Synthesis of Aminocyclohexitol *via* Carbon–Carbon Bond-Forming Radical Cyclization of Oxime Ether

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The stannyl radical mediated-cyclization of oxime ether, derived from D-glucose, gave the aminocyclohexitol derivative. Stereoselective C–C bond forming cyclization proceeded *via* favorable conformers minimizing $A^{1,3}$-strain between the oxime ether group and α-substituents.

Key words radical reaction; oxime ether; cyclization

The aminocyclitols such as mannostatin, trehazolin, and allosamindin are well known to be powerful inhibitors of glycosidases.[2] Recently, our group and Marco-Contelles/Chiaira's group have independently reported the investigations into the radical cyclization of oxime ethers as a useful method for preparing various types of five-membered aminocyclitols.[3—8] In contrast, the synthesis of six-membered aminocyclitols has not been widely studied; thus, the synthesis of aminocyclohexitols based on the radical cyclization of oxime ethers derived from saccharides has been a subject of current interest due to their therapeutic applications.[9]

Marco-Contelles/Chiaira's group reported the SmI_2-mediated radical cyclization of oxime ether **1** giving the aminocyclohexitols **2** and **3** with low selectivity (Chart 1).[3,4] In our recent studies on the radical reaction of oxime ether **4**, we found that $A^{1,3}$-strain effect between the oxime ether group and α-substituents is important for stereocontrol of the benzyloxyamino group on product **5** (Chart 2).[10] In this paper, we report that the radical cyclization of oxime ether **6** proceeded with an excellent selectivity concerning the stereochemistry of the benzyloxyamino group on product **7** *via* favorable conformers minimizing $A^{1,3}$-strain around the oxime ether group.

Results and Discussion

Oxime ether **6** was prepared as shown in Chart 3. According to the literature,[11] the commercially available 1,2,3,4,6-pentaacetyl-D-glucose **8** was treated with *p*-TolSH in the presence of $BF_3 \cdot OEt_2$ to give **9**. Deacetylation of **9** followed by selective protection of 4,6-hydroxyl groups using *p*-anisaldehyde dimethylacetal gave **10** in 96% yield.[12] Benzylation of **10** using benzyl bromide and NaH followed by treatment with $NaBH_3CN$ in the presence of trifluoroacetic acid (TFA) gave alcohol **12**.[13] Treatment of **12** with *N*-iodosuccinimide (NIS) in the presence of AcOH gave the acetate **13** in 98% yield.[14] Subsequent deacetylation of **13** afforded the hemiacetal **14** in 96% yield, which was then treated with *O*-benzylhydroxyamine hydrochloride in pyridine to give oxime ether **15** in 91% yield, as an *E*/*Z* mixture in a 9 : 2 ratio. Treatment of **15** with 2,2-dimethoxypropane in the presence of *p*-TsOH gave the acetonide **16** in 94% yield. Deprotection of methoxyphenylmethyl (MPM) group of **16** by treatment with DDQ followed by mild oxidation of the resulting alcohol **17** with chromium(VI) oxide-pyridine afforded the aldehyde **6** as an *E*/*Z* mixture. In the recent studies on the radical reaction of oxime ether, we have observed no remarkable effect of the geometry of the starting oxime ether group on either the chemical yield or stereoselectivity by employing geometrically pure *E*- and *Z*-isomer.[15] Thus, oxime ether **6** was subjected to the following radical reactions, without the separation of *E*/*Z*-isomers.

We next examined the stannyl radical-promoted cyclization of oxime ether **6**. Treatment of an *E*/*Z* mixture of **6** with tributyltin hydride in the presence of AIBN in boiling benzene gave a 3 : 1 mixture of two cyclized products *trans*-**7** and *cis*-**7** in 81% combined yield in favor of *trans*-**7**. As expected, the configuration of the benzyloxyamino group on product **7** was highly controlled in the radical cyclization of **6** as a result of $A^{1,3}$-strain effect around oxime ether group (Fig. 1). The preferential formation of the *trans*-**7** could be

