Facile Syntheses of Valiolamine and Its Diastereomers from (−)-Quinic Acid.[1] Nucleophilic Substitution Reactions of 5-(Hydroxymethyl)cyclohexane-1,2,3,4,5-pentol

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Valiolamine (**1**), 1-*epi*-valiolamine (**2**), 2-*epi*-valiolamine (**3**), (1*R*,2*R*)-valiolamine (**4**), and 2-amino regioisomer **17** have been prepared from (−)-quinic acid (**6**) in 14 (8.4% overall yield), 13 (9.0%), 15 (4.3%), 17 steps (2.5%), and 12 steps (13%), respectively. Charged nucleophilic ring-openings of cyclic sulfate (1*R*,2*S*,3*S*,4*S*,5*S*)-4,5-di-*O*-acetyl-3-*O*-benzyl-5-(benzyloxymethyl)-1,2-*O*,*O*-sulfonylcyclohexane-1,2,3,4,5-pentol (**11**) occurred regioselectively at C-2, whereas the corresponding ring-openings of its (1*S*,2*R*)-diastereomer **34** proceeded preponderantly at C-1. (1*R*,2*S*,3*R*,4*S*,5*S*)-2,4,5-Tri-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)-1-*O*-(trifluoromethanesulfonyl)cyclohexane-1,2,3,4,5-pentol (**24**) underwent novel internal displacement spontaneously to form (1*S*,2*S*,3*R*,4*S*,5*S*)-1,2,4-tri-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-1,2,3,4,5-pentol (**25**), whereas its 2-epimer was inert under the same conditions. Ruthenium-catalyzed dihydroxylation of alkene, (3*R*,4*S*,5*S*)-4,5-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)-1-cyclohexene-3,4,5-triol (**31**), gave the desired β-1,2-diol **32** in higher yield and stereoselectivity than the osmium tetraoxide protocol. The regioselectivity of charged nucleophilic ring-openings of cyclic sulfates **11**, **34**, and **38** is discussed.

1. Introduction

There has been increasing interest in the chemistry and biochemistry of glycosidase inhibitors[2] because of their potential use as chemotherapeutic agents, which are being actively investigated.[3] Glycosidases are enzymes for the cleavage of glycosidic bonds and are responsible for glycoprotein processing on the surface of the cell wall and for carbohydrate digestion in animals. Inhibition of these enzymes has significant implications for both antiviral and antidiabetic chemotherapy.[4] Several studies have confirmed the value of the inhibitors of the processing enzyme glucosidase I in inhibiting the human immunodeficiency virus (HIV) replication—the etiologic agent for acquired immune deficiency syndrome (AIDS) and AIDS-related complex.[5] It has also been demonstrated that inhibition of the glycoprotein processing enzyme mannosidase I may provide leads for the treatment of AIDS.[6] In addition, these compounds may have therapeutic application for the treatment of hyperglycemia and disorders related to these conditions such as obesity and diabetes mellitus.[7]

In 1984, naturally occurring valiolamine (**1**) was isolated from the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneus* IFO12703,[8] which also produces antibiotic validamycin. Valiolamine has been shown to be the most potent α-glucosidase inhibitor among the pseudoaminosugars (carbaaminosugars)[9] valienamine, validamine,[10] and hydroxyvalidamine obtained from chemical or microbial degradation[11] of validamycin. The structure of valiolamine was deduced to be (2*S*)-(1,2,4,5/3)-1-amino-5-*C*-(hydroxymethyl)-2,3,4,5-cyclohexanetetrol (sugar numbering is adopted for all synthetic compounds) on the basis of spectral studies, and its absolute configuration was confirmed by a stereoselective transformation from valienamine or validamine.[12] The *N*-[2-hydroxy-1-(hydroxymethyl)ethyl]valiolamine (**5**), coded as AO-128, displayed higher activities than the parent valiolamine and is undergoing clinical trials for the treatment of diabetes.[13] Figure 1 shows the structural resemblance between valiolamine and α-D-glucose (sugar numbering is adopted for all synthetic intermediates and target molecules). Since valiolamine (**1**) is a potent α-D-glucosidase inhibitor, (1*R*)-valiolamine (**2**) (1-*epi*-valiolamine), which possesses a β-amino group, might be a β-D-glucosidase inhibitor. Along this vein of reasoning, (2*R*)- and (1*R*,2*R*)-valiolamine, i.e., (**3**) (2-*epi*-valiolamine) and (**4**), may be an α-D-mannosidase or a β-D-mannosidase inhibitor, respectively. Hence, syntheses of these four carba-sugars are relevant with respect to their potential use as antidiabetic or antiviral agents.

Three total syntheses of valiolamine (**1**) have been reported with one starting from a Diels−Alder (furan−

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(1) (−)-quinic acid in organic synthesis. 7. Part 6: (a) Shing, T. K. M.; Tai, V. W.-F. *J. Org. Chem.* **1995**, *60*, 5332. Part 5: (b) Tai, V. W.-F.; Fung, P.-H.; Wong, Y.-S.; Shing, T. K. M. *Tetrahedron: Asymmetry* **1994**, *5*, 1353.

(2) (a) Winchester, B; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199. (b) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319.

(3) (a) Fleet, G. W. J.; Fellows, L. E. In *Natural Product Isolation*; Wagman, G. H., Cooper, R., Eds; Elsevier: Amsterdam, 1988; p 540. (b) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1752. (c) Elbein, A. *Annu. Rev. Biochem.* **1987**, *56*, 497.

(4) Fleet, G. W. J. *Chem. Br.* **1989**, *25*, 287.

(5) Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237*, 128 and references cited therein.

(6) Montefoiori, D. C.; Robinson, W. E.; Mitchell, W. M. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9248.

(7) (a) Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 288. (b) Arends, J.; Willms, B. H. L. *Horm. Metab. Res.* **1986**, *18*, 761;

(8) Kameda, Y.; Asano, N.; Yoshikawa, M.; Takeuchi, M.; Yamaguchi, T.; Matsui, K.; Horii, S.; Fukase, H. *J. Antibiot.* **1984**, *37*, 1301.

(9) For a recent review on pseudosugars, see: (a) Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21. For general pseudosugar synthesis, see: (b) Ogawa, S. *J. Synth. Org. Chem. Jpn.* **1985**, *43*, 26. (c) Pingli, L.; Vandewalle, M. *Synlett* **1994**, 228 and references cited therein.

(10) Kameda, Y.; Horii, S. *J. Chem. Soc., Chem. Commun.* **1972**, 746.

(11) Horii, S.; Iwasa, T.; Mizuta, E.; Kameda, Y. *J. Antibiot.* **1971**, *24*, 59.

(12) Horii, S.; Fukase, H.; Kameda, Y. *Carbohydr. Res.* **1985**, *140*, 185.

(13) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. L. *J. Med. Chem.* **1986**, *29*, 1038.

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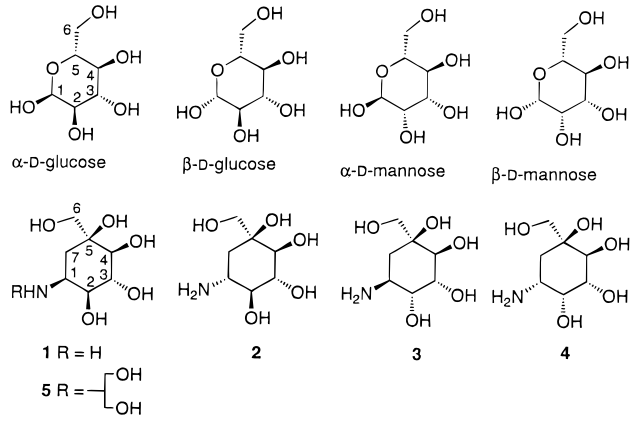


Figure 1. Structural relationship between sugars and hydroxylated cyclohexylamine inhibitors of glycosidases.

acrylic acid) cycloadduct,[14] one from D-glucose via a Ferrier rearrangement[15] and the third one from 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone employing an aldol reaction as the key step.[16] The last synthesis[16] also provided a fabrication of 1-*epi*-valiolamine (**2**). However, the constructions of polyhydroxylated amines **3** and **4** have not been described. Our endeavors in pseudosugar synthesis from (−)-quinic acid (**6**) have already furnished 2-((crotonyloxy)methyl)-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone (COTC),[17] pseudo-β-D-mannopyranose, pseudo-β-D-fructopyranose,[18] pseudo-α-D-glucopyranose, pseudo-α-D-mannopyranose,[19] cyclophellitol and its diastereomers,[20] peracetyl-validamine and -2-*epi*-validamine.[1a] In continuation with our investigation into the preparation of potential glycosidase inhibitors, we now report in detail on the versatility of this approach in the facile syntheses[21] of pseudoaminosaccharides **1**, **2**, **3**, **4**, and **17** and also on a novel acetyl migration and internal displacement reactions involving neighboring group participation.

Examination of the structures of the four target molecules **1**−**4** shows that the stereogenic centers from C-3 to C-5 of all the target molecules are the same. Hence, the synthetic strategy was divided into two parts: (i) to establish the chirality from C-3 to C-5 first and then (ii) to establish the chirality of C-1 and C-2 as well as the introduction of a nitrogen functionality with the desired stereochemistry to C-1 (Figure 2).

2. Results and Discussion

2.1. Syntheses of 2-*epi*-Valiolamine (3) and 2-Amino Regioisomer 17. Our previous work has demonstrated that (−)-quinic acid (**6**) could be easily transformed into the alkene **7** in five steps with an overall yield of 47%.[20b] *cis*-Dihydroxylation of the double bond in **7** with a catalytic amount of osmium tetraoxide[22] gave

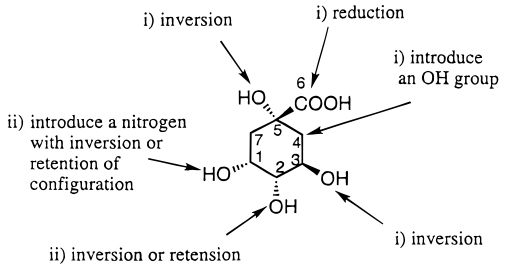
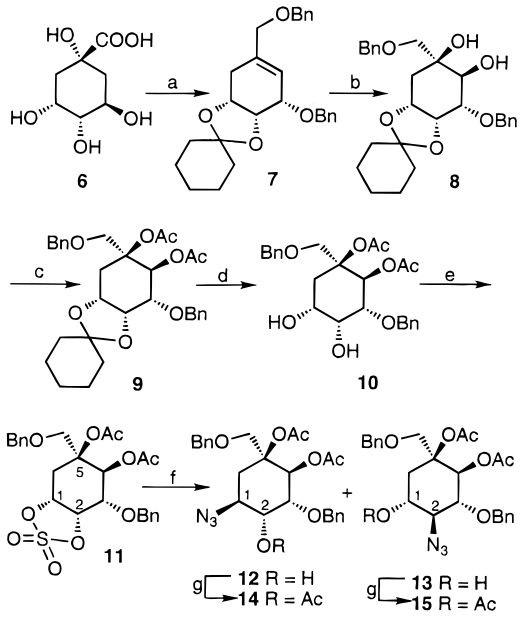


Figure 2. Synthetic strategy.

Scheme 1[a]



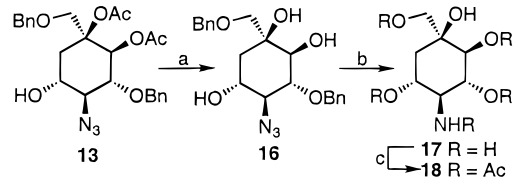
[a] Key: (a) five steps, (47%), see ref 20; (b) OsO_4, H_2O, Me_3NO, pyridine, Bu^{t}OH, reflux, (75%); (c) Ac_2O, DMAP, Et_3N, reflux, (90%); (d) TFA, H_2O, CH_2Cl_2, (90%); (e) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, then $RuCl_3 \cdot H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O, 0 °C (86%); (f) LiN_3, DMF, then 20% H_2SO_4, THF, (80%, **12**:**13** = 1:10); (g) Ac_2O, DMAP, Et_3N, CH_2Cl_2 (80% for **14**; 86% for **15**).

8 diastereoselectively as the sole product (Scheme 1). Enhanced by the steric hindrance of the *O*-benzyl group at the α-face of the alkene in **7**, the osmium reagent was more favored to add to the double bond from the less hindered convex face (β-face) of the bicyclic skeleton. This facial selectivity is predominately governed by the latter factor as pointed out by one reviewer. The resultant β-diol in compound **8** was then protected as the diacetate. The tertiary hydroxy group in **8** was unreactive toward acetic anhydride (3 equiv), triethylamine, or pyridine (5 equiv) and a catalytic amount of DMAP in methylene chloride at room temperature or at reflux. Fortunately, when a triethylamine (as solvent) solution of **8** was heated under reflux with an excess of acetic anhydride and 0.5 equiv of DMAP, the reaction was complete within 3 h and gave diacetate **9** as a colorless syrup.

The key intermediate **10** in the present synthetic excursion was then obtained by hydrolytic removal of the cyclohexylidene ketal in **9** with aqueous trifluoroacetic acid in dichloromethane. The diol **10** was converted into a relatively unstable cyclic sulfate **11** by the Sharpless method.[23] As in our previous synthesis of validamine,[1a] azide anion was employed to introduce a nitrogen func-

(14) Ogawa, S.; Shibata, Y. *Chem. Lett.* **1985**, 1581.
(15) Hayashido, M.; Sakairi, N.; Kuzuhara, H. *J. Carbohydr. Chem.* **1988**, *7*, 83.
(16) Fukase, H.; Horii, S. *J. Org. Chem.* **1992**, *57*, 3642 and 3651.
(17) (a) Shing, T. K. M.; Tang, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 312; (b) *Tetrahedron* **1990**, *46*, 6584.
(18) (a) Shing, T. K. M.; Tang, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 748; (b) *Tetrahedron* **1991**, *47*, 4571.
(19) (a) Shing, T. K. M.; Cui, Y.-X.; Tang, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 756; (b) *Tetrahedron* **1992**, *48*, 2349.
(20) (a) Shing, T. K. M.; Tai, V. W.-F. *J. Chem. Soc., Chem. Commun.* **1993**, 995; (b) *J. Chem. Soc., Perkin Trans. 1* **1994**, 2017.
(21) Shing, T. K. M.; Wan, L. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1643.
(22) (a) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449. (b) Review: Schroder, M. *Chem. Rev.* **1980**, *80*, 187.
(23) (a) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655. (b) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.

Scheme 2.[a] Synthesis of 2-Amino Regioisomer 17



[a] Key: (a) K_2CO_3, MeOH (100%); (b) $Pd(OH)_2$, H_2, EtOH (70%); (c) Ac_2O, pyridine, cat. DMAP (75%).

