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Synthetic studies towards a new scaffold, spirobicycloimidazoline

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Abstract—A new scaffold consisting of a carbocycle and a substituted imidazoline in an orthogonal arrangement was synthesized as a potential specific inhibitor of glycosidases. The spirobicycloimidazoline, (5*R*,6*R*,7*R*,8*R*)-8-(hydroxymethyl)-2-phenyl-1,3-diaza-spiro[4.4]non-1-ene-6,7-diol, was synthesized from methyl 2-*O*-*p*-methoxybenzyl-3,4-di-*O*-benzyl-α/β-D-*gluco*-6-enopyranoside via (1*R*,2*S*,3*S*,4*R*,5*S*)-3,4-bis(benzyloxy)-2-(4-methoxybenzyloxy)-5-vinyl-cyclopentanol. The ring contraction of the 6-enopyranoside in the presence of zirconocene equivalent ('Cp_2Zr') reagent gave exclusively the corresponding cyclopentanol without cleavage of the PMB protecting group. In the course of the study, a new α-mannosidase inhibitor, (1*R*,2*R*,3*R*,5*R*)-5-amino-3-hydroxy-methyl-cyclopentane-1,2-diol, was also discovered.

Keywords: Glycosidase inhibitors; Spiro compounds; Imidazoline; Carbocyclic compounds

1. Introduction

The glycosidases, which are related to the control of various biological phenomena, are one of the most important families of carbohydrate-related enzymes.[1,2] Inhibitors of glycosidases are useful tools when investigating biochemical processes,[3–5] in enzyme purification as affinity ligands,[6,7] and also as drug candidates.[8–11] Thus, many compounds, either isolated from natural sources or chemically synthesized, have been reported as inhibitors of glycosidases. Recent advances in three-dimensional analysis based on the crystal structures of glycosidases have also been used to design inhibitors of these enzymes. A majority of compounds in the class carry a cationic moiety in the structure that mimics the oxocarbenium ion species in the transition state.

One well-known family of glycosidase inhibitors with a five-membered ring is hydroxylated pyrrolidines, represented by DMDP and DAB-1 (Chart 1).[12,13] It is believed that the powerful inhibitory activities are the result of a strong charge interaction between the ammonium group and the carboxylate group in the active site of glycosidase. A combinatorial chemistry approach is expected to result in further improvement of activity.[14,15] Cyclopentitols having a sugar-like carbocycle are another class of inhibitors that deserve attention. Mannostatin A, isolated from *Streptoverticillium verticillus*, is a specific and potent inhibitor of Golgi α-mannosidase II.[16,17] The structure of Mannostatin A does not resemble the three-dimensional structure of a mannopyranoside, the substrate of the mannosidase, and the inhibitory mechanism is thus of great interest.

Bicyclic cyclopentitol-related compounds have also been studied as potential inhibitors of various glycosidases. Trehazoline and allosamidin are known to be good inhibitors of trehalase and chitinase, respectively.[18,19] Despite the accumulated information regarding inhibitory activities, the prediction of enzyme specificity in the inhibition by five-membered ring compounds is, in general, difficult because of the conformational freedom of these rings and the resulting unpredictable three-dimensional placement of functional groups.

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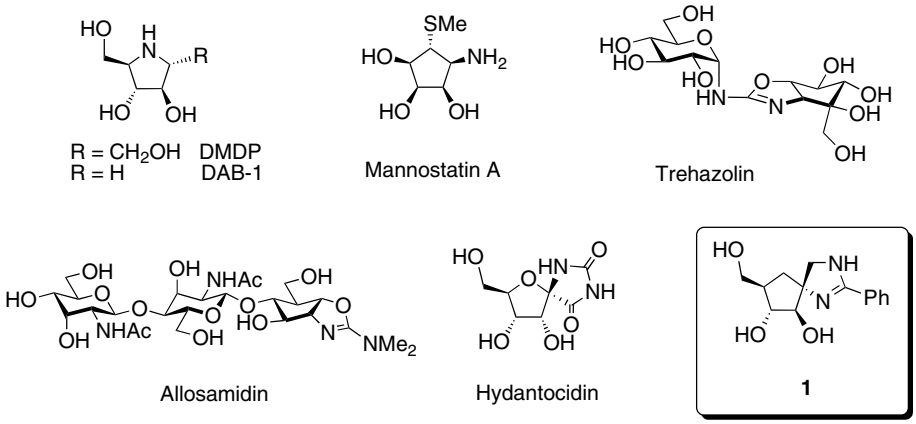


Chart 1.

Hydantocidin, a naturally occurring spiroribofuranose derivative, was reported to show strong herbicidal activity with no toxicity to microorganisms or animals.[20,21] An analogue of hydantocidin, in which the endocyclic oxygen of the sugar moiety has been replaced by a methylene group, is known.[22–24] This type of compound, having a fused ring system in an orthogonal arrangement, might provide valuable information and hopefully serve as a source of potent glycosidase inhibitors. This consideration was based on fact that the natural product salacinol with a 'semi-' spiro system as the result of intramolecular ion pairing, showed potent inhibitory activity against α-glucosidase.[25] However, cancellation of charge in the molecule is considered to be unfavourable for glycosidase inhibition. We thus designed a new scaffold consisting of a carbocycle and a substituted imidazoline, where the hydroxylated carbocycle ring mimics the glycon moiety, the imidazoline moiety provides hydrogen-bonding capability in the catalytic site of the enzyme, and an aglycon moiety can be incorporated at the amidino-group. We report here the synthesis of spirobicycloimidazoline (**1**), which is expected to become a compound in a novel class of compounds. In the course of these studies a new α-mannosidase inhibitor, (1*R*,2*R*,3*R*,5*R*)-5-amino-3-hydroxymethyl-cyclopentane-1,2-diol, was also discovered.

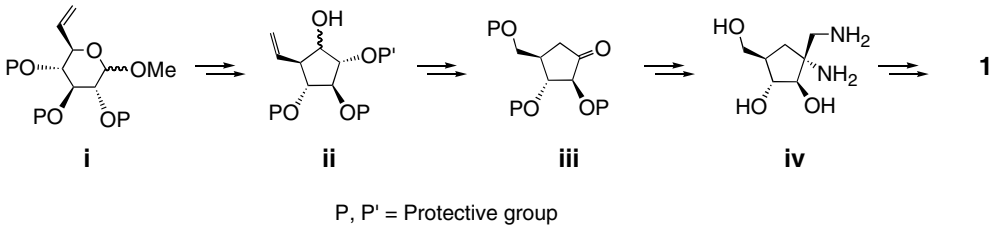
2. Results and discussion

2.1. Synthesis

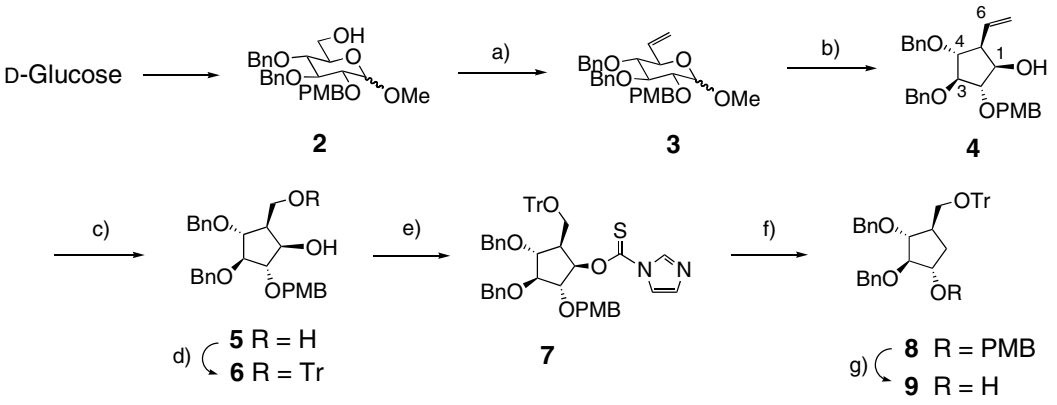
Our target bicyclospiro compound, imidazoline (**1**), consists of a five-membered carbocycle and an imidazoline. In this study, we selected as a target backbone 5-amino-3-hydroxymethyl-cyclopentane-1,2-diol, which might provide new information when searching for and/or designing new inhibitors of glycosidases. In the construction of this scaffold we chose an approach in which the key steps were a ring contraction of an enopyranoside (**i**) to provide a cyclopentitol derivative (**ii**), subsequent conversion of **ii** into a ketone (**iii**) and finally introduction of a C–C bond into **iii** leading eventually to **iv**. Diamine **iv** is a precursor to imidazoline **1** (Scheme 1).

A suitably protected 6-enopyranoside (**3**), which was to be subjected to the ring contraction, was synthesized from D-glucose (Scheme 2). The 2-OH of compound **2**, which is transformed to the spiro-centre of **1**, should be distinct from other hydroxyl groups, so we chose *p*-methoxybenzyl (PMB) ether as the protecting group. Compound **2** was obtained in high yield by conventional protection of the hydroxyl groups, and the spectral data matched the reported data.[26,27] Oxidation of the hydroxymethyl group of **2** gave the corresponding aldehyde, which was converted into **3** by a Wittig reaction.

It had been reported that the ring contraction of 6-enopyranoside was promoted by a zirconocene equivalent ('Cp_2Zr') reagent.[28] Although the reaction generally required a Lewis acid to assist with elimination of the aglycone group when methyl glycosides were used as substrates, Ito et al. reported that this reaction sometimes proceeded in the absence of a Lewis acid.[29] However, the details of the reaction conditions were not revealed in the paper, and it was also anticipated that in our case that the use of Lewis acid could prove troublesome due to cleavage of the PMB group. After some experimentation, we found suitable reaction conditions. In the absence of a Lewis acid, the ring contraction of the olefin–Zr complex, which was generated in situ at −78 °C, proceeded smoothly by rapidly increasing the temperature. This suggests that multiple intermediates may exist, although it does not indicate that all of them become precursors of carbocyclic compound (**4**). Although we could not determine the structure of these species, compounds **3α** and **3β** were efficiently converted into compound **4** accompanied by small amounts of



Scheme 1.



