A Stereodivergent Access to Naturally Occurring Aminocarbasugars from (Phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane Derivatives. Total Synthesis of Penta-*N*,*O*-acetyl-(±)-validamine and Its C_1 and C_2 Stereoisomers

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The total syntheses of the antibiotic component validamine **1** and its three diastereomers **2**–**4** have been accomplished as their racemic penta-*N*,*O*-acetates *via* stereocontrolled nucleophilic epoxidation of polyhydroxylated cyclohexenyl sulfones, obtained from (phenylsulfonyl)-7-oxabicyclo-[2.2.1]heptanes. The diastereoselectivity of the epoxidation can be readily controlled by careful choice of the hydroxyl protecting groups. Ring opening of the resulting α,β-epoxy sulfones followed by stereocontrolled introduction of an amine precursor led to the four C_1 and C_2 diastereomers of 1-aminocarbasugars.

Introduction

Carbasugars (often called pseudosugars[1a]) and related compounds are products of biological relevance because they may act as enzyme inhibitors, sweeteners, antibiotics, etc.[1b] Considerable efforts directed toward the development of syntheses of these compounds have been made.[1,2] 1-Aminocarbasugars such as validamine **1**[3] (Figure 1) are some of the most important and attractive members of the carbasugar family due to their enzyme inhibitory activity against various glucose hydrolases.[4] 1-Aminocarbasugars are also constituents of the antibiotic validamycin complex,[5] isolated from the fermentation broth of *streptomyces hygroscopicus* subsp. *limonenus*, which shows growth inhibition activity against bacterial diseases of rice plants.[6]

Although there are several syntheses of 1-aminocarbasugars,[7] in many cases these methods suffer from a lack of versatility in terms of both regio- and stereocontrol. One of the most widely used intermediates in the syntheses of carbasugars are 7-oxanorbornenic systems,[1,8,9] which are readily available both as racemates as well as pure enantiomers.[10] A crucial transformation in these synthetic sequences employing oxabicyclic intermediates is the cleavage of the oxygen bridge to produce highly functionalized cyclohexenol derivatives.[11] In this paper, we describe a short and stereodivergent route of penta-*N*,*O*-acetyl-(±)-validamine **17** and its C_1 and C_2 stereoisomers **19**, **22**, and **23** from the cyclohexenyl sulfones **7** (Scheme 1). These compounds are available by our previously described methodology based on the strain-directed bridge cleavage of 7-oxanorbornanic sulfones **6** with *n*-BuLi, and they have been employed in the total synthesis of carba-α-DL-glucopyranose.[8] Sulfones **6** are readily available in four steps from acid **5**.[12]

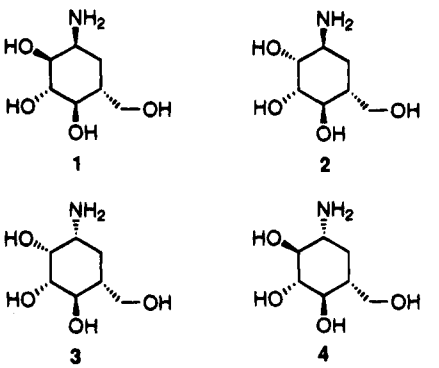
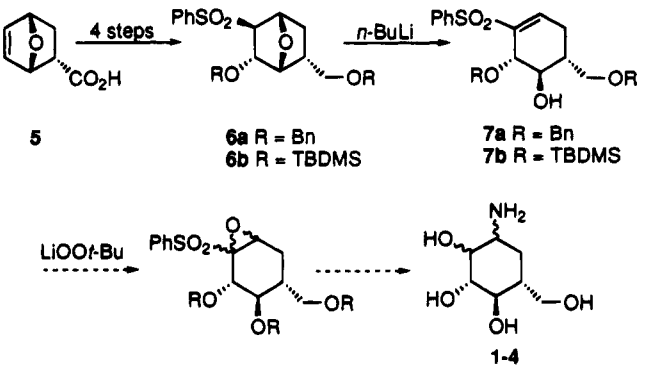


Figure 1.

Scheme 1



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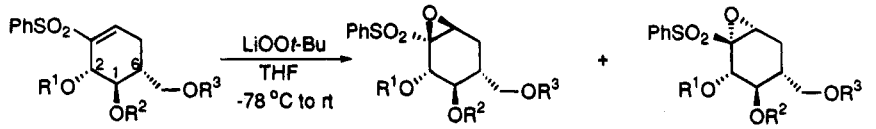
Scheme 2



7a $R^1 = R^3 =$ Bn, $R^2 = H$
7b $R^1 = R^3 =$ TBDMS, $R^2 = H$
7c $R^1 =$ Bn, $R^2 = R^3 = -CH_2-$
7d $R^1 = R^3 =$ Bn, $R^2 =$ TBDMS
7e $R^1 = R^2 = R^3 =$ TBDMS

The key step of our synthetic plan involves the diastereoselective nucleophilic epoxidation of sulfones **7**. This kind of epoxidation is a well-known process.[13] The reaction has been studied in terms of diastereoselectivity on acyclic[14] and cyclic[15] oxygenated vinyl sulfones. Coordination and/or conformational effects have been invoked in order to explain the diastereoselectivity of the process. With the appropiate α,β-epoxy sulfone in our hands, the stereoselective introduction of an amine group precursor by epoxide cleavage would produce the 1-aminocarbasugars **1**–**4**.

Results and Discussion

We first examined methylene acetal **7c**, obtained by reaction of sulfone **7a** with $(MeO)_2CH_2$[8] (Scheme 2). This compound, which presents a fixed conformation, by treatment with LiOO-*t*-Bu[13b] afforded a 60:40 mixture of epoxides **8c** and **9c** (Table 1, entry 3). In contrast with this disappointing result, dibenzyl ether **7a**, under identical reaction conditions, gave a single α,β-epoxy sulfone (**8a**) (entry 1). In the case of disilyl sulfone **7b**, a high diastereoselectivity (95:5) in the same sense was observed (entry 2).[16] In contrast, sulfones **7d** and **7e**, obtained by silylation (TBDMSOTf, Et_3N, THF, −78 °C) of **7a** and **7b**, respectively, displayed high or total diastereoselectivity, but in the opposite direction (entries 4 and 5). Thus, the diastereoselectivity of the nucleophilic epoxidation of our polyhydroxycyclohexenyl sulfones can be controlled by the choice of the protecting groups.

