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Convenient synthesis of (+)-valiolamine and (−)-1-epi-valiolamine from (−)-*vibo*-quercitol

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Convenient and practical synthesis of (+)-valiolamine and (−)-1-epi-valiolamine from (−)-*vibo*-quercitol, 1-deoxy-L-*myo*-inositol, readily obtained by bioconversion of *myo*-inositol, is described.

myo-Inositol is the most abundant cyclitol occurring in nature. Among nine stereoisomers, seven are meso compounds. Therefore, synthetic studies of inositol derivatives of biological interest have often been accompanied by some difficulty in obtaining the desired optically active compounds. When *myo*-inositol is chosen as a starting material, chemical synthesis featuring modification and/or substitution of one of the four hydroxyl groups on C-1(3) and 4(6) leads to compounds of racemic modification. Their optical resolution is needed at an early stage of the preparative processing, with determination of absolute structures. Bioconversion of inositols has therefore been a very attractive route to provide several optically pure raw materials for cyclitol synthesis (Fig. 1), although some problems have arisen in isolation and purification of the desired compounds when complex mixtures of products are formed.

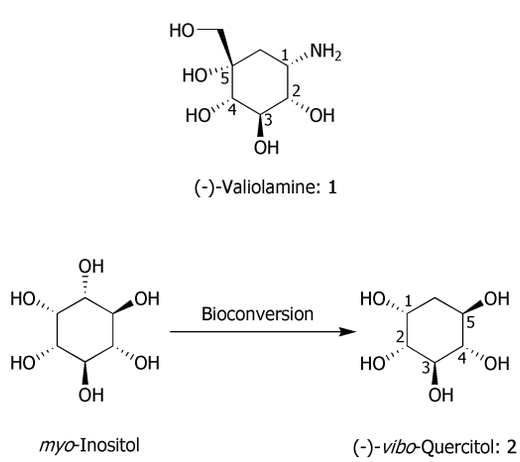

Fig. 1 (+)-Valiolamine and preparation of (−)-*vibo*-quercitol by bioconversion of *myo*-inositol.

Recently, bio-deoxygenation of *myo*-inositol has successfully been carried out employing bacterial strains[1] to produce mainly (−)-*vibo*-quercitol **2**, together with (+)-*epi* and (+)-*proto*-quercitol. These quercitols, or deoxyinositols, can be readily separated and purified by a combination of chromatography on ion-exchange-resin columns and subsequent recrystallization, and the major product, (−)-*vibo*-quercitol is now commercially available. We have become interested in application of these optically pure cyclitols as sources for the development of biologically active compounds.[2,3] In this paper, we describe recent results regarding bioconversion of **2** to the optically active deoxyinososе **3**, from which a convenient and practical synthesis of biologically important valiolamine (**1**) can be carried out.

Valiolamine[4] **1** was first isolated from fermentation broth of antibiotic validamycins, later being found[5,6] to be one of the components of validamycin G. The absolute structure was established by comparison[7] with that of validamine. Since **1** very strongly inhibits α-glucosidase and maltase,[4] its chemical modification has been extensively investigated, leading to the preparation of the *N*-(1,3-dihydroxyprop-2-yl) derivative,[8] a clinically very useful agent for control of diabetes. Several syntheses of **1** have already been accomplished, starting from the Diels–Alder *endo*-adduct[9] of furan and acrylic acid, D-glucose,[10,11] L-quinic acid,[12] and D-arabinose.[13]

1L-(1,2,4/3,5)-1,2,3,4,5-Cyclohexanepentol[1,13] (**2**), (−)-*vibo*-quercitol, which can readily be obtained by stereospecific microbial dehydration of *myo*-inositol, is biochemically oxidized under the influence of *Gluconobacter* sp. AB10277 to produce about 80% yield of crude 2-deoxy-*scyllo*-inosose,[14] 2L-(2,4/3,5)-2,3,4,5-tetrahydroxycyclohexan-1-one (**3**), $[\alpha]^{25}_{D}$ −27° (H_2O) (Scheme 1). Based on its ^{1}H-NMR spectral data, this compound was shown to be a mixture of the keto and hydrate forms in water, but the former seems to be the major component in DMSO. Although several synthetic procedures are possible for C–C bond formation at the keto function of cyclitol derivatives, protection of their hydroxyl groups is usually indispensable for carrying out the process successfully. In fact, under direct protection such as conventional acylation or etherification, inososes often suffer serious structural changes *via* epimerization and/or elimination. Therefore, we attempted to subject the crude ketone directly to simple C–C bond-formation conditions, among which a reaction with diazomethane would be considered to be adequate in polar and protic solvents. Treatment of **3** with 2 molar equiv. of diazomethane–diethyl ether was carried out in methanol for 7 h at room temperature. On addition of excess diethyl ether, a sole spiro epoxide **4** crystallized out from the reaction mixture in 44% yield. Isolated yields are rather variable,[15] partly depending on a ratio of the keto- and hydrate-forms of **3** in the reaction medium. Diazomethane is likely to attack the carbonyl group at the rear of the adjacent 2-hydroxyl group in an equatorial orientation. Hydrolysis of **4** with 3 M aqueous potassium hydroxide for 6 h at 100 °C gave, after chromatography, a crystalline (−)-β-valiol **5** in 32% yield. On the other hand, nucleophilic substitution of **4** with excess of sodium acetate in 80% aqueous DMF for 3 h at 120 °C afforded, after acetylation with acetic anhydride in pyridine, the penta-*O*-acetyl derivative **6**

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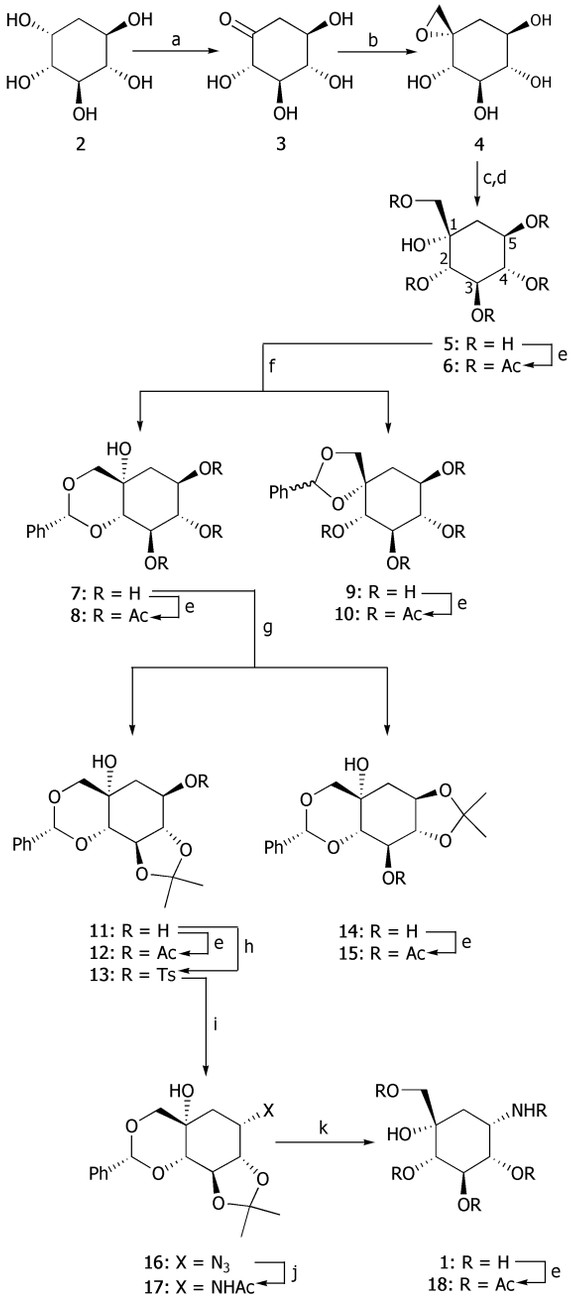