Scheme 2. Reagents and conditions: (a) (1) $(COCl)_2$, Me_2SO, *i*-Pr_2NEt, CH_2Cl_2, −78 °C; (2) Ph_3PCH_3I, *t*-BuOK, toluene; 7:3, α/β, 64%; (b) Cp_2ZrCl_2, *n*-BuLi, THF, −78 then 25 °C, 55% from **3-α**, 50% from **3-β**; (c) O_3 then $NaBH_4$, MeOH, CH_2Cl_2, 76%; (d) TrCl, pyridine, 83%; (e) $(Im)_2C{=}S$, DMAP, THF, 96%; (f) *n*Bu_3SnH, AIBN, toluene, 94%; (g) DDQ, CH_2Cl_2, H_2O, 91%.

their respective diastereomers (65% yield, 85:12:3, **4**: 1*S*,2*S* isomer:1*S*5*R* isomer). Under these conditions, it was found that the PMB group was not at all affected.

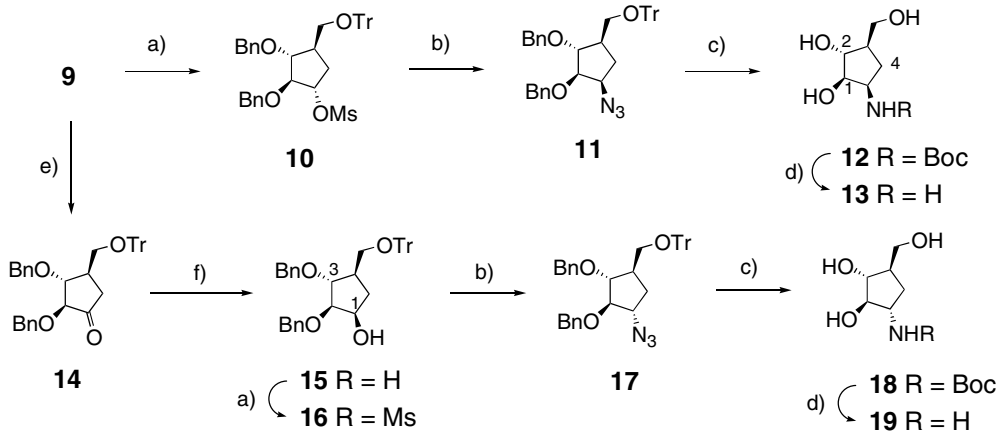
Compound **4** was converted into diol (**5**) by ozonolysis and successive reduction using $NaBH_4$ (76% yield). After tritylation of the primary alcohol, the secondary alcohol of compound **6** was deoxygenated by radical reduction to afford cyclopentitol (**8**). Compound **9**, obtained by cleavage of the PMB group in **8** (91%), is the common precursor for the synthesis of amino-cyclopentitols (**13** and **19**) (Scheme 3).

The azido group in compound **11** was introduced by substitution of the corresponding mesylate (**10**, obtained by mesylation of **9**) with NaN_3 in an S_N2 fashion (95%). Deprotection of **11** was accomplished by hydrogenolysis under acidic conditions to afford **13**, whose amino group was protected as *t*-butyl carbamate (**12**, 86%) to facilitate purification of some minor alkylation by-products. Upon treatment with trifluoroacetic acid (TFA), compound **12** was converted into known **13**[30] as a pure TFA salt, in quantitative yield.

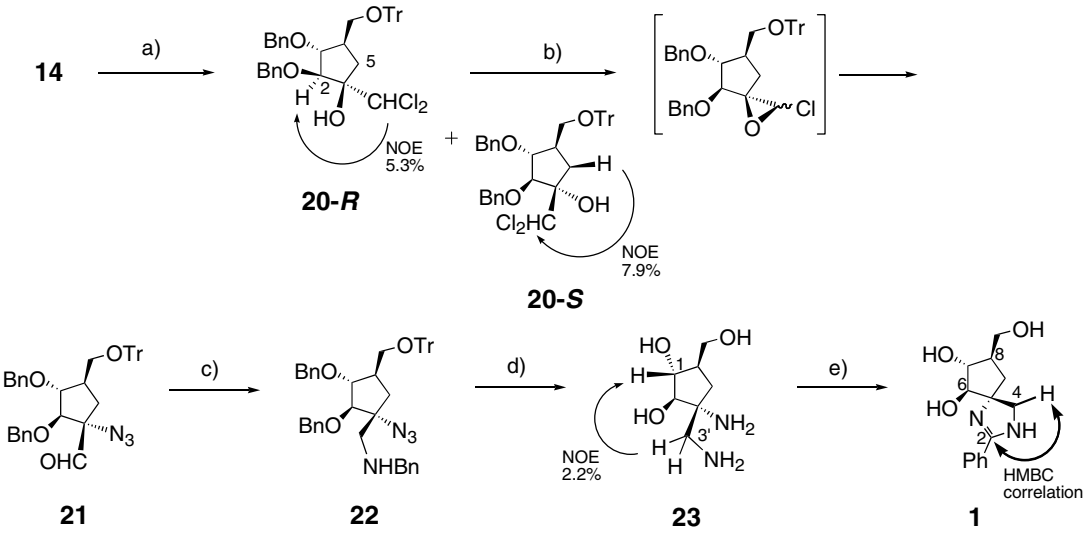
Alternatively, the hydroxyl group in **9** was successfully epimerized by an oxidation–reduction procedure via ketone (**14**) to afford **15** (89%) together with **9** (10%). The diastereoselectivity of the reduction was controlled by steric effects, with the hydride attacking the ketone in **14** from the less-hindered side. Compound **19** was obtained from **15** by way of azido compound **17** in the same manner as described for **13**.

For the synthesis of **1**, construction of a quaternary carbon including the amino-functionality on the cyclopentitol frame was required. This step was achieved by introducing an azide via and α-chloroepoxide intermediate (Scheme 4).[31,32] Nucleophilic addition of dichloromethyllithium to ketone (**14**) generated two isomeric branched-cyclopentitols (**20-*R*** and **20-*S***) in 67% and 13% yield, respectively. An NOE was observed between the dichloromethyl protons and H-2, which supported an *R* configuration of **20-*R***. The structure of the isomeric **20-*S*** was also supported by an NOE between H-5 and the dichloromethyl protons. The diastereoselectivity of this reaction was similar to the hydride reduction described for compound **15**. The major isomer (**20-*R***) was converted into α-azido aldehyde (**21**) with stereochemical inversion at the quaternary carbon (79%).

The stereochemistry of **21** was supported by the NOE experiments of diamine (**23**), the synthesis of which follows. Introduction of the second nitrogen atom of the imidazoline ring was achieved by reductive amination of **21** using $BnNH_2$ and $NaBH_3CN$ (86%).[33] Diamine (**23**), obtained from **22** by hydrogenolysis under acidic conditions, was easily purified by protection as an *N*-Boc derivative, which was quantitatively converted back into diamine (**23**) as the TFA salt. The NOE shown in the structure suggested the relative stereochemistry of **23**. Condensation of **23** with benzaldehyde using *N*-bromosuccinimide (NBS) gave imidazoline (**1**; 33% after



Scheme 3. Reagents and conditions: (a) MsCl, DMAP, pyridine; (b) NaN_3, DMF, 90% for **11**, 92% for **17**; (c) (1) H_2, $Pd(OH)_2$–C, HCl, MeOH, THF; (2) $(Boc)_2O$, Et_3N, H_2O, MeOH, 86% for **12**, 84% for **18**; (d) TFA, CH_2Cl_2, quant.; (e) Dess–Martin periodinane, CH_2Cl_2, 91%; (f) $NaBH_4$, MeOH, THF, 89%.



Scheme 4. Reagents and conditions: (a) *i*-Pr_2NH, *n*-BuLi, CH_2Cl_2, THF, **20-*R*** 67%, **20-*S*** 13%; (b) NaN_3, 15-crown-5, Me_2SO, 79%; (c) BnNH, $NaBH_3CN$, AcOH, TFA, 86%; (d) (1) H_2, $Pd(OH)_2$–C, HCl, MeOH, THF; (2) $(Boc)_2O$, Et_3N, MeOH, H_2O; (3) TFA, CH_2Cl_2, 64%; (e) PhCHO, NBS, Et_3N, MeOH, 33%.

purification using HPLC) whose imidazoline structure was supported by a correlation between C-2 and H-4 in the HMBC spectrum.[34]

2.2. Glycosidase inhibition studies

The inhibitory activities of compounds **13**, **19** and **1** against various glycosidases, namely, α/β-glucosidases, β-*N*-acetylglucosaminidase, α-mannosidase and β-galactosidase, were investigated. The sources of enzymes and substrates are as follows: α-glucosidase (EC 3.2.1.20) from yeast, β-glucosidase (EC 3.2.1.21) from almond, β-*N*-acetylglucosaminidase (EC 3.2.1.52) from jack beans, β-galactosidase (EC 3.2.1.23) from *Aspergillus oryzae* and α-mannosidase (EC 3.2.1.24) from jack bean. It was observed that **13** and **19** had low activities against α-glucosidase ($IC_{50} = 0.16$–0.18 mM), high activity against α-mannosidase (**13**: $IC_{50} = 1.55$ μM, $K_i = 0.85$ μM; **19**: $IC_{50} = 17.5$ μM, $K_i = 16.0$ μM), and no activity against other glycosidases. Although **13** does not have a *cis*-diol moiety, of which the presence has been considered to be essential for α-mannosidase inhibition, the inhibitory activity was found to be as powerful as swainsonine.[35] This might suggest that the amino group of **13** mimics a hydroxyl group, possibly 2-OH of mannose. However, the observed inhibitory activity of **19** against α-mannosidase seems to be a contradiction to this hypothesis because all functional groups are pre-

sented in trans-orientation. Thus, detailed analysis and further investigation are required to determine the inhibitory mechanism. Only low activities against α/β-glucosidase (17% inhibition at 0.3 mM against α-glucosidase and 17% inhibition at 0.5 mM against β-glucosidase) were observed for imidazoline (**1**). We speculate that the reasons for the lower activity of **1** compared with **13** and **19** are either the steric hindrance at an aglycon site in the enzymes or a change of conformation of the carbocycle resulting from the fused imidazoline.

2.3. Conclusion

A novel spirobicycloimidazoline expected to have potent inhibitory activity against glucosidase was synthesized. Although the compound was found to have only weak inhibitory activity, it is hoped that the related compounds may be more potent. However, these studies did identify an amino-cyclopentitol that was a good inhibitor of α-mannosidase. In the synthesis of the target, a key ring-contraction reaction in the presence of zirconocene was achieved without using a Lewis acid, which allowed us to use an acid labile protecting group such as a PMB ether. Expansion of the choice of protecting groups is advantageous for the synthesis of additional cyclopentitol derivatives and analogues.