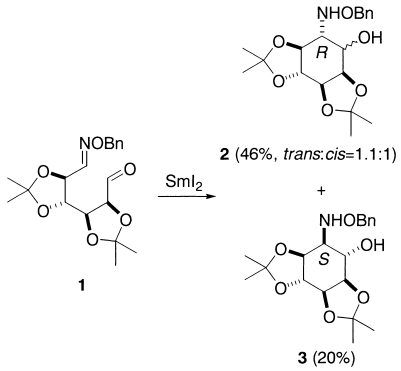

Chart 1

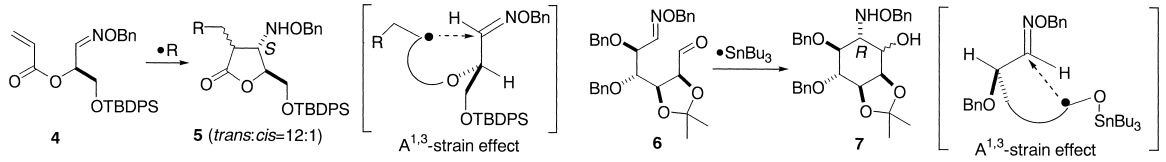

Chart 2

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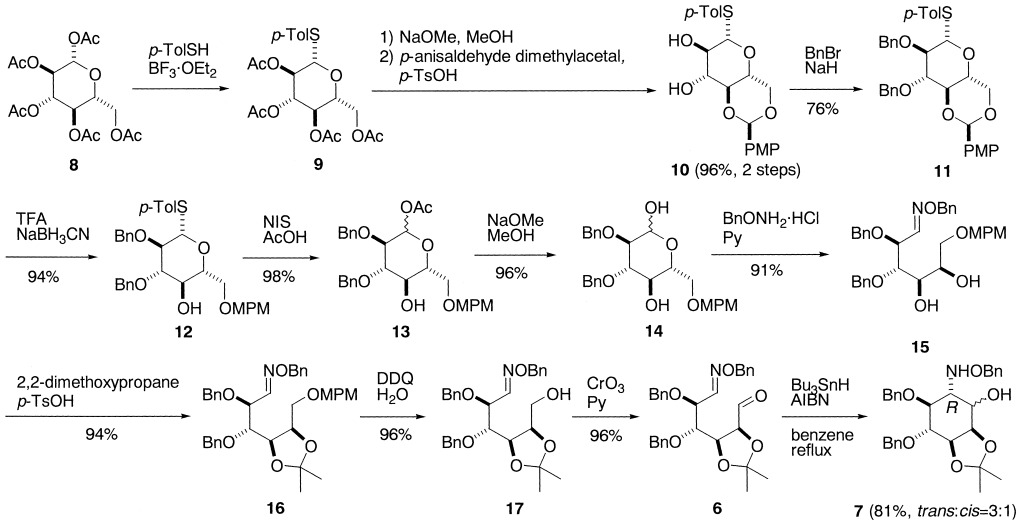

Chart 3

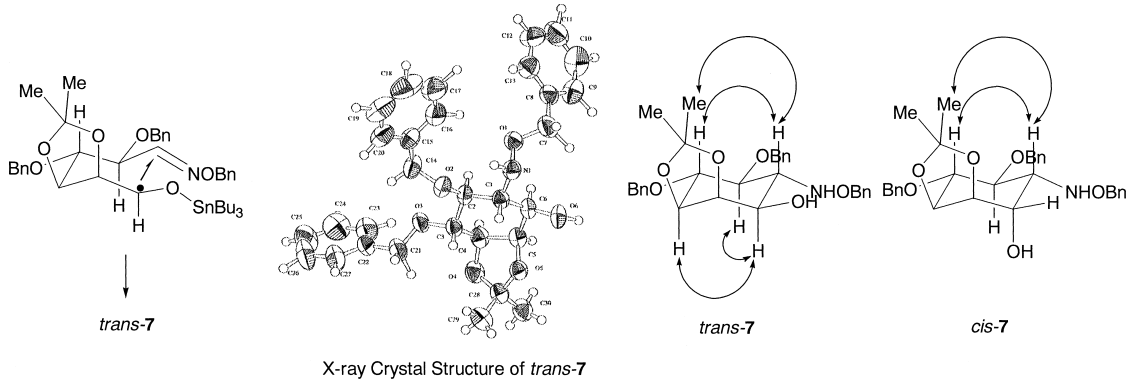

Fig. 1. Stereochemical Feature, X-Ray Crystal Structure of *trans*-**7** and NOE Correlations of *trans*-**7** and *cis*-**7**

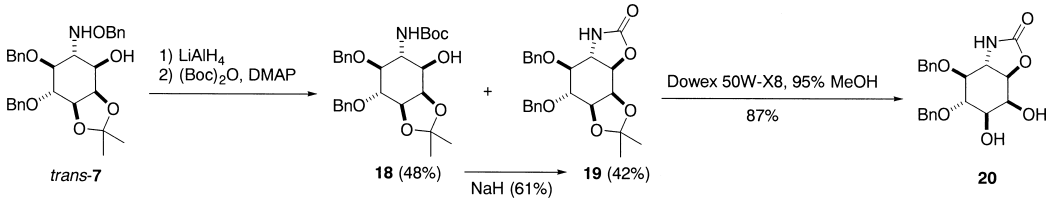

Chart 4

explained by less steric and electronic repulsions of the ketyl radical moiety and the oxime ether group. The rationale of the reaction pathway of this 6-*exo*-*trig* radical cyclization is that the stannyl radical initially reacted with the oxygen atom of the formyl group to form the ketyl radical which attacked intramolecularly the oxime ether group to give the cyclized products.