Table 1. Nucleophilic Epoxidation of Vinyl Sulfones 7a–e

entry	substrate	$J_{1,2}$[a]	$J_{1,6}$[a]	8	9	8:9 ratio[b]	yield,[c] %
1	**7a**	6.8	9.8	**8a**		100:0	92
2	**7b**	4.9	7.4	**8b**[d]	**9b**	95:5	85
3	**7c**	7.6	11.0	**8c**	**9c**	60:40	82
4	**7d**	2.9	2.9	**8d**	**9d**	10:90	88
5	**7e**	2.7	2.7		**9e**	0:100	80

[a] In Hz. [b] Measured by integration of the ^1H NMR spectra of the crude reaction mixtures. [c] Overall yield of pure products. [d] Epoxide **8b** experimented a migration of silyl group from R_1 to R_2 position.[16]

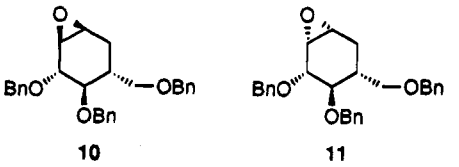


Figure 2.

The stereochemistry of the resulting epoxides was tentatively established from their ^1H NMR spectra. The crucial data were the chemical shifts of the protons linked at the β-alkoxy substituents to the phenylsulfonyl groups, which are more deshielded for compounds **9b**–**d** due to the *syn* effect of the sulfone. This assignment was further secured by chemical correlations of the sulfonyl oxiranes with the known tribenzyl epoxides **10** and **11**[17] (Figure 2).

The stereochemical outcome of the nucleophilic epoxidation of our substrates can be rationalized on the basis of the conformational behavior of the starting polyoxy-

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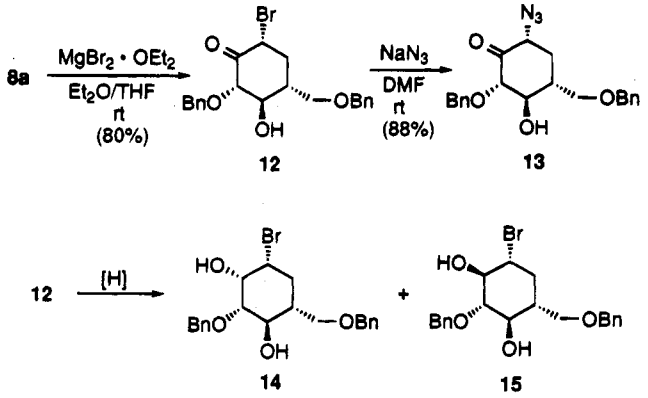
(16) Epoxide **8b** experimented a migration of silyl group from R_1 to R_2 position. The structural assignement for compound **8b** was performed by ^1H NMR spectroscopy. This analysis showed an apparent triplet for H-1 (3.83 ppm, J = 6.8 Hz) indicating coupling (confirmed by selective decoupling) with the free hydroxyl group (3.14 ppm, d, J = 7.1 Hz) and with H-6 (3.44 ppm, dd, J = 6.7 Hz)

Scheme 3



genated cyclohexenyl sulfones along with coordinative effects of the remote hydroxyl group. Inspection on the $J_{1,2}$ and $J_{1,6}$ coupling constant data (Table 1) shows that **7a–c** present similar ground state conformational equilibria; however, the selectivity of the process is clearly controlled by the free homoallylic hydroxyl group. Finally, the striking reversal of diastereoselectivity found for **7d** and **7e** presumably reflects the intrinsic steric bias of the molecule[15] as a result of its very different conformation (see $J_{1,2}$ and $J_{1,6}$ in Table 1).

The epoxide ring opening with concomitant loss of the phenylsulfonyl group was the next step of our synthetic plan. The introduction of an azide group in the epoxide **9e** would produce an α-azido ketone with the same configuration on the azide group as in validamine. Unfortunately, when **9e** was treated with NaN_3 in DMF at reflux,[18] the desired α-azido ketone was not obtained.[19] Therefore, the approach to this product was performed indirectly by means of the reaction of **8a** with $MgBr_2{\cdot}OEt_2$[20] (Scheme 3), affording α-bromo ketone **12** along with its epimer in 89:11 ratio (90% overall yield). After chromatographic separation, **12** was transformed into the related α-azido ketone **13**[21] by halogen displacement with NaN_3 (88% yield). This reaction occured at room temperature and with overall net retention of configuration due to equilibration of the product.[22]

Compound **13** can serve as the precursor of compounds **3** and **4**, by reduction of the carbonyl group followed by azide hydrogenation. At this point, we reasoned that stereocontrolled reduction of the carbonyl group in **12** would produce both diols **14** and **15**. Azide displacement in each case with inversion of configuration and subsequent reduction of the azide to amine would afford validamine **1** and its epimer **2**. Thus, the stereochemistry of the reduction of the carbonyl group of **12** was explored.

(17) Ogawa, S.; Tonegawa, T. *Carbohydr. Res.* **1990**, *204*, 51–64. For instance, **8a** was benzylated with NaH/BnBr and desulfonylated with Na–Hg to obtain the epoxide **10**, and **9e** was converted to **11** by desilylation with *n*-Bu_4NF, benzylation, and desulfonylation.

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(21) Proton H-6 in both ketones **12** and **13** shows an axial–axial constant coupling (13.6 and 13.2 Hz, respectively) and an axial–equatorial constant coupling (6.1 and 5.3 Hz).