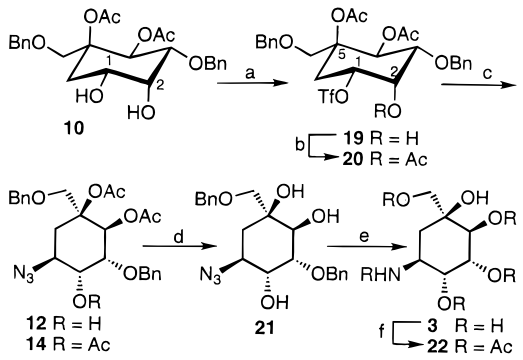
tionality to C-1. However, ring-opening reaction of the cyclic sulfate **11** occurred regioselectively (vide infra) at the undesired C-2 position, affording a mixture of azido alcohols **12** and **13** with the latter regioisomer as the preponderant product (**12**:**13** = 1:10).[24] The regio- and stereochemical assignments were based on ^{1}H NMR spectral analyses of their respective azido acetates **14** and **15**. The H-2 in **14** resonated at δ 5.04 as a doublet of doublets ($J_{2,3}$ = 3.3, $J_{2,1}$ = 7.2 Hz), indicating that the C-2 acetyl group was at the axial position. The H-2 and H-1 in **15** appeared at δ 3.58 and 4.86 as a triplet (J = 9.9 Hz) and a doublet of doublets of doublets ($J_{1,2}$ = 9.9, $J_{1,7eq}$ = 4.7, $J_{1,7ax}$ = 12.1 Hz), respectively, demonstrating that both the C-2 azido and the C-1 acetyl groups were at the equatorial positions. These assignments were confirmed by spin−spin decoupling experiments, thus providing evidence that the nucleophilic opening reactions of the cyclic sulfate **11** were stereospecific and proceeded with inversion of configuration, a corollary consistent with our previous findings.[1,20b]

Deacetylation of the diacetate **13** gave triol **16**, which was subjected to the removal of benzyl protecting groups via hydrogenolysis and to hydrogenation of the azide moiety to yield 2-amino regioisomer **17** (Scheme 2). Compound **17** was thus prepared from quinic acid in 12 steps with an overall yield of 13% and was characterized as its pentaacetate **18**.

Since the azido alcohol **12** was only obtained in poor yield (*ca.* 5.5%) from the ring-opening of cyclic sulfate **11**, an alternate approach was investigated in order to afford **12** in good overall yield. Examination of the conformation of **10** shows that the OH-1 is at the equatorial position while the other free alcohol is at the axial position. Hence, selective esterification of the less hindered OH-1 by 1 equiv of triflic anhydride in pyridine gave the monotriflate **19** in 93% yield. When the triflate **19** was subjected to azide displacement in DMF, the azido alcohol **12**, obtained in fair yield (60%) (Scheme 3), was identical in all respects to the minor product from the azide opening of **11**. If the monotriflate **19** was first acetylated to **20** and then followed by azide attack, azido acetate **14** was obtained and the yield of the substitution reaction was improved from 60% to 80%. Deprotection of the triacetate **14** with basic methanol provided triol **21**, which was hydrogenolyzed to give 2-*epi*-valiolamine (**3**) for the first time. Thus, the target molecule **3** was synthesized form (−)-quinic acid (**6**) in 15 steps with an overall yield of 4.3%. Acetylation of **3** furnished the corresponding *N*,*O*-pentaacetate **22** for characterization.

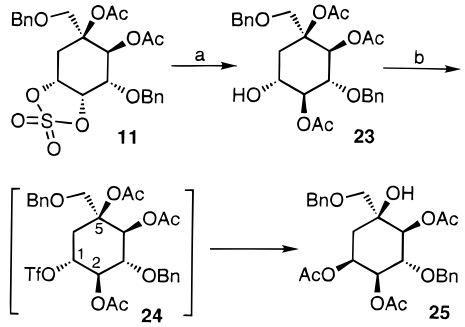
2.2. Synthesis of Valiolamine (1). Unexpected Internal Displacement. For the synthesis of valiolamine, the avenue involving the cyclic sulfate **11** was

Scheme 3.[a] Synthesis of 2-*epi*-Valiolamine (3)



[a] Key: (a) Tf_2O (1 equiv), CH_2Cl_2, pyridine, 0 °C (93%); (b) Ac_2O, Et_3N, CH_2Cl_2 (90%); (c) NaN_3, benzo-15-crown-5, DMF (**19** → **12**, 60%; **20** → **14**, 80%); (d) K_2CO_3, MeOH (72% from **14**; 80% from **12**); (e) H_2, $Pd(OH)_2$, EtOH (80%); (f) Ac_2O, pyridine, cat. DMAP (60%).

Scheme 4.[a] Unexpected Internal Displacement of Triflate 24



[a] Key: (a) Bu^n_4NOAc, THF then 20% H_2SO_4, THF (85%); (b) Tf_2O, CH_2Cl_2, pyridine, 0 °C (76%).

investigated initially and the configurations at C-1 and C-2 of **11** had to be inverted. The aforedescribed chemistry of **11** predicted that the ring openings of the cyclic sulfate moiety with nucleophiles would occur at C-2 preponderantly (vide supra). Tetrabutylammonium acetate was used to invert the chirality at C-2, and the reaction gave acetate **23** with excellent regioselectivity in 85% yield (Scheme 4). The C-1 regiosiomer could not be detected by TLC or NMR spectroscopy.

To introduce a nitrogen functionality to C-1 with inversion of configuration via an S_N2 displacement, activation of the free alcohol at this site as a sulfonate ester was investigated and the preparation of a triflate ester was attempted first. Treatment of the alcohol **23** with triflic anhydride and pyridine in dichloromethane led to an unexpected 1,2,4-triacetate **25**, and none of the desired product, triflate ester **24**, was isolated. We believed that the triflate **24** was formed initially and then underwent a facile and efficient intramolecular substitution by the tertiary acetate at C-5 to give the C-1 β-acetate **25**. Formation of the less nucleofugal mesylate from the alcohol **23** was successful, and the desired α-mesylate **26** was harvested without incident (Scheme 5). However, the subsequent intermolecular substitution of **26** with tetrabutylammonium azide at 100 °C did not afford any C-1 azide, and the only product isolated was also **25**, presumably derived from a similar internal displacement.

Examination of the molecular models of sulfonate esters **24** and **26** (OTf-1 or OMs-1 and OAc-2 *trans*-disposed) shows that the tertiary acetate (OAc-5) is in

(24) For reviews on the chemistry of cyclic sulfates, see: (a) Lohray B. B. *Synthesis* **1992**, 1035. (b) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

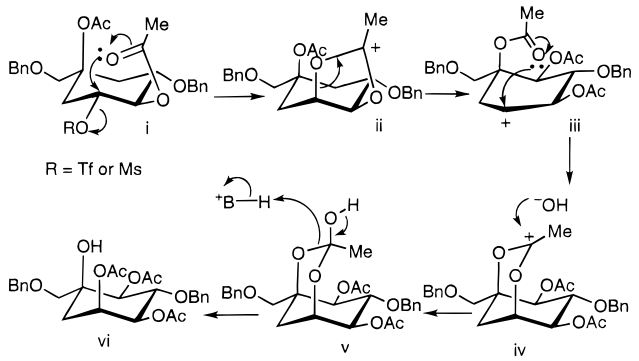
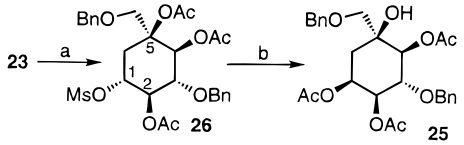


Figure 3. Proposed pathway for the unexpected intramolecular displacement involving neighboring *trans*-disposed acetyl group participation. The nucleophile in iv could also be water during the workup. For clarity, the C-4 acetate in i or in ii is not illustrated.

Scheme 5.[a] Unexpected Internal Displacement of Mesylate 25



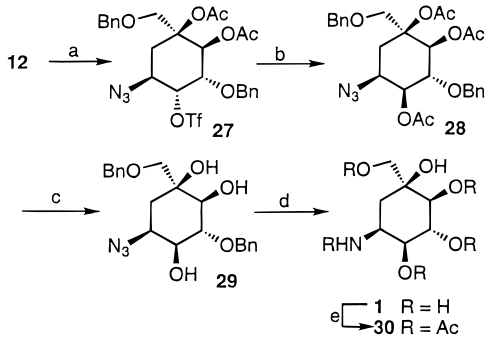
[a] Key: (a) MsCl, pyridine (80%); (b) $Bu^n_4NN_3$, DMF, 100 °C (80%).

close proximity to the sulfonate leaving group and intramolecular displacement should be facilitated. However, the dominance of the juxtaposed acetate (OAc-2) over the tertiary acetate (OAc-5) in initiating the intramolecular displacement is indicated by the fact that the cyclic sufate **11** (with OAc-5 but no juxtaposed acetate) did not yield an internal displacement product when subjected to azide treatment (cf. **11** → **12** + **13**). Furthermore, the importance of the stereochemistry of OAc-2 relative to the sulfonate-1 is demonstrated by the fact that the 2-epimer of **24**, i.e., the triflate acetate **20** (OTf-1 and OAc-2 *cis*-disposed), *did not* undergo the internal substitution process. Only **24** and **26**, both with OAc-2 *trans* to the C-1 sulfonate, underwent intramolecular inversion probably via neighboring group participation. In fact, the ionization of a mesylate assisted by a neighboring *trans*-disposed acetate is not uncommon in carbohydrate chemistry.[25] The reaction pathway for the internal displacement is proposed in Figure 3, and the involvement of OAc-5 in the ionization of C-1 sulfonate to give vi directly is unlikely on the basis of the aforedescribed findings.

The strategy for the construction of **1** was revised, and the nitrogen functionality had to be introduced to C-1 in **10** first before inverting the C-2 configuration. Hence, the diol **10** was transformed into the azido alcohol **12** as described previously, and the stereogenic center at C-2 was inverted by trifluoromethanesulfonylation and subsequent displacement with tetrabutylammonium acetate to give azido triacetate **28** (Scheme 6). Deacetylation of **28** with basic methanol gave triol **29**, which was hydrogenolyzed to valiolamine (**1**) as a white amorphous solid. Valiolamine (**1**) was thus synthesized from quinic acid (**6**) in 14 steps with an overall yield of 8.4%. All the

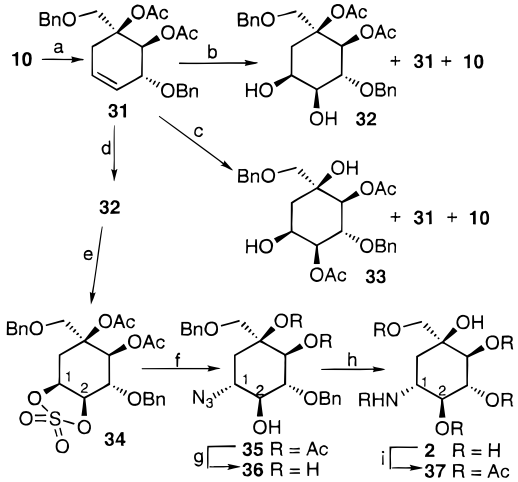
(25) For related internal displacement in sugars involving neigboring group participation, see: Goodman, L. *Adv. Carbohydr. Chem.* **1967**, *22*, 109.

Scheme 6.[a] Synthesis of Valiolamine (1)



[a] Key: (a) Tf_2O, pyridine, CH_2Cl_2, 0 °C (90%); (b) Bu^n_4NOAc, THF (80%); (c) K_2CO_3, MeOH (91%); (d) H_2, $Pd(OH)_2$, EtOH (80%); (e) Ac_2O, pyridine, cat. DMAP (70%).

Scheme 7.[a] Synthesis of 1-*epi*-Valiolamine (2)



[a] Key: (a) 1,1′-(thiocarbonyl)diimidazole, toluene, reflux, then $P(OMe)_3$, reflux, (64% overall); (b) OsO_4, H_2O, pyridine, Me_3NO, ButOH, 10^{-2} M, reflux, **32** (20%), **31** (60%), **10** (10%); (c) OsO_4, H_2O, pyridine, Me_3NO, Bu^tOH, 10^{-1} M, reflux, **33** (29%), **31** (46%), **10** (14%); (d) $RuCl_3 \cdot H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O, 0 °C (81%); (e) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, then $RuCl_3 \cdot H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O, 0 °C (74%); (f) LiN_3, DMF, then 20% H_2SO_4, THF (50%) (g) K_2CO_3, MeOH (88%); (h) H_2, $Pd(OH)_2$/C, EtOH (85%); (i) Ac_2O, pyridine, cat. DMAP (80%).

physical data of **1** from this synthesis were in good agreement with those reported by Kameda et al.[11] ($[\alpha]^{22}_D$ +14.5 (lit.[11] $[\alpha]^{20}_D$ +18.8)) except for the ^1H NMR spectral data; the NMR peaks overlapped heavily within the δ 3.4−3.9 region. Therefore, valiolamine (**1**) was derivatized as its *N*,*O*,*O*,*O*,*O*-pentaacetate **30** whose physical data (mp = 137−138 °C and $[\alpha]^{20}_D$ −17.8 (lit.[11] mp = 137−138 °C and $[\alpha]^{25}_D$ −14.8)) including the ^1H NMR spectral data were in good agreement with those reported.[11]

2.3. Syntheses of 1-*epi*-Valiolamine (2) and (1*R*,2*R*)-Valiolamine (4). Unexpected Acetyl Migration. The aforedescribed diol **10** was converted into alkene **31** uneventfully by the Corey−Winter reaction[26] in 64% overall yield (Scheme 7). *cis*-Dihydroxylation of a 10^{-2} M solution of the alkene **31** via osmium tetraoxide catalysis[27] resulted in 20% yield of the desired β-diol **32**,

(26) Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677.
(27) (a) Schroder, M. *Chem. Rev.* **1980**, *80*, 187. (b) Singh, H. S. In *Organic Syntheses by Oxidation with Metal Compounds*; Mijs, W. J., de Jonge, C. R. H. I., Eds.; Academic Press: New York, London, 1986; p 633.

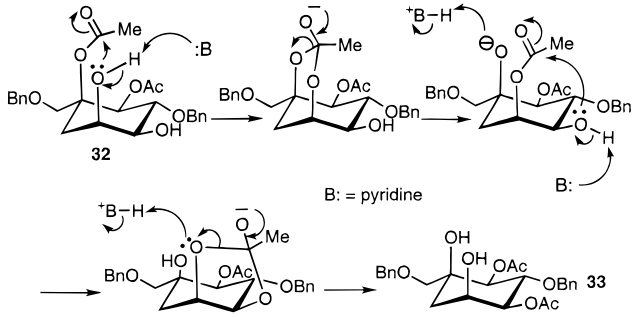


Figure 4. Proposed pathway for the unexpected acetyl migration.