We were able to separate and purify isomers of *trans*-**7** and *cis*-**7** by the medium-pressure column chromatography. The configuration of the major product *trans*-**7** was determined by X-ray analysis. The stereostructure of the minor product *cis*-**7** was deduced from comparison of the ^{1}H-NMR spectrum with that of the major product *trans*-**7** and from nuclear Overhanser effect (NOE) correlations.

The major product *trans*-**7** was converted into the aminocyclohexitol derivative **20** (Chart 4). Reduction of the benzyloxyamino group of *trans*-**7** with $LiAlH_4$ followed by *N*-acylation of the resulting crude amine with $(Boc)_2O$ afforded the *N*-Boc derivative **18** in 48% yield and the oxazolidone **19** in 42% yield. The *N*-Boc derivative **18** could be converted into the oxazolidone **19** in 61% yield by treatment with NaH in THF. The aminocyclohexitol derivative **20** was prepared by treatment of **19** with Dowex 50W-X8 in MeOH.

In conclusion, we have shown an $A^{1,3}$-strain effect on the stannyl radical mediated-cyclization of oxime ether derived from D-glucose for preparing the aminocyclohexitol derivative.

Experimental

General Melting points are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded at 500, 300, and 200 MHz and at 125, 75, and 50 MHz, respectively. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$). Medium-pressure column chromatography was

performed using Lobar größe B (E. Merck 310-25, Lichroprep Si60). Flash column chromatography was performed using E. Merck Kieselgel 60 (230—400 mesh).

4-Methylphenyl (*S*)-4,6-*O*-[(4-Methoxyphenyl)methylene]-1-thio-β-D-glucopyranoside (10) To a solution of **9**[11] (50.0 g, 0.11 mol) in MeOH (600 ml) was added NaOMe (28% in MeOH, 2.57 ml) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 1 h, Dowex 50W-X8 was added to the reaction mixture. The reaction mixture was filtered and the filtrate was concentrated at reduced pressure to afford the alcohol. To a solution of the resulting alcohol in MeCN (350 ml) were added *p*-anisaldehyde dimethylacetal (37.5 ml, 0.22 mol) and *p*-TsOH (1.4 g, 7.26 mol) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 20 h, Et_3N (1.0 ml, 7.26 mmol) was added to the reaction mixture. After the reaction mixture was concentrated at reduced pressure, the resulting residue was diluted with AcOEt and then the organic phase was washed with 3% HCl, water, saturated $NaHCO_3$, water, and saturated NaCl. The extract was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by recrystallization (hexane/AcOEt 3 : 1) afforded **10** (42.8 g, 96%) as colorless crystals. mp 152—157 °C. $[\alpha]_D^{25}$ −36.1° (*c*=1.00, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 2.68 (1H, br s), 2.83 (1H, br s), 3.39—3.55 (3H, m), 3.70—3.90 (2H, m), 4.35 (1H, dd, *J*=10, 3.5 Hz), 3.79 (3H, s), 4.56 (1H, d, *J*=9.5 Hz), 5.48 (1H, s), 6.86—7.45 (8H, m). ^{13}C-NMR ($CDCl_3$) δ: 21.0, 55.1, 68.3, 70.2, 72.4, 74.3, 80.0, 88.5, 101.6, 113.6, 127.5, 129.3, 129.7, 133.3, 138.4, 160.1. Some carbon peaks were missing due to their overlapping. IR ($CHCl_3$) cm^{-1}: 3592. High resolution (HR)-MS (electron impact (EI)) *m/z*: 404.1289 (Calcd for $C_{21}H_{24}O_6S$ (M^+): 404.1294). *Anal.* Calcd for $C_{21}H_{24}O_6S \cdot 3/2H_2O$: C, 58.45; H, 6.31. Found: C, 58.34; H, 6.05.