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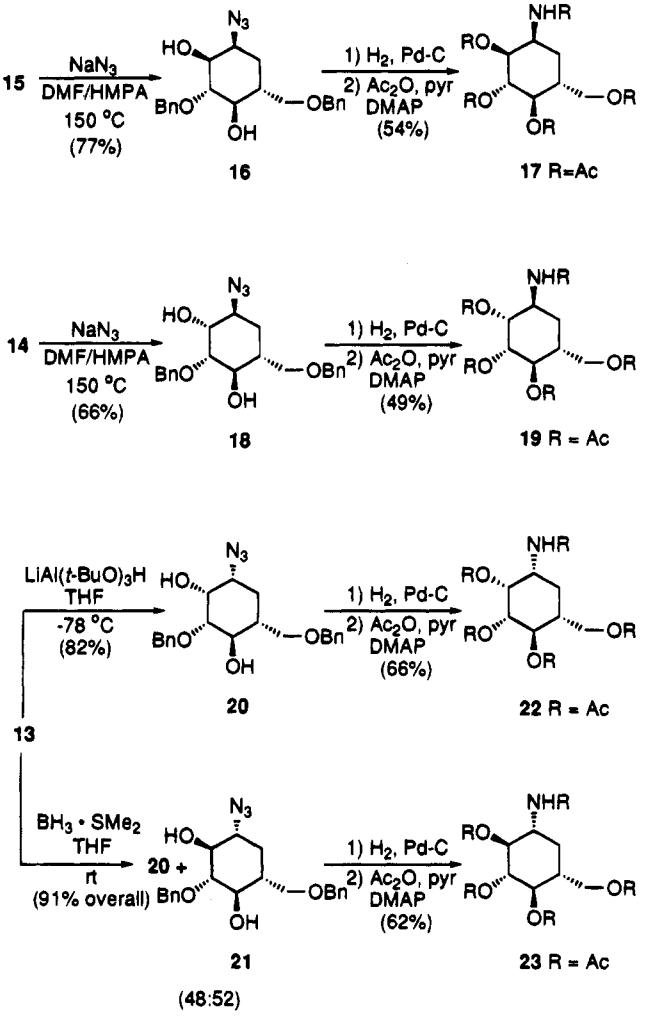
Table 2. Stereochemistry of the Reduction of Ketone 12

reagent	temperature, °C	14:15 ratio
$LiAl(t\text{-}BuO)_3H$	−78	100:0
$NaBH_4$	0	91:9
$LiAlH_4$	0	91:9
DIBAL-H	0	91:9
$NaBH_4/CeCl_3$	−78	71:29
$NaBH_4/CeCl_3$	rt	50:50
$BH_3{\cdot}SMe_2$	−78	40:60
$BH_3{\cdot}SMe_2$	rt	18:82

Scheme 4



A wide range of reagents and temperatures were tested for the reduction of ketone **12** (Table 2). Treatment of **12** with $LiAl(t\text{-}BuO)_3H$ at −78 °C gave axial alcohol **14** as single diastereomer (85% yield). Other reducing agents ($NaBH_4$, $LiAlH_4$, DIBAL-H, $NaBH_4/CeCl_3$) afforded mixtures of both diastereomers, but **14** was always the major product due to preferential equatorial attack. Finally, reduction with $BH_3{\cdot}SMe_2$ at room temperature yielded the desired equatorial alcohol **15** as the major diastereomer in a 82:18 ratio (94% overall yield). These diols were easily separated by column chromatography.

The synthesis of validamine was then addressed from bromohydrin **15**. Substitution with NaN_3 gave azide **16** (77% yield) (Scheme 4). The dissappearance of the carbonyl group allowed for the reaction to occur with inversion of configuration. This transformation required an increase of the reaction temperature to 150 °C and

the addition of HMPA as cosolvent.[23] Reduction of the azido group and concurrent removal of benzyl groups by catalytic hydrogenation (H_2, Pd–C, MeOH) followed by acetylation (Ac_2O, pyr, DMAP) provided penta-*N,O*-acetyl-(±)-validamine **17** (54% overall yield). Its spectral features were identical to those reported in the literature.[3]

Similarly, we achieved the syntheses of diastereomers **19**, **22**, and **23**. Thus, the reaction of *cis*-bromohydrin **14** with NaN_3 afforded **18** (66% yield) followed by hydrogenation under the same conditions as before provided 2-epivalidamine (5a-carba-α-mannopyranosylamine, **2**), which was characterized as the pentaacetate **19** (49% overall yield).[7f] On the other hand, reduction of α-azido ketone **13** was carried out in the same manner as in the case of **12**. Treatment of **13** with $LiAl(t\text{-}BuO)_3H$ at −78 °C produced **20** as a single diastereomer (82% yield), whereas in the presence of $BH_3{\cdot}SMe_2$, a 48:52 mixture of **20** and **21** was obtained (91% overall yield). Compound **21** was easily separated by chromatography for the synthesis of **4**. Catalytic hydrogenation of **20** afforded 5a-carba-β-mannopyranosylamine **3**, and the same procedure in the case of **21** yielded the 1-epivalidamine (5a-carba-β-glucopyranosylamine, **4**). These products were fully characterized as pentaacetates **22**[24] and **23**[25] respectively.

In summary, an efficient, regio- and stereocontrolled route to 5a-carba-D,L-glycopyranosylamine from (phenylsulfonyl)-7-oxanorbornanic systems has been developed. Useful control of the diastereoselectivity of the nucleophilic epoxidation of polyoxygenated cyclohexenyl sulfones by choosing the protecting groups and subsequent oxirane opening with concomitant loss of the phenylsulfonyl group provided an α-bromo ketone, key intermediate for the synthesis of (±)-validamine and its C_1 and C_2 stereoisomers.

Experimental Section

General Methods. All reactions were carried out under a positive pressure of dry argon. Reagents and solvents were handled by using standard syringe techniques. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone, *N,N*-dimethylformamide, triethylamine, and hexamethylphosphoramide (HMPA) from CaH_2. Commercial *n*-butyllithium (solution 1.6 M in hexane) was purchased from Aldrich and titrated prior to use.[26] Flash chromatography was performed using E. Merck 230–400 mesh silica gel. Analytical TLC was carried out on 0.20 mm E. Merck precoated silica gel plates (60F-254), with detection by UV light, acidic vanillin solution, and a 10% solution of phosphomolybdic acid in ethanol. Melting points were determined on a Büchi 512 apparatus and are uncorrected. Infrared spectra were recorded on either a Perkin-Elmer 781 or 257 grating spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on Brüker AM-200, Varian XL-300, or Varian VXR-300S instruments using $CDCl_3$ or C_6D_6 as solvent. The following abbreviations are used to describe peak patterns when appropiate: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

General Procedure for the Epoxidation of Vinyl Sulfones 7a–e. To a cold (−78 °C) solution of 2 equiv of *t*-BuOOH (80% in *t*-BuOO*t*-Bu) in THF (3 mL × mmol) was added 2 equiv of *n*-BuLi. After15 min of stirring at −78 °C, a solution of the corresponding vinyl sulfone in THF (3 mL × mmol) was added. The mixture was slowly warmed to room temperature and stirred overnight. Saturated aqueous NaCl was added, and the crude mixture was extracted with EtOAc, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, using the appropiate eluent.