10% of α-diol **10**, and 60% of the starting alkene **31**. The stereochemistry of the *β*-1,2-diol **32** was supported by the ^{1}H NMR coupling constant data ($J_{1,2}$ = 3.2, $J_{1,7eq}$ = 2.7, $J_{1,7ax}$ = 2.8, $J_{2,3}$ = 9.2 Hz). When the reaction was repeated in a more concentrated solution (10^{-1} M), the acetyl-migrated *β*-1,5-diol **33** (29% yield), α-diol **10** (14% yield), and the starting alkene (46%) were obtained. The acetyl-migration process is believed to be promoted by pyridine and hence displayed a concentation effect. Related acyl migrations have been observed in carbohydrates[28] and inositols.[29]

The mechansim for the acetyl-migration process is proposed in Figure 4. This proposal is supported by the fact that no corresponding migration was observed for the α-diol **10** because the two hydroxy groups (OH-1,2) are *trans* to the tertiary acetate (OAc-5). Since the tertiary *O*-acetyl group is located at the axial position, it tends to migrate to the relatively more stable secondary axial hydroxy group and then to the most stable equatorial hydroxy group under equilibrating conditions.

The inertness of **31** may be due to its formation of the very stable osmate ester with osmium tetraoxide. In fact, formation of very stable osmate ester of some olefin with osmium tetraoxide was reported and catalytic process is not feasible in such situation.[30,31] Addition of methanesulfonamide described by Sharpless[31] could increase the rate of hydrolysis of osmate ester but such reagent showed no improvement to our system at 25 °C, at 60 °C, or at reflux. Besides, the diastereoselectivity of the reaction was also poor. Attempts to use potassium ferricyanide ($K_3Fe(CN)_6$)[32] as an oxidant to replace trimethylamine *N*-oxide and to improve the stereoselectivity gained no advantage. As an alternate approach, the alkene **31** was subjected to the *cis*-hydroxyamination procotol described by Sharpless,[33] but the reaction was not effective. The reaction was repeated under phase transfer conditions,[33] but only a trace amount of *cis*-dihydroxylated products were obtained and no hydroxyaminated products were isolated (Scheme 8).

In order to synthesize **2**, the (1*S*,2*S*)-diol **32** is the key precursor from which cyclic sulfate **34** can be derived. As discussed above, the yield of **32** from **31** via OsO_4-catalyzed dihydroxylation was not acceptable from a synthetic view point. A fruitless alternative had been attempted to access **32** by Mitsunobu inversion[34] of the two hydroxy groups in **10** with trifluoroacetic acid in the presence of sodium benzoate.[35] Fortunately, the new dihydroxylation protocol via ruthenium catalysis developed by us[36] greatly improved the yield, the diastereoselectivity, the reaction time, and the workup procedure. Thus, when the alkene **31** was treated with 0.1 equiv of $RuCl_3 \cdot H_2O$ and 1.7 equiv of $NaIO_4$ in CCl_4-CH_3CN-water, the *cis*-dihydroxylation reaction was complete within minutes at 0 °C. The yield of the desired *β*-diol **32** was improved from 20% to 81%, and no diastereomer, acetyl-migrated product, or starting material was detected. The diol **32** was then converted into 1,2-cyclic sulfate **34** according to the Sharpless protocol[23] (Scheme 7). The cyclic sulfate **34** was opened regioselectively by lithium azide in DMF and was subsequently hydrolyzed to give azide **35**. The regio- and stereochemical assignments were based on ^{1}H NMR spectral analyses ($J_{1,2}$ = 9.6, $J_{1,7eq}$ = 4.4, $J_{1,7ax}$ = 12.3, $J_{2,3}$ = 9.3 Hz). If the azide anion had opened the ring at C-2, the dihedral angle between H_1 and H_2 would be about 60° (Figure 5) and the coupling constant between them would have been *ca.* 3−5 Hz.

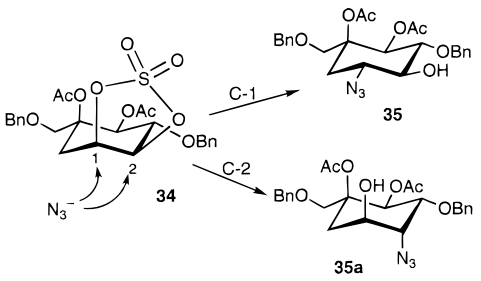
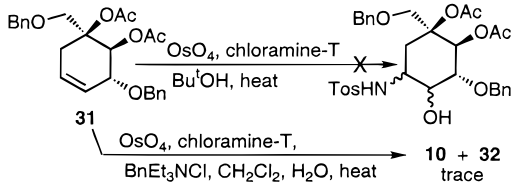


Figure 5.

Scheme 8. Attempted Hydroxyamination

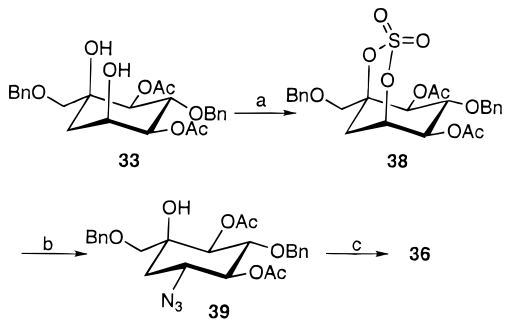


Deacetylation of the azido acetate **35** with basic methanol afforded azido triol **36**. On the other hand, if we started with the rearranged diol **33** (the unblocked diol moiety in a 1,3-diaxial relationship) and followed the presented reaction sequence (**32** → **34** → **35** → **36**), the same product **36** would be obtained (Scheme 9). Hence, the diol **33** was readily converted into 1,3-cyclic sulfate **38**. Nucleophilic ring opening of the 1,3-cyclic sulfate **38** with azide ion gave azide **39** which on deacetylation afforded the identical hydroxy azide **36**.

Hydrogenolysis of the benzyl ethers and reduction of the azide in **36**, catalyzed by 10% $Pd(OH)_2$ on charcoal, proceeded smoothly to give the target molecule 1-*epi*-valiolamine (**2**) in 85% yield (Scheme 7). Starting from (−)-quinic acid, 13 steps were required to prepare **2** with

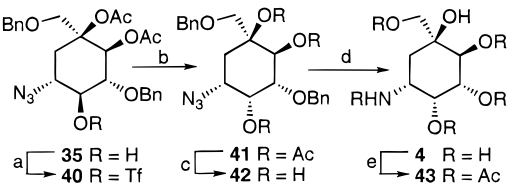
(28) Rowell, R. M. *Carbohydr. Res.* **1972**, *23*, 417.
(29) (a) Shvets, V. I. *Russian Chem Rev.* **1974**, *43*, 488. (b) Chung, S.-K.; Chang, Y.-T.; Ryu, Y. *Pure Appl. Chem.* **1996**, *68*, 931.
(30) Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063.
(31) Sharpless, K. B.; Amberg, W.; Bennani, Y.; Crispino, G.; Hartung, J.; Jeong, K.; Kwong, H.-L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768
(32) Kwong H.-L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 2999.
(33) (a) Sharpless, K. B.; Hori, T. *J. Org. Chem.* **1976**, *41*, 177. (b) Herranz, E.; Sharpless, K. B. *Ibid.* **1978**, *43*, 2544.
(34) Mitsunobu, O. *Synthesis* **1981**, 1.
(35) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235.
(36) (a) Shing, T. K. M.; Tam, E. K. W.; Tai, V. W.-F.; Chung, I. H. F.; Jiang, Q. *Chem. Eur. J.* **1996**, *2*, 50. (b) Shing, T. K. M.; Tai, V. W.-F.; Tam, E. K. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2312.

Scheme 9[a]



[a] Key: (a) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C then $RuCl_3 \cdot H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O, 0 °C (80%); (b) LiN_3, DMF, then 20% H_2SO_4, THF (80%); (c) K_2CO_3, MeOH (88%).

Scheme 10.[a] **Synthesis of (1*R*,2*R*)-Valiolamine (4)**



[a] (a) Tf_2O, pyridine, CH_2Cl_2 (78%); (b) Bu^n_4NOAc, THF (95%); (c) K_2CO_3, MeOH (80%); (d) H_2, $Pd(OH)_2$, EtOH (73%); (e) Ac_2O, pyridine, cat. DMAP (80%).

9.0% overall yield. 1-*epi*-Valiolamine (**2**) was acetylated to the corresponding *N*,*O*,*O*,*O*,*O*-pentaacetate **37** for characterization. The spectral data and physical constants of our synthetic compound **2** are in close agreement with those reported by Fukase ($[\alpha]^{20}_D$ −27.9 (lit.[11] $[\alpha]^{24}_D$ −23.2)).

Since (1*R*,2*R*)-valiolamine (**4**) is the 2-epimer of **2**, **4** could readily be accessed by inverting the OH-2 in compound **2**. Thus, activation of the OH-2 in **35** with trifluoromethanesulfonic anhydride afforded triflate **40**, which was subjected to nucleophilic substitution with tetrabutylammonium acetate, leading to the protected target molecule **41** (Scheme 10). Deacetylation of the triacetate **41** gave triol **42** which was hydrogenolyzed to furnish (1*R*,2*R*)-valiolamine (**4**) for the first time. The overall yield of the target molecule **4** from (−)-quinic acid is 2.5% in 17 steps. (1*R*,2*R*)-Valiolamine (**4**) was also characterized as its *N*,*O*,*O*,*O*,*O*-pentaacetate **43**.

2.4. Regiochemistry of Nucleophilic Attack of Cyclic Sulfates 34, 11 and 38. Cyclic sulfates, from a synthetic view point, are more or less the same as epoxides. They can be opened by nucleophiles and give vicinal alcohols after acid hydrolysis.[24] If the epoxide or the cyclic sulfate is located within a six-membered ring, the regioselectivities of their ring openings are different. For epoxides, nucleophilic attacks leading to diaxial products are much more favored.[37] For cyclic sulfates, on the basis of our previous work summarized in Figure 6,[1,20b] there are two major factors that govern the regioselectivity of charged nucleophilic openings, namely a stereoelectronic factor[37] (alignment of dipoles)[38] and a steric factor[1a,20b] (conformation of the substrate and the size of the nucleophile).

(37) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983.

(38) Buchanan, J. G. In *MTP International Review of Science, Organic Chemistry Series One*; Aspinall, A. O., Ed.; University Park Press: New York, 1973; Vol. 7, p 33.

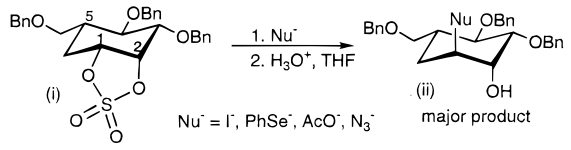


Figure 6.

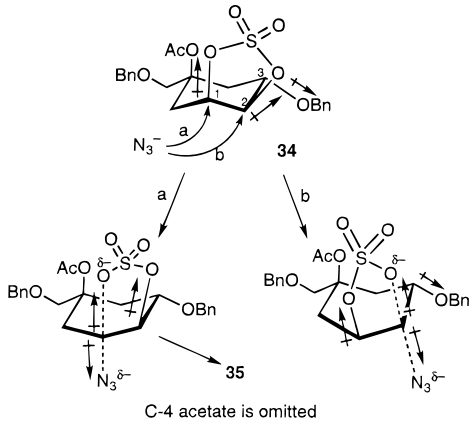


Figure 7.

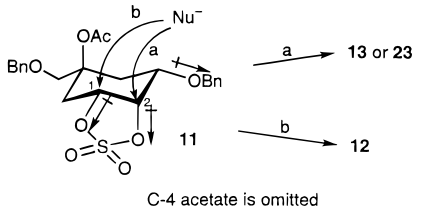


Figure 8.

For the ring opening of **34**, nucleophilic attack at C-2 (path b) would induce dipoles that are aligned with two existing dipoles at the vicinal carbon atoms (i.e., C-1 and C-3), and the transition state energy is correspondingly increased[20b,38] (Figure 7). In addition, the 1,3-diaxial interaction between the H-4 and the incoming nucleophile also deters the process. However, if the nucleophilic attack takes place at C-1, the induced dipole is only aligned with one existing vicinal dipole and the 1,3-diaxial interaction between OAc-5 and C-1 substitutent is diminishing in the transition state, path a is therefore preferred and only **35** was obtained.

For **11**, the nucleophilic attack was also favored at C-1, attributable to the stereoelectronic factor as described above. However, due to the presence of the axial acetate group at C-5, the 1,3-diaxial steric interaction is dominant over the electronic effect and the attack at C-2 takes precedence. The ring-opening reaction with lithium azide furnished mainly **13** and only a small amount of **12** (Figure 8). Since steric interaction increases with the size of nucleophile, the regioselectivity should increase from using azide to using acetate as the nucleophile. This has been shown to be the case and reaction of **11** with tetrabutylammonium acetate gave the C-2 acetate **23** as the sole product. The effect of the size of nucleophile on regioselectivity is in accord with our previous findings.[1a]

For the 1,3-cyclic sulfate **38**, both the electronic and steric effects favored the nucleophilic attack at C-1, and hence, C-1 azide **39** was produced as the sole product (Figure 9).

Finally, it is noteworthy that all the nucleophilic ring openings of cyclic sulfates studied in this and in our

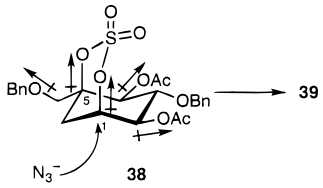


Figure 9.

previous work[1,20b] are stereospecific and proceed with inversion of configuration.

3. Experimental Section

Melting points were determined with a Reichert apparatus and are reported in °C (uncorrected). Optical rotations were measured with an automatic digital polarimeter, operating at 589 nm. IR spectra were recorded on an FT-IR spectrometer as thin films on NaCl disks. Unless stated to the contrary, NMR spectra were measured in solutions of $CDCl_3$ at 250 MHz (^{1}H) or at 62.9 MHz (^{13}C). All chemical shifts were recorded in ppm downfield from tetramethylsilane on the δ scale. 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[39] chromatographic technique. Pyridine was distilled over barium oxide and stored in the presence of potassium hydroxide pellets. Absolute methanol was distilled over magnesium and stored in the presence of 4 Å molecular sieves. THF was distilled from sodium benzophenone ketyl under a nitrogen atmosphere. CH_2Cl_2 was distilled over phosphorous pentoxide and stored in the presence of 4 Å molecular sieves.