4-Methylphenyl (*S*)-4,6-*O*-[(4-Methoxyphenyl)methylene]-2,3-bis-*O*-(phenylmethyl)-1-thio-β-D-glucopyranoside (11) To a suspension of NaH (60% in mineral oil, 7.7 g, 0.19 mol) in DMF (50 ml) was added **10** (32.0 g, 76.5 mol) under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 30 min, benzyl bromide (20.2 ml, 0.17 mol) was added to the reaction mixture at 20 °C. After being stirred at the same temperature for 20 h, the reaction mixture was diluted with Et_2O and then the organic phase was washed with water, saturated $NaHCO_3$, water, and saturated NaCl. The extract was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by recrystallization (hexane) afforded **11** (34.2 g, 76%) as colorless crystals. mp 135—136 °C. $[\alpha]_D^{24}$ −32.1° (*c*=1.03, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s), 3.43 (1H, ddd, *J*=10, 9, 5 Hz), 3.47 (1H, dd, *J*=9.5, 9 Hz), 3.66 (1H, t, *J*=9 Hz), 3.78 (1H, t, *J*=10 Hz), 3.79 (3H, s), 3.81 (1H, t, *J*=9 Hz), 4.35 (1H, dd, *J*=10, 5 Hz), 4.68 (1H, d, *J*=9.5 Hz), 4.76, 4.92 (2H, ABq, *J*=11 Hz), 4.81, 4.86 (2H, ABq, *J*=11 Hz), 5.54 (1H, s), 6.89—7.44 (18H, m). ^{13}C-NMR ($CDCl_3$) δ: 20.9, 55.1, 68.4, 70.0, 75.0, 75.6, 80.2, 81.2, 82.8, 88.3, 100.9, 113.4, 127.1, 127.5, 127.6, 127.9, 128.0, 128.2, 129.0, 129.6, 132.8, 137.9, 138.1, 159.8. Some carbon peaks were missing due to their overlapping. HR-MS (EI) *m/z*: 584.2249 (Calcd for $C_{35}H_{36}O_6S$ (M^+): 584.2233). *Anal.* Calcd for $C_{35}H_{36}O_6S$: C, 71.89; H, 6.26. Found: C, 71.90; H, 6.21.

4-Methylphenyl (*S*)-6-*O*-[(4-Methoxyphenyl)methyl]-2,3-bis-*O*-(phenylmethyl)-1-thio-β-D-glucopyranoside (12) To a solution of **11** (10 g, 17.1 mmol), $NaBH_3CN$ (5.4 g, 85.5 mmol), and 4A MS (3.0 g) in DMF (30 ml) was added a solution of TFA (13.2 ml, 0.17 mol) in DMF (30 ml) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 20 h, acetone (5 ml) and Et_3N (23.8 ml, 0.17 mmol) were added to the reaction mixture at 0 °C. The reaction mixture was diluted with Et_2O and then the organic phase was washed with 3% HCl, water, saturated $NaHCO_3$, water, and saturated NaCl. The extract was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by flash column chromatography (AcOEt/hexane 1 : 2) afforded **12** (9.4 g, 94%) as colorless crystals. mp 66—67 °C (Hexane). $[\alpha]_D^{27}$ −8.81° (*c*=1.11, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.31 (3H, s), 2.60 (1H, br d, *J*=2 Hz), 3.43 (1H, br t, *J*=10 Hz), 3.44 (1H, dd, *J*=10, 9 Hz), 3.52 (1H, t, *J*=9 Hz), 3.63 (1H, br dt, *J*=9, 2 Hz), 3.70—3.77 (2H, m), 3.81 (3H, s), 4.48, 4.50 (2H, ABq, *J*=11.5 Hz), 4.61 (1H, d, *J*=10 Hz), 4.73, 4.91(2H, ABq, *J*=10.5 Hz), 4.78, 4.89 (2H, ABq, *J*=11.5 Hz), 6.87—7.46 (18H, m). ^{13}C-NMR ($CDCl_3$) δ: 20.9, 55.0, 69.9, 71.6, 73.1, 75.1, 75.2, 77.9, 80.2, 85.0, 87.7, 113.6, 127.6, 127.7, 128.1, 128.2, 128.4, 129.2, 129.4, 129.5, 129.6, 129.8, 132.4, 137.5, 137.9, 138.3, 159.1. IR ($CHCl_3$) cm^{-1}: 3586. HR-MS (EI) *m/z*: 586.2370 (Calcd for $C_{35}H_{38}O_6S$ (M^+): 586.2389). *Anal.* Calcd for $C_{35}H_{38}O_6S$: C, 71.65; H, 6.53. Found: C, 71.48; H, 6.51.