D,L-(1,3,4/2,6)-3,4-Anhydro-2-*O*-benzyl-6-((benzyloxy)methyl)-3-*C*-(phenylsulfonyl)-1,2,3,4-cyclohexanetetrol (8a). From 630 mg (1.36 mmol) of **7a**,[8] 600 mg of **8a** was obtained as a white solid (92% yield). R_f = 0.19 (hexane:EtOAc, 2:1). Mp: 58–59 °C. IR ($CHCl_3$): 3600–3300, 2960, 2940, 1450, 1330, 1160, 1100 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.80–1.90 (m, 2 H), 2.12 (dd, 1 H, J = 10.5, 2.7 Hz), 3.05 (br s, 1 H), 3.39 (dd, 1 H, J = 9.3, 5.9 Hz), 3.54 (dd, 1 H, J = 9.3, 3.9 Hz), 3.63 (dd, 1 H, J = 9.5, 6.8 Hz), 3.66 (br s, 1 H), 3.89 (dd, 1 H, J = 6.8, 1.0 Hz), 4.45 (s, 2 H), 4.60 (d, 1 H, J = 11.2 Hz), 4.82 (d, 1 H, J = 11.2 Hz), 7.23–7.35 (m, 10 H), 7.40 (t, 2 H, J = 7.8 Hz), 7.58 (t, 1 H, J = 7.3 Hz), 7.79 (d, 2 H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 25.0, 33.6, 57.0, 71.7, 72.1, 73.3, 75.1, 75.2, 79.8, 127.6, 127.8, 128.3, 128.4, 128.7, 129.1, 133.7, 137.4, 137.5, 137.9. Anal. Calcd for $C_{27}H_{28}O_6S$: C, 67.48; H, 5.87. Found: C, 66.90; H, 5.93.

D,L-(1,5/2,3,6)-2,3-Anhydro-6-*O*-(*tert*-butyldimethylsilyl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-*C*-(phenylsulfonyl)-1,2,3,6-cyclohexanetetrol (8b) and D,L-(1/2,3,4,6)-3,4-Anhydro-2-*O*-(*tert*-butyldimethylsilyl)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-*C*-(phenylsulfonyl)-1,2,3,4-cyclohexanetetrol (9b). From 1 g (1.95 mmol) of **7b**,[8] a mixture of 835 mg of **8b** as a white solid (81% yield) and 40 mg of **9b** as a colorless oil (4% yield) was obtained. Data for **8b**: R_f = 0.26 (hexane:EtOAc, 5:1). Mp: 87–88 °C. IR ($CHCl_3$): 3700–3300, 2980, 2940, 1470, 1450, 1310, 1260, 1100 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.01 (s, 6 H), 0.02 (s, 3 H), 0.04 (s, 3 H), 0.80 (s, 9 H), 0.85 (s, 9 H), 1.44–1.60 (m, 1 H), 1.90 (ddd, 1 H, J = 15.5, 12.7, 1.0 Hz), 2.15 (ddd, 1 H, J = 15.5, 4.4, 2.7 Hz), 3.14 (d, 1 H, J = 7.1 Hz), 3.44 (dd, 1 H, J = 10.4, 6.7 Hz), 3.51 (dd, 1 H, J = 10.0, 3.2 Hz), 3.62 (dd, 1 H, J = 10.0, 5.4 Hz), 3.73 (br s, 1 H), 3.83 (t, 1 H, J = 6.8 Hz), 7.54 (t, 2 H, J = 7.7 Hz), 7.66 (t, 1 H, J = 7.4 Hz), 7.94 (dd, 2 H, J = 7.3, 1.6 Hz). ^{13}C NMR ($CDCl_3$): δ −5.6, −5.3, −5.1, −4.0, 18.2, 25.9, 25.9, 36.2, 57.5, 62.5, 72.2, 72.7, 74.7, 128.9, 129.6, 134.3, 135.8. Anal. Calcd for $C_{25}H_{44}O_6SSi_2$: C, 56.78; H, 8.39. Found: C, 56.64; H, 8.01. Data for **9b**: R_f = 0.18 (hexane:AcOEt, 5:1). IR ($CHCl_3$): 3600–3200, 2980, 2960, 1470, 1450, 1330, 1260, 1150 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.01 (s, 6 H), 0.20 (s, 3 H), 0.28 (s, 3 H), 0.85 (s, 9 H), 0.96 (s, 9 H), 1.62–1.78 (m, 1 H), 1.79 (dd, 1 H, J = 14.5, 11.4 Hz), 1.98 (ddd, 1 H, J = 14.5, 4.6, 3.1 Hz), 2.91 (d, 1 H, J = 5.4 Hz), 3.27 (d, 1 H, J = 3.1 Hz), 3.50 (dd, 1 H, J = 10.1, 6.3 Hz), 3.51 (td, 1 H, J = 5.4, 3.1 Hz), 3.64 (dd, 1 H, J = 10.1, 5.4 Hz), 4.39 (dd, 1 H, J = 5.4, 1.0 Hz), 7.50 (dd, 2 H, J = 7.8, 7.3 Hz), 7.62 (t, 1 H, J = 7.5 Hz), 7.89 (d, 2 H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ −5.6, −5.6, −4.8, −3.9, 24.4, 25.7, 26.1, 36.6, 57.2, 65.7, 72.1, 73.0, 75.7, 128.6, 129.9, 134.0, 135.3.

