (1H, d, $J = 11.8$ Hz), 4.43 (2H, t, 11.4 Hz), 4.54 (1H, d, $J = 11.4$ Hz), 4.60 (2H, s), 5.70 (1H, s), 7.22−7.33 (15H, m); MS (FAB) *m*/*z* (relative intensity) 446 (MH^+, 26). Anal. Calcd for $C_{28}H_{31}NO_4$: C, 75.48; H, 7.01; N, 3.14. Found: C, 75.21; H, 6.86; N, 3.04.

2-*epi*-Valienamine (2) and (1*S*,2*R*,3*S*,4*R*)-1-Acetamido-5-(acetoxymethyl)-2,3,4-tri-*O*-acetylcyclohex-5-ene-2,3,4-triol [Penta-*N*,*O*-acetyl-2-*epi*-valienamine] (14). To a solution of the amine **13** (276 mg, 0.62 mmol) in dry THF (5 mL) and liquid NH_3 (20 mL) was added sodium (150 mg, 6.52 mmol) at −78 °C. The reaction mixture was stirred for 4 h at −78 °C. Solid NH_4Cl (100 mg) was added to the mixture at −78 °C. After disappearance of the blue color of the mixture, NH_3 and solvent were removed under reduced pressure to give crude 2-*epi*-valienamine (**2**). The crude product **2** was dissolved in pyridine (10 mL), and acetic anhydride (2 mL) containing a catalytic amount of DMAP (2 mg) was added. 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 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (hexanes−EtOAc, 1:4) gave the pentaacetate **14** (165 mg, 70%) as white plate crystals.

Pentaacetate **14**: mp 143−146 °C; $R_f = 0.29$ (hexanes−EtOAc, 1:4); $[\alpha]^{20}_D$ +11.3 ($c = 1.1$, $CHCl_3$); IR (film) 3264, 1733, 1665 cm^{-1}; ^1H NMR δ 1.91 (3H, s), 1.92−2.03 (12H, m), 4.38 and 4.52 (2H, ABq, $J = 13.2$ Hz), 4.80 (1H, br t, $J = 8.1$ Hz), 5.09 (1H, dd, $J = 8.1$, 2.4 Hz), 5.19−5.22 (1H, m), 5.34 (1H, d, $J = 3.9$ Hz), 5.82 (1H, m), 6.02 (1H, br d, $J = 8.5$ Hz); ^{13}C NMR δ 20.6, 23.1, 47.3, 63.6, 67.6, 69.4, 69.6, 130.0, 131.2, 169.4, 169.5, 169.9, 170.2, 170.7; MS (L-SIMS) *m*/*z* (relative intensity) 386 (MH^+, 0.6). Anal. Calcd for $C_{17}H_{23}NO_9$: C, 52.98; H, 6.02; N, 3.63. Found: C, 53.18; H, 6.08; N, 3.62.

(1*S*,2*R*,3*S*,4*R*)-1-Azido-3,4-di-*O*-benzyl-5-(benzyloxymethyl)-2-*O*-trifluoromethanesulfonylcyclohex-5-ene-2,3,4-triol (15). To a solution of the alcohol **11** (48 mg, 0.10 mmol) in dry CH_2Cl_2 (10 mL) and pyridine (0.04 mL, 0.5 mmol) was added dropwise Tf_2O (0.04 mL, 0.24 mmol) for 10 min at 0 °C, and the mixture was stirred for 3 h at 0 °C. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (hexane−diethyl ether, 3:1) gave the triflate **15** (58.4 mg, 95%) as a colorless oil.

Triflate **15**: IR (film) 2105, 1400 1200 cm^{-1}; ^1H NMR δ 3.88 (1H, d, $J = 12.8$ Hz), 3.62−4.07 (3H, m), 4.32 (1H, d, $J = 11.4$ Hz), 4.35 (1H, d, $J = 11.8$ Hz), 4.45−4.46 (2H, m), 4.50−4.51 (2H, m), 4.63 (1H, d, $J = 11.8$ Hz), 5.05 (1H, dd, $J = 8.5$, 2.2 Hz), 5.58 and 4.72 (2H, ABq, $J = 12$ Hz), 5.78 (1H, m), 7.16−7.36 (15H, m).

(1*S*,2*S*,3*S*,4*R*)-2-*O*-Acetyl-1-azido-3,4-di-*O*-benzyl-5-(benzyloxymethyl)cyclohex-5-ene-2,3,4-triol (17). (a) From Triflate 15. To a solution of the triflate **15** (58 mg, 0.097 mmol) in DMF (5 mL) was added *n*-Bu_4NOAc (90 mg, 0.30 mmol) at room temperature, and the resulting mixture was stirred overnight at 80 °C. The reaction mixture was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (hexane−diethyl ether, 4:1) gave the aromatic compound **16** (20 mg, 50%) as a white solid and the desired azidoacetate **17** (14 mg, 27%) as a colorless oil.