6-*O*-[(4-Methoxyphenyl)methyl]-2,3-bis-*O*-(phenylmethyl)-D-glucopyranose-1-acetate (13) To a suspension of NIS (383 mg, 1.70 mmol) in Et_2O (8.5 ml) and CH_2ClCH_2Cl (8.5 ml) was added AcOH (9.8 ml, 0.17 mol) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 10 min, **12** (1.0 g, 1.70 mmol) was added to the reaction mixture at 20 °C. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with saturated sodium thiosulfate and CH_2Cl_2. The organic phase was washed with saturated $NaHCO_3$, water, and saturated NaCl, dried over $MgSO_4$, and concentrated at reduced pressure. Purification by flash column chromatography (AcOEt/hexane 1 : 2) afforded **13** (870 mg, 98%) as a colorless oil (a mixture of α/β-isomer). ^{1}H-NMR of major isomer ($CDCl_3$) δ: 2.15 (3H, s), 2.56 (1H, d, *J*=2.5 Hz), 3.60—3.84 (6H, m), 3.80 (3H, s), 4.46, 4.51 (2H, ABq, *J*=12 Hz), 4.62, 4.69 (2H, ABq, *J*=11.5 Hz), 4.75, 4.96 (2H, ABq, *J*=11.5 Hz), 6.34 (1H, d, *J*=3.5 Hz), 6.85—7.36 (14H, m). IR ($CHCl_3$) cm^{-1}: 3554, 1752. HR-MS (EI) *m/z*: 522.2233 (Calcd for $C_{30}H_{34}O_8$ (M^+): 522.2254).

6-*O*-[(4-Methoxyphenyl)methyl]-2,3-bis-*O*-(phenylmethyl)-D-glucopyranose (14) To a solution of **13** (2.9 g, 5.57 mmol) in MeOH (30 ml) was added NaOMe (28% in MeOH, 0.12 ml) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 11 h, Dowex 50W-X8 was added to the reaction mixture. The reaction mixture was filtered and the filtrate was concentrated at reduced pressure. Purification by recrystallization (AcOEt) afforded **14** (2.6 g, 96%) as colorless crystals (a mixture of α/β-isomer). mp 111—114 °C. ^{1}H-NMR of major isomer ($CDCl_3$) δ: 2.41 (1H, d, *J*=2.5 Hz), 2.99 (1H, d, *J*=2.5 Hz), 3.52—3.64 (4H, m), 3.78 (1H, t, *J*=9 Hz), 3.79 (3H, s), 3.98 (1H, dt, *J*=9.5, 4 Hz), 4.46, 4.51 (2H, ABq, *J*=11.5 Hz), 4.69, 4.75 (2H, ABq, *J*=12Hz), 4.76, 4.97 (2H, ABq, *J*=11.5 Hz), 5.22 (1H, t, *J*=3 Hz), 6.84—7.37 (14H, m). IR ($CHCl_3$) cm^{-1}: 3594. HR-MS (EI) *m/z*: 480.2158 (Calcd for $C_{28}H_{32}O_7$ (M^+): 480.2148). *Anal.* Calcd for $C_{28}H_{32}O_7$: C, 69.98; H, 6.71. Found: C, 69.94; H, 6.71.

6-*O*-[(4-Methoxyphenyl)methyl]-2,3-bis-*O*-(phenylmethyl)-D-glucose *O*-(Phenylmethyl)oxime (15) To a solution of **14** (24 mg, 0.05 mmol) in pyridine (0.3 ml) was added *O*-benzylhydroxylamine hydrochloride (8 mg, 0.05 mmol) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 20 h, the reaction mixture was diluted with AcOEt and then the organic phase was washed with 3% HCl, water, saturated $NaHCO_3$, water, and saturated NaCl. The extract was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt/hexane 1 : 1) afforded **15** (26.6 mg, 91%) as a colorless oil (*E* : *Z*=9 : 2). ^{1}H-NMR of *E*-isomer ($CDCl_3$) δ: 2.40 (1H, d, *J*=5 Hz), 2.50 (1H, d, *J*=9 Hz), 3.50—3.74 (4H, m), 3.79 (3H, s), 4.00 (1H, dd, *J*=7, 1.5 Hz), 4.28 (1H, dd, *J*=8.5, 7 Hz), 4.40, 4.58 (2H, ABq, *J*=12 Hz), 4.45, 4.47 (2H, ABq, *J*=11 Hz), 4.60, 4.80 (2H, ABq, *J*=11 Hz), 5.12 (2H, s), 6.85—7.37 (19H, m), 7.49 (1H, d, *J*=8.5 Hz). IR ($CHCl_3$) cm^{-1}: 3561. HR-MS (EI) *m/z*: 585.2723 (Calcd for $C_{35}H_{39}NO_7$ (M^+): 585.2727).