(1*S*,2*S*,3*R*,4*S*,5*S*)-1-Amino-5-(hydroxymethyl)cyclohexane-2,3,4,5-tetrol (Valiolamine) (1). To a solution of the dibenzyl ether **29** (18 mg, 0.045 mmol) in EtOH (5 mL) was added 20% $Pd(OH)_2$ on charcoal (10 mg), and H_2 was bubbled through the mixture with stirring until no UV-active species was shown by TLC. The solution was filtered through a pad of Celite and the filtrate concentrated. Flash column chromatography ($CHCl_3$:MeOH:NH_3(aq), 9:8:3) of the residue gave the crude product, which was further purified by Amberlite CG-50 (NH_4^+) chromatography to yield valiolamine (**1**) (7 mg, 80%) as a white amorphous solid: TLC R_f 0.14 ($CHCl_3$:MeOH:NH_3(aq), 9:8:3); $[\alpha]^{22}_D$ +15.4 (c = 2.2, H_2O) (lit.[8] $[\alpha]^{20}_D$ +18.8 (c = 1.0, H_2O)); IR (neat) 3342 cm^{-1}; ^{1}H NMR (D_2O) δ 1.90 (1H, dd, J = 3.9, 15.9 Hz), 2.11 (1H, dd, J = 2.4, 15.9 Hz), 3.4−3.9 (6H, m); ^{13}C NMR (D_2O, dioxane as the reference peak at 67.8 ppm) δ 33.34, 51.57, 66.74, 72.42, 74.30, 74.93, 77.06 (lit.[8] δ 35.0, 52.9, 68.2, 73.8, 76.3, 76.4, 78.7); MS m/z (CI) 194 (M^+ + 1, 100).

(1*R*,2*S*,3*R*,4*S*,5*S*)-1-Amino-5-(hydroxymethyl)cyclohexane-2,3,4,5-tetrol (1-*epi*-Valiolamine) (2). To a solution of the dibenzyl ether **36** (29 mg, 0.073 mmol) in EtOH (7 mL) was added 20% $Pd(OH)_2$ on charcoal (30 mg), and H_2 was bubbled through the mixture with stirring until no UV-active species was shown by TLC. The solution was filtered through a pad of Celite and the filtrate concentrated. Flash column chromatography ($CHCl_3$:MeOH:NH_3(aq), 10:7:3) of the residue gave the crude product, which was further purified by Amberlite CG-50 (NH_4^+) to give 1-*epi*-valiolamine (**2**) as a white amorphous solid (11 mg, 85%): TLC R_f 0.15 ($CHCl_3$:MeOH:NH_3(aq), 10:7:3); $[\alpha]^{20}_D$ −27.9 (c = 0.5, H_2O) (lit.[16] $[\alpha]^{24}_D$ −23.2 (c = 0.5, H_2O)); IR (neat) 3351 cm^{-1}; ^{1}H NMR (D_2O) δ 1.65 (1H, t*, J = 3.2 Hz), 2.06 (1H, dd, J = 1.0, 3.5 Hz), 3.20−3.75 (6H, m) (*apparent splitting pattern); ^{13}C NMR (D_2O, dioxane at 67.40 ppm) δ 34.96, 50.76, 66.58, 73.99 74.75, 75.12, 75.77; MS m/z (CI) 194 (M^+ + 1, 11.07). Anal. Calcd for $C_7H_{15}O_5N\cdot 0.45H_2O$: C, 41.77; H, 7.96; N, 6.95. Found: C, 41.73; H, 7.84; N, 6.84.

(1*S*,2*R*,3*R*,4*S*,5*S*)-1-Amino-5-(hydroxymethyl)cyclohexane-2,3,4,5-tetrol (2-*epi*-Valiolamine) (3). To a solution of the dibenzyl ether **21** (32.8 mg, 0.082 mmol) in EtOH (5 mL) was added 20% $Pd(OH)_2$ on charcoal (30 mg), and H_2 was bubbled through the mixture under stirring until no UV active species was shown by TLC. The solution was filtered through a pad of Celite and the filtrate concentrated. Flash column chromatography ($CHCl_3$:MeOH:NH_3(aq), 9:8:3) of the residue followed by Amberlite CG-50 (NH_4^+) chromatography afforded 2-*epi*-valiolamine (**3**) as a white amorphous solid (13 mg, 80%): TLC R_f 0.14 ($CHCl_3$:MeOH:NH_3(aq), 9:8:3); $[\alpha]^{22}_D$ −11.1 (c = 0.4, H_2O); IR (neat) 3339 cm^{-1}; ^{1}H NMR (D_2O) δ 1.78 (1H, dd, J = 4.8, 14.8 Hz), 2.02 (1H, dd, J = 4.4, 14.8 Hz), 3.38 (1H, q*, J = 4.5 Hz), 3.51 and 3.62 (2H, ABq, J = 11.7 Hz), 3.75 (1H, d, J = 8.0 Hz), 3.8−4.1 (2H, m) (*apparent splitting pattern); ^{13}C NMR (D_2O, dioxane at 67.40 ppm) δ 31.05, 50.90, 66.22, 70.11, 71.42, 71.86, 76.22; MS m/z (CI) 194(M^+ + 1, 100). Anal. Calcd for $C_7H_{15}O_5N\cdot 0.5H_2O$: C, 41.58; H, 7.98; N, 6.93. Found: C, 41.53; H, 7.93; N, 6.75.

(1*R*,2*R*,3*R*,4*S*,5*S*)-1-Amino-5-(hydroxymethyl)cyclohexane-2,3,4,5-tetrol ((1*R*,2*R*)-Valiolamine) (4). To a solution of the dibenzyl ether **42** (31 mg, 0.078 mmol) in EtOH (5 mL) was added 20% $Pd(OH)_2$ on charcoal (100 mg), and H_2 was bubbled through the mixture under stirring until no UV-active species was shown by TLC. The solution was filtered through a pad of Celite and the filtrate concentrated. Flash column chromatography ($CHCl_3$:MeOH:NH_3(aq), 9:8:3) of the residue followed by Amberlite CG-50 (NH_4^+) chromatography furnished (1*R*,2*R*)-valiolamine (**4**) (11 mg, 73%) as a white amorphous solid: TLC R_f 0.14 ($CHCl_3$:MeOH:NH_3(aq), 9:8:3); $[\alpha]^{19}_D$ −13.7 (c = 0.5, H_2O); ^{1}H NMR (D_2O) δ 1.80-2.00 (2H, m), 3.50−3.65 (1H, m), 3.50 and 3.60 (2H, ABq, J = 11.3 Hz), 3.68 (1H, d, J = 9.9 Hz), 3.78 (1H, dd, J = 2.9, 9.9 Hz), 4.13 (1H, br s); ^{13}C NMR (D_2O, dioxane at 67.4 ppm) δ 31.63, 48.38, 66.40, 67.40*, 70.48, 71.62, 74.20 (*overlapped with dioxane); MS m/z (CI) 194 (M^+ + 1, 100). Anal. Calcd for $C_7H_{15}O_5N\cdot 0.8H_2O$: C, 40.50; H, 8.06; N, 6.75. Found: C, 40.79; H, 8.20; N, 6.36.

(1*R*,2*R*,3*S*,4*S*,5*S*)-3-*O*-Benzyl-5-((benzyloxy)methyl)-1,2-*O*-cyclohexylidenecyclohexane-1,2,3,4,5-pentol (8). To a solution of the alkene **7**[20b] (7.03 g, 16.7 mmol) in Bu^{t}OH (70 mL) were added Me_3NO (2.6 g, 23.3 mmol), pyridine (9 mL, 103.3 mmol), H_2O (1.6 mL, 90 mmol), and OsO_4 (2.5 wt%, 0.25 mL). The reaction mixture was refluxed for 12 h and then cooled to rt, quenched with saturated $Na_2S_2O_3$(aq) (20 mL), and filtered through a short column of silica gel. The organic phase was washed with brine (2 × 20 mL), dried ($MgSO_4$), filtered and the filtrate was concentrated. Flash column chromatography (hexane:Et_2O, 1:1) of the residue afforded the diol **8** (5.7 g, 75%) as a white solid: mp 101−103 °C; TLC R_f 0.34 (hexane:Et_2O, 1:2); $[\alpha]^{25}_D$ −27 (c = 1.0, $CHCl_3$); IR (neat) 3460 cm^{-1}; ^{1}H NMR δ 1.3-1.8 (11H, m), 2.02 (1H, dd, J = 6.4, 14.4 Hz), 2.51 (1H, s), 2.75 (1H, s), 3.43 and 3.48 (2H, ABq, J = 9.1 Hz), 3.80 (1H, dd, J = 3.9, 9.5 Hz), 4.00 (1H, d, J = 9.5 Hz), 4.25−4.45 (2H, m), 4.55 (2H, s), 4.70 and 4.80 (2H, ABq, J = 12.0 Hz), 7.2−7.5 (10H, m); MS m/z (EI) 538 (M^+, 0.43), 241(M^+ − 43, 84.7), 55 (100). Anal. Calcd for $C_{27}H_{34}O_6$: C, 71.34; H, 7.54. Found: C, 71.33; H, 7.50.

(1*R*,2*S*,3*S*,4*S*,5*S*)-4,5-Di-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)-1,2-*O*-cyclohexylidenecyclohexane-1,2,3,4,5-pentol (9). The diol **8** (2.9 g, 6.39 mmol) was dissolved in Et_3N (20 mL) and Ac_2O (4.8 mL, 51.1 mmol). A catalytic amount of DMAP was added to the solution at rt, and the mixture was refluxed for 3 h. The cooled mixture was quenched with saturated NH_4Cl(aq) solution (20 mL), extracted with Et_2O (2 × 40 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated. Flash chromatography (hexane:Et_2O, 1:1) of the crude product provided the diacetate **9** (6.0 g, 90%) as a colorless syrup: TLC R_f 0.5 (hexane:Et_2O, 1:1); IR (neat) 1744 cm^{-1}; ^{1}H NMR δ 1.2−1.7 (11H, m), 1.88

(39) Still, W. C.; Kahn, M.; Mitra, *A. J. Org. Chem.* **1978**, *43*, 2923.

(3H, s), 1.93 (3H, s), 2.72 (1H, dd, J = 6.15, 14.6 Hz), 3.62 and 3.79 (2H, ABq, J = 9.18 Hz), 3.90 (1H, dd, J = 4.3, 10.0 Hz), 4.00−4.08 (1H, m), 4.29 (1H, m), 4.30 and 4.38 (2H, ABq, J = 12 Hz), 4.63 (2H, br s), 5.42 (1H, d, J = 10.0 Hz), 7.18−7.31 (10H, m); MS m/z (EI) 538 (M^+, 0.43), 91(C_7H_7, 100). Anal. Calcd for $C_{31}H_{38}O_8$: C, 69.13; H, 7.11. Found: C, 68.9; H, 7.29.

(1*R*,2*R*,3*R*,4*S*,5*S*)-4,5-Di-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-1,2,3,4,5-pentol (10). To a solution of the ketal **9** (4.8 g, 8.92 mmol) in CH_2Cl_2 (20 mL) were added TFA (0.5 mL) and H_2O (1 mL). The mixture was stirred vigorously at rt for 24 h. Then the reaction mixture was quenched with saturated $NaHCO_3$(aq) solution and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography (Et_2O:hexane, 3:1) provided the diol **10** (3.5 g, 90%) as a white amorphous solid: TLC R_f 0.19 (hexane:Et_2O 1:3); $[\alpha]^{25}_D$ −13.5 (c = 0.4, $CHCl_3$); IR (neat) 3425, 1740 cm^{-1}; ^1H NMR δ 1.93 (3H, s), 2.00−2.01 (1H, m,), 2.04 (3H, s), 2.62 (1H, br s), 2.74 (1H, dd, J = 4.8, 13.8 Hz), 3.71 and 3.92 (2H, ABq, J = 9.0 Hz), 3.73 (2H, dd, J = 2.9, 10.0 Hz), 4.20 (1H, br s), 4.37 and 4.45 (2H, ABq, J = 11.7 Hz), 4.60 and 4.66 (2H, ABq, J = 12.1 Hz), 5.46 (1H, d, J = 10.0 Hz), 7.20−7.40 (10H, m); MS m/z (EI) 458 (M^+, 0.08), 367 ($M^+ - C_7H_7$, 0.18), 261 ($M^+ - C_7H_7 - C_7H_6O$, 73.4), 91 (100). Anal. Calcd for $C_{25}H_{30}O_8$: C, 65.49; H, 6.60. Found: C, 65.57; H, 6.84.

(1*R*,2*S*,3*S*,4*S*,5*S*)-4,5-Di-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)-1,2-*O*,*O*-sulfonylcyclohexane-1,2,3,4,5-pentol (11). A solution of the α-1,2-diol **10** (494 mg, 1.07 mmol) and Et_3N (0.47 mL, 4.31 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C. $SOCl_2$ (0.28 mL, 3.77 mmol) was added with stirring for 0.5 h. After a further 15 min at 0 °C, cold Et_2O (10 mL) and cold H_2O (15 mL) were added. The aqueous phase was extracted with Et_2O (2 × 15 mL). The combined extracts were dried ($MgSO_4$) and filtered and the filtrate concentrated. The residue was pumped under high vacuum for 1 h. The residue was dissolved in CCl_4−CH_3CN (1:1) (20 mL) and the resulting solution cooled to 0 °C. Then $NaIO_4$ (0.92 g, 4.32 mmol), H_2O (10 mL), and a catalytic amount of $RuCl_3 \cdot H_2O$ was added. The reaction mixture was stirred vigorously for 1 h at 0 °C, and cold Et_2O (5 mL) was added. The aqueous phase was extracted by Et_2O (2 × 15 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated. The crude product was purified by flash chromatography (Et_2O:hexane, 1:2) to give the cyclic sulfate **11** as a white amorphous solid (0.48 g, 86%): TLC R_f 0.48 (hexane:Et_2O, 1:3); ^1H NMR δ 1.95 (3H, s), 2.03 (3H, s), 2.39 (1H, dd, J = 10.7, 14.7 Hz), 3.19 (1H, dd, J = 6.5, 14.6 Hz), 3.64 and 3.90 (2H, ABq, J = 9.2 Hz), 4.00 (1H, dd, J = 3.8, 9.3 Hz), 4.37 and 4.47 (2H, ABq, J = 12.1 Hz), 4.66 and 4.72 (2H, ABq, J = 12.1 Hz), 4.90 (1H, ddd, J = 4.5, 6.5, 10.9 Hz), 5.20 (1H, t*, J = 4.1 Hz), 5.52 (1H, d, J = 9.4 Hz), 7.1−7.5 (10H, m) (*apparent splitting pattern); MS m/z (EI) 429 ($M^+ - C_7H_7$, 0.22), 323 ($M^+ - C_7H_7 - C_7H_6O$, 1.79), 91 (100).