Scheme 1 Synthesis of (+)-valiolamine (**1**) from (−)-*vibo*-quercitol (**2**). *Reagents and conditions:* (a) *Gluconobacter* sp. AB 10277; (b) CH_2N_2/Et_2O, MeOH; (c) 3 M aqueous KOH, 100 °C; (d) NaOAc, 80% aqueous DMF; NaOMe/MeOH; (e) Ac_2O, pyridine; (f) $PhCH(OMe)_2$, $TsOH{\cdot}H_2O$, DMF, 50 °C; (g) 2-methoxypropene (2.5 molar equiv.), $TsOH{\cdot}H_2O$, DMF, room temperature; (h) TsCl, pyridine; (i) NaN_3 (4 molar equiv.), DMF, 120 °C; (j) H_2, Raney Ni, EtOH, Ac_2O; (k) 2 M HCl; Dowex 50W × 2 (H^+) resin, aqueous 1% NH_3.

(~100%), which was treated with methanolic sodium methoxide to give **5** quantitatively. The ^{1}H NMR spectral data were shown to be identical with those of known racemic[16] **6**. These results also verified both the proposed absolute configuration of **3** and the stereochemistry of the spiro-epoxide **4**. Thus, optically active (−)-β-valiol **5** is readily available in large scale from *myo*-inositol through a standard sequence of reactions.

Our aim was to establish a simple synthesis of biologically valuable valiolamine **1** from **5**. The important key-step was considered to be incorporation of an amino function at C-5 by replacement of the 5-hydroxyl group *via* Walden-inversion. In the initial attempts to provide 5-hydroxyl unprotected derivatives, the primary hydroxyl group was first blocked by a triphenylmethyl group and the trityl ether obtained was subjected to conventional isopropylidenation conditions using 2-methoxypropene, expecting preferential formation of the *cis*-1,2-*O*-isopropylidene group. Although generation of two di-*O*-isopropylidene derivatives was observed, these compounds were not sufficiently stable for the usual purification using a silica gel column. When 1,1-dimethoxycyclohexane was used as an acetalation reagent, surprisingly, the major product was found to be the 2,3:4,5-di-*O*-cyclohexylidene derivative (~80%). Then, benzylidenation of **5** was carried out by treatment with α,α-dimethoxytoluene and $TsOH{\cdot}H_2O$ in dry DMF for 4 h at room temperature, giving the desired 2,7-*O* **7** (59%) and a spiro-type 1,7-*O*-benzylidene derivative **9** (26%). Compounds **7** and **9** were converted into the tri- **8** and tetra-*O*-acetyl derivatives **10**, respectively, and their structures confirmed.

Compound **9** was convertible to **7** by regeneration of **5**, followed by benzylidenation.

Treatment of **7** with 2.5 molar equiv. of 2-methoxypropene in the presence of $TsOH{\cdot}H_2O$ in DMF for 4 h at room temperature gave a mixture of the products, which were easily fractionated on a silica gel column to give the 3,4-**11** and 4,5-*O*-isopropylidene derivatives[17,18] **14** in 41% and 36% yields, respectively, their structures being established by converting them into the acetyl derivatives **12** and **15**, respectively.

Treatment of **11** with excess *p*-toluenesulfonyl chloride in pyridine gave the tosylate **13** (~100%). Direct nucleophilic substitution of **13** with an azide anion in the presence of 15-crown-5 ether in DMF proceeded smoothly at 120 °C to afford a single azide **16** (88%) selectively. Formation of elimination products was not observed. Hydrogenation of **16** with Raney nickel catalyst in ethanol in the presence of excess acetic anhydride gave the amide **17** (76%). This compound was deacylated with 2 M hydrochloric acid at 80 °C to give, after purification over a column of Dowex 50 W × 2 (H^+) resin with 5% aqueous ammonia, valiolamine **1** (90%) as a syrup. Synthetic valiolamine was further characterized as the penta-*N*,*O*-acetyl derivative **18**. Physical data, including ^{1}H and ^{13}C-NMR spectral data,[6] were shown to be identical with those of authentic samples. Thus, (+)-valiolamine **1** could be readily synthesized from the crude deoxyinososе **3** through conventional processing in more than 10% total yield.

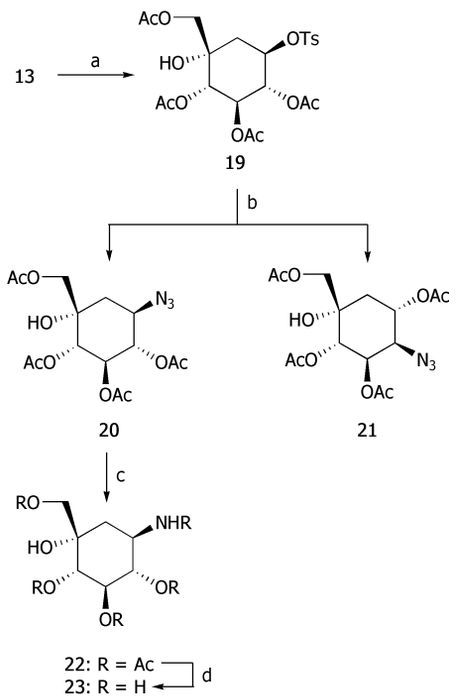
The 1-epimer[11] (β-valiolamine) **23** of **1** was also prepared from the tosylate **13**. Hydrolysis of **13** followed by conventional acetylation gave the tetra-acetyl tosylate **19** (Scheme 2). Treatment of **19** with sodium azide in aqueous 90% 2-methoxyethanol proceeded *via* formation of an intermediate acetoxonium ion by neighboring participation of 4-acetoxyl at C-4 to give rise to two products, the 5-azide **20** (65%) and the 4-azide **21** (28%). Compound **20** was similarly hydrogenolyzed and the penta-*N*,*O*-acetyl derivative **22** (68%) obtained converted into the free amine **23**, which showed medium inhibitory activity toward α-glucosidase.

The present synthesis demonstrates that optically active inositol derivatives generated by biogenesis of *myo*-inositol are promising key intermediates for the preparation of biologically interesting carba-amino sugar derivatives. The first syntheses of two racemic 5a-carba-hexopyranoses from *myo*-inositol were reported by Suami[19] and one of us some time ago. Ready accessibility of a quantity of the key-intermediate spiro-epoxide **4** would much improve the previous route employed, being generally applicable for provision of optically pure 5a-carba-sugars and their derivatives. Compound **4** has also been successfully transformed[20] into the useful 5-methylene compound almost quantitatively.