3. Experimental

3.1. General methods

Thin-layer chromatography was performed on Merck Art. 5715, Kieselgel 60 F_{254}/0.25 mm thickness plates. Visualization was accomplished with UV light and 1% $Ce(SO_4)_2$–1.5% $(NH_4)_6MoO_{24}{\cdot}4H_2O$–10% H_2SO_4 solution or 0.5% ninhydrin *n*-BuOH solution followed by heating. Silica gel column chromatography was conducted on Kieselgel 60 (Merck Art. 7734) or Silica Gel 60 Spherical (Kanto Chemical). The HPLC was performed with Waters-LCMS system (Column: Unizon C-18; Mobile phase: 60% MeCN, 40% H_2O; Flow rate: 4.0 mL/min). Mass spectra were obtained on SHIMADZU-LCQIT-TOF (Shimadzu) coupled with an electrospray interface. Melting points were measured with Yanaco MP-S3 micro melting point apparatus. Optical rotations were measured in a 1.0 dm tube with a Horiba SEPA-200 polarimeter. ^{1}H NMR (500 MHz) spectra were recorded with an AVANCE 500 spectrometer (Bruker Biospin Inc.) in deuterated solvent using Me_4Si (0.00 ppm) or the solvent peak (HDO; 4.65 ppm or CD_3OH; 4.87 ppm) as the internal standard. ^{13}C NMR (125 MHz) spectra were recorded with an AVANCE 500 spectrometer (Bruker Biospin Inc.) in deuterated solvent using Me_4Si (0.00 ppm) or the solvent peak ($CDCl_3$; 77.0 ppm, CD_3OD; 49.0 ppm or C_6D_6; 128.0 ppm) as the internal standard.

3.2. Methyl 2-*O*-*p*-methoxybenzyl-3,4-di-*O*-benzyl-α/β-D-gluco-6-enopyranoside (3)

A solution of Me_2SO (0.73 mL, 10.3 mmol) in CH_2Cl_2 (4.40 mL) was added to a solution of $(COCl)_2$ (2 M in CH_2Cl_2, 2.57 mL, 5.14 mmol) under a nitrogen atmosphere at −78 °C. To the mixture was added after 50 min a solution of **2** (1.27 g, 2.57 mmol, 3:1, α/β) in CH_2Cl_2 (30.0 mL), and then after stirring for 1 h a solution of *N*,*N*′-diisopropylethylamine (2.68 mL, 15.4 mmol) at −65 °C. The mixture was poured into H_2O, and the organic layer was washed successively with 2% aq HCl, H_2O and brine, dried over Na_2SO_4, concentrated in vacuo and co-evaporated with toluene three times. To the toluene (8.40 mL) solution of the residue (1.27 g) was added $Ph_3P{=}CH_2$ (0.3 M in toluene, 17.1 mL, 51.4 mmol) over 0.5 h at −10 °C. After being stirred for 2 h at rt, to the mixture was added large excess of acetone. The mixture was concentrated, and the residue was purified by silica gel chromatography (6:1 *n*-hexane–EtOAc) to afford **3** (810 mg, 64%, 3:1, α/β):**3**α; $R_f = 0.57$ (2:1 *n*-hexane–EtOAc); $[\alpha]_D^{29}$ −11.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.37–7.26 (m, 12H, aromatic), 6.86 (d, 2H, $J = 8.6$ Hz, *p*-OMe-*Ph*), 5.91 (ddd, 1H, $J_{5,6} = 6.5$ Hz, $J_{6,7\text{-cis}} = 10.5$ Hz, $J_{6,7\text{-trans}} = 17.2$ Hz, H-6), 5.42 (d, 1H, H-7-cis), 5.26 (d, 1H, H-7-trans), 4.96 (d, 1H, $J = 10.8$ Hz, PhCH_2), 4.83 (d, 1H, $J = 10.8$ Hz, PhCH_2), 4.79 (d, 1H, $J = 10.7$ Hz, PhCH_2), 4.75 (d, 1H, $J = 11.8$ Hz, PhCH_2), 4.62 (d, 2H, $J = 11.3$ Hz, PhCH_2), 4.55 (d, 1H, $J_{1,2} = 3.2$ Hz, H-1), 4.09 (dd, 1H, $J_{4,5} = 9.7$ Hz, H-5), 3.98 (t, 1H, $J_{2,3} = J_{3,4} = 9.3$ Hz, H-3), 3.81 (s, 3H, Ph–OCH_3), 3.52 (dd, 1H, H-2), 3.38 (s, 3H, OCH_3), 3.26 (t, 1H, H-4); ^{13}C NMR ($CDCl_3$): δ 138.6, 138.2 (aromatic *C*), 135.3 (C-6), 130.3–127.6 (aromatic *C*), 118.2 (C-7), 113.9 (aromatic *C*), 98.2 (C-1), 82.3 (C-4), 81.7 (C-3), 79.5 (C-2), 75.9, 75.2, 73.1 (Ph*C*H_2×3), 55.3 (Ph–O*C*H_3), 55.2 (O*C*H_3). ESIMS *m*/*z* calcd for $[C_{30}H_{34}O_6{+}Na]^+$: 513.2248. Found: 513.2248: **3**β; $R_f = 0.66$ (2:1, *n*-hexane–EtOAc); mp 93.0–95.0 °C; $[\alpha]_D^{23}$ −2.4 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.34–7.26 (m, 12H, aromatic), 6.84 (d, 2H, $J = 8.7$ Hz, *p*-MeO-*Ph*), 5.96 (ddd, 1H, $J_{5,6} = 6.0$ Hz, $J_{6,7\text{-cis}} = 10.6$ Hz, $J_{6,7\text{-trans}} = 17.3$ Hz, H-6), 5.45 (d, 1H, H-7-cis), 5.28 (d, 1H, H-7-trans), 4.89 (d, 1H, $J = 10.9$ Hz, PhCH_2), 4.83 (d, 1H, $J = 10.6$ Hz, PhCH_2), 4.79 (d, 1H, $J = 10.9$ Hz, PhCH_2), 4.76 (d, 1H, $J = 10.6$ Hz, PhCH_2), 4.64 (d, 1H, $J = 10.6$ Hz, PhCH_2), 4.61 (d, 1H, $J = 10.6$ Hz, PhCH_2), 4.34 (d, 1H, $J_{1,2} = 7.8$ Hz, H-1), 3.79 (s, 3H, Ph–OCH_3), 3.77 (dd, 1H, $J_{4,5} = 9.5$ Hz, H-5), 3.62 (t, 1H, $J_{2,3} = J_{3,4} = 9.1$ Hz, H-3), 3.59 (s, 3H, OCH_3), 3.41 (dd, 1H, H-2), 3.30 (t, 1H, H-4); ^{13}C NMR ($CDCl_3$): δ 138.6, 138.0 (aromatic

C), 134.6 (C-6), 130.6–127.6 (aromatic *C*), 117.9 (C-7), 113.8 (aromatic *C*), 104.5 (C-1), 84.2 (C-3), 82.0 (C-2), 82.0 (C-4), 75.8 (Ph*C*H_2), 75.6 (C-5), 75.2, 74.5 (Ph*C*H_2 × 2), 57.2 (Ph–O*C*H_3), 55.3 (O*C*H_3). ESIMS *m*/*z* calcd for $[C_{30}H_{34}O_6+Na]^{+\cdot}$: 513.2248. Found: 513.2255.

3.3. (1*R*,2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-2-(4-methoxybenzyloxy)-5-vinyl-cyclopentanol (4)