6-*O*-[(4-Methoxyphenyl)methyl]-4,5-*O*-(1-methylethylidene)-2,3-bis-*O*-(phenylmethyl)-D-glucose *O*-(Phenylmethyl)oxime (16) To a solution of **15** (5.4 g, 9.20 mmol) in 2,2-dimethoxypropane (50 ml) was added *p*-TsOH (65 mg, 0.34 mmol) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 20 h, Et_3N (0.05 ml, 0.36 mmol) was added to the reaction mixture, and then the reaction mixture was concentrated at reduced pressure. The residue was diluted with AcOEt and then the organic phase was washed with 3% HCl, water, saturated $NaHCO_3$, water, and saturated NaCl. The extract was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by flash column chromatography (AcOEt/hexane 1 : 2) afforded **16** (5.4 g, 94%) as a colorless oil (*E* : *Z*=5 : 1). ^{1}H-NMR of *E*-isomer ($CDCl_3$) δ: 1.33 (3H, s), 1.42 (3H, s), 3.42 (2H, d, *J*=6 Hz), 3.58 (1H, t, *J*=4.5 Hz), 3.76 (3H, s), 4.06 (1H, q, *J*=6 Hz), 4.23—4.67 (8H, m), 5.09 (2H, s), 6.79—7.36 (19H, m), 7.56 (1H, d, *J*=7.5 Hz). HR-MS (EI) *m/z*: 625.3026 (Calcd for $C_{38}H_{43}NO_7$ (M^+): 625.3040).

4,5-*O*-(1-Methylethylidene)-2,3-bis-*O*-(phenylmethyl)-D-glucose *O*-(Phenylmethyl)oxime (17) To a solution of **16** (488 mg, 0.78 mmol) in CH_2Cl_2 (7.9 ml) and H_2O (0.5 ml) was added DDQ (267 mg, 1.17 mmol) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with CH_2Cl_2 and then the organic phase was washed with water and saturated NaCl. The extract was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by flash column chromatography (AcOEt/hexane 1 : 2) afforded **17** (377 mg, 96%) as a colorless oil (*E* : *Z*=4 : 1). ^{1}H-NMR of *E*-isomer ($CDCl_3$) δ: 1.33 (3H, s), 1.46 (3H, s), 2.26 (1H, br s), 3.53 (2H, br m), 3.67 (1H, br t, *J*=5 Hz), 3.92 (1H, br q, *J*=6 Hz), 4.22 (1H, dd, *J*=8, 5 Hz), 4.30, 4.59 (2H, ABq, *J*=12 Hz), 4.47 (1H, t, *J*=6 Hz), 4.59, 4.69 (2H, ABq, *J*=11 Hz), 5.11 (2H, s), 7.21—7.37 (15H, m), 7.57 (1H, d, *J*=8 Hz). IR ($CHCl_3$) cm^{-1}: 3497. HR-MS (EI) *m/z*: 505.2465 (Calcd for $C_{30}H_{35}NO_6$ (M^+): 505.2464).

4,5-*O*-(1-Methylethylidene)-2,3-bis-*O*-(phenylmethyl)-D-gluco-hexodialdose 1-[*O*-(Phenylmethyl)oxime] (6) To a solution of pyridine (3.1 ml, 38.8 mmol) in CH_2Cl_2 (31 ml) was portionwise added CrO_3 (1.9 g, 19.4

mmol) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 15 min, a solution of **17** (982 mg, 1.94 mmol) in CH_2Cl_2 (7.8 ml) was added to the reaction mixture. After the reaction mixture was stirred at the same temperature for 30 min, the solvent was evaporated at reduced pressure. After the resulting residue was diluted with Et_2O and filtered through a pad of Celite, the filtrate was concentrated at reduced pressure. Purification by flash column chromatography (AcOEt/hexane 1 : 2) afforded **6** (937 mg, 96%) as a colorless oil ($E:Z=5:1$). ^{1}H-NMR of *E*-isomer ($CDCl_3$) δ: 1.34 (3H, s), 1.55 (3H, s), 3.65 (1H, dd, J=7, 2 Hz), 4.13, 4.70 (2H, ABq, J=11 Hz), 4.25 (1H, dd, J=8, 2.5 Hz), 4.37, 4.59 (2H, ABq, J=12 Hz), 4.39 (1H, dd, J=8, 7 Hz), 4.74 (1H, dd, J=8, 2 Hz), 5.12 (2H, s), 7.21—7.37 (15H, m), 7.61 (1H, d, J=8 Hz), 9.49 (1H, d, J=2.5 Hz). IR ($CHCl_3$) cm^{-1}: 1725. HR-MS (EI) *m/z*: 503.2290 (Calcd for $C_{30}H_{33}NO_6$ (M^+): 503.2308).

Radical Reaction of Oxime Ether 6 To a boiling solution of **6** (937 mg, 1.86 mmol) in benzene (14 ml) was added portionwise (5 ml/h) a solution of Bu_3SnH (1.0 ml, 3.72 mmol) and AIBN (61 mg, 0.37 mmol) in benzene (4.0 ml) under a nitrogen atmosphere. The reaction mixture was heated at reflux for 1.5 h and then the solvent was evaporated at reduced pressure. The resulting residue was diluted with MeCN and the MeCN phase was washed with hexane and concentrated at reduced pressure. Purification by medium-pressure column chromatography (AcOEt/hexane 1 : 2) afforded *cis*-**7** (207 mg, 22%) as a colorless oil and *trans*-**7** (522 mg, 59%) as colorless crystals.