D,L-(1,3,4/2,6)-3,4-Anhydro-2-*O*-benzyl-6-(hydroxymethyl)-3-*C*-(phenylsulfonyl)-1,2,3,4-cyclohexanetetrol, 1,7-Methylene Acetal (8c) and D,L-(1/2,3,4,6)-3,4-Anhydro-2-*O*-benzyl-6-(hydroxymethyl)-3-*C*-(phenylsulfonyl)-1,2,3,4-cyclohexanetetrol, 1,7-Methylene Acetal (9c). From 100 mg (0.26 mmol) of **7c**,[8] a mixture of 50 mg of **8c** (48% yield) and 35 mg of **9c** (34% yield) was obtained, both as colorless oils. Data of **8c**: R_f = 0.28 (hexane:AcOEt, 1:1). IR ($CHCl_3$): 2930, 2860, 1450, 1330, 1190, 1150, 1000 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.54 (dd, 1 H, J = 14.9, 12.6 Hz), 1.82–1.98 (m, 1 H), 2.02 (ddd, 1 H, J = 14.9, 4.2, 2.7 Hz), 3.26 (t, 1 H, J = 11.0 Hz), 3.49 (dd, 1 H, J = 10.9, 7.7 Hz), 3.73 (s, 1 H), 3.97 (d, 1 H, J = 7.9 Hz), 3.98 (dd, 1 H, J = 11.2, 3.5 Hz), 4.37 (d, 1 H, J = 10.9 Hz), 4.60 (d, 1 H, J = 6.4 Hz), 4.83 (d, 1 H, J = 10.9 Hz), 5.02 (d, 1 H, J = 6.4 Hz), 7.28–7.40 (m, 7 H), 7.57 (t, 1 H, J = 7.5 Hz), 7.78 (d, 2 H, J = 7.9 Hz). ^{13}C NMR ($CDCl_3$): δ 24.2, 28.4, 55.8, 70.3, 71.9, 75.3, 76.3, 82.9, 93.6, 127.4, 127.5, 128.1, 128.7, 129.0, 133.7, 137.5, 137.7. Data for **9c**: R_f = 0.32 (hexane:EtOAc, 1:1). IR ($CHCl_3$): 2940, 2900, 1450, 1320,

(23) When the reaction was performed in refluxing DMF, compound **16** was obtained in only 50% yield.

(24) A derivative of **3** with different protecting groups was described: Ogawa, S.; Tonegawa, T.; Nishi, K.; Yokoyama, J. *Carbohydr. Res.* **1992**, *229*, 173–182.

(25) Ogawa, S.; Oya, M.; Toyokuni, T.; Chida, N.; Suami, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1441–1445.

(26) Watson, S. C.; Eastham, J. E. *J. Organomet. Chem.* **1967**, *9*, 165–168.

1190, 1160, 1000 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.46 (dd, 1 H, J = 14.3, 11.1 Hz), 1.98–2.18 (m, 2 H), 3.23 (t, 1 H, J = 10.8 Hz), 3.53 (dd, 1 H, J = 10.2, 8.4 Hz), 4.02 (dd, 1 H, J = 11.4, 4.5 Hz), 4.14 (d, 1 H, J = 5.2 Hz), 4.56 (d, 1 H, J = 6.4 Hz), 4.63 (d, 1 H, J = 10.9 Hz), 4.66 (d, 1 H, J = 8.2 Hz), 4.93 (d, 1 H, J = 10.9 Hz), 5.05 (d, 1 H, J = 6.4 Hz), 7.01–7.03 (m, 2 H), 7.21–7.35 (m, 5 H), 7.44 (t, 1 H, J = 7.6 Hz), 7.77 (d, 2 H, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$): δ 24.4, 34.8, 58.8, 69.9, 74.6, 75.6, 76.4, 80.8, 93.5, 127.3, 127.3, 127.6, 128.5, 129.0, 133.6, 137.9.

D,L-(1,2,4/3,5)-1,2-Anhydro-3-*O*-benzyl-5-((benzyloxy)methyl)-4-*O*-(*tert*-butyldimethylsilyl)-2-*C*-(phenylsulfonyl)-1,2,3,4-cyclohexanetetrol (8d) and D,L-(1,2,3,5/4)-1,2-Anhydro-3-*O*-benzyl-5-((benzyloxy)methyl)-4-*O*-(*tert*-butyldimethylsilyl)-2-*C*-(phenylsulfonyl)-1,2,3,4-cyclohexanetetrol (9d). From 100 mg (0.17 mmol) of **7d**, a mixture of 8 mg of **8d** (8% yield) and 82 mg of **9d** (80% yield) was obtained, both as colorless oils. Data for **8d**: R_f = 0.23 (hexane:EtOAc, 5:1). IR ($CHCl_3$): 2970, 2880, 1450, 1330, 1260, 1100, 840 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.16 (s, 3 H), −0.10 (s, 3 H), 0.73 (s, 9 H), 1.82–1.94 (m, 1 H), 2.03 (ddd, 1 H, J = 15.3, 8.9, 2.4 Hz), 2.21 (ddd, 1 H, J = 15.3, 5.6, 2.6 Hz), 3.28 (dd, 1 H, J = 9.2, 7.0 Hz), 3.34 (dd, 1 H, J = 9.2, 5.0 Hz), 3.67 (t, 1 H, J = 2.5 Hz), 3.74 (dd, 1 H, J = 6.1, 4.0 Hz), 3.91 (d, 1 H, J = 4.0 Hz), 4.38 (AB system, 2 H), 4.67 (AB system, 2 H), 7.22–7.33 (m, 10 H), 7.40 (t, 2 H, J = 7.8 Hz), 7.57 (t, 1 H, J = 7.4 Hz), 7.81 (d, 2 H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ −4.6, −4.5, 17.8, 24.2, 25.7, 37.8, 56.1, 70.4, 71.1, 71.9, 73.1, 74.0, 78.8, 127.6, 127.7, 128.2, 128.4, 128.7, 129.3, 133.7, 137.2, 137.7, 138.3. Data for **9d**: R_f = 0.20 (hexane:AcOEt, 5:1). IR ($CHCl_3$): 2980, 2950, 1450, 1370, 1260, 1100, 850 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.88 (s, 9 H), 2.00–2.12 (m, 2 H), 2.25 (ddd, 1 H, J = 16.0, 6.9, 2.6 Hz), 3.34 (dd, 1 H, J = 9.2, 7.0 Hz), 3.57 (dd, 1 H, J = 9.2, 7.4 Hz), 3.94 (br s, 1 H), 4.01 (dd, 1 H, J = 4.0, 3.3 Hz), 4.27 (d, 1 H, J = 11.2 Hz), 4.32 (s, 2 H), 4.39 (d, 1 H, J = 2.9 Hz), 4.46 (d, 1 H, J = 11.2 Hz), 6.92 (dd, 2 H, J = 7.4, 1.9 Hz), 7.14–7.32 (m, 8 H), 7.45 (dd, 2 H, J = 8.3, 6.9 Hz), 7.57 (t, 1 H, J = 7.5 Hz), 7.91 (dd, 2 H, J = 7.0, 1.7 Hz). ^{13}C NMR ($CDCl_3$): δ −5.0, −4.8, 17.9, 21.7, 25.7, 38.2, 57.4, 66.4, 70.7, 72.2, 72.6, 72.8, 75.3, 127.3, 127.3, 127.5, 128.0, 128.2, 129.0, 129.1, 134.0, 136.9, 137.3, 138.5.