(1*S*,2*R*,3*R*,4*S*,5*S*)-1-Azido-4,5-di-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-2,3,4,5-tetrol (12). To a solution of the hydroxy triflate **19** (185 mg, 0.031 mmol) in dry DMF (8 mL) were added NaN_3 (0.06 g, 0.92 mmol) and benzo-15-crown-5 (0.27 g, 1.0 mmol). The mixture was stirred overnight at rt and then diluted with CH_2Cl_2 (20 mL), washed with brine (2 × 40 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography ($CHCl_3$:MeOH:hexane, 3:5:65) afforded azido alcohol **12** (60%) as a colorless syrup: TLC R_f 0.46 (hexane:Et_2O, 1:2); $[\alpha]^{27}_D$ +9.9 (c = 1.6, $CHCl_3$); IR (neat) 3425, 2108, 1738.2 cm^{-1}; ^1H NMR δ 2.00 (3H, s), 2.03 (3H, s), 2.37 (1H, br s), 2.39 (1H, br s), 2.57 (1H, br s), 3.6−3.7 (1H, m), 3.71 and 3.99 (2H, ABq, J = 9.8 Hz,), 3.8-3.9 (2H, m), 4.36 and 4.50 (2H, ABq, J = 11.9 Hz), 4.58 and 4.69 (2H, ABq, J = 11.5 Hz), 5.67(1H, d, J = 6.7 Hz), 7.2−7.4 (10H, m); MS m/z (EI) 392 ($M^+ - C_7H_7$, 3.36), 286 ($M^+ - C_7H_7 - C_7H_6O$, 100), 376 ($M^+ - C_7H_7O$, 4.02). Anal. Calcd for $C_{25}H_{29}O_7N_3$: C, 62.10; H, 6.05; N, 8.69. Found: C, 62.14; H, 5.97; N, 8.59.

(1*R*,2*S*,3*R*,4*S*,5*S*)-2-Azido-4,5-di-*O*-acetyl-3-*O*-benzyl-5-((benyloxy)methyl)cyclohexane-1,3,4,5-tetrol (13). To a solution of the cyclic sulfate **11** (0.19 g, 0.37 mmol) in dry DMF (20 mL) was added LiN_3[40] (0.16 g, 2.42 mmol), and the solution was stirred for 6 h at rt. The solvent was evaporated and the residue was dissolved in THF (20 mL). Then 20% H_2SO_4(aq) (2.5 mL) was added and the mixture was allowed to stir at rt. After 1 h, saturated Na_2CO_3(aq) solution (20 mL) was added and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the residue (Et_2O: hexane, 1:1) furnished the 1-azide **12** (13 mg, 7.3%) and 2-azide **13** (0.13 g, 73%) as a colorless syrup: TLC R_f 0.53 (hexane: Et_2O, 1:2); $[\alpha]^{25}_D$ −62.6 (c = 0.9, $CHCl_3$); IR (neat) 3450, 2106, 1744 cm^{-1}; ^1H NMR δ 1.64 (1H, dd, J = 11.7, 14.4 Hz), 1.79 (3H, s), 1.99 (3H, s), 2.29 (1H, br s), 2.88 (1H, dd, J = 4.6, 14.0 Hz), 3.35 (1H, t*, J = 9.6 Hz), 3.40−3.55 (1H, m), 3.57 and 3.85 (2H, ABq, J = 9.0 Hz), 3.64 (1H, t*, J = 9.7 Hz), 4.28 and 4.36 (2H, ABq, J = 11.6 Hz), 4.58 and 4.75 (2H, ABq, J = 10.9 Hz), 5.20 (1H, d, J = 9.8 Hz), 7.1−7.34 (10H, m) (*apparent splitting pattern); MS m/z (EI) 377($M^+ - C_7H_6O$, 1.22), 91 (100). Anal. Calcd for $C_{25}H_{29}O_7N_3$: C, 62.10; H, 6.05; N, 8.69. Found: C, 61.93; H, 5.81; N, 8.46.

(1*S*,2*R*,3*R*,4*S*,5*S*)-1-Azido-2,4,5-triacetyl-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-2,3,4,5-tetrol (14). (a) From 20. To a solution of the triflate **20** (0.11 g, 0.17 mmol) in dry DMF (5 mL) were added NaN_3 (0.023 g, 0.34 mmol) and benzo-15-crown-5 (0.1 g, 0.38 mmol). The mixture was stirred overnight, and the solvent was then evaporated. The residue was purified by flash chromatography (hexane:Et_2O 2:1) to give the azido acetate **14** (0.07 g, 80%) as a colorless syrup: TLC R_f 0.35 (hexane:Et_2O, 3:2); $[\alpha]^{28}_D$ −5.0 (c = 1.0, $CHCl_3$); IR (neat) 2108, 1744 cm^{-1}; ^1H NMR δ 1.94 (3H, s), 1.96 (3H, s), 1.98 (3H, s), 2.15−2.50 (2H, m), 3.60−3.80 (1H, m), 3.74 and 3.97 (2H, ABq, J = 10.0 Hz), 3.88 (1H, dd, J = 3.4, 6.6 Hz), 4.32 and 4.45 (2H, ABq, J = 11.9 Hz), 4.50 (2H, s), 5.04 (1H, dd, J = 3.3, 7.2 Hz), 5.61 (1H, d, J = 6.6 Hz), 7.10−7.40 (10H, m); MS m/z (EI) 434 ($M^+ - C_7H_7$, 0.4), 328 ($M^+ - C_7H_7 - C_7H_6O$, 7.1). Anal. Calcd for $C_{27}H_{31}O_8N_3$: C, 61.71; H, 5.95. Found: C, 61.69; H, 6.09.

(b) From 12. To a solution of the azido alcohol **12** (0.1 g) in dry CH_2Cl_2 (1 mL) were added excess Ac_2O, Et_3N, and a catalytic amount of DMAP. The mixture was stirred for 1 h at rt. The reaction mixture was quenched with H_2O (1 mL), washed with brine (2 × 10 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated. Flash chromatography purification of the crude product (hexane:Et_2O, 1:1) afforded the azido acetate **14** as a colorless syrup in 90% yield.

(1*R*,2*S*,3*R*,4*S*,5*S*)-2-Azido-1,4,5-tri-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-1,3,4,5-tetrol (15). To a solution of the azido alcohol **13** (31 mg, 0.064 mmol) in dry CH_2Cl_2 (5 mL) were added Ac_2O (9.1 μL, 0.096 mmol), Et_3N (20.9 μL, 0.19 mmol), and a catalytic amount of DMAP. The mixture was stirred for 1 h and then quenched with saturated NH_4Cl(aq) (1 mL), washed with brine (2 × 10 mL), dried ($MgSO_4$), and filtered and the filtrate concentrated. Flash chromatography of the crude product (hexane:Et_2O, 1:1) afforded the azido acetate **15** (29 mg, 86%) as a white amorphous solid: TLC R_f 0.56 (Et_2O:hexane 2:1); ^1H NMR δ 1.75 (1H, dd, J = 12.3, 14.2 Hz), 1.89 (3H, s), 2.07 (3H, s), 2.10 (3H, s), 2.96 (1H, dd, J = 4.8, 14.3 Hz), 3.58 (1H, t*, J = 9.9 Hz), 3.59 and 3.98 (2H, ABq, J = 8.9 Hz), 3.71 (1H, t*, J = 9.8 Hz), 4.34 and 4.42 (2H, ABq, J = 11.5 Hz), 4.63 and 4.84 (2H, ABq, J = 11.0 Hz), 4.86 (1H, ddd, J = 4.7, 9.9, 12.1 Hz), 5.30 (1H, d, J = 9.7 Hz), 7.1−7.4 (10H, m) (*apparent splitting pattern).

(1*R*,2*S*,3*R*,4*S*,5*S*)-2-Azido-3-*O*-benzyl-5-((benzyloxy)-methyl)-cyclohexane-1,3,4,5-tetrol (16). To a solution of the diacetate **13** (0.47 g, 0.97 mmol) in MeOH (20 mL) was added K_2CO_3 (0.1 g). The solution was stirred at rt for 1.5 h. Then the solvent was evaporated, and H_2O (20 mL) was added. The aqueous phase was extracted with Et_2O (2 × 20 mL), the combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (Et_2O:hexane, 1:1) to afford the triol **16** (0.38 g, 100%) as a white solid: mp 100−101 °C; TLC R_f

(40) Hofmann-Bang, N. *Act. Chem. Scand.* **1957**, *11*, 581.

0.28 (hexane:Et_2O, 1:2); $[\alpha]^{25}_D$ −79.1 (*c* = 0.9, $CHCl_3$); IR (neat) 3400, 2100 cm^{-1}; ^1H NMR δ 1.47 (1H, t*, *J* = 12.3 Hz), 2.06 (1H, dd, *J* = 4.8, 13.9 Hz), 2.50 (1H, br s), 2.81 (1H, br s), 2.89 (1H, br d, *J* = 3.1 Hz), 3.25 (1H, t*, *J* = 9.8 Hz), 3.42 (2H, s), 3.52 (1H, t*, *J* = 9.4 Hz), 3.68 (1H, dd, *J* = 2.6, 9.1 Hz), 3.65-3.85 (1H, m), 4.51 (2H, s), 4.79 and 4.88 (2H, ABq, *J* = 10.9 Hz), 7.2−7.5 (10H, m) (*apparent splitting pattern); MS *m*/*z* (EI) 308.1 ($M^+ - C_7H_7$, 1.03), 217.1 ($M^+ - 2C_7H_7$, 0.14), 202 (M^+- C_7H_7 − C_7H_6O, 0.44), 91 (100). Anal. Calcd for $C_{21}H_{25}O_5N_3$: C, 63.15, H, 6.31, N, 10.52. Found: C, 63.3; H, 6.15; N, 10.43.

(1*R*,2*S*,3*R*,4*S*,5*S*)-2-Amino-5-(hydroxymethyl)cyclohexane-1,3,4,5-tetrol (17). To a solution of the azide **16** (538 mg, 0.135 mmol) in EtOH (15 mL) was added 20% $Pd(OH)_2$ on charcoal (0.4 g), and H_2 was bubbled through the mixture with stirring until no UV-active species was shown by TLC. The solution was filtered through a pad of Celite and the filtrate concentrated. Flash column chromatography ($CHCl_3$:MeOH:NH_3(aq), 9:8:3) followed by purification with Amberlite CG-50 (NH_4^+) gave the 2-amino-regioisomer **17** (18 mg, 70%) as a white amorphous solid: TLC R_f 0.13 ($CHCl_3$:MeOH:NH_3(aq), 9:8:3); $[\alpha]^{21}_D$ −8.5 (*c* = 0.6, H_2O); IR (neat) 3333 cm^{-1}; ^1H NMR (D_2O) δ 1.60 (1H, t*, *J* = 12.4, 13.0 Hz), 2.06 (1H, dd, *J* = 4.6, 13.7 Hz), 2.89 (1H, *J* = 10.4 Hz), 3.47 (1H, d, *J* = 9.4 Hz), 3.47 and 3.56 (2H, ABq, *J* = 11.5 Hz), 3.68 (1H, t*, *J* = 9.9 Hz), 3.87 (1H, dt*, *J* = 4.7, 0.7 Hz) (*apparent splitting pattern); ^{13}C NMR (D_2O, dioxane at 67.39 ppm) δ 38.66, 60.19, 66.37, 66.70, 71.59, 74.14, 74.36; MS *m*/*z* (CI) 194 (M^+ + 1, 100). Anal. Calcd for $C_7H_{17}O_6N{\cdot}0.2H_2O$: C, 42.72; H, 7.89; N, 7.12. Found: C, 42.74; H, 7.92; N, 6.83.

(1*R*,2*S*,3*R*,4*S*,5*S*)-2-Acetamido-1,3,4-tri-*O*-acetyl-5-((acetyloxy)methyl)-cyclohexane-1,3,4,5-tetrol (18). To a solution of the amino alcohol **17** (0.05 g) in pyridine (3 mL) were added Ac_2O (0.25 mL) and a catalytic amount of DMAP. The reaction mixture was allowed to stir at rt overnight, and the solvent was then removed under reduced pressure. The crude product was purified by flash chromatography with 5% MeOH in chloroform to afford *N*,*O*-pentaacetate **18** (78 mg, 75%) as a white solid: mp 200−201 °C; TLC R_f 0.27 (MeOH:$CHCl_3$, 5:95); $[\alpha]^{27}_D$ −8.54 (*c* = 0.8, $CHCl_3$); IR (neat) 3400, 1747, 1666 cm^{-1}; ^1H NMR δ 1.92 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.08 (3H, s), 2.10 (3H, s), 2.18 (1H, dd, *J* = 4.8, 13.7 Hz), 3.36 (1H, br s), 3.86 and 4.03 (2H, ABq, *J* = 11.4 Hz), 4.33 (1H, q*, *J* = 10.2 Hz), 5.21 (1H, d, *J* = 9.7 Hz), 5.30 (1H, t*, *J* = 9.9 Hz), 5.1−5.3 (1H, m), 6.13 (1H, br d, *J* = 9.9 Hz, NHAc) (*apparent splitting pattern); MS *m*/*z* (CI) 404 (M^+ + 1, 70.75). Anal. Calcd for $C_{17}H_{25}O_{10}N$: C, 50.62; H, 6.25; N, 3.47. Found: C, 50.24; H, 6.08; N, 3.35.

(1*R*,2*S*,3*R*,4*S*,5*S*)-4,5-Di-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)-1-*O*-(trifluoromethanesulfonyl)cyclohexane-1,2,3,4,5-pentol (19). To a solution of the 1,2-diol **10** (941 mg, 0.21 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C were added Tf_2O (37 μL, 0.23 mmol) and pyridine (33 μL, 0.41 mmol). After 1 h, the mixture was quenched with H_2O (1 mL), washed with brine (2 × 10 mL), dried ($MgSO_4$), and filtered and the filtrate concentrated. Flash chromatography (hexane:Et_2O, 2:1) of the residue afforded the triflate **19** (115.5 mg, 93%) as white crystals: mp 100−101 °C; TLC R_f 0.33 (hexane:Et_2O, 3:2); $[\alpha]^{25}_D$ −19.1 (*c* = 0.5, $CHCl_3$); IR (neat) 3423, 1728 cm^{-1}; ^1H NMR δ 1.94 (3H, s), 2.07 (3H, s), 2.59 (1H, dd, *J* = 12.8, 13.4 Hz), 2.89 (1H, dd, *J* = 4.4, 14.7 Hz), 3.66 and 3.97 (2H, ABq, *J* = 9.1 Hz), 3.74 (1H, dd, *J* = 2.7, 9.9 Hz), 4.37 and 4.46 (2H, ABq, *J* = 11.7 Hz), 4.59 and 4.67 (2H, ABq, *J* = 11.7 Hz), 24.89 (1H, ddd, *J* = 2.8, 4.3, 12.4 Hz), 5.50 (1H, d, *J* = 9.9 Hz), 7.2-7.4 (10H, m).