To a THF (20.0 mL) solution of bis(cyclopentadienyl)zirconium dichloride (1.87 g, 6.39 mmol) was added *n*-BuLi (2 M in *n*-hexane, 8.50 mL, 13.6 mmol) at −78 °C. After being stirred for 1 h, to the solution was added 3α (2.09 g, 4.26 mmol) in a cold (−78 °C) THF (25.0 mL) solution over 20 min. After the mixture was stirred for 15 min at −78 °C, the reaction temperature was quickly elevated to rt. The reaction was stopped by addition of 5% aq NaOH at 0 °C, and insoluble materials were filtered through a Celite pad. The organic layer of filtrate was washed with brine, followed by extraction with CH_2Cl_2, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (3:1 *n*-hexane–EtOAc) to afford **4** (1.09 g, 55%) and its diastereomers (1*S*,2*S* isomer, 149 mg, 8% and 1*S*,5*R* isomer, 39 mg, 2%). The products were obtained from **3β** by reacting in the same manner as described for **3α**:**4**; $R_f = 0.31$ (3:1 *n*-hexane–EtOAc); $[\alpha]_D^{25}$ +17.4 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.36–7.26 (m, 12H, aromatic), 6.88 (d, 2H, $J = 8.6$ Hz, *p*-MeO-*Ph*), 5.93 (ddd, 1H, $J_{5,6} = 7.8$ Hz, $J_{6,7\text{-cis}} = 10.3$ Hz, $J_{6,7\text{-trans}} = 17.4$ Hz, H-6), 5.28 (d, 1H, H-7-cis), 5.25 (d, 1H, H-7-trans), 4.62–4.52 (m, 6H, PhCH_2), 4.11 (ddd, 1H, $J_{1,2} = 2.9$ Hz, $J_{1,5} = 5.6$ Hz, $J_{1,OH} = 4.3$ Hz, H-1), 4.02 (dd, 1H, $J_{3,4} = 5.1$ Hz, $J_{4,5} = 8.1$ Hz, H-4), 3.95 (t, 1H, $J = 4.2$ Hz, H-3), 3.80 (s, 3H, Ph–OCH_3), 3.79 (t, 1H, $J = 3.5$ Hz, H-2), 2.90 (ddd, 1H, $J = 7.9$ Hz, H-5), 1.75 (d, 1H, O*H*); ^{13}C NMR ($CDCl_3$): δ 138.2, 138.0 (aromatic C), 134.6 (C-6), 130.0–127.6 (aromatic C), 119.0 (C-7), 113.8 (aromatic C), 88.3 (C-3), 86.7 (C-2), 84.7 (C-4), 75.5 (C-1), 72.0, 71.9, 71.4 (PhCH_2×3), 55.3 (Ph–OCH_3), 50.9 (C-5). ESIMS *m*/*z* calcd for $[C_{29}H_{32}O_5+Na]^+$: 483.2142. Found: 483.2148. **1*S*,2*S* Isomer**; $R_f = 0.31$ (3:1 *n*-hexane–EtOAc); ^{1}H NMR (C_6D_6): δ 7.34–7.09 (m, 12H, aromatic), 6.76 (d, 2H, $J = 8.6$ Hz, *p*-MeO-*Ph*), 5.93 (ddd, 1H, $J_{5,6} = 7.9$ Hz, $J_{6,7\text{-cis}} = 10.3$ Hz, $J_{6,7\text{-trans}} = 17.1$ Hz, H-6), 5.23 (d, 1H, H-7-trans), 5.07 (d, 1H, H-7-cis), 4.61–4.30 (m, 6H, PhCH_2), 4.10 (t, 1H, $J = 3.6$ Hz, H-3), 3.88 (ddd, 1H, $J_{1,2} = 5.3$ Hz, $J_{1,5} = 8.5$ Hz, $J_{1,OH} = 8.5$ Hz, H-1), 3.75 (m, 2H, H-2, H-4), 3.28 (s, 3H, Ph–OCH_3), 2.90 (q, 1H, $J = 8.1$ Hz, H-5), 2.38 (d, 1H, O*H*); ^{13}C NMR ($CDCl_3$): δ 138.2, 138.0 (aromatic *C*), 134.6 (C-6), 130.0–127.6 (aromatic *C*), 119.0 (C-7), 113.8 (aromatic *C*), 88.3 (C-3), 86.7 (C-2), 84.7 (C-4), 75.5 (C-1), 72.0, 71.9, 71.4 (PhCH_2 × 3), 55.3 (Ph–OCH_3), 50.9 (C-5). ESIMS *m*/*z* calcd for $[C_{29}H_{32}O_5+Na]^+$: 483.2142. Found: 483.2146. **1*S*,5*R* Isomer**; $R_f = 0.31$ (3:1, *n*-hexane–EtOAc); ^{1}H NMR ($CDCl_3$): δ 7.36–7.28 (m, 12H, aromatic), 6.88 (d, 2H, $J = 8.6$ Hz, *p*-MeO-*Ph*), 6.14 (ddd, 1H, $J_{6,5} = 9.3$ Hz, $J_{6,7\text{-cis}} = 10.2$ Hz, $J_{6,7\text{-trans}} = 17.2$ Hz, H-6), 5.25 (br d, 1H, H-7-cis), 5.22 (br d, 1H, H-7-trans), 4.62, 4.52 (each d, 2H, $J = 11.4$ Hz, PhCH_2), 4.51 (s, 4H, PhCH_2 and *p*-MeO–PhCH_2), 4.16–4.11 (m, 2H, H-1, H-3), 3.86 (dd, 1H, $J_{3,4} = 2.7$ Hz, $J_{4,5} = 5.9$ Hz, H-4), 3.83–3.79 (m, 1H, H-2), 3.81 (s, 3H, Ph–OCH_3), 2.82 (ddd, 1H, $J_{1,5} = 5.3$ Hz, H-5), 2.63 (d, 1H, $J = 8.6$ Hz, O*H*); ^{13}C NMR ($CDCl_3$): δ 159.33, 137.93, 137.73, 133.16, 129.85, 129.61, 128.38, 128.34, 127.79, 127.77, 127.73, 127.71, 118.48, 113.82, 88.30 (C-3), 84.89 (C-2), 84.33 (C-4), 73.44 (C-1), 71.80, 71.61, 71.52, 55.25, 49.81 (C-5).

3.4. (1*R*,2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-hydroxymethyl-2-(4-methoxybenzyloxy)-cyclopentanol (5)

Ozone was bubbled through a solution of **4** and **1*S*,2*S* isomer** (1.25 g, 2.71 mmol, 88:12, **4**/**1*S*,2*S* isomer**) in CH_2Cl_2–MeOH (1:1, 34.0 mL) at −78 °C until consumption of the olefin. To the solution was added $NaBH_4$ (1.03 g, 27.1 mmol), and the mixture was stirred for 1 h at −78 °C and for 1 h at rt. The reaction mixture was poured into satd NH_4Cl, then the products were extracted with EtOAc. The organic layer was washed successively with H_2O and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (1:1 *n*-hexane–EtOAc) to afford **5** (955 mg, 76%) and its **1*S* isomer** (128 mg, 10%): **5**; $R_f = 0.34$ (2:3 *n*-hexane–EtOAc); mp 84.5–86.0 °C; $[\alpha]_D^{25}$ +22.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.36–7.27 (m, 12H, aromatic), 6.88 (d, 2H, $J = 8.6$ Hz, *p*-MeO-*Ph*), 4.67–4.58 (m, 6H, PhCH_2), 4.28 (td, 1H, $J_{1,2} = J_{1,OH} = 4.2$ Hz, $J_{1,5} = 6.8$ Hz, H-1), 4.02 (dd, 1H, $J_{3,4} = 5.8$ Hz, $J_{4,5} = 8.1$ Hz, H-4), 3.93 (dd, 1H, $J_{2,3} = 5.2$ Hz, H-3), 3.92 (ddd, 1H, H-5a), 3.86 (ddd, 1H, $J_{5,5'b} = 5.9$ Hz, $J_{5'a,5'b} = 11.3$ Hz, $J_{5'b,OH} = 5.8$ Hz, H-5′b), 3.81 (s, 3H, Ph–OCH_3), 3.78 (t, 1H, $J =$ 4.5 Hz, H-2), 2.59 (d, 1H, $J = 4.5$ Hz, O*H*), 2.30 (m, 1H, H-5), 2.17 (t, 1H, $J = 5.6$ Hz, O*H*); ^{13}C NMR ($CDCl_3$): δ 138.2–127.7, 113.9 (aromatic *C*), 87.7 (C-3), 87.6 (C-2), 81.7 (C-4), 75.7 (C-1), 72.2, 72.1, 71.7 (Ph*C*H_2 × 3), 61.2 (C-5′), 55.3 (Ph–O*C*H_3), 46.6 (C-5). ESIMS *m*/*z* calcd for $[C_{28}H_{32}O_6+Na]^+$: 487.2091. Found: 487.2094. **1*S* Isomer** $R_f = 0.23$ (2:3 *n*-hexane–EtOAc); mp 101.0–103.5 °C; $[\alpha]_D^{28}$ +6.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.38–7.28 (m, 12H, aromatic), 6.88 (d, 2H, $J = 8.6$ Hz, *p*-MeO-*Ph*), 4.68–4.51 (m, 6H, PhCH_2), 4.00 (dd, 1H, $J_{2,3} = 3.9$ Hz, $J_{3,4} = 4.1$ Hz, H-3), 3.93 (ddd, 1H, $J_{1,2} = 7.8$ Hz, $J_{1,5} = 5.5$ Hz, $J_{1,OH} =$ 7.9 Hz, H-1), 3.83–3.78 (m, 5H, H-2, H-5′a, Ph–OCH_3), 3.74 (td, 1H, $J = 5.4$ Hz, $J_{5'a,5'b} = 10.7$ Hz,

H-5′b), 3.67 (dd, 1H, $J_{4,5} = 8.2$ Hz, H-4), 2.61 (d, 1H, $J = 7.9$ Hz, O*H*), 2.25 (m, 1H, H-5), 1.88 (t, 1H, J 5.3 Hz, O*H*). ^{13}C NMR ($CDCl_3$): δ 138.1–127.7, 113.9 (aromatic *C*), 86.6 (C-3), 82.6 (C-4), 81.6 (C-2), 72.1, 71.9, 71.7 (PhCH_2 × 3), 71.6 (C-1), 63.1 (C-5′), 55.3 (Ph–OCH_3), 50.6 (C-5). ESIMS m/z calcd for $[C_{28}H_{32}O_6+Na]^+$: 487.2091. Found: 487.2089.

3.5. (1*R*,2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-2-(4-methoxybenzyloxy)-5-trityloxymethyl-cyclopentanol (6)

To a pyridine (64.0 mL) solution of **5** (890 mg, 1.92 mmol) was added TrCl (695 mg, 2.50 mmol) and the mixture was stirred for 30 h at 70 °C under a nitrogen atmosphere. After the mixture was concentrated in vacuo, the residue was suspended in a mixed solvent (2:1 *n*-hexane–EtOAc) and filtered through a Celite pad. The filtrate was concentrated again, and the residue was purified by silica gel chromatography (7:2 *n*-hexane–EtOAc) to afford **6** (1.13 g, 83%) as a syrup: $R_f = 0.47$ (2:1, *n*-hexane–EtOAc); $[\alpha]_D^{28}$ +8.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.41–7.17 (m, 27H, aromatic), 6.86 (d, 2H, $J = 8.7$ Hz, *p*-MeO-*Ph*), 4.66–4.48 (m, 6H, PhCH_2), 4.25 (ddd, 1H, $J_{1,2} = 2.9$ Hz, $J_{1,5} = 6.0$ Hz, $J_{1,OH} = 3.0$ Hz, H-1), 4.15 (dd, 1H, $J_{4,3} = 6.2$ Hz, $J_{4,5} = 9.4$ Hz, H-4), 3.93 (dd, 1H, $J_{2,3} = 5.0$ Hz, H-3), 3.80 (dd, 1H, H-2), 3.79 (s, 3H, Ph–OCH_3), 3.45 (dd, 1H, $J_{5,5'a} = 6.1$ Hz, $J_{5'a,5'b} = 9.6$ Hz, H-5′a), 3.39 (dd, 1H, $J_{5,5'b} = 3.8$ Hz, H-6′), 3.09 (d, 1H, O*H*), 2.38 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 143.4, 138.4–127.2, 113.8 (aromatic *C*), 88.6 (C-3), 87.4 (C-2), 87.3 (*C*Ph_3), 82.0 (C-4), 74.9 (C-1), 72.2, 72.0, 71.3 (PhCH_2×3), 61.1 (C-5′), 55.3 (Ph–OCH_3), 45.6 (C-5). ESIMS m/z calcd for $[C_{47}H_{46}O_6+Na]^+$: 729.3187. Found: 729.3179.