Experimental

General methods

Melting points were determined with a Yanagimoto melting point apparatus MP-S3 and are uncorrected. Optical rotations



Scheme 2 Synthesis of (−)-1-epi-valiolamine from the tosylate **13**. *Reagents and conditions:* (a) 2 M HCl, 60 °C; Ac_2O, pyridine; (b) NaN_3 (4 molar equiv.), aqueous 90% $MeOCH_2OH$, 120 °C; (c) H_2, Raney Ni, EtOH, Ac_2O; (d) 2 M HCl, Dowex 50W × 2 (H^+) resin, 1% aqueous NH_3.

were measured with a JASCO DIP-370 polarimeter, and $[\alpha]_D$ values are given in 10^{-1} deg cm² g^{-1}. ^{1}H NMR spectra were recorded for solutions in deuteriochloroform and deuteriomethanol with internal tetramethylsilane (TMS) as a reference with a JEOL JNM LAMDA-300 (300 MHz) instrument. ^{13}C NMR spectra were recorded with the same instrument (75 MHz). IR spectra were recorded with a JASCO IR-810 or a HITACHI Bio-Rad Digital Lab FTS-65 spectrometer. Mass spectra were determined with a HITACHI M-8000 ion trap mass spectrometer using electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI). TLC was performed on silica gel 60 F-254 (E. Merck, Darmstadt). The silica gel used for a column chromatography was Wakogel C-300 (Wako Junyaku Kogyo Co., Osaka, 200–300 mesh) or silica gel 60 KO (Katayama Kagaku Kogyo Co., Osaka, 70–230 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated at >45 °C under diminished pressure. New compounds synthesized are more or less hygroscopic. Final characterization of all the compounds has therefore been done by mass spectra using ESI.

2L-(2,4/3,5)-2,3,4,5-Tetrahydroxycyclohexan-1-one 3

Compound **3** was prepared by the microbial conversion of 1L-(1,2,4/3,5)-1,2,3,4,5-cyclohexanepentaol (−)-*vibo*-quercitol **2**, which was easily obtained by stereospecific microbial dehydration[1] of *myo*-inositol.

A slant culture of *Gluconobacter* sp. AB10277, which was deposited in the National Institute of Advanced Industrial Science and Technology, Japan, with accession number of FERMP-19320, was inoculated into 100 mL (total volume is 5 L) of the medium consisting of compound **2** (5%), D-glucose (0.5%), yeast extract (0.4%), $(NH_4)_2SO_4$ (0.1%), K_2HPO_4 (0.7%), KH_2PO_4 (0.2%), and $MgSO_4{\cdot}7H_2O$ (0.01%) (pH 7.0 before autoclaving), and the mixture was incubated for 72 h at 27 °C. The supernatant (5 L) combined was successively passed through columns of Duolite C-20 (H^+, Sumitomo Chemical Co., Ltd.), activated charcoal, and Duolite A368S (OH^-, Sumitomo Chemical Co., Ltd.). The eluent was evaporated to give the ketone **3** (*ca.* 200 g, 80%), as a white powder, the ^{13}C-NMR spectrum (D_2O, 75 MHz) of which was superimposed to those of racemic 2-deoxy-*scyllo*-inosose.[14] The ^{1}H NMR spectral data (in D_2O) indicated the presence of two types of compounds, presumably the keto- and hydrate-forms, however the signals due to the keto-form were only observed when it was measured in $(CD_3)_2SO$.

$[\alpha]^{25}_D$ = −27 (*c* = 1.0, H_2O); ^{1}H-NMR [300 MHz, $(CD_3)_2SO$]: δ 2.33 (dd, 1 H, *J* 5.1 and 13.6 Hz, H-6eq), 2.53 (td, 1 H, *J* 1.3, 13.6 and 13.6 Hz, H-6ax), 3.02 (dd, 1 H, *J* 8.6 and 9.9 Hz, H-3), 3.30 (m, 1 H, *J* 5.1, 9.9 and 13.6 Hz, H-5), 3.40 (t, 1 H, *J* 8.6 and 9.9 Hz, H-4), 3.97 (dd, *J* 1.3 and 9.9 Hz, H-2); (in D_2O) (*inter alia*): δ 1.69 (dd, 0.3 H, *J* 10.0 and 10.5 Hz, H-6ax, hydrate), 2.21 (dd, 0.3 H, *J* 4.5 and 10.5 Hz, H-6eq, hydrate), 2.73 (d, 0.7 H, *J* 0.5 Hz, H-6ax, keto), 2.77 (br s, 0.7 H, H-6eq, keto), 3.63 (ddd, 0.3 H, *J* 5.0, 6.9, and 9.0 Hz, H-5, hydrate), 3.79 (dd, 0.7 H, *J* 9.2 and 9.2 Hz, H-4, keto), 4.34 (dd, 0.7 H, *J* 0.5 and 10.1 Hz, H-2, keto); ^{13}C-NMR [75 MHz, $(CD_3)_2SO$]: δ 206.14 (C-1), 78.16 (C-2), 76.74 (C-4), 74.81 (C-3), 68.51 (C-5), 45.28 (C-6); (in D_2O): 207.74 (C-1), 94.11 (C-1, hydrate), 78.66 (C-2,), 77.82 (C-2 or 3, hydrate), 77.08 (C-3 or 2, hydrate), 76.88 (C-4), 74.68 (C-3), 74.36 (C-3, hydrate), 69.30 (C-5, hydrate), 69.02 (C-5), 44.99 (C-6), 41.48 (C-6, hydrate); ITMS-ESI (negative mode): *m*/*z* 143 [M − H_2O − H]$^-$, 161 [M − H]$^-$.

(3*S*,4*S*,5*R*,6*S*,7*R*)-4,5,6,7-Tetrahydroxy-1-oxaspiro[2,5]octane 4

To a stirred solution of crude ketone **3** (20.0 g, 0.123 mmol) in methanol (300 mL) was added cautiously dropwise diazomethane etherate (*ca.* 0.8 M, 160 mL) over 0.5 h under ice cooling. An additional amount of the reagent (4 × 40 mL) was added portionwise in the interval of 1 h. Stirring was further continued until turbidity of the mixture turned clear. Diethyl ether (400 mL) was added and an insoluble material was removed by filtration and the filtrate was allowed to stand in a refrigerator overnight. Crystalline product was collected by filtration and washed thoroughly with diethyl ether to give the spiro epoxide **4** (9.7 g, 44%) as a hygroscopic powder, $[\alpha]^{20}_D$ = −1.3 (*c* 7.4, MeOH), −37 (*c* 0.72, H_2O); ^{1}H-NMR (300 MHz, CD_3OD) δ 3.63 (d, 1 H, *J* 9.4 Hz, H-2), 3.58 (m, 1 H, H-5), 3.34 (m, 1 H, H-3), 3.28 (m, 1 H, H-4), 2.97, 2.56 (2 d, each 1 H, *J* 5.1 Hz, C*H*$_2$O), 1.95 (dd, 1 H, *J* 11.7 and 13.8 Hz, H-6ax), 1.55 (dd, 1 H, *J* 5.1 and 13.8 Hz, H-6eq); ^{13}C-NMR (75 MHz, CD_3OD): δ 37.78 (C-8), 48.70 (C-2), 58.71 (C-3), 70.95 (C-7), 71.33 (C-4), 76.71 (C-5), 78.91 (C-6); ITMS-APCI (negative mode): *m*/*z* 157 [M − H_2O − H]$^-$, 175 [M − H]$^-$, 193 [M + H_2O − H]$^-$.

Practically, a crude syrupy **4** (8.86 g, purity: ~82%) was prepared from the crude ketone **3** (8.11 g, 50 mmol) by evaporation of the diethyl ether solution obtained by filtration of the reaction mixture.