(1*R*,2*S*,3*R*,4*S*,5*S*)-2,4,5-Tri-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)-1-*O*-(trifluoromethanesulfonyl)cyclohexane-1,2,3,4,5-pentol (20). To a solution of the alcohol **19** (116 mg, 0.20 mmol) in dry CH_2Cl_2 (8 mL) were added Ac_2O (92.8 mL, 0.98 mmol), pyridine (95.1 mL, 1.18 mmol), and a catalytic amount of DMAP. The mixture was stirred for 0.5 h, quenched with H_2O (1 mL), washed with brine (2 × 10 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated. Flash chromatography of the crude product (hexane:Et_2O, 2:1) afforded the triacetate **20** (0.11 g, 90%) as a colorless syrup: TLC R_f 0.39 (hexane:Et_2O, 1:1); IR (neat) 1754 cm^{-1}; ^1H NMR δ 1.95 (3H, s), 2.05 (3H, s), 2.17 (3H, s), 2.47 (1H, dd, *J* = 12.6, 13.7 Hz), 2.96 (1H, ddd, *J* = 0.59, 4.6, 13.8 Hz), 3.66 and 3.99 (2H, ABq, *J* = 9.2 Hz), 3.78 (1H, dd, *J* = 3.0, 10.1 Hz), 4.40 and 4.48 (2H, ABq, *J* = 12.0 Hz), 4.43 and 4.71 (2H, ABq, *J* = 11.7 Hz), 4.94 (1H, ddd, *J* = 3.1, 4.5, 12.6 Hz), 5.45 (1H, d, *J* = 10.1 Hz), 5.85−5.92 (1H, m), 7.2−7.4 (10H, m).

(1*S*,2*R*,3*R*,4*S*,5*S*)-1-Azido-3-*O*-benzyl-5-((benzyloxy)-methyl)cyclohexane-2,3,4,5-tetrol (21). (a) From 14. To solution of the azido acetate **14** (0.06 g, 0.11 mmol) in MeOH (5 mL) was added K_2CO_3 (0.01 g). The solution was allowed to stir at rt for 1.5 h. Then the solvent was evaporated, and H_2O (20 mL) was added. The aqueous phase was extracted with Et_2O (2 × 20 mL) and the combined organic phase was dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography (Et_2O:hexane, 2:1) afforded the triol **21** (33 mg, 72%) as a colorless syrup: TLC R_f 0.16 (hexane:Et_2O, 1:1); $[\alpha]^{26}_D$ +29.1 (*c* = 1.8, $CHCl_3$); IR (neat) 3445, 2106 cm^{-1}; ^1H NMR δ 1.84 (1H, dd, *J* = 6.5, 14.5 Hz), 2.03 (1H, dd, *J* = 4.4, 14.5 Hz), 2.56 (1H, br d, *J* = 3.7 Hz), 2.80 (1H, br s), 3.02 (1H, br s), 3.51 (2H, s), 3.71 (1H, dd, *J* = 6.2, 10.6 Hz), 3.83 (1H, dd, *J* = 3.2, 7.0 Hz), 3.85−4.0 (2H, m), 4.48 and 4.55 (2H, ABq, *J* = 12 Hz), 4.60 and 4.69 (2H, ABq, *J* = 11.5 Hz), 7.1−7.4 (10H, m); MS *m*/*z* (CI) 400 (M^+ + 1, 1.91). Anal. Calcd for $C_{21}H_{25}O_5N_3$: C, 63.15; H, 6.31; N, 10.52. Found: C, 63.37; H, 6.32; N, 10.45.

(b) From 12. To a solution of the azido alcohol **12** (21 mg, 0.043 mmol) in MeOH (5 mL) was added K_2CO_3 (5 mg). The solution was allowed to stir at rt for 3 h. Then the solvent was evaporated, and H_2O (10 mL) was added. The aqueous phase was extracted with Et_2O (2 × 20 mL), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated followed by flash chromatography (Et_2O:hexane, 2:1) to afford the triol **21** (15 mg, 80%) as a colorless syrup.

(1*S*,2*R*,3*R*,4*S*,5*S*)-1-*N*-Acetyl-2,3,4-tri-*O*-acetyl-5-((acetyloxy)methyl)cyclohexane-2,3,4,5-tetrol (22). To a solution of **3** (8 mg) in pyridine (2 mL) was added Ac_2O (0.5 mL) and a catalytic amount of DMAP. The reaction mixture was stirred at rt overnight, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography with 5% MeOH in chloroform to afford *N*,*O*-pentaacetate **22** (10 mg, 60%) as an amorphous solid: TLC R_f 0.29 (MeOH:$CHCl_3$, 5:95); $[\alpha]^{21}_D$ −18.1 (*c* = 1.3, $CHCl_3$); IR (neat) 3379, 1733, 1670 cm^{-1}; ^1H NMR (270 MHz) δ 1.97 (3H, s), 2.00 (3H, s), 2.09 (3H, s), 2.12 (3H, s), 2.13 (3H, s), 3.15 (1H, br s), 3.98 (2H, s), 4.1−4.2 (1H, m), 5.30 (1H, d, *J* = 10.2 Hz), 5.37 (1H, t*, *J* = 3.05 Hz), 5.42 (1H, dd, *J* = 2.9, 10.2 Hz), 7.03 (1H, br d, *J* = 7.8 Hz, NHAc) (*apparent splitting pattern); MS *m*/*z* (CI) 404 (M^+ + 1, 63.77).

(1*R*,2*S*,3*R*,4*S*,5*S*)-2,4,5-Tri-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-1,2,3,4,5-pentol (23). To a solution of the cyclic sulfate **11** (53 mg, 0.01 mmol) in 5 mL dry DMF (10 mL) was added Bu^n_4NOAc (0.02 g, 0.05 mmol), and the solution was stirred at rt for 6 h. The solvent was evaporated, the residue was dissolved in THF (10 mL), and 10% H_2SO_4(aq) (5 mL) was added. The mixture was stirred for 2 h, and then saturated Na_2CO_3(aq) (1 mL) solution was added. The aqueous phase was extracted with Et_2O (10 mL × 2), the combined organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated. The crude product was purified by flash chromatography (hexane:Et_2O, 1:2) to furnish the acetate **23** (43 mg, 85%) as a colorless syrup: TLC R_f 0.24 (hexane:Et_2O, 1:2); $[\alpha]^{21}_D$ −10.5 (*c* = 0.4, $CHCl_3$); IR (neat) 3500 and 1745 cm^{-1}; ^1H NMR δ 1.73 (1H, dd, *J* = 12.1, 14.5 Hz), 1.89 (3H, s), 2.02 (3H, s), 2.10 (3H, s), 2.99 (1H, dd, *J* = 4.8, 14.5 Hz), 3.67 and 3.95 (2H, ABq, *J* = 9.0 Hz), 3.75 (1H, ddd, *J* = 4.5, 9.4, 12.1 Hz), 3.85 (1H, t*, *J* = 9.8 Hz), 4.37 and 4.44 (2H, ABq, *J* = 11.5 Hz), 4.64 (2H, s), 4.96 (1H, t*, *J* = 9.6 Hz), 5.29 (1H, d, *J* = 10.0 Hz), 7.1−7.4 (10H, m) (*apparent splitting pattern); MS *m*/*z* (EI) 409($M^+ - C_7H_7$), 303 ($M^+ - C_7H_7 - C_7H_6O$, 100). Anal. Calcd for $C_{27}H_{32}O_9$: C, 64.79; H, 6.44. Found: C, 64.60; H, 6.47.

(1*S*,2*S*,3*R*,4*S*,5*S*)-1,2,4-Tri-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-1,2,3,4,5-pentol (25). (a) From 26. To a solution of the mesylate **26** (26 mg) in DMF (2 mL) was added an excess of Bu^n_4NOAc. The solution was heated to 100 °C for 1 d with stirring under N_2. After cooling, the

solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (hexane:Et_2O, 1:2) to afford 1,2,4-triacetate **25** (23 mg, 80%) as a colorless syrup: TLC R_f 0.39 (hexane:Et_2O, 1:2); $[\alpha]^{19}_D$ +20.0 (c = 1.2, $CHCl_3$); IR (neat) 3450, 1744 cm^{-1}; ^1H NMR (250 MHz) δ 1.92 (3H, s), 1.96 (3H, s), 2.12 (3H, s), 3.25 and 3.32 (2H, ABq, J = 9.1 Hz), 4.15 (1H, t*, J = 9.8 Hz), 4.42 and 4.48 (2H, ABq, J = 11.6 Hz), 4.62 and 4.72 (2H, ABq, J = 11.6 Hz), 4.96 (1H, dd, J = 3.4, 10.0 Hz), 5.18 (1H, d, J = 9.6 Hz), 5.43 (1H, q*, J = 3.4 Hz), 7.1−7.4 (10H, m) (*apparent splitting pattern); MS m/z (EI) 393 ($M^+ - C_7H_7O$), 303 ($M^+ - C_7H_7 - C_7H_6O$).

(b) From 23. To a solution of the alcohol **23** (50 mg, 0.01 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C were added Tf_2O (3.8 mL, 0.024 mmol) and pyridine (3.4 μL, 0.042 mmol). The mixture was warmed from 0 °C to rt in 3 h and then was quenched with H_2O (1 mL), washed with brine (2 × 10 mL), dried ($MgSO_4$), and filtered, and the filtrate concentrated. Flash chromatography (hexane:Et_2O, 1:2) of the crude residue afforded the triacetate **25** (38 mg, 76%).

(1*R*,2*R*,3*R*,4*S*,5*S*)-2,4,5-Tri-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)-1-*O*-(methanesulfonyl)cyclohexane-1,2,3,4,5-pentol (26). To a solution of the alcohol **23** (33 mg, 0.066 mmol) in pyridine (1 mL) under N_2 at 0 °C was added MsCl (0.26 mmol). The reaction mixture was stirred for 10 min and quenched with H_2O (10 mL). Then Et_2O (10 mL) was added, the mixture was washed with brine (2 × 10 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated. Flash chromatography (hexane:Et_2O, 1:2) of the residue afforded the mesylate **26** (31 mg, 80%) as a colorless syrup: TLC R_f 0.34 (hexane:Et_2O, 1:2); $[\alpha]^{19}_D$ −4.35 (c = 1.2, $CHCl_3$); IR (neat) 1746 cm^{-1}; ^1H NMR δ 1.90 (3H, s), 2.00 (3H, s), 2.13 (3H, s), 2.97 (3H, s), 3.12 (1H, dd, J = 5.0, 14.3 Hz), 3.61 and 3.98 (2H, ABq, J = 9.0 Hz), 3.89 (1H, t*, J = 9.8 Hz), 4.37 and 4.44 (2H, ABq, J = 11.6 Hz), 4.62 (2H, s), 4.6−4.7 (1H, m), 5.23 (1H, t*, J = 9.7 Hz), 5.32 (1H, d, J = 10.0 Hz), 7.1−7.4 (10H, m) (*apparent splitting pattern); MS m/z (EI) 487 ($M^+ - C_7H_7$, 0.16), 381 ($M^+ - C_7H_7 - C_7H_6O$, 24.94).

(1*S*,2*R*,3*S*,4*S*,5*S*)-1-Azido-4,5-di-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)-2-*O*-(trifluoromethanesulfonyl)cyclohexane-2,3,4,5-tetrol (27). To a solution of the azido alcohol **12** (105 mg, 0.22 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C were added Tf_2O (0.18 mL, 1.08 mmol) and pyridine (0.18 mL, 2.17 mmol). The mixture was stirred for 10 min and quenched with H_2O (10 mL). Et_2O (100 mL) was added, the organic phase was washed with brine (2 × 10 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated. Flash chromatography of the crude (hexane:Et_2O, 2:1) afforded the azido triflate **27** (0.12 g, 90%) as a colorless syrup: TLC R_f 0.40 (hexane:Et_2O, 3:2); $[\alpha]^{26}_D$ +11.0 (c = 1.0, $CHCl_3$); IR (neat) 2113, 1746 cm^{-1}; ^1H δ 2.00 (3H, s), 2.03 (3H, s), 2.26 (1H, dd, J = 8.5, 14.7 Hz), 2.59 (1H, dd, J = 4.5, 14.2 Hz), 3.7−3.9 (1H, m), 3.82 and 4.00 (2H, ABq, J = 10.3 Hz), 4.04 (1H, dd, J = 3.3, 6.0 Hz), 4.33 and 4.51 (2H, ABq, J = 12.0 Hz), 4.64 (2H, s), 4.82 (1H, dd, J = 3.3, 8.1 Hz), 5.73 (1H, J = 5.9 Hz), 7.1−7.5 (10H, m).

(1*S*,2*S*,3*R*,4*S*,5*S*)-1-Azido-2,4,5-tri-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-2,3,4,5-tetrol (28). To a solution of the azido triflate **27** (98 mg, 0.16 mmol) in dry THF (20 mL) was added Bu^n_4NOAc (0.14 g, 0.048 mmol), and the solution was stirred for 1 h at rt. The solvent was removed under reduced pressure and the residue purified by flash chromatography (hexane:Et_2O, 2:1) to afford the azido acetate **28** (67 mg, 80%) as a colorless syrup: TLC R_f 0.44 (hexane:Et_2O, 1:1); $[\alpha]^{25}_D$ −14.0 (c = 1.5, $CHCl_3$); IR (neat) 2102, 1743 cm^{-1}; ^1H NMR δ 1.91 (3H, s), 1.95 (1H, dd, J = 3.7, 16.3 Hz), 2.04 (3H, s), 2.09 (3H, s), 3.04 (1H, dd, J = 3.3, 15.9 Hz), 3.44 and 3.98 (2H, ABq, J = 8.8 Hz), 4.13 (1H, t*, J = 9.8 Hz), 4.1−4.2 (1H, m), 4.35 and 4.44 (2H, ABq, J = 11.6 Hz), 4.66 and 4.73 (2H, ABq, J = 11.7 Hz), 5.03 (1H, dd, J = 4.1, 9.8 Hz), 5.29 (1H, d, J = 9.7 Hz), 7.1−7.4 (10H, m) (*apparent splitting pattern); MS m/z (EI) 328 ($M^+ - C_7H_7 - C_7H_6O$, 43.49). Anal. Calcd for $C_{27}H_{31}O_8N_3$: C, 61.71; H, 5.95; N, 8.00. Found: C, 61.61; H, 5.98; N, 7.92.