3.6. (1*R*,2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-2-(4-methoxybenzyloxy)-5-trityloxymethyl-1-thiocarbonylimidazoyloxy-cyclopentanol (7)

The mixture of **6** (1.13 g, 1.60 mmol), 1,1′-thiocarbonyl diimidazole (1.27 g, 6.39 mmol) and DMAP (78 mg, 0.64 mmol) in THF (6.00 mL) was stirred for 20 h at 80 °C. After the mixture was concentrated in vacuo, the residue was purified by silica gel chromatography (5:2 *n*-hexane–EtOAc) to afford**7** (1.25 g, 96%) as a syrup: $R_f = 0.34$ (2:1 *n*-hexane–EtOAc); $[\alpha]_D^{25}$ +66.3 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.97 (s, 1H, imidazole), 7.32–7.14 (m, 28H, aromatic), 6.94 (s, 1H, imidazole), 6.87 (d, 2H, $J = 8.6$ Hz, *p*-MeO-*Ph*), 5.99 (br d, 1H, $J = 4.5$ Hz, H-1), 4.76 (d, 1H, $J = 11.8$ Hz, PhCH_2), 4.63 (d, 1H, $J = 11.8$ Hz, PhCH_2), 4.51 (d, 1H, $J = 11.8$ Hz, PhCH_2), 4.41 (d, 1H, $J = 11.8$ Hz, PhCH_2), 4.38 (s, 2H, PhCH_2), 3.99 (br s, 1H, H-3), 3.94 (br s, 1H, H-2), 3.82 (dd, 1H, $J_{3,4} = 4.9$ Hz, $J_{4,5} = 8.9$ Hz, H-4), 3.79 (s, 3H, Ph–OCH_3), 3.35 (dd, 1H, $J_{5,5'a} = 4.3$ Hz, $J_{5'a,5'b} = 9.1$ Hz, H-5′a), 3.01 (t, 1H, $J = 9.1$ Hz, H-5′b), 2.38 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ (O*C*=S), 143.4, 137.8–127.0, 113.9 (aromatic *C*), 88.9, 86.7 (*C*Ph_3), 84.0, 83.9, 83.0, 72.1, 71.9, 71.6 (PhCH_2 × 3), 59.8 (C-5′), 55.3 (Ph–OCH_3), 45.6 (C-5). ESIMS m/z calcd for $[C_{51}H_{48}N_2O_6S+Na]^+$: 839.3125. Found: 839.3117.

3.7. (1*S*,2*R*,3*S*,5*S*)-2,3-Bis(benzyloxy)-5-(4-methoxybenzyloxy)-3-trityloxymethyl-cyclopentane (8)

To a toluene (8.00 mL) solution of *n*-Bu_3SnH (0.61 mL, 2.25 mmol) was added a toluene (6.00 mL) solution of **7** (460 mg, 0.563 mmol) and azobisisobutyronitrile (AIBN, 28 mg, 0.169 mmol) at reflux under a nitrogen atmosphere. After being stirred for 1 h, the mixture was concentrated in vacuo. The residue was purified by silica gel chromatography (6:1 *n*-hexane–EtOAc) to afford **8** (365 mg, 94%) as a syrup: $R_f = 0.66$ (2:1 *n*-hexane–EtOAc); $[\alpha]_D^{27}$ +16.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.43–7.17 (m, 27H, aromatic), 6.86 (d, 2H, $J = 8.6$ Hz, *p*-MeO-*Ph*), 4.64–4.43 (m, 6H, PhCH_2), 3.94 (dd, 1H, $J_{1,5} = 2.7$ Hz, $J_{1,2} = 3.6$ Hz, H-1), 3.90 (m, 1H, H-5), 3.80 (m, 4H, H-2, Ph–OCH_3), 3.17 (dd, 1H, $J_{3,3'a} = 4.7$ Hz, $J_{3'a,3'b} = 9.2$ Hz, H-3′a), 3.10 (t, 1H, $J_{3,3'b} = 5.7$ Hz, H-3′b), 2.41 (m, 1H, H-3), 1.93 (m, 2H, H-4a, H-4b); ^{13}C NMR ($CDCl_3$): δ 144.1, 138.5–126.9, 113.7 (aromatic *C*), 90.0 (C-1), 86.3 (*C*Ph_3), 84.8 (C-2), 80.9 (C-5), 72.1, 72.0, 70.6 (PhCH_2 × 3), 63.8 (C-3′), 55.3 (Ph–OCH_3), 41.5 (C-3), 30.9 (C-4). ESIMS m/z calcd for $[C_{47}H_{46}O_5+Na]^+$: 713.3237. Found: 713.3236.

3.8. (1*S*,2*R*,3*R*,4*R*)-2,3-Bis(benzyloxy)-4-trityloxymethyl-cyclopentanol (9)

To a CH_2Cl_2 (62.4 mL) solution of **8** (455 mg, 0.659 mmol) were added H_2O (3.50 mL) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 299 mg, 1.32 mmol) at 0 °C. After being stirred for 2 h at rt, the mixture was filtered through a Celite pad and poured into satd $NaHCO_3$, then the product was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (3:1 *n*-hexane–EtOAc) to afford **9** (343 mg, 91%) as a syrup: $R_f = 0.36$ (3:1 *n*-hexane–EtOAc); $[\alpha]_D^{27}$ +25.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.47–7.21 (m, 25H, aromatic), 4.57 (s, 2H, PhCH_2), 4.53 (s, 2H, PhCH_2), 4.14 (br s, 1H, H-1), 3.83 (m, 2H, H-2, H-3), 3.13 (ddd, 2H, $J_{4,4'a} = 9.2$ Hz, $J_{4,4'b} = 6.5$ Hz, $J_{4'a,4'b} = 15.8$ Hz, H-4′a, H-4′b), 2.48 (m, 1H, H-4), 2.02 (d, 1H, $J_{1,OH} = 6.1$ Hz, O*H*), 1.92 (ddd, 1H, $J = 4.6$ Hz, $J = 8.9$ Hz, $J_{5a,5b} = 13.7$ Hz, H-5a), 1.85 (ddd, 1H, $J = 6.5$ Hz, $J = 7.7$ Hz, H-5b); ^{13}C NMR ($CDCl_3$): δ 144.1, 138.3, 128.8–127.0 (aromatic *C*), 90.0 (C-2), 86.5 (*C*Ph_3), 85.0 (C-3), 75.1 (C-1), 71.9

(PhCH$_2$×2), 64.9 (C-4′), 42.2 (C-4), 34.3 (C-5). ESIMS *m*/*z* calcd for $[C_{39}H_{38}O_4+Na]^+$: 593.2662. Found: 593.2662.

3.9. (1*S*,2*R*,3*R*,4*R*)-2,3-Bis(benzyloxy)-4-trityloxymethyl-cyclopentanoyl methanesulfonate (10)

To a pyridine (0.90 mL) solution of **9** (42.0 mg, μmol) were added DMAP (3.0 mg, 22.1 μmol) and methanesulfonyl chloride (17.0 μL, 0.221 mmol) at 0 °C under a nitrogen atmosphere. After being stirred for 20 h at rt, the mixture was poured into 5% $KHSO_4$ at 0 °C, then the product was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (3:1 *n*-hexane–EtOAc) to afford a corresponding mesylate **10** (45.3 mg, 95%) as a syrup; $R_f = 0.44$ (2:1 *n*-hexane–EtOAc); $[\alpha]_D^{28}$ +9.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.42–7.15 (m, 25H, aromatic), 5.04 (dt, 1H, $J = 4.6$ Hz, H-5), 4.68 (d, 1H, $J = 11.7$ Hz, PhCH_2), 4.61 (d, 1H, $J = 11.7$ Hz, PhCH_2), 4.44 (d, 1H, $J = 11.6$ Hz, PhCH_2), 4.40 (d, 1H, $J = 11.6$ Hz, PhCH_2), 4.10 (t, 1H, $J_{1,5} = J_{1,2} = 4.6$ Hz, H-1), 3.82 (dd, 1H, $J_{2,3} = 6.8$ Hz, H-2), 3.20 (dd, 1H, $J_{3,3'a} = 4.6$ Hz, H-3′a), 3.16 (dd, 1H, $J_{3,3'b} = 5.3$ Hz, H-3′b), 2.98 (s, 3H, SO_2CH_3), 2.41 (m, 1H, H-3), 2.15 (m, 2H, H-4a, H-4b); ^{13}C NMR ($CDCl_3$): δ 143.4, 137.9–127.0 (aromatic *C*), 88.5 (C-1), 86.6 (*C*Ph$_3$), 84.6 (C-2), 83.2 (C-5), 72.3, 72.2 (PhCH$_2$ × 2), 63.5 (C-3′), 41.9 (C-3), 38.5 (SO_2CH_3), 32.2 (C-4). ESIMS *m*/*z* calcd for $[C_{40}H_{40}O_6S+Na]^+$: 671.2438. Found: 671.2440.

3.10. (1*R*,2*R*,3*R*,5*S*)-5-Azido-1,2-bis(benzyloxy)-3-trityloxymethyl-cyclopentane (11)

To a DMF (0.87 mL) solution of this compound (45.3 mg, 0.698 mmol) were added NaN_3 (45.0 mg, 0.698 mmol), and the mixture was stirred for three days at 80 °C. After cooling, the mixture was poured into ice water then the product were extracted with a mixed solvent (4:1, *n*-hexane–EtOAc). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (10:1 *n*-hexane–EtOAc) to afford **10** (39.5 mg, 95%) as a syrup; $R_f = 0.57$ (3:1 *n*-hexane–EtOAc); $[\alpha]_D^{27}$ −10.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.42–7.19 (m, 25H, aromatic), 4.58–4.47 (m, 4H, PhCH_2), 3.87 (t, 1H, $J = 4.2$ Hz, H-1), 3.82 (t, 1H, $J = 4.3$ Hz, H-2), 3.76 (ddd, 1H, H-5), 3.17 (m, 2H, H-3′a, H-3′b), 2.22 (m, 1H, H-4), 2.15 (ddd, 1H, H-4a), 1.72 (dt, 1H, $J = 7.8$ Hz, $J_{4a,4b} = 13.0$ Hz, H-4b); ^{13}C NMR ($CDCl_3$): δ 144.1–127.0 (aromatic *C*), 86.6 (*C*Ph$_3$), 84.6 (C-1), 83.6 (C-2), 72.0, 71.9 (PhCH$_2$×2), 65.0 (C-3′), 60.6 (C-5), 42.2 (C-3), 29.6 (C-4). ESIMS *m*/*z* calcd for $[C_{39}H_{37}N_3O_3+Na]^+$: 618.2727. Found: 618.2729.