1L-(1,2,4/3,5)-1-*C*-(Hydroxymethyl)-1,2,3,4,5-cyclohexanepentol [1-*C*-(hydroxymethyl)-(−)-*vibo*-quercitol, (−)-β-valiol] 5

The epoxide **4** (20.56 g, 0.116 mol) was dissolved in 3 M aqueous potassium hydroxide (20 mL) and the mixture was stirred for 6 h at 100 °C. After cooling, the mixture was filtered through a column of CM-sephadix (100 mL) and washed with water (300 mL) thoroughly. The filtrate and washings were combined and concentrated to 50 mL and the solution was taken up on a column of active carbon (200 mL). Evaporation of the main fraction gave a syrup which was crystallized from aqueous methanol to give **5** (7.21 g, 32%) as colorless prisms : $[\alpha]^{20}_D$= −21 (*c* = 3.3, MeOH), mp 188–189 °C; ^{1}H-NMR (300 MHz, D_2O): δ 1.33 (dd, 1 H, *J* 11.9 and 13.8 Hz, H-6ax), 1.95 (dd, 1 H, *J* 4.8 and 13.8 Hz, H-6eq), 3.07 (t, 1 H, *J* 9.4 Hz, H-4), 3.25 (d, 1 H, *J* 9.5 Hz, H-2), 3.29 (d, 1 H, *J* 11.4 Hz, H-7), 3.37 (t, 1 H, *J* 9.4 Hz, H-3), 3.37 (d, 1 H, *J* 11.4 Hz, H-7), 3.56 (ddd, 1 H, *J* 5.0, 9.4 and 11.9 Hz, H-5); ^{13}C-NMR (75 MHz, CD_3OD):

δ 37.29 (C-6), 66.40 (C-7), 69.25 (C-5), 73.73 (C-2), 74.39 (C-3), 74.52 (C-1), 77.90 (C-4); ITMS-ESI (negative mode): ITMS-ESI (negative mode): *m*/*z* 193 $[M - H]^-$.

1L-(1,2,4/3,5)-1-*C*-(Acetoxymethyl)-2,3,4,5-tetra-*O*-acetyl-1,2,3,4,5-cyclohexanepentol [penta-*O*-acetyl-(−)-β-valiol] 6

A solution of **4** (0.10 g, 0.57 mmol) and anhydrous sodium acetate (0.37 g) in 80% aqueous DMF (2.0 mL) was stirred for 3 h at 80 °C. The mixture was evaporated and the residue was treated with acetic anhydride (1.3 mL) and pyridine (2.5 mL) for 13 h at room temperature. After addition of methanol (0.5 mL), the mixture was evaporated and the residue was chromatographed on a column of silica gel (25 g, acetone–hexane 1 : 7) as eluent to give **6** (0.24 g, ~100%) as crystals: $[\alpha]^{20}_D = -22$ (*c* = 1.1, MeOH), mp 129–131 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.43 (dd, 1 H, *J* 9.6 and 9.6 Hz, H-3), 5.28 (ddd, 1 H, *J* 4.9, 9.8 and 11.6 Hz, H-5), 5.17 (dd, 1 H, *J* 9.6 and 9.8 Hz, H-4), 5.10 (d, 1 H, *J* 9.6 Hz, H-2), 3.96 (d, 1 H, *J* 11.4 Hz, H-7), 3.82 (d, 1 H, *J* 11.4 Hz, H-7), 2.26 (dd, 1 H, *J* 4.9 and 13.8 Hz, H-6eq), 2.06, 2.05, 1.99, 1.96 (4 s, 3, 3, 6, 3 H, 5 × Ac), 1.69 (dd, 1 H, *J* 11.6 and 13.8 Hz, H-6ax); ^{13}C-NMR (75 MHz, CD_3OD): δ 20.48, 20.53, 20.56, 20.64, 20.76 (5 × *C*H_3CO), 36.12 (C-6), 67.09 (C-7) 70.20 (C-5), 72.61 (C-3), 72.75 (C-1), 73.46 (C-2), 74.75 (C-4), 171.49, 171.53, 171.58, 171.64, 172.10 (5 × CH_3*C*O); ITMS-ESI (positive mode): *m*/*z* 427 $[M + Na]^+$, 443 $[M + K]^+$.

Conventional de-*O*-acetylation of **6** with methanolic sodium methoxide in methanol afforded **5** quantitatively.

(1*S*,3*R*,6*S*,8*R*,9*S*,10*R*)-3-Phenyl-2,4-dioxabicyclo[4.4.0]decane-6,8,9,10-tetrol 7, and (2*R*,5*S*,6*S*,7*R*,8*S*,9*R*)- and (2*S*,5*S*,6*S*,7*R*,8*S*,9*R*)-2-phenyl-1,3-dioxaspiro-[4.5]decane-6,7,8,9-tetrol 9a,b

To a solution of **6** (5.77 g, 14.3 mmol) in methanol (90 mL) was added 1 M methanolic sodium methoxide (10 mL), and the mixture was stirred for 1 h at room temperature. The mixture was neutralized with Amberlite 1R B-120 (H^+) resin and then evaporated to dryness. The residue was dissolved in dimethylformamide (41 mL), to which were added α,α-dimethoxytoluene (6.34 ml, 42.8 mmol) and *p*-toluenesulfonic acid monohydrate (0.54 g, 2.9 mmol), and the mixture was stirred for 3 h at 50 °C. After neutralization with triethylamine, the reaction mixture was evaporated and the residue was chromatographed on a column of silica gel (400 g, chloroform–methanol 5 : 1 ⟶ 12 : 1) as eluent to give **7** (2.37 g, 59%) as a colorless syrup: R_f 0.32 (*n*-butanol–acetic acid–H_2O 2 : 1 : 1), and a diastereoisomeric mixture (1.04 g, 26%) of **9a**,**b**.

For **7**: $[\alpha]^{20}_D = -32$ (*c* = 1.2, MeOH), mp 220–222 °C; ^{1}H-NMR (300 MHz, CD_3OD): δ 7.51–7.24 (m, 5 H, Ph), 5.50 (s, 1 H, PhC*H*), 3.79 (ddd, 1 H, *J* 5.1, 9.0 and 11.5 Hz, H-8), 3.73 (br s, each 1 H, 2 × H-5), 3.66 (dd, 1 H, *J* 9.2 and 9.4 Hz, H-10), 3.50 (d, 1 H, *J* 9.4 Hz, H-1), 3.16 (dd, 1 H, *J* 9.0 and 9.2 Hz, H-9), 1.73 (dd, 1 H, *J* 5.1 and 13.2 Hz, H-7eq), 1.21 (dd, 1 H, *J* 11.5 and 13.2 Hz, H-7ax); ^{13}C-NMR (75 MHz, CD_3OD): δ 37.11 (C-7), 67.60 (C-6), 70.09 (C-8), 72.80 (C-10), 76.88 (C-5), 79.88 (C-9), 84.38 (C-1), 103.47 (C-3), 127.67 (C-3′, 5′), 129.00 (C-2′, 6′), 129.87 (C-4′), 139.48 (C-1′); ITMS-ESI (negative mode): *m*/*z* 281 $[M - H]^-$.