(1*S*,2*S*,3*R*,4*S*,5*S*)-1-Azido-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-2,3,4,5-tetrol (29). To a solution of the azido acetate **28** (81 mg, 0.16 mmol) in MeOH (10 mL) was added K_2CO_3 (58 mg). The solution was allowed to stir at rt for 2 h, and the solvent was evaporated. The residue was dissolved in Et_2O (20 mL), washed with brine, dried ($MgSO_4$), and filtered and the filtrate concentrated. The residue was purified by flash chromatography (hexane:Et_2O, 1:1) to afford the triol **29** (56 mg, 91%) as a colorless syrup: TLC R_f 0.17 (hexane:Et_2O, 1:1); $[\alpha]^{28}_D$ +12.7 (c = 2.6, $CHCl_3$); IR (neat) 3420, 2114 cm^{-1}; ^1H NMR δ 1.79 (1H, dd, J = 3.8, 15.2 Hz), 1.94 (1H, dd, J = 4.6, 15.2 Hz), 2.68 (1H, br d, J = 5.8 Hz), 2.78 (1H, br s), 3.22 (1H, s), 3.25 and 3.44 (2H, ABq, J = 9.2 Hz), 3.6-3.8 (3H, m), 3.90 (1H, q*, J = 3.6 Hz), 4.45 (2H, s), 4.65 and 4.90 (2H, ABq, J = 11.2 Hz), 7.1−7.4 (10H, m) (*apparent splitting pattern); MS m/z (EI) 308 ($M^+ - C_7H_7$, 1.38). Anal. Calcd for $C_{21}H_{25}O_5N_3$: C, 63.15; H, 6.31; N, 10.52. Found: C, 62.90; H, 6.37; N, 10.26.

(1*S*,2*S*,3*R*,4*S*,5*S*)-1-*N*-Acetyl-2,3,4-tri-*O*-acetyl-5-((acetyloxy)methyl)-cyclohexane-2,3,4,5-tetrol (30). To a solution of valiolamine (**1**) in pyridine (0.5 mL) were added Ac_2O (0.25 mL) and a catalytic amount of DMAP. The reaction mixture was allowed to stir at rt overnight, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with 5% MeOH in chloroform to afford the pentaacetate **30** (29 mg, 70%) as a white solid: mp 137−138 °C (lit.[8] mp 137−138 °C); TLC R_f 0.26 (MeOH:$CHCl_3$, 5:95); $[\alpha]^{20}_D$ −17.8 (c = 2.0, $CHCl_3$) (lit.[8] $[\alpha]^{25}_D$ −14.8 (c = 1.0, $CHCl_3$)); IR (neat) 3345, 1737, 1680 cm^{-1}; ^1H NMR δ 1.99 (6H, s), 2.02 (3H, s), 2.09 (3H, s), 2.10 (3H, s), 3.02 (1H, s), 3.85 and 3.96 (2H, ABq, J = 11.6 Hz), 4.7−4.8 (1H, m), 4.93 (1H, dd, J = 4.4, 10.7 Hz), 5.08 (1H, d, J = 9.8 Hz), 5.52 (1H, t*, J = 10.3 Hz), 7.01 (1H, br d, J = 8.7 Hz) (*apparent splitting pattern); MS m/z (CI) 404 (M^+ + 1, 9.98).

(3*R*,4*S*,5*S*)-4,5-*O*-Acetyl-3-*O*-benzyl-5-((benzyloxy)-methyl)-1-cyclohexene-3,4,5-triol (31). To a solution of the diol **10** (0.4 g, 0.96 mmol) in toluene (50 mL) was added 1,1′-(thiocarbonyl)diimidazole (0.19 g, 1.07 mmol). The reaction mixture was heated to 90 °C for 1.5 h and then refluxed overnight. Then saturated NH_4Cl(aq) (50 mL) was added, and the aqueous phase was extracted with Et_2O (2 × 25 mL). The combined extracts were washed with cold 0.1 N H_2SO_4(aq), saturated $KHCO_3$(aq), and brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography (hexane:Et_2O, 2:3) afforded the corresponding thiocarbonate as a white solid (0.42 g, 87%), mp 68−70 °C. The thiocarbonate was dissolved in $P(OMe)_3$ (10 mL), and the solution was refluxed for 24 h. Evaporation of the solvent under reduced pressure followed by flash column chromatography (hexane:Et_2O, 2:1) furnished the alkene **31** (0.27 g, 74%) as a colorless syrup: TLC R_f 0.53 (hexane:Et_2O, 1:1); $[\alpha]^{25}_D$ −50.6 (c = 1.6, $CHCl_3$); IR (neat) 3000−3200, 1746 cm^{-1}; ^1H NMR δ 1.93 (3H, s), 1.94 (3H, s), 2.54 (1H, ddd, J = 2.6, 4.4, 20.0 Hz), 2.82 (1H, d, J = 20.0 Hz), 3.81 and 3.94 (2H, ABq, J = 9.6 Hz), 4.12−4.20 (1H, m), 4.30 and 4.41 (2H, ABq, J = 11.9 Hz), 4.57 (2H, s), 5.56 (1H, d, J = 6.1 Hz), 5.6-5.7 (2H, m), 7.1−7.30 (10H, m); MS m/z (EI) 333 ($M^+ - C_7H_7$, 1.2), 227 ($M^+ - C_7H_7 - C_7H_6O$, 16.59), 242 ($M^+ - 2C_7H_7$, 1.31), 91 (100). Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.98; H, 6.84.

(1*S*,2*S*,3*R*,4*S*,5*S*)-4,5-Di-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-1,2,3,4,5-pentol (32). (a) By the OsO_4 Method. To a solution of the alkene **31** (0.23 g, 0.54 mmol), Me_3NO (0.09 g, 0.76 mmol), pyridine (0.27 mL, 3.37 mmol), H_2O (0.05 mL, 2.94 mmol) in Bu^tOH (20 mL) was added a catalytic amount of OsO_4. The solution was refluxed with stirring for 24 h under N_2. After cooling, the reaction mixture was quenched with saturated $Na_2S_2O_3$(aq) solution (20 mL) and was extracted with Et_2O (2 × 20 mL). The organic phase was filtered through a short column of silica gel and the column eluted with Et_2O (300 mL). Evaporation of solvent followed by flash chromatography (hexane:Et_2O, 1:3) afforded the α-1,2-diol **10** (25 mg 10%), the starting material **31** (0.14 g, 60%), and the desired β-1,2-diol **32** (white solid, 50 mg, 20%): mp 127−128 °C; TLC R_f 0.21 (hexane:Et_2O, 1:2); $[\alpha]^{25}_D$ +21.9 (c = 1.0, $CHCl_3$); IR (neat) 3450, 1737 cm^{-1}; ^1H NMR δ 1.73 (1H, dd, J = 2.8, 16 Hz), 1.96 (3H, s), 2.03 (3H, s), 2.54 (1H, br s), 2.75 (1H, br s), 3.13 (1H, dd, J = 2.7, 16.0 Hz), 3.48 and 3.97 (2H, ABq, J = 8.8 Hz), 3.62 (1H, dd, J = 3.2, 9.2 Hz), 4.04 (1H, dd, J = 9.2, 9.9 Hz), 4.1-4.2 (1H, m), 4.36 and 4.47

(2H, ABq, $J = 11.7$ Hz), 4.67 and 4.77 (2H, ABq, $J = 11.5$ Hz), 5.27 (1H, d, $J = 9.9$ Hz), 7.2−7.45 (10H, m); MS *m/z* (EI) 367 ($M^+ - C_7H_7$, 18.36), 261 ($M^+ - C_7H_7 - C_7H_6O$, 100). Anal. Calcd for $C_{25}H_{30}O_8$: C, 65.49; H, 6.60. Found: C, 65.03; H, 6.44.

(b) By the $RuCl_3$ Method. A solution of the alkene **31** (15 mg, 0.035 mmol) in (CCl_4:CH_3CN, 1:1) (5 mL) was cooled to 0 °C. Then solution of $NaIO_4$ (7.8 mg, 0.037 mmol) and a catalytic amount of $RuCl_3 \cdot H_2O$ in H_2O (5 mL) were added, and the mixture was stirred vigorously for several min. Then saturated $Na_2S_2O_3$(aq) (2 mL) and Et_2O (20 mL) were added. The aqueous phase was extracted with Et_2O (2 × 10 mL), the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and the filtrate was concentrated. Flash chromatography (hexane:Et_2O, 3:1) of the crude product afforded **32** (13 mg, 81%) as a white solid.

(1*S*,2*S*,3*R*,4*S*,5*S*)-2,4-Di-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-1,2,3,4,5-pentol (33). To a solution of the alkene **31** (0.26 g, 0.63 mmol), Me_3NO (0.26 g, 2.33 mmol), pyridine (0.25 mL, 13.2 mmol), and H_2O (56 μL, 3.15 mmol) in Bu^tOH (3 mL) was added a catalytic amount of OsO_4. The solution was refluxed for 2 d under N_2. After cooling, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution (20 mL) and extracted with Et_2O (2 × 20 mL). The organic phase was filtered through a short column of silica gel, and the column was eluted with Et_2O (300 mL). The eluent was concentrated, and the residue was purified by flash chromatography (hexane:Et_2O, 1:3) to afford the α-1,2-diol **10** (41 mg, 14%), the starting material **31** (0.12 g, 46%), and the acetyl-migrated β-1,5-diol **33** (85 mg, 29%) as a white solid: mp 105−107 °C; TLC R_f 0.21 (hexane:Et_2O, 1:2); $[\alpha]^{23}_D$ +21.5 ($c = 1.0$, $CHCl_3$); IR (neat) 3400, 1740 cm^{-1}; ^1H NMR δ 1.79 (1H, dd, $J = 2.8$, 15.2 Hz), 1.88 (3H, s), 2.06 (3H, s), 2.16 (1H, dd, $J = 3.4$, 15.4 Hz), 3.27 and 3.35 (2H, ABq, $J = 9.2$ Hz), 3.53 (1H, s), 3.57 (1H, s), 4.18 (1H, t*, $J = 10.0$ Hz), 4.2−4.3 (1H, m), 4.42 and 4.48 (2H, ABq, $J = 11.4$ Hz), 4.63 and 4.72 (2H, ABq, $J = 11.7$ Hz), 4.89 (1H, dd, $J = 3.1$, 10.1 Hz), 5.15 (1H, d, $J = 9.8$ Hz), 7.1−7.4 (10H, m) (*apparent splitting pattern); MS *m/z* (EI) 367 ($M^+ - C_7H_7$, 12.44), 276 ($M^+ - 2C_7H_7$, 0.25), 261 ($M^+ - C_7H_7 - C_7H_6O$, 59.12). Anal. Calcd for $C_{25}H_{30}O_8$: C, 65.49; H, 6.60. Found: C, 65.14; H, 6.4.

(1*S*,2*R*,3*S*,4*S*,5*S*)-4,5-Di-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)-1,2-*O*,*O*-sulfonylcyclohexane-1,2,3,4,5-pentol (34). A solution of the β-1,2-diol **32** (0.08 g, 0.18 mmol) and Et_3N (76 μL, 0.69 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C. Then $SOCl_2$ (45 μL, 0.61 mmol) was added. The mixture was allowed to stir for several min, and then cold Et_2O (5 mL) and cold water (15 mL) were added. The aqueous phase was extracted with Et_2O (2 × 10 mL), the combined extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated. The crude product was pumped under vacuum for 1 h. The residue was dissolved in CCl_4−CH_3CN (1:1) (20 mL), and the solution was cooled to 0 °C. Then $NaIO_4$ (187 mg, 0.87 mmol), H_2O (10 mL), and a catalytic amount of $RuCl_3 \cdot H_2O$ were added and the mixture stirred vigorously. After 1 h, Et_2O (5 mL) was added, and the aqueous phase was extracted by Et_2O (2 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography (hexane:Et_2O, 2:1) afforded the cyclic sulfate **34** (67 mg, 74%) as a white solid: mp 44−46 °C; TLC R_f 0.56 (hexane:Et_2O, 1:3); $[\alpha]^{21}_D$ +42.2 ($c = 3.9$, $CHCl_3$); IR (neat) 1740 cm^{-1}; ^1H NMR δ 1.91 (3H, s), 2.07 (3H, s), 2.15 (1H, dd, $J = 3.8$, 17.4 Hz), 3.43 and 4.05 (2H, ABq, $J = 8.7$ Hz), 3.52 (1H, dd, $J = 1.7$, 17.4 Hz), 4.33 and 4.47 (2H, ABq, $J = 11.8$ Hz), 4.50 (1H, dd, $J = 7.8$, 10.7 Hz), 4.64 and 4.84 (2H, ABq, $J = 11.5$ Hz), 4.96 (1H, dd, $J = 5.4$, 7.9 Hz), 5.17−5.25 (1H, m), 5.25 (1H, d, $J = 10.6$ Hz), 7.2−7.4 (10H, m); MS *m/z* (EI) 413 ($M^+ - C_7H_7$, 0.84), 323 ($M^+ - C_7H_7 - C_7H_6O$, 83.36). Anal. Calcd for $C_{25}H_{28}O_{10}S$: C, 57.68, H 5.42, S, 6.16. Found: C, 57.71; H, 5.46, S, 6.14.

(1*R*,2*S*,3*R*,4*S*,5*S*)-1-Azido-4,5-di-*O*-acetyl-3-*O*-benzyl-5-(benzyloxy)methyl)cyclohexane-2,3,4,5-tetrol (35). To a solution of the cyclic sulfate **34** (67 mg, 0.13 mmol) in dry DMF (20 mL) was added LiN_3[40] (33 mg, 0.52 mmol), and the solution was stirred for 6 h at rt. The solvent was evaporated, the residue was dissolved in THF (20 mL), and 20% H_2SO_4(aq) (2.5 mL) was added. The mixture was allowed to stir for 1 h and then quenched with saturated Na_2CO_3(aq) solution (20 mL). The aqueous phase was extracted with Et_2O (2 × 10 mL), the combined extracts were dried ($MgSO_4$) and filtered, and the filtrate concentrated. The crude product was purified by flash chromatography (hexane:Et_2O, 1:1) to afford the hydroxy azide **35** (0.03 g, 50%) as a colorless syrup: TLC R_f 0.37 (hexane:Et_2O, 1:1); $[\alpha]^{27}_D$ −3.4 ($c = 0.9$, $CHCl_3$); IR (neat) 3470, 2105, 1739 cm^{-1}; ^1H NMR δ 1.62 (1H, dd, $J = 12.6$, 14.7 Hz), 1.92 (3H, s), 2.12 (3H, s), 2.62 (1H, br d, $J = 2.4$ Hz), 2.90 (1H, dd, $J = 4.4$, 14.6 Hz), 3.46 (1H, ddd, $J = 4.4$, 9.6, 12.3 Hz), 3.59 (1H, dt*, $J = 2.4$, 9.3 Hz), 3.62 and 3.94 (2H, ABq, $J = 9.0$ Hz), 3.73 (1H, dd, $J = 9.0$, 9.8 Hz), 4.36 and 4.44 (1H, ABq, $J = 11.6$ Hz), 4.68 and 4.75 (1H, d, $J = 11.5$ Hz), 5.21 (1H, d, $J = 9.9$ Hz), 7.1−7.4 (10H, m) (*apparent splitting pattern); MS *m/z* (EI) 377 ($M^+ - C_7H_6O$, 3.46), 286 ($M^+ - C_7H_7 - C_7H_6O$, 1.76), 285 ($M^+ - C_7H_7 - C_7H_7O$, 1.37), 91 (100). Anal. Calcd for $C_{25}H_{29}O_7N_3$: C, 62.10; H, 6.05; N, 8.69. Found: C, 62.21; H, 6.12; N, 8.33.