3.11. (1*R*,2*R*,3*R*,5*S*)-5-*t*-Butyloxycarbonylamino-3-hydroxymethyl-cyclopentane-1,2-diol (12)

To a THF–MeOH (1:1, 1.16 mL) solution of **11** (20.7 mg, 34.8 μmol) were added $Pd(OH)_2$–C (ca. 10.0 mg) and 10% HCl (MeOH solution, 0.12 mL). The mixture was stirred for 20 h under a hydrogen atmosphere, filtered through a Celite pad then concentrated in vacuo. To a MeOH–H_2O solution (1:1, 1.16 mL) of the residue were added Et_3N (10.0 μL, 69.5 μmol) and a MeOH (0.29 mL) solution of Boc_2O (16.0 mg, 69.5 μmol) at 0 °C. After being stirred for 3 h at rt, the mixture was concentrated in vacuo. The residue was purified by silica gel chromatography (30:1, EtOAc–MeOH) to afford **12** (7.4 mg, 86%) as a syrup: $R_f = 0.37$ (10:1, EtOAc–MeOH); $[\alpha]_D^{25}$ +28.0 (*c* 0.2, MeOH); ^{1}H NMR (CD_3OD): δ 3.96 (m, 1H, H-5), 3.76 (dd, 1H, $J_{1,2} = 4.9$ Hz, $J_{1,5} = 3.2$ Hz, H-1), 3.66 (dd, 1H, $J_{2,3} = 4.4$ Hz, H-2), 3.60 (dd, 2H, $J_{3,3'a} = 5.7$ Hz, $J_{3'a,3'b} = 10.6$ Hz, H-3′a), 3.51 (dd, 1H, $J_{3,3'b} = 6.6$ Hz, H-3′b), 2.11 (dt, 1H, $J = 8.0$ Hz, $J_{4a,4b} = 12.6$ Hz, H-4a), 1.87 (m, 1H, H-3), 1.41 (s, 9H, *t*-Bu), 1.35 (dt, 1H, $J = 9.4$ Hz, H-4b); ^{13}C NMR (CD_3OD): δ 157.9 (NH–*C*O), 80.1 (*C*Me$_3$), 80.0 (C-2), 78.7 (C-1), 65.1 (C-3′), 53.3 (C-5), 47.3 (C-3), 32.3 (C-4), 28.7 (Me). ESIMS *m*/*z* calcd for $[C_{11}H_{21}NO_5+Na]^+$: 270.1312. Found: 270.1308.

3.12. (1*R*,2*R*,3*R*,5*S*)-5-Amino-3-hydroxymethyl-cyclopentane-1,2-diol (13)

To a CH_2Cl_2 (0.42 mL) solution of **12** (2.8 mg, 11.3 μmol) was added TFA (0.14 mL) at 0 °C. The mixture was stirred for 1 h under a nitrogen atmosphere, and concentrated in vacuo. The residue was dissolved in H_2O then filtered through Millex® filter. The filtrate was concentrated in vacuo to afford **13** (3.0 mg, quant.) as a TFA salt: $R_f = 0.39$ (5:2:3, *n*-BuOH–AcOH–H_2O); $[\alpha]_D^{23}$ +23.6 (*c* 0.6, MeOH); ^{1}H NMR (D_2O): δ 4.06 (t, 1H, $J = 8.5$ Hz, H-1), 3.80 (dd, 1H, $J_{1,2} = 5.3$ Hz, $J_{1,5} = 6.9$ Hz, H-2), 3.69 (m, 1H, H-5), 3.68 (dd, 1H, $J_{3,3'a} = 5.0$ Hz, $J_{3'a,3'b} = 11.2$ Hz, H-3′a), 3.59 (dd, 1H, $J_{3,3'b} = 6.5$ Hz, H-3′b), 2.34 (td, 1H, $J = 8.1$ Hz, $J_{4a,4b} = 13.6$ Hz, H-4a), 1.99 (m, 1H, H-3), 1.88 (ddd, 1H, $J_{4b,5} = 9.6$ Hz, $J_{3,4b} = 8.4$ Hz, H-4b); ^{13}C NMR (CD_3OD): δ 79.3 (C-2), 77.3 (C-1), 64.2 (C-3′), 53.0 (C-5), 47.3 (C-3), 30.5 (C-4). HRMS *m*/*z* calcd for $[C_6H_{13}NO_3+H]^+$: 148.0968. Found: 148.0966.

3.13. (2*S*,3*R*,4*R*)-2,3-Bis(benzyloxy)-4-trityloxymethyl-cyclopentanone (14)

A mixture of **9** (209 mg, 0.366 mmol) and Dess–Martin Periodinane (311 mg, 0.732 mmol) in CH_2Cl_2 (7.30 mL) was stirred for 20 h at rt. To the mixture was added satd $NaHCO_3$ and stirred for 5 min at

0 °C. The organic layer was washed with brine, followed by extraction with CH_2Cl_2, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel chromatography (6:1 *n*-hexane–EtOAc) to afford **14** (190 mg, 91%) as a syrup: $R_f = 0.57$ (3:1, *n*-hexane–EtOAc); $[\alpha]_D^{25}$ +16.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.41–7.14 (m, 25H, aromatic), 5.07 (d, 1H, $J = 11.4$ Hz, PhCH_2), 4.74 (d, 1H, $J = 11.5$ Hz, PhCH_2), 4.71 (d, 1H, $J = 11.5$ Hz, PhCH_2), 4.47 (d, 1H, $J = 11.5$ Hz, PhCH_2), 4.12 (t, 1H, $J = 7.4$ Hz, H-3), 4.06 (dd, $J_{2,3} = 8.7$ Hz, $J_{2,5} = 1.6$ Hz, H-2), 3.30 (d, 2H, $J = 3.9$ Hz, H-4′a, H-4′b), 2.55 (ddd, 1H, $J_{4,5a} = 8.8$ Hz, $J_{5a,5b} = 19.1$ Hz, H-5a), 2.37 (m, 1H, H-4), 2.43 (dd, 1H, $J_{4,5b} = 10.8$ Hz, H-5b); ^{13}C NMR ($CDCl_3$): δ 213.1 (C-1),143.7, 137.9–127.0 (aromatic *C*), 87.0 (C-2), 86.4 (*C*Ph$_3$), 80.9 (C-3), 73.02, 72.98 (Ph*C*H$_2$ × 2), 61.2 (C-6), 38.2 (C-5), 37.7 (C-4). ESIMS *m*/*z* calcd for $[C_{39}H_{36}O_4+Na]^+$: 591.2506. Found: 591.2506.

3.14. (1*R*,2*R*,3*R*,4*R*)-2,3-Bis(benzyloxy)-4-trityloxymethyl-cyclopentanol (15)

To a THF–MeOH (1:1, 2.80 mL) solution of **14** (81.0 mg, 0.142 mmol) was added $NaBH_4$ (54.0 mg, 1.42 mmol) at −78 °C, then stirred for 1 h. After being stirred for 1 h at 0 °C, the mixture was poured into satd NH_4Cl. The organic layer was washed with brine, followed by extraction with EtOAc, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel chromatography (5:1, *n*-hexane–EtOAc) to afford **15** (73.0 mg, 89%) and **9** (8.0 mg, 10%): $R_f = 0.49$ (5:2, *n*-hexane–EtOAc); $[\alpha]_D^{24}$ +11.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (C_6D_6): δ 7.58–7.00 (m, 25H, aromatic), 4.59 (s, 2H, PhCH_2), 4.32 (d, 1H, $J = 11.9$ Hz, PhCH_2), 4.27 (d, 1H, $J = 11.8$ Hz, PhCH_2), 4.03 (m, 1H, H-1), 3.99 (t, 1H, $J = 5.2$ Hz, H-3), 3.68 (t, 1H, $J = 4.8$ Hz, H-2), 3.37 (dd, 1H, H-4′a), 3.13 (dd, 1H, H-4′b), 2.23 (m, 1H, H-4), 2.21 (d, 1H, $J = 4.9$ Hz, O*H*), 1.90 (ddd, 1H, H-5a), 1.68 (ddd, 1H, H-5b); ^{13}C NMR (C_6D_6): δ 144.9, 139.5–127.2 (aromatic *C*), 87.0 (*C*Ph$_3$), 86.4 (C-2), 84.7 (C-3), 72.0, 71.8 (Ph*C*H$_2$×2), 70.6 (C-1), 66.2 (C-6), 42.3 (C-4), 33.3 (C-5). ESIMS *m*/*z* calcd for $[C_{39}H_{38}O_4+Na]^+$: 593.2662. Found: 593.2663.

3.15. (1*R*,2*R*,3*R*,4*R*)-2,3-Bis(benzyloxy)-4-trityloxymethyl-cyclopentanoyl methanesulfonate (16)

Compound **16** was obtained from **15** by reacting in the same manner as described for **10**. Corresponding mesylate **16** was purified by silica gel chromatography (7:2, *n*-hexane–EtOAc) to afford a syrup (92%); $R_f = 0.29$ (3:1, *n*-hexane–EtOAc); $[\alpha]_D^{26}$ −12.7 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.44–7.20 (m, 25H, aromatic), 5.14 (ddd, 1H, H-5), 4.67–4.51 (m, 4H, PhCH_2), 3.91 (dd, 1H, $J_{1,5} = 4.5$ Hz, $J_{1,2} = 4.7$ Hz, H-1), 3.89 (dd, 1H, $J_{2,3} = 6.8$ Hz, H-2), 3.19 (dd, 1H, $J_{3,3'a} = 9.0$ Hz, H-3′a), 3.18 (dd, 1H, $J_{3,3'b} = 9.0$ Hz, H-3′b), 2.89 (s, 3H, SO_2CH_3), 2.27 (ddd, 1H, H-4a), 2.26 (m, 1H, H-3), 1.94 (dt, 1H, $J = 4.9$ Hz, $J_{4a,4b} = 8.7$ Hz, H-4b); ^{13}C NMR ($CDCl_3$): δ 144.0, 138.2–127.0 (aromatic *C*), 86.6 (*C*Ph$_3$), 83.9 (C-1), 83.3 (C-2), 79.4 (C-5), 72.4, 72.3 (Ph*C*H$_2$ × 2), 64.7 (C-3′), 40.9 (C-3), 38.7 (SO_2CH_3), 30.6 (C-4). ESIMS calcd for $[C_{40}H_{40}O_6S+Na]^+$: 671.2438. Found: 671.2432.