D,L-(1,2,3,5/4)-1,2-Anhydro-3,4-bis-*O*-(*tert*-butyldimethylsilyl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-*C*-(phenylsulfonyl)-1,2,3,4-cyclohexanetetrol (9e). From 500 mg (0.80 mmol) of **7e**, 410 mg of **9e** was obtained as a colorless oil (80% yield). R_f = 0.33 (hexane:EtOAc, 10:1). IR ($CHCl_3$): 2960, 2920, 1460, 1310, 1250, 1100, 1050, 830 cm^{-1}. ^1H NMR ($CDCl_3$): δ −0.02 (s, 3 H), 0.01 (s, 3 H), 0.02 (s, 3 H), 0.04 (s, 3 H), 0.08 (s, 3 H), 0.12 (s, 3 H), 0.78 (s, 9 H), 0.83 (s, 9 H), 0.84 (s, 9 H), 1.80–1.90 (m, 1 H), 1.90 (ddd, 1 H, J = 15.7, 6.6, 2.4 Hz), 2.08 (td, 1 H, J = 15.7, 1.5 Hz), 3.53 (dd, 1 H, J = 10.3, 5.6 Hz), 3.54 (br s, 1 H), 3.64 (dd, 1 H, J = 10.3, 9.3 Hz), 3.72 (dd, 1 H, J = 3.2, 2.7 Hz), 4.61 (dd, 1 H, J = 2.7, 1.0 Hz), 7.51 (t, 2 H, J = 8.1 Hz), 7.62 (t, 1 H, J = 7.3 Hz), 7.88 (dd, 2 H, J = 7.7, 2.1 Hz). ^{13}C NMR ($CDCl_3$): δ −5.3, −5.3, −5.0, −4.7, −3.6, 17.9, 18.3, 19.7, 25.7, 25.8, 25.9, 40.9, 57.9, 63.3, 67.8, 69.6, 129.0, 129.1, 129.5, 134.0.

D,L-(2,4,6/3)-2-*O*-Benzyl-4-((benzyloxy)methyl)-6-bromo-2,3-dihydroxycyclohexanone (12). To a suspension of 357 mg (1.38 mmol) of $MgBr_2{\cdot}OEt_2$ in 4.6 mL of Et_2O was added a solution of 442 mg (0.92 mmol) of **8a** in 4.6 mL of THF. The mixture was stirred at room temperature for 4 h, and then it was quenched with a saturated aqueous solution of NaCl and extracted with Et_2O. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, affording a mixture of 310 mg of **12** (80% yield) and 40 mg of its C_6 epimer (10% yield), both as colorless oils. R_f = 0.28 (hexane:EtOAc, 2:1). IR ($CHCl_3$): 3600–3200, 2920, 2850, 1740, 1450, 1360, 1120, 1030, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.93 (q, 1 H, J = 13.4 Hz), 2.11–2.17 (m, 1 H), 2.61 (ddd, 1 H, J = 13.4, 6.1, 3.5 Hz), 2.92 (s, 1 H), 3.58 (dd, 1 H, J = 9.2, 5.7 Hz), 3.67 (dd, 1 H, J = 9.2, 3.7 Hz), 3.68 (t, 1 H, J = 9.4 Hz), 4.00 (dd, 1 H, J = 9.5, 1.3 Hz), 4.46 (d, 1 H, J = 11.1 Hz), 4.50 (s, 2 H), 4.59 (ddd, 1 H, J = 13.6, 6.1, 1.1 Hz), 4.93 (d, 1 H, J = 11.1 Hz), 7.27–7.42 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 36.6, 41.9, 52.1, 69.9, 73.1, 73.4, 74.0, 86.1, 127.5, 127.7, 128.2, 128.3, 128.4, 128.6, 137.0, 137.8, 197.2.

D,L-(2,4,6/3)-6-Azido-2-*O*-benzyl-4-((benzyloxy)methyl)-6-bromo-2,3-dihydroxycyclohexanone (13). To a suspension of sodium azide (194 mg, 2.98 mmol) in 3 mL of DMF was added a solution of **12** (250 mg, 0.60 mmol) in 3 mL of DMF. The mixture was stirred at room temperature for 1 h, and then it was diluted with distilled water. The aqueous layer was extracted with a mixture Et_2O/CH_2Cl_2, 7:3. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded 200 mg of **13** as a white solid (88% yield). R_f = 0.37 (hexane:EtOAc, 1:1). Mp: 102–104 °C. IR ($CHCl_3$): 3600–3200, 2900, 2110, 1740, 1450, 1360, 1130, 1050 cm^{-1}. ^1H NMR (C_6D_6): δ 1.24 (q, 1 H, J = 13.2 Hz), 1.61–1.70 (m, 1 H), 1.89 (ddd, 1 H, J = 13.2, 6.2, 3.7 Hz), 2.81 (br s, 1 H), 3.03 (dd, 1 H, J = 13.2, 5.3 Hz), 3.24 (dd, 1 H, J = 8.9, 6.3 Hz), 3.37 (t, 1 H, J = 9.6 Hz), 3.42 (dd, 1 H, J = 9.1, 3.8 Hz), 3.52 (d, 1 H, J = 9.4 Hz), 4.23 (s, 2 H), 4.28 (d, 1 H, J = 11.4 Hz), 4.84 (d, 1 H, J = 11.4 Hz), 7.08–7.21 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 30.9, 39.1, 63.5, 69.9, 73.0, 73.2, 74.0, 85.9, 127.4, 127.7, 128.1, 128.2, 128.3, 128.5, 136.9, 137.7, 200.9. Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02. Found: C, 65.95; H, 6.04; N, 10.65.