For **9a**: ^{1}H-NMR (300 MHz, CD_3OD): δ 6.02 (s, 1 H, PhC*H*), 3.61 (t, 1 H, *J* 9.3 Hz, H-7), 3.40 (d, 1 H, *J* 9.5 Hz, H-6), 3.26 (t, 1 H, *J* 9.2 Hz, H-8), 2.18 (dd, 1 H, *J* 4.6 and 13.3 Hz, H-10eq), 1.63 (dd, 1 H, *J* 12.1 and 13.3 Hz, H-10ax); for **9b**: δ 5.91 (s, 1 H, PhC*H*), 3.54 (t, 1 H, *J* 9.2 Hz, H-7), 3.41 (d, 1 H, *J* 9.7 Hz, H-6), 3.28 (t, 1 H, *J* 9.2 Hz, H-8), 2.33 (dd, 1 H, *J* 4.7 and 13.7 Hz, H-10eq), 1.55 (dd, *J* 11.5 and 13.7 Hz, H-10ax); ITMS-ESI (negative mode): *m*/*z* 281 $[M - H]^-$.

(1*S*,3*R*,6*S*,8*R*,9*S*,10*R*)-8,9,10-Triacetoxy-3-phenyl-2,4-dioxabicyclo[4.4.0]decan-6-ol 8

Compound **7** (26 mg, 0.093 mmol) was treated with acetic anhydride (0.5 mL) and pyridine (1.0 mL) for 17 h at room temperature. After addition of methanol (0.5 mL), the reaction mixture was evaporated and the residual product was chromatographed on a silica gel column (4 g, acetone–hexane 1 : 2) as eluent to give **8** (38 mg, 92%) as crystals: $[\alpha]^{20}_D = -35$ (*c* = 1, MeOH), mp 226–229 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.45–7.43 (m, 5 H, Ph), 5.54 (s, 1 H, PhC*H*), 5.51 (dd, 1 H, *J* 9.6 and 9.8 Hz, H-10), 5.42 (ddd, 1 H, *J* 5.2, 9.6 and 11.6 Hz, H-8), 5.20 (dd, 1 H, *J* 9.6 and 9.6 Hz, H-9), 3.96 (d, 1 H, *J* 11.2 Hz, H-5), 3.81 (d, 1 H, *J* 9.8 Hz, H-1), 3.79 (d, 1 H, *J* 11.2 Hz, H-5), 2.20 (dd, 1 H, *J* 5.2 and 13.2 Hz, H-7eq), 2.04 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 1.40 (dd, 1 H, *J* 11.6 and 13.2 Hz, H-7ax); ^{13}C-NMR [75 MHz, $(CD_3)_2CO$]: δ 20.54, 20.65, 20.76 (3 × *C*H_3CO), 33.62 (C-7), 66.94 (C-6), 70.13 (C-8), 71.71 (C-10), 74.40 (C-9), 75.86 (C-5), 81.00 (C-1), 102.37 (C-3), 127.22 (C-3′, 5′), 128.75 (C-2′, 6′), 129.57 (C-4′), 138.91 (C-1′), 170.07, 170.14, 171.00 (3 × CH_3*C*O); ITMS-ESI (positive mode): *m*/*z* 431 $[M + Na]^+$, 447 $[M + K]^+$.

(2*R*,5*S*,6*S*,7*R*,8*S*,9*R*)- and (2*S*,5*S*,6*S*,7*R*,8*S*,9*R*)-6,7,8,9-Tetraacetoxy-2-phenyl-1,3-dioxaspiro[4.5]decane 10a,b

The mixture (28 mg, 0.144 mmol) of **9a**,**b** was treated with acetic anhydride (0.5 mL) and pyridine (1.0 mL) in the usual manner. The products were purified by silica gel chromatography (4 g, acetone–hexane 2 : 5) to give a diastereoisomeric mixture (32 mg, 72%) of **10a**,**b** (3.5 : 1): R_f 0.20 (acetone–hexane 2 : 5).

For **10a**: ^{1}H-NMR (300 MHz, CD_3OD): δ 5.99 (s, 1 H, H-2), 4.00 and 3.90 (ABq, each 1 H, *J* 8.8 Hz, 2 × H-4); for **10b**: δ 5.94 (s, 1 H, H-2), 4.12 and 3.80 (ABq, each 1 H, *J* 8.8 Hz, 2 × H-4); ITMS-ESI (positive mode): *m*/*z* 473 $[M + Na]^+$, 489 $[M + K]^+$.

(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*)-12,12-Dimethyl-4-phenyl-3,5,11,13-tetra-oxatricyclo[8.3.0.0^{2,7}]tridecane-7,9-diol 11 and (1*R*,2*S*,3*S*,5*R*,8*S*,10*R*)-12,12-dimethyl-5-phenyl-4,6,11,13-tetra-oxatricyclo[8.3.0.0^{3,8}]tridecane-2,8-diol 14

To a solution of **7** (1.76 g, 6.23 mmol) in DMF (35 mL) was added 2-methoxypropene (1.49 ml, 15.6 mmol) and $TsOH \cdot H_2O$ (1.12 g, 0.62 mmol), and the mixture was stirred for 4 h at room temperature. After neutralization with triethylamine, the mixture was evaporated and the residue was chromatographed on a column of silica gel (200 g, ethyl acetate–hexane 2 : 3 ⟶ 3 : 2) as eluent to give the isopropylidene derivatives **11** (0.82 g, 41%) as crystals and **14** (0.73 g, 36%) as crystals.

For **11**: $[\alpha]^{20}_D = -37$ (*c* = 1, MeOH), mp 182–186 °C; ^{1}H-NMR (300 MHz, CD_3OD): δ 7.48–7.24 (m, 5 H, Ph), 5.56 (s, 1 H, PhC*H*), 4.05 (ddd, 1 H, *J* 4.7, 10.0 and 10.4 Hz, H-9), 3.80 (m, 2 H, 2 × H-4), 3.34 (dd, 1 H, *J* 10.0 and 10.0 Hz, H-10), 1.80 (dd, 1 H, *J* 4.7 and 13.3 Hz, H-8eq), 1.35, 1.32 (2 s, each 3 H, CMe_2), 1.21 (dd, 1 H, *J* 10.4 and 13.3 Hz, H-8ax); ^{13}C-NMR (75 MHz, CD_3OD): δ 27.06 (C-1″, 2″), 39.07 (C-8), 68.14 (C-9), 69.34 (C-7), 76.85 (C-2, 6), 82.49 (C-1), 84.25 (C-10), 103.01 (C-4), 112.25 (C-12), 127.52 (C-3′, 5′), 129.05 (C-2′, 6′), 129.94 (C-4′), 139.15 (C-1′); ITMS-ESI (positive mode): *m*/*z* 345 $[M + Na]^+$.

For **14**: $[\alpha]^{20}_D = -31$ (*c* = 1, MeOH), mp 175–178 °C; ^{1}H-NMR (300 MHz, CD_3OD): δ 7.28–7.23 (m, 5 H, Ph), 5.50 (s, 1 H, PhC*H*), 3.91 (ddd, 1 H, *J* 4.2, 9.4 and 14.0 Hz, H-10), 3.86 (d, 1 H, *J* 9.7 Hz, H-3), 3.80 (m, 2 H, 2 × H-7), 3.55 (dd, 1 H, *J* 9.4 and 9.7 Hz, H-2), 3.28 (dd, 1 H, *J* 9.4 and 9.4 Hz, H-1), 1.86 (dd, 1 H, *J* 4.2 and 12.2 Hz, H-9eq), 1.43 (dd, 1 H, *J* 12.2 and 14.0 Hz, H-9ax), 1.34, 1.32 (2 s, each 3 H, CMe_2); ^{13}C-NMR (75 Hz, CD_3OD): δ 27.12 (C-1″ or 2″), 27.14 (C 2″ or 1″), 33.04 (C-9), 69.47 (C-8), 70.80 (C-2), 74.97 (C-10), 77.05 (C-7), 83.59 (C-1), 86.19 (C-3), 103.95 (C-5), 111.72 (C-12), 127.65 (C-3′,5′), 129.02 (C-2′,6′), 129.93 (C-4′), 139.28 (C-1′); ITMS-ESI (positive mode): *m*/*z* 345 $[M + Na]^+$, 361 $[M + K]^+$.