Compound **16**: mp 42−44 °C; $R_f = 0.67$ (hexane−diethyl ether, 10:1); IR (film) 1478, 1454, 735, 696 cm^{-1}; ^1H NMR δ 4.52 (2H, s), 4.56 (2H, s), 5.03 (2H, s), 5.14 (2H, s), 6.96−7.08 (3H, m), 7.28−7.47 (15H, m); HRMS (EI) calcd for $C_{28}H_{26}O_3$ 410.1882 (M), found 410.1871 (M).

Acetate **17**: $R_f = 0.42$ (hexane−diethyl ether, 3:1); $[\alpha]^{20}_D$ = +35.6 ($c = 1.0$, $CHCl_3$); IR (film) 2103, 1746 cm^{-1}; ^1H NMR δ 2.04 (3H, s), 3.99 (1H, d, $J = 13$ Hz), 4.12−4.21 (3H, m), 4.31 (1H, br t, $J = 4.3$ Hz), 4.44 and 4.52 (2H, ABq, $J = 11.8$ Hz), 4.59 and 4.70 (2H, ABq, $J = 11$ Hz), 4.74 and 4.80 (2H, ABq, $J = 11.4$ Hz), 5.09−5.15 (1H, m), 5.84 (1H, d, $J = 4.9$ Hz), 7.21−7.37 (15H, m); MS (EI) *m*/*z* (relative intensity) 514 (MH^+, 10); HRMS (ESI) calcd for $C_{30}H_{31}N_3O_5Na^+$ 536.2154, found 536.2160.

(b) From Mesylate 18. To a solution of the mesylate **18** (123 mg, 0.22 mmol) in DMF (5 mL) was added *n*-Bu_4NOAc at room temperature, and the resultant mixture was stirred overnight at 80 °C. The cooled reaction mixture was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (hexane−diethyl ether, 4:1) gave the acetate **17** (65 mg, 61%) as a colorless oil.

(1*S*,2*R*,3*S*,4*R*)-1-Azido-3,4-di-*O*-benzyl-5-(benzyloxymethyl)-2-*O*-methanesulfonylcyclohex-5-ene-2,3,4-triol (18). To a solution of the alcohol **11** (31 mg, 0.07 mmol) in CH_2Cl_2 (10 mL) and Et_3N (0.04 mL) was added methanesulfonyl chloride (0.01 mL, 0.13 mmol) at 0 °C, and the mixture was stirred for 1 h at 0 °C. The reaction mixture was then diluted with CH_2Cl_2 (15 mL) and washed with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the

filtrate followed by flash chromatography (hexane−diethyl ether, 3:1) gave the mesylate **18** (36 mg, 98%) as a colorless oil.

Mesylate **18**: R_f = 0.43 (hexane−diethyl ether, 2:1); $[\alpha]^{20}_D$ +27.1 (c = 1.2, $CHCl_3$); IR (film) 3031, 2105, 1454, 1179 cm^{-1}; ^1H NMR δ 3.06 (3H, s), 3.87 (1H, d, J = 12.8 Hz), 3.92 (1H, br d, J = 3.4 Hz), 4.04 (1H, d, J = 12.8 Hz), 4.15−4.17 (1H, m), 4.31 (1H, d, J = 11.3 Hz), 4.34 (1H, d, J = 11.8 Hz), 4.44−4.53 (3H, m), 4.72 and 5.58 (2H, ABq, J = 12 Hz), 4.84 (1H, dd, J = 8.4, 2.2 Hz), 5.75−5.76 (1H, m), 7.18−7.36 (15H, m); MS (ESI) m/z (relative intensity) 549 (M^+, 0.45). Anal. Calcd for $C_{29}H_{31}N_3O_6S$: C, 63.37; H, 5.68; N, 7.65; S, 5.83. Found: C, 63.05; H, 5.88; N, 7.32; S, 5.45.

(1*S*,2*S*,3*R*,4*R*)-1-Azido-3,4-di-*O*-benzyl-5-(benzyloxymethyl)cyclohex-5-ene-2,3,4-triol (19). To a solution of the acetate **17** (120 mg, 0.23 mmol) in MeOH (10 mL) was added a catalytic amount of K_2CO_3 (3 mg), and the mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with EtOAc (10 mL) and washed with saturated NH_4Cl (10 mL). The aqueous layer was extracted with EtOAc (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (hexane−diethyl ether, 2:1) gave the alcohol **19** (110 mg, 100%) as a colorless oil.