3.16. (1*R*,2*R*,3*R*,5*R*)-5-Azido-1,2-bis(benzyloxy)-3-trityloxymethyl-cyclopentane (17)

Compound **17** was obtained from **16** by reacting in the same manner as described for **11**. Compound **17** was purified by silica gel chromatography (8:1 *n*-hexane–EtOAc) to afford a syrup (quant.); $R_f = 0.69$ (3:1 *n*-hexane–EtOAc); $[\alpha]_D^{28}$ +18.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.43–7.18 (m, 25H, aromatic), 4.66 (d, 1H, $J = 11.6$ Hz,PhCH_2), 4.59 (d, 1H, $J = 11.6$ Hz, PhCH_2), 4.50 (d, 1H, $J = 11.6$ Hz, PhCH_2), 4.45 (d, 1H, $J = 11.6$ Hz, PhCH_2), 4.10 (dd, 1H, $J_{1,5} = 4.5$ Hz, $J_{1,2} = 4.7$ Hz, H-1), 3.82 (dd, 1H, $J_{2,3} = 6.8$ Hz, H-2), 3.18 (dd, 1H, $J_{3,3'a} = 5.1$ Hz, $J_{3'a,3'b} = 9.3$ Hz, H-3′a), 3.16 (dd, 1H, $J_{3,3'b} = 5.8$ Hz, H-3′b), 2.33 (m, 1H, H-3), 2.00 (dt, 1H, $J = 7.2$ Hz, $J_{4a,4b} = 13.6$ Hz, H-4a), 1.91 (ddd, 1H, $J = 6.5$ Hz, $J = 8.6$ Hz, H-4b); ^{13}C NMR ($CDCl_3$): δ 144.0, 138.2–127.1 (aromatic *C*), 89.3 (C-2), 86.6 (*C*Ph$_3$), 85.0 (C-1), 72.4, 72.2 (Ph*C*H$_2$ × 2), 63.9 (C-3′), 63.7 (C-5), 41.8 (C-3), 30.5 (C-4). ESIMS *m*/*z* calcd for $[C_{39}H_{37}N_3O_3+Na]^+$: 618.2727. Found: 618.2732.

3.17. (1*R*,2*R*,3*R*,5*R*)-5-*t*-Butyloxycarbonylamino-3-hydroxymethyl-cyclopentane-1,2-diol (18)

Compound **18** was obtained from **17** by reacting in the same manner as described for **12**. Compound **18** was purified by silica gel chromatography (30:1 EtOAc–MeOH) to afford a syrup (84%): $R_f = 0.43$ (10:1 EtOAc–MeOH); $[\alpha]_D^{25}$ +38.2 (*c* 0.2, MeOH); ^{1}H NMR (CD_3OD): δ 3.63–3.51 (m, 4H, H-1, H-2, H-5, H-3′a), 3.47 (dd, 1H, $J_{3,3'b} = 6.6$ Hz, $J_{3'a,3'b} = 10.6$ Hz, H-3′b), 1.92 (m, 1H, H-3), 1.88 (dt, 1H, $J = 7.0$ Hz, $J_{4a,4b} = 13.0$ Hz, H-4a), 1.61 (m, 1H, H-4b), 1.41 (s, 9H, *t*-Bu); ^{13}C NMR (CD_3OD): δ 83.3 (C-1 or 2), 80.0 (*C*Me$_3$), 78.6 (C-1 or 2), 64.5 (C-3′), 55.3 (C-5), 44.7 (C-3), 31.1 (C-4), 28.8, 28.5 (Me). ESIMS *m*/*z* calcd for $[C_{11}H_{21}NO_5+Na]^+$: 270.1312. Found: 270.1309.

3.18. (1*R*,2*R*,3*R*,5*R*)-5-Amino-3-hydroxymethyl-cyclopentane-1,2-diol (19)

Compound **19** was quantitatively obtained from **18** by reacting in the same manner as described for **13**: $R_f = 0.40$ (5:2:3 *n*-BuOH–AcOH–H_2O); $[\alpha]_D^{23}$ +47.6 (*c*

0.4, MeOH); ^{1}H NMR (D_2O): δ 3.88 (t, 1H, $J = 8.5$ Hz, H-1), 3.67 (t, 1H, $J = 8.5$ Hz, H-2), 3.65 (dd, 1H, $J_{3,3'a} = 4.6$ Hz, $J_{3'a,3'b} = 11.2$ Hz, H-3′a), 3.54 (dd, 1H, $J_{3,3'b} = 6.6$ Hz, H-3′b), 3.37 (q, 1H, J=8.7 Hz, H-5), 2.10 (m, 1H, H-3), 1.98 (ddd, 1H, H-4a), 1.88 (ddd, 1H, H-4b); ^{13}C NMR (CD_3OD): δ 81.3 (C-1), 77.8 (C-2), 63.5 (C-3′), 55.0 (C-5), 44.6 (C-3), 28.1 (C-4). ESIMS m/z calcd for $[C_6H_{13}NO_3+H]^+$: 148.0968. Found: 148.0966.

3.19. (1*R*,2*S*,3*R*,4*R*)-2,3-Bis(benzyloxy)-1-dichloromethyl-4-trityloxymethyl-cyclopentanol (20-*R*) and (1*S*,2*S*,3*R*,4*R*)-2,3-bis(benzyloxy)-1-dichloromethyl-4-trityloxymethyl-cyclopentanol (20-*S*)

To a THF (1.20 mL) solution of *N*,*N*′-diisopropylamine (47.0 μL, 0.333 mmol) were added *n*-BuLi (1.6 M in *n*-hexane, 0.21 mL) and the mixture was stirred for 1 h at −78 °C under nitrogen atmosphere. To the mixture were added THF (0.15 mL) solution of CH_2Cl_2 (0.214 mL, 3.33 mmol) and THF (0.30 mL) solution of **14** (47.4 mg, 83.4 μmol), successively. After being stirred for 1 h, the mixture was poured into satd NH_4Cl. The products were extracted with CH_2Cl_2 then washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel chromatography (8:1 *n*-hexane–EtOAc) to afford **20-*R*** (36.4 mg, 67%) and **20-*S*** (7.0 mg, 13%): **20-*R***; $R_f = 0.56$ (7:2, *n*-hexane–EtOAc); $[\alpha]_D^{24}$ +10.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.44–7.14 (m, 25H, aromatic), 5.56 (s, 1H, C*H*Cl_2), 4.77 (d, 1H, $J = 11.1$ Hz, PhCH_2), 4.70 (d, 1H, $J = 11.1$ Hz, PhCH_2), 4.49 (d, 1H, $J = 11.4$ Hz, PhCH_2), 4.45 (d, 1H, $J = 11.4$ Hz, PhCH_2), 4.15 (d, 1H, $J = 7.1$ Hz, H-2), 3.95 (t, 1H, $J = 7.5$ Hz, H-3), 3.40 (s, 1H, O*H*), 3.31 (dd, 1H, $J_{4,4'a} = 5.4$ Hz, $J_{4'a,4'b} = 9.3$ Hz, H-4′a), 3.18 (dd, 1H, $J_{4,4'b} = 5.8$ Hz, H-4′b), 2.39 (dd, $J_{4,5a} = 9.5$ Hz, $J_{5a,5b} = 14.5$ Hz, H-5a), 2.18 (m, 1H, H-4), 1.91 (dd, $J_{4,5b} = 8.0$ Hz, H-5b); ^{13}C NMR ($CDCl_3$): δ 144.0, 128.7–127.0 (aromatic *C*), 86.6 (*C*Ph_3), 85.6 (C-3), 84.6 (C-2), 80.0 (C-1), 77.2 (*C*HCl_2), 73.7, 73.0 (Ph*C*H_2×2), 63.9 (C-4′), 40.1 (C-4), 34.1 (C-5). ESIMS m/z calcd for $[C_{40}H_{38}Cl_2O_4+Na]^+$: 675.2039. Found: 675.2044. **20-*S***; $R_f = 0.43$ (7:2, *n*-hexane–EtOAc); $[\alpha]_D^{25}$ +28.9 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.42–7.13 (m, 25H, aromatic), 6.03 (s, 1H, C*H*Cl_2), 4.58 (d, 1H, $J = 12.0$ Hz, PhCH_2), 4.53 (d, 1H, $J = 12.0$ Hz, PhCH_2), 4.37 (d, 1H, $J = 10.9$ Hz, PhCH_2), 4.29 (d, 1H, $J = 10.9$ Hz, PhCH_2), 3.85 (d, 1H, $J = 3.5$ Hz, H-3), 3.72 (s, 1H, H-2), 3.20 (dd, 1H, $J_{4,4'a} = 5.5$ Hz, $J_{4'a,4'b} = 9.1$ Hz, H-4′a), 3.07 (dd, 1H, $J_{4,4'b} = 7.6$ Hz, H-4′b), 3.02 (s, 1H, O*H*), 2.74 (m, 1H, H-4), 2.15 (dd, $J_{4,5a} = 8.1$ Hz, $J_{5a,5b} = 13.4$ Hz, H-5a), 1.67 (dd, $J_{4,5b} = 10.4$ Hz, H-5b); ^{13}C NMR ($CDCl_3$): δ 144.0, 128.7–127.0 (aromatic *C*), 87.9 (C-2), 86.6 (*C*Ph_3), 85.7 (C-1), 84.6 (C-3), 76.4 (*C*HCl_2), 71.8, 71.6 (Ph*C*H_2 × 2), 65.0 (C-4′), 44.9 (C-4), 38.3 (C-5). ESIMS m/z calcd for $[C_{40}H_{38}Cl_2O_4+Na]^+$: 675.2039. Found: 675.2043.

3.20. (1*S*,2*R*,3*R*,4*R*)-1-Azido-2,3-bis(benzyloxy)-4-trityloxymethyl-cyclopentane-carbaldehyde (21)

To a Me_2SO (0.40 mL) solution of **20-*R*** (22.0 mg, 33.7 μmol) were added 15-crown-5-ether (20.0 μL) and NaN_3 (22.0 mg, 0.337 mmol) and the mixture was stirred for two days at 80 °C under a nitrogen atmosphere. To the mixture was added NaN_3 (22.0 mg, 0.337 mmol) again. After being stirred for 20 h, the mixture was diluted with EtOAc, and poured into an ice water. The organic layer was washed with brine, followed by extraction with EtOAc, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel chromatography (100:1, toluene–EtOAc) to afford **21** (16.6 mg, 79%) as a syrup: $R_f = 0.34$ (40:1, toluene–EtOAc); $[\alpha]_D^{26}$ +25.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 9.65 (s, 1H, C*H*O), 7.42–7.13 (m, 25H, aromatic), 4.55 (d, 1H, $J = 11.4$ Hz, PhCH_2), 4.53 (d, 1H, $J = 11.3$ Hz, PhCH_2), 4.48 (d, 1H, $J = 11.5$ Hz, PhCH_2), 4.42 (d, 1H, $J = 11.4$ Hz, PhCH_2), 4.04 (d, 1H, $J = 5.7$ Hz, H-2), 4.01 (dd, 1H, $J_{3,2} = 5.9$ Hz, $J_{3,4} = 7.8$ Hz, H-3), 3.26 (m, 2H, H-4′a, H-4′b), 2.43 (m, 1H, H-4), 2.38 (dd, $J_{4,5a} = 11.4$ Hz, $J_{5a,5b} = 13.1$ Hz, H-5a), 1.95 (dd, $J_{4,5b} = 7.1$ Hz, H-5b); ^{13}C NMR ($CDCl_3$): δ 197.1 (*C*HO), 143.9, 128.7–127.1 (aromatic *C*), 91.0 (C-2), 86.6 (*C*Ph_3), 84.1 (C-3), 75.0 (C-1), 72.8, 72.7 (Ph*C*H_2 × 2), 62.5 (C-4′), 42.3 (C-4), 31.1 (C-5). ESIMS m/z calcd for $[C_{40}H_{37}N_3O_4+Na]^+$: 646.2676. Found: 646.2670.