(1*R*,2*S*,3*R*,4*S*,5*S*)-1-Azido-3-*O*-benzyl-5-((benzyloxy)-methyl)cyclohexane-2,3,4,5-tetrol (36). (a) From 35. To a solution of the diacetate **35** (0.04 g, 0.083 mmol) in MeOH (10 mL) was added K_2CO_3 (0.01 g). The solution was allowed to stir at rt for 1.5 h. Then the solvent was evaporated, and H_2O (20 mL) was added. The aqueous phase was extracted with Et_2O (2 × 20 mL), and the combined organic phase was dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography (hexane:Et_2O, 1:1) afforded the triol **36** (0.029 g, 88%) as a colorless syrup: TLC R_f 0.3 (hexane:Et_2O, 2:3); $[\alpha]^{23}_D$ −14.6 ($c = 1.0$, $CHCl_3$); IR (neat) 3450, 2103 cm^{-1}; ^1H NMR δ 1.41 (1H, t*, $J = 13.3$ Hz), 2.03 (1H, dd, $J = 4.5$, 14 Hz), 2.68 (1H, br d, $J = 2.0$ Hz), 2.83 (1H, s), 2.88 (1H, d, $J = 3.08$ Hz), 3.42 (3H, m), 3.54 (1H, t*, $J = 8.9$ Hz), 3.63 (1H, dd, $J = 2.8$, 8.9 Hz), 3.74 (1H, ddd, $J = 4.7$, 9.6, 12.4 Hz), 4.52 (2H, s), 4.84 (2H, ABq, $J = 11.5$ Hz), 7.2−7.5 (10H, m) (*apparent splitting pattern); MS *m/z* (CI) 400 ($M^+ + 1$, 1.56). Anal. Calcd for $C_{21}H_{25}O_5N_3$: C, 63.15; H, 6.31; N, 10.52. Found: C, 63.21; H, 6.46; N, 10.07.

(b) From 39. To a solution of the diacetate **39** (53 mg, 0.11 mmol) in MeOH (10 mL) was added K_2CO_3 (0.05 g), and the resulting mixture was stirred at rt for 24 h. Then the solvent was removed under reduced pressure, and Et_2O (20 mL) was added. The aqueous phase was extracted with Et_2O (2 × 20 mL), the combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated. The crude product was purified by flash chromatography (hexane:Et_2O, 1:1) to afford **36** (0.04 g, 80%) as a colorless syrup.

(1*R*,2*S*,3*R*,4*S*,5*S*)-1-*N*-Acetyl-2,3,4-tri-*O*-acetyl-5-((acetyloxy)methyl)cyclohexane-2,3,4,5-tetrol (37). To a solution of **2** (20 mg) in pyridine (2 mL) were added Ac_2O (0.5 mL) and a catalytic amount of DMAP. The reaction mixture was allowed to stir at rt overnight, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with 5% MeOH in chloroform to afford *N*,*O*-pentaacetate **37** (33.4 mg, 80%) as a white solid: mp 231−232 °C; TLC R_f 0.26 (MeOH:$CHCl_3$, 5:95); $[\alpha]^{21}_D$ −14.2 ($c = 2.3$, $CHCl_3$); IR (neat) 3386, 3274, 1731, 1660 cm^{-1}; ^1H NMR (270 MHz) δ 1.58 (1H, t*, $J = 13.0$ Hz), 1.91 (3H, s), 1.97 (3H, s), 2.03 (3H, s), 2.05 (6H, s), 2.25 (1H, dd, $J = 4.6$, 14.3 Hz), 3.65 (1H, br s), 3.79 and 4.01 (2H, ABq, $J = 11.1$ Hz), 4.4−4.6 (1H, m), 4.93 (1H, t*, $J = 9.7$ Hz), 5.05 (1H, d, $J = 10.0$ Hz), 5.53 (1H, t*, $J = 10.0$ Hz), 5.89 (1H, br s, NHAc) (*apparent splitting pattern); MS *m/z* (CI) 404 ($M^+ + 1$, 22.07). Anal. Calcd for $C_{17}H_{25}O_{10}N$: C, 50.62; H, 6.25; N, 3.47. Found: C, 50.35; H, 6.20; N, 3.34.

(1*S*,2*R*,3*R*,4*S*,5*S*)-2,4-Di-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)-1,5-*O*,*O*-sulfonylcyclohexane-1,2,3,4,5-pentol (38). A solution of the 1,3-diol **33** (85 mg, 0.17 mmol) and Et_3N (59 mg, 0.74 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C. Then $SOCl_2$ (0.03 g, 0.28 mmol) was added, and the mixture was stirred for 15 min. Then cold Et_2O (50 mL) and cold water (25 mL) were added. The aqueous phase was extracted with Et_2O (100 mL), dried ($MgSO_4$), and filtered, and the filtrate concentrated. The crude product was pumped under vacuum for 1 h. The residue was dissolved in CCl_4−

CH_3CN (1:1) (25 mL) and cooled to 0 °C. Then $NaIO_4$ (0.12 g, 0.056 mmol), H_2O (10 mL), and a catalytic amount of $RuCl_3 \cdot H_2O$ were added, and the mixture was stirred vigorously. After 1 h, Et_2O (50 mL) was added. The aqueous phase was extracted with Et_2O (100 mL), and the combined organic phase was washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography (hexane:Et_2O, 1:1) afforded the cyclic sulfate **38** (77 mg, 80%) as a white solid: mp 147−148 °C; TLC R_f 0.53 (hexane:Et_2O, 1:2); IR (neat) 1752 cm^{-1}; ^1H NMR δ 1.94 (3H, s), 2.06 (3H, s), 2.15 (1H, d, J = 16.5 Hz), 3.42 (1H, dd, J = 4.8, 16.4 Hz), 3.50 (2H, s), 4.25 (1H, t*, J = 9.4 Hz), 4.43 and 4.53 (2H, ABq, J = 11.6 Hz), 4.64 and 4.73 (2H, ABq, J = 11.6 Hz), 4.96 (1H, dd, J = 2.1, 9.5 Hz), 5.11 (1H, m), 5.38 (1H, d, J = 9.4 Hz), 7.1−7.5 (10H, m) (*apparent splitting pattern); MS m/z (EI) 429 ($M^+ - C_7H_7$, 5.46), 323 ($M^+ - C_7H_7 - C_7H_6O$, 39.08). Anal. Calcd for $C_{25}H_{28}O_{10}S$: C, 57.68; H, 5.42. Found: C, 57.36; H, 5.36.

(1*R*,2*S*,3*R*,4*S*,5*S*)-1-Azido-2,4-di-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-2,3,4,5-tetrol (39). To a solution of the cyclic sulfate **38** (0.1 g, 0.21 mmol) in dry DMF (10 mL) was added LiN_3[40] (excess), and the solution was stirred for 6 h. The solvent was evaporated, the residue was dissolved in THF (10 mL), and 20% H_2SO_4(aq) (2 mL) was added. The mixture was stirred for 1 h and then quenched with saturated Na_2CO_3(aq) solution (10 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL), the combined phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated. Flash chromatography of the crude product (Et_2O:hexane, 3:1) afforded the azido alcohol **39** (82 mg, 80%) as a white solid: mp 98−100 °C: TLC R_f (hexane:Et_2O, 1:1); $[\alpha]^{21}_D$ +14.0 (c = 0.4, $CHCl_3$); IR (neat) 3408, 2101, 1740 cm^{-1}; ^1H NMR δ 1.51 (1H, t*, J = 12.8 Hz), 1.84 (3H, s), 2.01 (3H, s), 2.12 (1H, dd, J = 4.7, 14.0 Hz), 2.80 (1H, s), 3.27 and 3.39 (2H, ABq, J = 9.1 Hz), 3.84 (1H, ddt*, J = 4.7, 10.2, 12.4 Hz), 3.90 (1H, t*, J = 9.7 Hz), 4.44 (2H, s), 4.59 (2H, s), 5.05 (1H, t*, J = 9.9 Hz, H-2), 5.05 (1H, d, J = 9.8 Hz), 7.1−7.4 (10H, m) (*apparent splitting pattern); MS m/z (CI) 484 (M^+ + 1, 16.0). Anal. Calcd for $C_{25}H_{29}O_7N_3$: C, 62.10; H, 6.05; N, 8.69. Found: C, 61.99; H, 6.00; N, 8.41.

(1*R*,2*S*,3*S*,4*S*,5*S*)-1-Azido-4,5-di-*O*-acetyl-3-*O*-benzyl-5-((benzyloxy)methyl)-2-*O*-(trifluoromethanesulfonyl)cyclohexane-2,3,4,5-tetrol (40). To a solution of the alcohol **35** (57.8 mg, 0.12 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C were added Tf_2O (0.2 mL, 1.22 mmol) and pyridine (0.2 mL, 2.44 mmol). The mixture was stirred for 1 h, quenched with H_2O (10 mL), washed with brine (2 × 10 mL), dried ($MgSO_4$), and filtered and the filtrate concentrated. Flash chromatography of the crude residue (hexane:Et_2O, 2:1) afforded the triflate **40** (58 mg, 78%) as a colorless syrup: TLC R_f 0.57 (hexane:Et_2O, 1:1); $[\alpha]^{28}_D$ −20.0 (c = 0.6, $CHCl_3$); IR (neat) 2111, 1747 cm^{-1}; ^1H NMR δ 1.82 (3H, s), 1.82 (1H, t*, J = 12.8 Hz), 2.15 (3H, s), 3.12 (1H, dd, J = 4.9, 14.8 Hz), 3.61 and 3.95 (2H, ABq, J = 9.0 Hz), 3.67 (1H, ddd, J = 4.8, 10.1, 12.8 Hz), 3.95 (1H, t*, J = 9.8 Hz), 4.35 and 4.43 (2H, ABq, J = 11.5 Hz), 4.59 and 4.84 (2H, ABq, J = 10.8 Hz), 4.66 (1H, t*, J = 9.8 Hz), 5.28 (1H, d, J = 10.0 Hz), 7.25−7.40 (10H, m) (*apparent splitting pattern).

(1*R*,2*R*,3*R*,4*S*,5*S*)-1-Azido-2,4,5-triacetyl-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-2,3,4,5-tetrol (41). To a solution of the triflate **40** (58 mg, 0.094 mmol) in dry THF (7 mL) was added Bu^n_4NOAc (excess), and the solution was stirred for 1 h at rt. The solvent was evaporated and the residue was flash chromatographed (hexane:Et_2O, 2:1) to give the azido acetate **41** (47 mg, 95%) as a colorless syrup: TLC R_f 0.40 (hexane:Et_2O, 1:1); $[\alpha]^{29}_D$ −61.5 (c = 0.7, $CHCl_3$); IR (neat) 2102, 1747 cm^{-1}; ^1H NMR δ 1.93 (3H, s), 2.05 (3H, s), 2.18 (3H, s), 2.18 (1H, t*, J = 12.3 Hz), 2.84 (1H, ddd, J = 1.5, 4.3, 14.1 Hz), 3.44 (1H, ddd, J = 2.8, 4.3, 13.0 Hz), 3.70 and 3.98 (2H, ABq, J = 9.1 Hz), 3.73 (1H, dd, J = 3.0, 10.2 Hz), 4.40 and 4.47 (2H, ABq, J = 11.7 Hz), 4.42 and 4.71 (2H, ABq, J = 11.8 Hz), 5.40 (1H, d, J = 10.2 Hz), 5.75 (1H, br), 7.33 (10H, m) (*apparent splitting pattern); MS m/z (EI) 328 ($M^+ - C_7H_7 - C_7H_6O$, 25.16), 91 (100). Anal. Calcd for $C_{27}H_{31}O_8N_3$: C, 61.71; H, 5.95; N, 8.00. Found: C, 61.88; H, 6.08; N, 7.73.

(1*R*,2*R*,3*R*,4*S*,5*S*)-1-Azido-3-*O*-benzyl-5-((benzyloxy)methyl)cyclohexane-2,3,4,5-tetrol (42). To a solution of the triacetate **41** (52 mg, 0.1 mmol) in MeOH (10 mL) was added K_2CO_3 (0.05 g). The solution was allowed to stir at rt for 1.5 h, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (20 mL), washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography (hexane:Et_2O, 1:1) afforded the triol **42** (32 mg, 73%) as a white solid: mp 100−102 °C; TLC R_f 0.29 (hexane:Et_2O, 1:1); $[\alpha]^{21}_D$ −47.9 (c = 2.2, $CHCl_3$); IR (neat) 3492, 3415, 3344, 2104 cm^{-1}; ^1H NMR δ 1.88 (1H, dd, J = 4.4, 13.3 Hz), 2.07 (1H, t*, J = 12.9 Hz), 2.48 (1H, br s), 2.80 (1H, br s), 2.85 (1H, br d, J = 2.5 Hz), 3.44 and 3.49 (2H, ABq, J = 9.2 Hz), 3.49 (1H, dd, J = 2.5, 10.6 Hz), 3.58 (1H, ddd, J = 2.4, 4.4, 12.3 Hz), 3.93 (1H, dd, J = 2.0, 9.2 Hz), 4.20 (1H, br s), 4.53 (2H, s), 4.63 and 4.69 (2H, ABq, J = 11.7 Hz), 7.20−7.40 (10H, m) (*apparent splitting pattern); MS m/z (CI) 400 (M^+ + 1, 3.19). Anal. Calcd for $C_{21}H_{25}O_5N_3$: C, 63.15; H, 6.31; N, 10.52. Found: C, 63.10; H, 6.36; N, 10.37.

(1*R*,2*R*,3*R*,4*S*,5*S*)-1-*N*-Acetyl-2,3,4-tri-*O*-acetyl-5-((acetyloxy)methyl)cyclohexane-2,3,4,5-tetrol (43). To a solution of **4** (10 mg, 0.052 mmol) in pyridine (2 mL) were added Ac_2O (0.25 mL) and a catalytic amount of DMAP. The reaction mixture was allowed to stir at rt overnight, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with 5% MeOH in chloroform to afford *N*,*O*-pentaacetate **43** (16.7 mg, 80%) as a white solid: mp 273−275 °C; TLC R_f 0.19 (MeOH:$CHCl_3$, 5:95); $[\alpha]^{22}_D$ −15.6 (c = 0.6, $CHCl_3$); IR (neat) 3422, 1728, 1660 cm^{-1}; ^1H NMR δ 1.96 (6H, s), 2.10 (6H, s), 2.28 (3H, s), 2.94 (1H, br s), 3.91 and 4.02 (2H, ABq, J = 11.4 Hz), 4.6−4.7 (1H, m), 5.26 (1H, d, J = 10.3 Hz), 5.34 (1H, dd, J = 2.7, 10.4 Hz), 5.45−5.55 (2H, m); MS m/z (CI) 404 (M^+ + 1, 36.68).

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