(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*)-9-Acetoxy-12,12-dimethyl-4-phenyl-3,5,11,13-tetra-oxatricyclo[8.3.0.0^{2,7}]tridecan-7-ol 12

Compound **11** (33 mg, 0.10 mmol) was treated with acetic anhydride (0.5 mL) and pyridine (1.0 mL) for 13 h at room

temperature. The product was chromatographed on a silica gel (4 g, ethyl acetate–hexane 1 : 3) as eluent to give **12** (39 mg, ~100%) as crystals: $[\alpha]^{20}_{D} = -26$ ($c = 1$, MeOH), mp 186–188 °C; ^{1}H-NMR (300 MHz, CD_3OD): δ 7.60–7.36 (m, 5 H, Ph), 5.68 (s, 1 H, PhC*H*), 5.33 (ddd, 1 H, *J* 5.1, 10.3 and 10.3 Hz, H-5), 4.12–4.03 (m, 2 H, H-2, H-1), 3.88 (ABq, each 1 H, *J* 11.3 Hz, 2 × H-6), 2.07 (s, 3 H, Ac), 1.46, 1.44 (2 s, each 3 H, CMe_2); ITMS-ESI (positive mode): *m*/*z* 365 $[M + H]^+$, 387 $[M + Na]^+$, 403 $[M + K]^+$.

(1*R*,2*S*,3*S*,5*R*,8*S*,10*R*)-2-Acetoxy-12,12-dimethyl-5-phenyl-4,6,11,13-tetra-oxatricyclo[8.3.0.0^{3,8}]tridecan-8-ol 15

Compound **14** was similarly converted into the acetyl derivative **15** as crystals: $[\alpha]^{20}_{D} = -16$ ($c = 1$, MeOH), mp 182–186 °C; ^{1}H-NMR (300 MHz, CD_3OD): δ 7.53–7.50 (m, 5 H, Ph), 5.58 (s, 1 H, PhC*H*), 5.43 (dd, 1 H, *J* 9.6 and 9.6 Hz, H-3), 4.13 (ddd, 1 H, *J* 4.2, 9.3 and 12.1 Hz, H-10), 3.88 (m, 3 H, H-2, 2 × H-7), 3.58 (dd, 1 H, *J* 9.3 and 9.6 Hz, H-1), 2.07 (s, 3 H, Ac), 2.01 (dd, 1 H, *J* 4.2 and 12.2 Hz, H-9eq), 1.55 (dd, 1 H, *J* 12.1 and 12.2 Hz, H-9ax), 1.43 (br s, 6 H, CMe_2); ITMS-ESI (positive mode): *m*/*z* 387 $[M + Na]^+$, 403 $[M + K]^+$.

(1*S*,2*S*,4*R*,7*S*,9*R*,10*S*)-12,12-Dimethyl-4-phenyl-9-tosyloxy-3,5,11,13-tetra-oxatricyclo[8.3.0.0^{2,7}]tridecan-7-ol 13

To a solution of **11** (20.3 mg, 0.063 mmol) in pyridine (0.3 mL) were added tosyl chloride (84 mg, 0.44 mmol) and a catalytic amount of DMAP, and the mixture was stirred for 16 h at room temperature. The mixture was diluted with ethyl acetate (30 mL), and the solution was washed with saturated aqueous sodium hydrogen carbonate and saline, dried, and evaporated. The residue was chromatographed on a column of silica gel (2 g, ethyl acetate–hexane 1 : 4) as eluent to give **13** (31 mg, ~100%) as colorless crystals: $[\alpha]^{20}_{D} = -40$ ($c = 1$, MeOH), mp 135–137 °C; ^{1}H-NMR (300 MHz, CD_3OD): δ 7.91–7.81 (m, 4 H, C_6H_4Me), 7.53–7.34 (m, 5 H, Ph), 5.62 (s, 1 H, PhC*H*), 3.88 (m, 3 H, H-2, H-1, H-9), 3.58 (dd, 1 H, *J* 9.2 and 9.2 Hz, H-10), 3.32 (br s, 2 H, 2 × H-6), 2.46 (s, 3 H, PhCH_3), 2.05 (dd, 1 H, *J* 4.9 and 12.9 Hz, H-8eq), 1.59 (dd, 1 H, *J* 11.7 and 12.9 Hz, H-8ax), 1.34, 1.26 (2 s, each 3 H, CMe_2); ^{13}C-NMR (75 MHz, CD_3OD): δ 21.57 (C-7″), 26.67 (C-1‴ or 2‴), 26.88 (C-1‴ or 2‴), 37.03 (C-8), 69.27 (C-7), 76.35 (C-6), 76.84 (C-1), 78.60 (C-9 or 10), 80.63 (C-10 or 9), 81.59 (C-2), 102.96 (C-4), 112.69 (C-12), 127.50 (C-3′, 5′), 129.05 (C-2′, 6′), 129.28 (C-2″, 6″), 129.97 (C-4′), 130.81 (C-3″, 5″), 135.27 (C-4″), 138.97 (C-1′), 146.42 (C-1″); ITMS-ESI (positive mode): *m*/*z* 476 $[M + H]^+$, 499 $[M + Na]^+$, 515 $[M + K]^+$.

(1*S*,2*S*,4*R*,7*S*,9*S*,10*S*)-9-Azido-12,12-dimethyl-4-phenyl-3,5,11,13-tetra-oxatricyclo[8.3.0.0^{2,7}]tridecan-7-ol 16

A mixture of **13** (0.260 g, 0.544 mmol), sodium azide (0.354 mg, 5.44 mmol), and dimethylformamide (3.9 mL) was stirred for 14 h at 120 °C, and then evaporated to dryness. The residue was suspended in ethyl acetate (45 mL) and the mixture was washed with water and saturated aqueous sodium chloride thoroughly, dried, and evaporated. The residual product was chromatographed on a column of silica gel (18 g, ethyl acetate–hexane 7 : 12) as eluent to give **16** (0.170 g, 88%) as a colorless syrup : R_f 0.20 (chloroform–methanol 4 : 1); R_f 0.64 (*n*-butanol–acetic acid–H_2O 2 : 1 : 1); $[\alpha]^{20}_{D} = -14.5$ ($c = 1.1$, MeOH); ^{1}H-NMR (300 MHz, CD_3OD): δ 7.57–7.33 (m, 5 H, Ph), 5.66 (s, 1 H, PhC*H*), 4.33 (dd, 1 H, *J* 9.3 and 10.0 Hz, H-1), 4.30 (ddd, 1 H, *J* 2.3, 3.4 and 3.9 Hz, H-9), 3.96 (d, 1 H, *J* 10.0 Hz, H-2), 3.85 (m, 2 H, 2 × H-6), 3.68 (dd, 1 H, *J* 3.4 and 9.3 Hz, H-10), 1.89 (dd, 1 H, *J* 2.3 and 15.3 Hz, H-8eq), 1.63 (dd, 1 H, *J* 3.9 and 15.3 Hz, H-8ax), 1.45, 1.44 (2 s, each 3 H, CMe_2); ^{13}C-NMR (75 MHz, CD_3OD): δ 26.61 (C-1″ or 2″), 27.25 (C-1″ or 2″), 33.46 (C-8), 57.37 (C-9), 69.46 (C-7), 73.78 (C-1), 76.71 (C-6), 81.08 (C-10), 83.26 (C-2), 103.11 (C-4), 112.37 (C-12), 127.51 (C-3′, 5′), 129.08 (C-2′, 6′), 129.98 (C-4′), 139.06 (C-1′); ITMS-ESI (positive mode): *m*/*z* 348 $[M + H]^+$, 370 $[M + Na]^+$, 386 $[M + K]^+$.