Alcohol **19**: R_f = 0.24 (hexane−diethyl ether, 2:1); $[\alpha]^{20}_D$ +37.2 (c = 1.3, $CHCl_3$); IR (film) 3452, 2104 cm^{-1}; ^1H NMR δ 2.99 (1H, d, J = 6.1 Hz), 3.92−4.05 (3H, m), 4.09−4.21 (3H, m), 4.42 and 4.50 (2H, ABq, J = 11.8 Hz), 4.57 and 4.68 (2H, ABq, J = 11.2 Hz), 4.67 and 4.75 (2H, ABq, J = 11.5 Hz), 5.86 (1H, d, J = 3.6 Hz), 7.23−7.38 (15H, m); MS (EI) m/z (relative intensity) 470 (M^+ − H, 6). Anal. Calcd for $C_{28}H_{29}N_3O_4$: C, 71.32; H, 6.20; N, 8.91. Found: C, 71.28; H, 6.20; N, 8.80.

(1*S*,2*S*,3*R*,4*R*)-1-Amino-3,4-di-*O*-benzyl-5-(benzyloxymethyl)cyclohex-5-ene-2,3,4-triol (20). To a solution of the alcohol **19** (54 mg, 0.12 mmol) in pyridine (5 mL) and aqueous NH_3 (32%, 1 mL) was added PPh_3 (45 mg, 0.17 mmol) at room temperature, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine. The aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were dried over $MgSO_4$ and filtered. Concentration of the filtrate followed by flash chromatography ($CHCl_3$−MeOH, 12:1) gave the amine **20** (50 mg, 97%) as a white solid.

Amine **20**: mp 84−85 °C; R_f = 0.43 ($CHCl_3$−MeOH, 10:1); $[\alpha]^{20}_D$ +18.7 (c = 1.0, $CHCl_3$); IR (film) 3365 $cm^{-1;}$ ^1H NMR δ 2.19 (3H, br s), 3.54 (1H, br s), 3.80−3.82 (2H, m), 3.90 and 4.21 (2H, ABq, J = 12 Hz), 4.07−4.08 (1H, m), 4.40 and 4.49 (2H, ABq, J = 11.8 Hz), 4.58 (1H, d, J = 11 Hz), 4.70−4.77 (2H, m), 4.79 (1H, d, J = 11.6 Hz), 5.82 (1H, d, J = 3.1 Hz), 7.22−7.35 (15H, m); MS (FAB) m/z (relative intensity) 446 (MH^+, 14). Anal. Calcd for $C_{28}H_{31}NO_4$: C, 75.48; H, 7.01; N, 3.14. Found: C,75.43; H, 7.03; N, 3.12.

Valienamine (1) and (1*S*,2*S*,3*S*,4*R*)-1-Acetamido-5-(acetoxymethyl)-2,3,4-tri-*O*-acetylcyclohex-5-ene-2,3,4-triol [Penta-*N*,*O*-acetylvalienamine] (21). To a solution of the amine **20** (204 mg, 0.46 mmol) in dry THF (10 mL) and liquid NH_3 (30 mL) was added sodium (80 mg, 3.48 mmol) at −78 °C. The reaction mixture was stirred for 4 h at −78 °C. Solid NH_4Cl (120 mg) was added to the mixture at −78 °C. After 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 (20 mL) and acetic anhydride (4 mL) containing a catalytic amount of DMAP (2 mg). The mixture was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography (hexane−EtOAc, 1:4) gave pentaacetate **21** (120 mg, 68%) as a white solid.

Pentaacetate **21**: mp 92−94 °C (lit.[5] mp 95 °C) (lit.[23] mp 92.5−95 °C); R_f = 0.29 (hexane−EtOAc, 1:4); $[\alpha]^{20}_D$ +20.1 (c = 0.8, $CHCl_3$) {lit.[5] $[\alpha]^{23}_D$ +32.2 ($CHCl_3$), lit.[23] $[\alpha]^{21}_D$ +20 (c = 1.04, $CHCl_3$)}; 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, br d, J = 6.3 Hz), 5.43 (1H, dd, J = 9.3, 6.3 Hz), 5.80 (1H, br d, J = 8.6 Hz), 5.87 (1H, dd, J = 5, 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; MS (FAB) m/z (relative intensity) 386 (MH^+, 0.4). Anal. Calcd for $C_{17}H_{23}NO_9$: C, 52.98; H, 6.02; N, 3.63. Found: C, 52.60; H, 6.25; N, 3.47.

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Supporting Information Available: Copies of the ^1H NMR spectra for compounds **6**, **10**, **11**, **12**, **15**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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