D,L-(1,2,4,6/3)-2-*O*-Benzyl-4-((benzyloxy)methyl)-6-bromo-1,3-cyclohexanediol (14). To a cold (−78 °C) suspension of 115 mg (0.48 mmol) of $LiAl(t\text{-}BuO)_3H$ in 1 mL of THF was added a solution of 100 mg (0.24 mmol) of **12** in 1 mL of THF, and the mixture was stirred at −78 °C. After 1 h, the reaction mixture was quenched with 0.5 N HCland extracted with EtOAc. The organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified on silica gel, and 85 mg of **14** was obtained as a colorless oil (85% yield). R_f = 0.27 (hexane:EtOAc, 2:1). IR ($CHCl_3$): 3600–3200, 2900, 1450, 1360, 1100, 1030, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.70–1.80 (m, 1 H), 2.04–2.21 (m, 2 H), 2.54–2.62 (br s, 2 H), 3.30 (dd, 1 H, J = 9.1, 2.8 Hz), 3.51 (dd, 1 H, J = 9.2, 6.0 Hz), 3.62 (dd, 1 H, J = 9.1, 5.4 Hz), 3.85 (dd, 1 H, J = 10.4, 9.1 Hz), 4.05 (ddd, 1 H, J = 12.0, 5.5, 2.2 Hz), 4.27 (t, 1 H, J = 2.1 Hz), 4.50 (s, 2 H), 4.69 (AB system, 2 H), 7.27–7.37 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 32.2, 42.3, 50.7, 70.1, 70.6, 72.0, 72.1, 73.4, 82.9, 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.7, 137.6, 137.9.

D,L-(1,3/2,4,6)-2-*O*-Benzyl-4-((benzyloxy)methyl)-6-bromo-1,3-cyclohexanediol (15). To a solution of 419 mg (1 mmol) of **12** in 5 mL of THF was added 0.19 mL (2 mmol) of $BH_3{\cdot}SMe_2$. The reaction mixture was stirred at room temperature for 1 h. After that time, it was quenched with 5% aqueous solution of $NaHCO_3$. The crude product was extracted with EtOAc, and the organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography on silica gel gave a mixture of 325 mg of **15** (77% yield) as a white solid and 72 mg of **14** (17% yield) as a colorless oil. R_f = 0.32 (hexane:EtOAc, 2:1). Mp: 102–104 °C. IR (KBr): 3500–3300, 2900–2850, 1450, 1360, 1110, 740, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.75–1.83 (m, 2 H), 2.31 (td, 1 H, J = 9.9, 4.6 Hz), 2.68 (d, 1 H, J = 2.2 Hz), 2.99 (d, 1 H, J = 1.7 Hz), 3.24 (dd, 1 H, J = 8.9, 7.7 Hz), 3.53–3.60 (m, 3 H), 3.64 (td, 1 H, J = 9.2, 2.1, Hz), 3.88 (ddd, 1 H, J = 12.0, 10.0, 4.4 Hz), 4.51 (s, 2 H), 4.83 (d, 1 H, J =11.5 Hz), 4.95 (d, 1 H, J = 11.5 Hz), 7.29–7.38 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 35.2, 41.8, 54.0, 71.4, 73.5, 73.7, 75.3, 78.1, 85.7, 127.6, 127.8, 128.0, 128.1, 128.5, 128.6, 137.9, 138.5. Anal. Calcd for $C_{21}H_{25}BrO_4$: C, 59.87; H, 5.98. Found: C, 59.48; H, 5.86.

D,L-(1,3,4/2,6)-4-Azido-2-*O*-benzyl-6-((benzyloxy)methyl)-1,3-cyclohexanediol (16). To a solution of 324 mg (0.77 mmol) of **15** in 3.8 mL of DMF was added 500 mg (7.7 mmol) of sodium azide, and then 3.8 mL of HMPA was added. The mixture was heated at 150 °C for 1.5 h, after which time distilled water was added. The reaction was extracted with a mixture Et_2O/CH_2Cl_2, 7:3. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, and 227 mg of **16** was obtained as a colorless oil (77% yield).

R_f = 0.25 (hexane:EtOAc, 2:1). IR ($CHCl_3$): 3600–3300, 2910, 2850, 2100, 1490, 1450, 1365, 1095, 700 cm^{-1}. ^1H NMR (C_6D_6): δ 0.80 (ddd, 1 H, J = 14.3, 12.8, 2.9 Hz), 1.30 (dt, 1 H, J = 14.4, 3.7 Hz), 1.98–2.10 (m, 1 H), 2.22 (br s, 1 H), 2.99 (br s, 1 H), 3.11 (dd, 1 H, J = 9.2, 6.1 Hz), 3.28 (dd, 1 H, J = 9.2, 4.5 Hz), 3.28 (dd, 1 H, J = 9.2, 4.5 Hz), 3.40 (q, 1 H, J = 3.2 Hz), 3.42 (t, 1 H, J = 9.4 Hz), 3.63 (t, 1 H, J = 9.1 Hz), 4.17 (AB system, 2 H), 4.68 (d, 1 H, J = 11.6 Hz), 4.93 (d, 1 H, J = 11.6 Hz), 7.07–7.21 (m, 8 H), 7.28 (d, 2 H, J = 7.9 Hz). ^{13}C NMR ($CDCl_3$): δ 28.5, 37.4, 61.0, 72.5, 73.5, 74.0, 75.4, 75.7, 83.7, 127.6, 127.8, 128.0, 128.5, 128.6, 137.8, 138.6.