(1*S*,2*S*,4*R*,7*S*,9*S*,10*S*)-9-Acetamido-12,12-dimethyl-4-phenyl-3,5,11,13-tetra-oxatricyclo[8.3.0.0^{2,7}]tridecan-7-ol 17

A solution of **16** (0.170 g, 0.48 mmol) and ethanol (2.0 mL) containing acetic anhydride (0.9 mL, 9.6 mmol) was hydrogenated in the presence of Raney nickel (one spoonful) under atmospheric pressure of H_2 for 3 h at room temperature. The reaction mixture was filtered through a Celite bed and the filtrate was evaporated to dryness. The product was purified by a silica-gel column (17 g, acetone–hexane 2 : 3) to give the *N*-acetyl derivative **17** (0.134 g, 76%) as needles; R_f 0.72 (chloroform–methanol 4 : 1), 0.77 (*n*-butanol–acetic acid–H_2O 2 : 1 : 1); $[\alpha]^{20}_{D} = -23$ ($c = 1$, MeOH), mp 214–218 °C; ^{1}H-NMR (300 MHz, CD_3OD): δ 7.58–7.32 (m, 5 H, Ph), 5.65 (s, 1 H, PhC*H*), 4.67 (t, 1 H, *J* 2.5, 3.9 and 4.2 Hz, H-9), 4.15 (dd, 1 H, *J* 9.3 and 10.0 Hz, H-1), 4.01 (d, 1 H, *J* 10.0 Hz, H-2), 3.88 (ABq, each 1 H, *J* 12.9 Hz, 2 × H-6), 3.62 (dd, 1 H, *J* 3.9 and 9.3 Hz, H-10), 2.00 (s, 3 H, Ac), 1.74 (dd, 1 H, *J* 2.5 and 15.0 Hz, H-8eq), 1.67 (dd, 1 H, *J* 4.2 and 15.0 Hz, H-8ax), 1.42, 1.39 (2 s, each 3 H, CMe_2); ^{13}C-NMR (75 MHz, CD_3OD): δ 22.94 (*C*H_3CO), 26.74 (C-1″ or 2″), 27.18 (C-1″ or 2″), 33.77 (C-8), 46.53 (C-9), 70.64 (C-7), 74.21 (C-1), 76.46 (C-6), 80.16 (C-10), 83.05 (C-2), 102.95 (C-4), 111.85 (C-12), 127.46 (C-3′, 5′), 129.08 (C-2′, 6′), 129.98 (C-4′), 139.08 (C-1′), 172.88 (CH_3*C*O); ITMS-ESI (positive mode): *m*/*z* 364 $[M + H]^+$, 386 $[M + Na]^+$, 402 $[M + K]^+$.

1L-(1,2,4,5/3)-5-Amino-1-*C*-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol [(+)-valiolamine] 1

A solution of **17** (0.114 g, 0.31 mmol) and 2 M hydrochloric acid (3.4 mL) was stirred for 3 h at 80 °C, and then evaporated. The residual product was eluted from a column of Dowex 50 (NH_4^+) resin (6 g) with 1% aqueous ammonia to give a free amine **1** (54 mg, 90%): R_f 0.26 (*n*-butanol–acetic acid–H_2O 2 : 1 : 1); $[\alpha]^{23}_{D} = +18.5$ ($c = 1$, H_2O); ref. 6 $[\alpha]^{20}_{D} = +18.8$ ($c = 1$, H_2O); ^{1}H-NMR (300 MHz, D_2O): δ 3.66 (dd, 1 H, *J* 9.5 and 9.8 Hz, H-3), 3.44 (dd, 1 H, *J* 4.2 and 9.8 Hz, H-4), 3.37, 3.29 (ABq, each 1 H, *J* 11.4 Hz, 2 × H-7), 3.26 (d, 1 H, *J* 9.5 Hz, H-2), 3.22 (m, 1 H, H-5), 1.75 (dd, 1 H, *J* 2.8 and 15.2 Hz, H-6eq), 1.55 (dd, 1 H, *J* 3.8 and 15.2 Hz, H-6ax); ^{13}C-NMR (75 MHz, D_2O): δ 32.94 (C-6), 51.10 (C-5), 66.21 (C-7), 71.87 (C-3), 74.04 (C-4), 74.42 (C-2), 76.72 (C-1); ITMS-ESI (positive mode): *m*/*z* 194 $[M + H]^+$, 216 $[M + Na]^+$.

The synthetic **1** has been demonstrated to possess enzyme-inhibitory activity: IC_{50} 1.2 and 20 μM against sucrase (rat) and maltase (rat), respectively.

1L-(1,2,4,5/3)-5-Acetamido-1-*C*-(acetoxymethyl)-2,3,4-tri-*O*-acetyl-1,2,3,4-cyclohexanetetrol (penta-*N*, *O*-acetylvaliolamine) 18

Compound **1** (12 mg, 0.063 mmol) was conventionally acetylated and the product was purified by a silica-gel column (3 g, acetone–hexane 2 : 3) to give **18** (25 mg, ~100%) as colorless crystals; $[\alpha]^{20}_{D} = -18$ ($c = 1$, MeOH), mp 137–138 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.06 (br d, 1 H, *J* 7.4 Hz, N*H*Ac), 5.53 (dd, 1 H, *J* 9.9 and 9.9 Hz, H-3), 5.09 (d, 1 H, *J* 9.9 Hz, H-2), 4.94 (dd, 1 H, *J* 4.3 and 9.9 Hz, H-4), 4.75 (m, 1 H, H-5), 3.98, 3.83 (ABq, each 1 H, *J* 11.4 Hz, 2 × H-7), 3.33 (br s, 1 H, OH), 2.10, 2.08, 2.02, 1.99 (4 s, 3, 3, 3, 6 H, 4 × Ac); ^{13}C-NMR (75 MHz, CD_3OD): δ 20.53, 20.62, 20.67, 20.75, 23.11 (5 × *C*H_3CO), 33.80 (C-6), 46 89 (C-5), 67.03 (C-7), 70.42 (C-3), 73.77 (C-4), 74.05 (C-2), 75.25 (C-1), 171.50, 171.77, 171.83, 172.08, 172.78 (5 × CH_3*C*O); ITMS-ESI (positive mode): *m*/*z* 404 $[M + H]^+$, 426 $[M + Na]^+$, 442 $[M + K]^+$.