5-Deoxy-1,2-*O*-(1-methylethylidene)-5-[(phenylmethoxy)amino]-3,4-bis-*O*-(methylphenyl)-L-chiro-inositol (*cis*-7) $[\alpha]_D^{27}$ −72.8° (c=0.79, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, s), 1.44 (3H, s), 2.83 (1H, br s), 3.22 (1H, dd, J=9.5, 2.5 Hz), 3.58 (1H, t, J=9.5 Hz), 3.66 (1H, dd, J=9.5, 7 Hz), 4.26—4.29 (2H, m), 4.31 (1H, dd, J=7, 6 Hz), 4.47, 4.92 (2H, ABq, J=11 Hz), 4.63, 4.67 (2H, ABq, J=12 Hz), 4.71, 4.88 (2H, ABq, J=11 Hz), 6.11 (1H, br s), 7.19—7.38 (15H, m). ^{13}C-NMR ($CDCl_3$) δ: 25.9, 27.8, 61.5, 66.8, 73.4, 74.8, 74.9, 76.2, 76.3, 79.7, 84.4, 109.0, 127.4, 127.7, 127.8, 127.9, 128.1 (2C), 128.3, 128.4, 128.6, 137.0, 138.0, 138.3. IR ($CHCl_3$) cm^{-1}: 3513. HR-MS (CI) *m/z*: 505.2465 (Calcd for $C_{30}H_{35}NO_6$ (M^+): 505.2464).

4-Deoxy-1,2-*O*-(1-methylethylidene)-4-[(phenylmethoxy)amino]-5,6-bis-*O*-(phenylmethyl)-D-myo-inositol (*trans*-7) mp 112—114 °C (Hexane). $[\alpha]_D^{28}$ −71.2° (c=2.14, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, s), 1.47 (3H, s), 2.77 (1H, br d), 2.94 (1H, t, J=10 Hz), 3.63 (1H, t, J=10 Hz), 3.71 (1H, br dd, J=10, 6.5 Hz), 3.97 (1H, ddd, J=10, 4, 2 Hz), 4.18 (1H, dd, J=6.5, 5.5 Hz), 4.48 (1H, dd, J=5.5, 4 Hz), 4.62, 4.91 (2H, ABq, J=10.5 Hz), 4.68, 4.71 (2H, ABq, J=11 Hz), 4.72, 4.91 (2H, ABq, J=12 Hz), 6.27 (1H, br s), 7.26—7.38 (15H, m). ^{13}C-NMR ($CDCl_3$) δ: 26.0, 27.7, 62.4, 65.7, 73.4, 75.2, 75.5, 75.9, 79.4, 84.1, 109.9, 127.5, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 137.2, 138.3. Some carbon peaks were missing due to their overlapping. IR ($CHCl_3$) cm^{-1}: 3536. HR-MS (SIMS) *m/z*: 506.2548 (Calcd for $C_{30}H_{35}NO_6$ ($M+H^+$): 506.2540). *Anal.* Calcd for $C_{30}H_{35}NO_6$: C, 71.27; H, 6.98; N, 2.77. Found: C, 71.26; H, 7.05; N, 2.77. Crystal data of *trans*-**7**: $C_{30}H_{35}NO_6$, space group $P2_12_12_1$ with a=18.845(2), b=24.499(4), c=5.879(4) Å, V=2714(1) Å, final R value 0.0684 for 2009 reflections.

Conversion of *trans*-7 to 18 and 19 To a solution of *trans*-**7** (522 mg, 1.09 mmol) in THF (8.7 ml) was added $LiAlH_4$ (249 mg, 6.55 mmol) under a nitrogen atmosphere at 20 °C. After the reaction mixture was heated at reflux for 1 h, the mixture was carefully diluted with Et_2O and then excess of the reagent was decomposed by addition of water. The organic phase was washed with saturated NaCl, dried over $MgSO_4$, and concentrated at reduced pressure to afford the amine. To a solution of the resulting amine in MeCN (20 ml) were added DMAP (122 mg, 1.09 mmol) and $(Boc)_2O$ (0.3 ml, 1.20 mmol) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 20 h, the reaction mixture was concentrated at reduced pressure. Purification by medium-pressure column chromatography (AcOEt/hexane 1 : 1) afforded **18** (263 mg, 48%) as colorless crystals and **19** (193 mg, 42%) as colorless crystals.