Penta-*N,O*-acetyl-(±)-validamine (17). To a solution of 120 mg (0.31 mmol) of **16** in 10 mL of MeOH were added 333 mg of 10% Pd–C and a few drops of AcOH. The mixture was stirred for 24 h in a Parr hydrogenator at 60 psi. After that time, the crude was filtered on silica gel with MeOH and then concentrated under reduced pressure. The residue was acetylated with acetic anhydride (1.5 mL), pyridine (1.5 mL), and DMAP (ca 15 mg) for 3 days, after which time the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using EtOAc as eluent to give 65 mg of the pure pentaacetate **17** (54% yield). Its spectral features were identical to those reported in the literature.[3]

D,L-(1,4/2,3,6)-4-Azido-2-*O*-benzyl-6-((benzyloxy)methyl)-1,3-cyclohexanediol (18). According to the procedure described above for the synthesis of **16**, from 200 mg (0.48 mmol) of **14**, 120 mg of **18** was obtained as a colorless oil (66% yield). R_f = 0.25 (hexane:EtOAc, 2:1). IR ($CHCl_3$): 3600–3300, 2910, 2850, 2100, 1490, 1450, 1365, 1095, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.71 (ddd, 1 H, J = 14.4, 3.9, 3.1 Hz), 1.84 (td, 1 H, J = 14.4, 2.9 Hz), 1.96–2.10 (m, 1 H), 2.51 (s, 1 H), 3.03 (d, 1 H, J = 1.3 Hz), 3.52 (dd, 1 H, J = 9.0, 3.1 Hz) 3.55 (dd, 1 H, J = 9.2, 5.9 Hz), 3.60 (dd, 1 H, J = 9.2, 5.0 Hz), 3.80 (t, 1 H, J = 9.5 Hz), 3.95 (q, 1 H, J = 3.2 Hz), 3.98 (t, 1 H, J = 3.2 Hz), 4.53 (s, 2 H), 4.70 (AB system, 2 H), 7.27–7.38 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 25.8, 37.2, 59.8, 68.5, 71.4, 72.4, 72.7, 73.3, 81.1, 127.6, 127.7, 127.9, 128.1, 128.4, 128.6, 137.8, 137.9.

Penta-*N,O*-acetyl-5a-carba-α-mannopyranosylamine (Penta-*N,O*-acetyl-2-epivalidamine), (19). According to the procedure described above for the synthesis of **17**, from 80 mg (0.21 mmol) of **18**, 40 mg of **19** (49% yield) was obtained as a colorless oil. Its spectral features were identical to those reported in the literature.[7f]

D,L-(1/2,3,4,6)-4-Azido-2-*O*-benzyl-6-((benzyloxy)methyl)-1,3-cyclohexanediol (20). According to the procedure described above for the synthesis of **14**, from 100 mg (0.26 mmol) of **13**, 82 mg of **20** was obtained as a colorless oil (82% yield). R_f = 0.19 (hexane:EtOAc, 2:1). IR ($CHCl_3$): 3600–3200, 2900, 2100, 1450, 1360, 1100, 1070 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.71–1.79 (m, 1 H), 1.83–1.90 (m, 2 H), 3.20–3.26 (m, 2 H), 3.56 (dd, 1 H, J = 9.1, 5.6 Hz), 3.66 (dd, 1 H, J = 9.2, 5.5 Hz), 3.82 (t, 1 H, J = 9.7 Hz), 4.21 (t, 1 H, J = 2.5 Hz), 4.53 (s, 2 H), 4.69 (AB system, 2 H), 7.27–7.38 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 27.7, 39.7, 59.4, 69.2, 70.9, 72.2, 72.3, 73.5, 82.8, 127.6, 127.7, 127.9, 128.1, 128.4, 128.7, 137.7, 137.9.

D,L-(1,3/2,4,6)-4-Azido-2-*O*-benzyl-6-((benzyloxy)methyl)-1,3-cyclohexanediol (21). According to the procedure described above for the synthesis of **15**, from 170 mg (0.45 mmol) of **13**, a mixture of 80 mg of **21** (47% yield) and 75 mg of **20** (44% yield) was obtained, both as colorless oils. R_f = 0.24 (hexane:EtOAc, 2:1). IR ($CHCl_3$): 3700–3300, 2910, 2880, 2110, 1450, 1360, 1100, 1030 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.21 (q, 1 H, J = 12.6 Hz), 1.78–1.87 (m, 1 H), 1.91 (dt, 1 H, J = 13.1, 4.0 Hz), 2.58 (d, 1 H, J = 2.0 Hz), 3.20 (d, 1 H, J = 1.7 Hz), 3.24 (t, 1 H, J = 8.9 Hz), 3.36 (td, 1 H, J = 9.6, 4.4 Hz), 3.42 (td, 1 H, J = 8.9, 2.0 Hz), 3.49–3.60 (m, 3 H), 4.50 (s, 2 H), 4.86 (AB system, 2 H), 7.26–7.36 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 29.5, 39.5, 62.6, 72.2, 73.5, 74.7, 75.3, 76.1, 85.8, 127.6, 127.9, 128.0, 128.5, 128.7, 137.7, 138.5.

Penta-*N,O*-acetyl-5a-carba-β-mannopyranosylamine (22). According to the procedure described above for the synthesis of **17**, from 150 mg of **20**, 100 mg of **22** was obtained as a white solid (66% yield). R_f = 0.35 (EtOAc). Mp: 174–176 °C. IR ($CHCl_3$): 3500–3300, 2980, 2940, 1750, 1670, 1510, 1430, 1380, 1250, 1150 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.60 (q, 1 H, J = 12.6 Hz), 1.95 (s, 3 H), 1.96 (s, 3 H), 1.97–2.10 (m, 2 H), 2.04 (s, 3 H), 2.06 (s, 3 H), 2.20 (s, 3 H), 3.97 (dd, 1 H, J = 11.3, 3.7 Hz), 4.05 (dd, 1 H, J = 11.3, 6.1 Hz), 4.27 (m, 1 H), 4.95 (dd, 1 H, J = 10.2, 2.9 Hz), 5.17 (t, 1 H, J = 10.5 Hz), 5.45 (t, 1 H, J = 2.7 Hz), 5.49 (d, 1 H, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$): δ 20.4, 20.6, 20.6, 20.9, 23.1, 28.8, 38.1, 46.9, 63.8, 69.1, 71.6, 72.7, 169.2, 169.6, 170.1, 170.2, 170.6. Anal. Calcd for $C_{17}H_{25}NO_9$: C, 52.71; H, 6.50; N, 3.62. Found: C, 52.68; H, 6.31; N, 3.35.

Penta-*N,O*-acetyl-5a-carba-β-glucopyranosylamine (Penta-*N,O*-acetyl-1-epivalidamine) (23). According to the procedure described above for the synthesis of **17**, from 80 mg (0.21 mmol) of **21**, 50 mg of **23** was obtained as a colorless oil (62% yield). Its spectral features were identical to those reported in the literature.[25]

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Supplementary Material Available: Experimental and spectroscopic data for compounds **7d–e**, **10**, **11**, and the epimer of **12** (2 pages). This material is contained in libraries on microfiche, inmediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.