3.21. (1*R*,2*R*,3*R*,5*R*)-3-Azido-3-benzylaminomethyl-1,2-bis(benzyloxy)-5-trityloxymethyl-cyclopentane (22)

To a THF (1.10 mL) solution of **21** (23.5 mg, 37.7 μmol), $BnNH_2$ (21.0 μL, 0.188 mmol) and AcOH (22.0 μL, 0.377 mmol) was added $NaBH_3CN$ (1 M in THF solution, 0.113 mL) and the mixture was stirred for 2 h at 0 °C under a nitrogen atmosphere. The mixture was poured into 5% aq NaOH, and the product was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel chromatography (6:1 *n*-hexane–EtOAc) to afford **22** (23.2 mg, 86%) as a syrup: $R_f = 0.63$ (7:2 *n*-hexane–EtOAc); $[\alpha]_D^{25}$ +28.8 (*c* 0.2, $CHCl_3$); ^{1}H NMR (C_6D_6): δ 7.54–7.00 (m, 30H, aromatic), 4.59 (d, 1H, $J = 12.0$ Hz, PhCH_2), 4.47 (d, 1H, $J = 12.0$ Hz, PhCH_2), 4.41 (d, 1H, $J = 11.5$ Hz, PhCH_2), 4.35 (d, 1H, $J = 11.5$ Hz, PhCH_2), 4.02 (d, 1H, $J = 4.1$ Hz, H-2), 3.96 (dd, 1H, $J_{1,2} = 4.3$ Hz, $J_{1,5} = 6.8$ Hz, H-1), 3.59 (s, 2H, NH–CH_2Ph), 3.20 (dd, 1H, $J_{5,5'a} = 5.4$ Hz, $J_{5'a,5'b} = 9.2$ Hz, H-5′a), 3.07 (dd, 1H, $J_{5,5'b} = 5.2$ Hz, H-5′b), 2.87

(d, 1H, $J = 12.3$ Hz, CH_2NHBn), 2.75 (d, 1H, $J = 12.3$ Hz, CH_2NHBn), 2.52 (m, 1H, H-5), 1.98 (dd, $J_{4a,5} = 10.8$ Hz, $J_{4a,4b} = 13.7$ Hz, H-4a), 1.87 (dd, $J_{4b,5} = 8.4$ Hz, H-4b); ^{13}C NMR (C_6D_6): δ 144.6, 128.7–127.1 (aromatic *C*), 88.8 (C-2), 87.0 (*C*Ph$_3$), 85.3 (C-1), 72.6, 72.3 (PhCH_2×2), 71.8 (C-3), 64.3 (C-5′), 54.6 (N–CH_2Ph), 53.6 (CH_2NHBn), 43.0 (C-5), 34.6 (C-4). ESIMS *m*/*z* calcd for $[C_{47}H_{46}N_4O_3+H]^+$: 715.3643. Found: 715.3637.

3.22. (1*R*,2*R*,3*R*,5*R*)-3-Amino-3-aminomethyl-5-hydroxymethyl-cyclopentane-1,2-diol (23)

To a THF–MeOH (1:1, 0.80 mL) solution of **22** (13.1 mg, 18.3 μmol) were added 20% Pd(OH)$_2$–C (ca. 10.0 mg) and 10% HCl–MeOH (65.0 μL). The mixture was stirred for 20 h under a hydrogen atmosphere, filtered through a Celite pad then concentrated in vacuo. To a H_2O solution (0.30 mL) of the residue were added Et_3N (10.0 μL, 73.3 μmol) and a MeOH (0.30 mL) solution of Boc_2O (16.0 mg, 73.3 μmol) at 0 °C. After being stirred for 4 h at rt, the mixture was concentrated in vacuo. The residue was purified by silica gel chromatography (30:1 EtOAc–MeOH) to afford a corresponding Boc derivative (4.4 mg, 64%). To a CH_2Cl_2 (0.36 mL) solution of the Boc derivative (3.5 mg, 9.3 μmol) was added TFA (0.12 mL) at 0 °C. The mixture was stirred for 2 h under a nitrogen atmosphere, and concentrated in vacuo. The residue was dissolved in H_2O then filtered through Millex®filter. The filtrate was concentrated in vacuo to afford **23** (3.8 mg, quant.) as a TFA salt: $R_f = 0.21$ (5:2:3, *n*-BuOH–AcOH–H_2O); ^{1}H NMR (D_2O): δ 4.08 (d, 1H, $J = 8.0$ Hz, H-2), 3.80 (dd, 1H, $J_{1,2} = 8.1$ Hz, $J_{1,5} = 8.4$ Hz, H-1), 3.65 (dd, 1H, H-5′a), 3.56 (dd, 1H, $J_{5,5'b} = 3.7$ Hz, $J_{5'a,5'b} = 11.5$ Hz, H-5′b), 3.42 (d, 1H, $J = 14.5$ Hz, CH_2NH$_2$), 3.29 (d, 1H, $J = 14.5$ Hz, CH_2NH$_2$), 2.13 (m, 2H, H-4a, H-5), 1.78 (dd, $J_{4b,5} = 13.2$ Hz, $J_{4a,4b} = 18.7$ Hz, H-4b); ^{13}C NMR (D_2O): δ 81.7 (C-2), 76.0 (C-1), 61.2 (C-5′), 58.4 (C-3), 43.1 (*C*H$_2$NH$_2$), 41.4 (C-5), 32.3 (C-4). HRMS *m*/*z* calcd for $[C_7H_{16}N_2O_3+H]^+$: 177.1234. Found: 177.1238. NOE (CH_2NH$_2$); 2.2% (H-3), 1.3% (H-5′).

3.23. (5*R*,6*R*,7*R*,8R)-8-(Hydroxymethyl)-2-phenyl-1,3-diazaspiro[4.4]non-1-ene-6,7-diol (1)

A MeOH (1.00 mL) solution of **23** (8.0 mg, 32 μmol), Et_3N (22.0 μL), 0.161 mmol and benzaldehyde (10.0 μL, 96.3 μmol) was stirred for 0.5 h at 0 °C. To the mixture was added NBS (17.0 mg, 96.3 μmol). After being stirred for 20 h at rt, the mixture was concentrated in vacuo then filtered through Dowex®-1 × 8, followed by eluting with H_2O. The product was purified by HPLC to afford **1** (2.8 mg, 33%) as a syrup: $R_f = 0.34$ (10:10:1, *i*-PrOH–H_2O–Et_3N); ^{1}H NMR (D_2O): δ 7.74–7.49 (m, 5H, aromatic), 3.96 (d, 1H, $J = 9.1$ Hz, H-6), 3.95 (d, 1H, $J = 11.7$ Hz, H-4a), 3.66 (dd, 1H, $J_{8,8'a} = 4.8$ Hz, $J_{8'a,8'b} = 11.3$ Hz, H-8′a), 3.59 (t, 1H, $J = 8.9$ Hz, H-7), 3.54 (dd, 1H, $J_{8,8'b} = 6.6$ Hz, H-8′b), 3.45 (d, 1H, $J = 11.6$ Hz, H-4b), 2.25 (dd, 1H, $J_{8,9a} = 11.2$ Hz, $J_{9a,9b} = 14.1$ Hz, H-9a), 2.07 (m, 1H, H-8), 1.73 (dd, 2H, $J_{8,9b} = 6.1$ Hz, H-9b). HRMS *m*/*z* calcd for $[C_{14}H_{18}N_2O_3+H]^+$: 263.1390. Found: 263.1392.

3.24. Glycosidase assay

3.24.1. Materials. *p*-Nitrophenyl-α-D-glucopyranoside (PNP-α-Glc), *p*-nitrophenyl-β-D-glucopyranoside (PNP-β-Glc), *p*-nitrophenyl-*N*-acetyl-2-deoxy-β-D-glucopyranoside (PNP-β-GlcNAc), *p*-nitrophenyl-β-D-galactopyranoside (PNP-β-Gal) and *p*-nitrophenyl-α-D-mannopyranoside (PNP-α-Man) were from Sigma–Aldrich Inc. (St. Louis, MO, USA). α-Glucosidase (EC 3.2.1.20) from yeast was purchased from Wako Pure Chemical Industries Ltd (Osaka, Japan), β-Glucosidase (EC 3.2.1.21) from almond, β-*N*-acetylglucosaminidase (EC 3.2.1.52) from jack beans, β-galactosidase (EC 3.2.1.23) from *Aspergillus oryzae* and α-mannosidase (EC 3.2.1.24) from jack bean were purchased from Sigma–Aldrich Inc. (St. Louis, MO, USA). α-Glucosidase was used in the phosphate buffer (25 mM, pH 7.0). β-*N*-Acetylglucosaminidase was used in citrate buffer (50 mM, pH 4.5). β-Glucosidase, α-mannosidase and β-galactosidase were used in phosphate buffer (25 mM, pH 5.8). Concentrations of enzymes were optimized and arranged between 0.1 and 0.2 U/mL. PNP-glycosides except PNP-α-Glc (0.5 mM) were used at 0.35 mM in solution.

3.24.2. Methods. Assays were performed on a BD Falcon microtest 96-well assay plate. After the mixture of PNP-glycosides, various amounts of inhibitors (75–500 μM) and various glycosidases in buffer solution (90 μL) were incubated for 7 min at 25 °C, the reaction was terminated by addition of 50 mM glycin buffer (180 μL, pH 10.0). Concentrations of *p*-nitrophenol generated in the each well were detected by absorbance at 405 nm using Wallac 1420-ARVOsx multilabel counter Version 2.0.

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