4-Deoxy-1,2-*O*-(1-methylethylidene)-4-[[(1,1-dimethylethoxy)carbonyl]amino]-5,6-bis-*O*-(phenylmethyl)-D-myo-inositol (18) mp 156—157 °C (Et_2O/Hexane). $[\alpha]_D^{21}$ −21.9° (c=0.94, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, s), 1.45 (9H, s), 1.50 (3H, s), 3.20 (1H, br s), 3.35 (1H, br t, J=8.5 Hz), 3.74—3.84 (3H, m), 4.23 (1H, t, J=6 Hz), 4.43 (1H, dd, J=6, 3 Hz), 4.51 (1H, br s), 4.58, 4.83 (2H, ABq, J=12 Hz), 4.69, 4.84 (2H, ABq, J=11 Hz), 7.26—7.38 (10H, m). ^{13}C-NMR ($CDCl_3$) δ: 25.7, 27.5, 28.2, 54.3, 69.6, 73.3, 74.0, 75.8, 78.5, 80.0, 82.6, 96.8, 109.8, 127.6, 127.9, 128.2, 128.2, 128.4, 137.9, 138.1, 156.8. Some carbon peaks were missing due to their overlapping. IR ($CHCl_3$) cm^{-1}: 3691, 1707. HR-MS (EI) *m/z*: 500.2657 (Calcd for $C_{28}H_{38}NO_7$ ($M+H^+$): 500.2648). *Anal.* Calcd for $C_{28}H_{37}NO_7$: C, 67.31; H, 7.46; N, 2.80. Found: C, 67.02; H, 7.68; N, 2.77.

4-Deoxy-1,2-*O*-(1-methylethylidene)-4-(carboxyamino)-5,6-bis-*O*-(phenylmethyl)-D-myo-inositol Intramol. 3,4-Ester (19) mp 157—158 °C (Et_2O). $[\alpha]_D^{28}$ −9.3° (c=0.55, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, s), 1.55 (3H, s), 3.71 (1H, br dd, J=9, 1.5 Hz), 3.87 (1H, dd, J=3, 1.5 Hz), 4.01 (1H, ddd, J=12, 9, 1.5 Hz), 4.32 (1H, dd, J=12, 3 Hz), 4.40, 4.65 (2H, ABq, J=12 Hz), 4.56, 4.60 (2H, ABq, J=11 Hz), 4.57 (1H, br dd, J=7, 3 Hz), 4.69 (1H, dd, J=7, 3 Hz), 4.96 (1H, br s), 7.26—7.28 (10H, m). ^{13}C-NMR ($CDCl_3$) δ: 23.9, 25.9, 54.0, 70.1, 71.8, 72.3, 75.6, 77.8, 80.1, 82.7, 111.3, 127.7, 127.9, 128.2, 128.4, 128.5, 128.6, 136.9, 137.4, 159.4. IR ($CHCl_3$) cm^{-1}: 3438, 1769. HR-MS (CI) *m/z*: 425.1845 (Calcd for $C_{24}H_{27}NO_6$ (M^+): 425.1838). *Anal.* Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.70; H, 6.50; N, 3.35.

4-Deoxy-4-(carboxyamino)-5,6-bis-*O*-(phenylmethyl)-D-myo-inositol, Intramol. 3,4-Ester (20) To a solution of **19** (50 mg, 0.12 mmol) in MeOH/H_2O (20 : 1, 5.2 ml) was added Dowex 50W-X8 (55 mg) under a nitrogen atmosphere at 20 °C. After being refluxed for 24 h, the reaction mixture was filtered and the filtrate was concentrated at reduced pressure. Purification by preparative TLC (AcOEt/hexane 1 : 1) afforded **20** (39 mg, 87%) as a colorless oil. $[\alpha]_D^{28}$ −31.4° (c=1.32, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 3.15 (2H, br s), 3.44 (1H, br dd), 3.56—3.65 (2H, br m), 3.75 (1H, br d), 4.01 (1H, br dd), 4.34 (1H, br s), 4.62, 4.76 (2H, ABq, J=12 Hz), 4.79, 4.80 (2H, ABq, J=11 Hz), 5.59 (1H, br s), 7.25—7.33 (10H, m). *J*-Values of three proton signals (δ: 3.44, 3.75, 4.01) were not correctly calculated due to the broad spectrum. ^{13}C-NMR ($CDCl_3$) δ: 55.0, 66.4, 73.3, 73.8, 75.7, 78.5, 80.8, 84.0, 127.7, 127.8, 128.0, 128.4, 128.5, 137.8, 138.2, 160.6. Some carbon peaks were missing due to their overlapping. IR ($CHCl_3$) cm^{-1}: 3562, 3429, 1773. HR-MS (EI) *m/z*: 385.1527 (Calcd for $C_{21}H_{23}NO_6$ (M^+): 385.1525).

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