1L-(1,2,4/3,5)-1-*C*-(Acetoxymethyl)-2,3,4-tri-*O*-acetyl-5-*O*-tosyl-1,2,3,4,5-cyclohexanepentol 19

A mixture of **13** (30 mg) and 2 M hydrochloric acid (0.9 mL) was stirred for 0.5 h at 60 °C, and then evaporated to dryness. The residue was treated with acetic anhydride (0.5 mL) and pyridine (1 mL) for 17 h at room temperature. After being quenched by the addition of MeOH, the mixture was evaporated and the residue was chromatographed on silica gel (3 g, acetone–hexane 1 : 3) to give **19** (25 mg, ~100%) as a syrup: R_f 0.56 (acetone–hexane 1 : 1); $[\alpha]^{20}_D = -39$ (c = 0.82, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.80–7.35 (m, 4 H, Ph), 5.38 (dd, 1 H, J 9.7 and 9.8 Hz, H-3), 5.17 (dd, 1 H, J 9.7 and 9.8 Hz, H-4), 5.10 (d, 1 H, J 9.8 Hz, H-2), 5.28 (ddd, 1 H, J 5.0, 9.6 and 11.8 Hz, H-5), 3.97, 3.82 (ABq, each 1 H, J 11.3 Hz, CH_2OAc), 2.73 (s, 1 H, OH), 2.46 (s, 3 H, PhCH_3), 2.36 (dd, 1 H, J 5.4 and 13.9 Hz, H-6eq), 2.10, 2.09, 1.96, 1.76 (4 s, each 3 H, 4 × Ac), 1.92 (dd, 1 H, J 12.0 and 13.9 Hz, H-6ax); ITMS-APCI (positive mode): m/z 457 $[M - AcO]^+$, 499 $[M - H_2O + H]^+$.

1L-(1,2,4/3,5)-1-*C*-(Acetoxymethyl)-2,3,4-tri-*O*-acetyl-5-azido-1,2,3,4-cyclohexanetetrol 20 and 1L-(1,2,5/3,4)-1-*C*-(acetoxymethyl)-2,3,5-tri-*O*-acetyl-4-azido-1,2,3,5-cyclohexanetetrol 21

A mixture of **19** (0.459 g, 1.14 mmol), sodium azide (289 mg, 4.4 mmol), and aqueous 90% 2-methoxyethanol (46 mL) was stirred for 21 h at 120 °C, and then evaporated. The residue was treated with acetic anhydride (1 mL) and pyridine (2 mL) for 1 h at room temperature. The mixture was evaporated and the residual compounds were fractionated over a silica gel column (50 g, ethyl acetate–hexane 1 : 2) to give **20** (224 mg, 65%) and **21** (129 mg, 28%) as a colorless syrup:

For **20**: R_f 0.57 (ethyl acetate–hexane 2 : 1); $[\alpha]^{20}_D = -10$ (c = 1.5, $CHCl_3$), mp 182–186 °C; ^{1}H-NMR (300 MHz, CD_3OD): δ 5.40 (dd, 1 H, J 9.8 and 9.9 Hz, H-3), 5.10 (d, 1 H, J 9.9 Hz, H-2), 5.06 (dd, 1 H, J 9.8 and 9.9 Hz, H-4), 3.99 (m, 1 H, H-5), 3.93 (ABq, each 1 H, J 11.5 Hz, CH_2OAc), 2.47 (s, 1 H, OH), 2.23–1.99 (m, 12 H, 4 × Ac); ITMS-ESI (positive mode): m/z 370 $[M - H_2O + H]^+$.

For **21**: R_f 0.36 (ethyl acetate–hexane 2 : 1); $[\alpha]^{20}_D = -6.6$ (c = 0.19, $CHCl_3$), mp 175–178 °C; ^{1}H-NMR (300 MHz, CD_3OD): δ 5.54 (dd, 1 H, J 3.3 and 9.6 Hz, H-3), 5.40 (d, 1 H, J 9.6 Hz, H-2), 5.07 (m, 1 H, H-5), 4.11 (dd, 1 H, J 3.3 and 3.5 Hz, H-4), 4.00, 3.86 (ABq, each 1 H, J 11.3 Hz, CH_2OAc), 2.52 (s, 1 H, OH), 2.17–1.99 (m, 14 H, 4 × Ac, 2 × H-6); ITMS-ESI (positive mode): m/z 370 $[M - H_2O + H]^+$.

1L-(1,2,4/3,5)-5-Acetamido-1-*C*-(acetoxymethyl)-2,3,4-tri-*O*-acetyl-1,2,3,4-cyclohexanetetrol [penta-*N*, *O*-acetyl-1-epi-valiolamine] 22

A solution of **20** (155 mg, 0.40 mmol) in ethanol (2 mL) containing acetic anhydride (0.08 mL) was hydrogenated in the presence of Raney nickel T-4 under atmospheric pressure of H_2 for 8 h at room temperature. The catalyst was removed by filtration and the filtrate was evaporated. The residue was chromatographed on a silica gel (20 g, acetone–hexane 2 : 3) to give **21** (109 mg, 68%) as crystals: R_f 0.30 (acetone–toluene 2 : 1); $[\alpha]^{20}_D = -12$ (c = 2.7, $CHCl_3$), mp 214–218 °C; ^{1}H-NMR (300 MHz, CD_3OD): δ 5.97–5.80 (br d, 1 H, NHAc), 5.56 (dd, 1 H, J 9.8 and 9.9 Hz, H-3), 5.08 (d, 1 H, J 9.9 Hz, H-2), 4.96 (dd, 1 H, J 9.8 and 10.3 Hz, H-4), 4.50 (dddd, 1 H, J 4.4, 7.9, 10.3 and 13.0 Hz, H-5), 4.03, 3.83 (ABq, each 1 H, J 11.3 Hz, CH_2OAc), 2.28 (dd 1 H, J 4.4 and 14.0 Hz, H-6eq), 2.08, 2.06, 1.99, 1.94, 1.60 (5 s, each 3 H, 5 × Ac), 1.60 (dd, 1 H, J 13.0 and 14.0 Hz, H-6ax); ITMS-ESI (positive mode): m/z 404 $[M + H]^+$, 426 $[M + Na]^+$, 442 $[M + K]^+$.

1L-(1,2,4/3,5)-5-Amino-1-*C*-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol [(−)-1-epi-valiolamine] 23

A solution of **21** (5.1 mg, 0.13 mmol) and 2 M hydrochloric acid (0.3 mL) was stirred for 4 h at 80 °C and then evaporated. The residue was chromatographed on a column of Dowex 50 W × 2 (0.5 g, 1% aqueous ammonia) to give **23** (2.4 mg, ~100%): R_f 0.50 (H_2O–AcOH–n-butanol 1 : 1 : 2); $[\alpha]^{20}_D = -17$ (c = 0.42, H_2O); ref. 9 $[\alpha]^{24}_D = -23.2$ (c = 0.5, H_2O); ^{1}H-NMR (300 MHz, D_2O): δ 3.44 (dd, 1 H, J 9.4 and 9.5 Hz, H-3), 3.44, 3.35 (ABq, each 1 H, J 11.5 Hz, CH_2OH), 3.29 (d, 1 H, J 9.4 Hz, H-2), 3.10 (dd, 1 H, J 9.5 and 10.1 Hz, H-4), 2.95 (ddd, 1 H, J 4.0, 10.1 and 12.7 Hz, H-5), 1.83 (dd, 1 H, J 4.0 and 13.9 Hz, H-6eq), 1.39 (dd, 1 H, J 12.7 and 13.9 Hz, H-6ax); ITMS-ESI (positive mode): m/z 194 $[M + H]^+$.

Compound **23** has been shown to possess enzyme-inhibitory activity: IC_{50} 36 μM against α-glucosidase (yeast).

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