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 α-glucose, gave the aminocyclohexitol derivative. Stereoselective C–C bond forming cyclization proceeded via favorable conformers minimizing A1,3-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 SmI2-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 A1,3-strain effect between the oxime ether group and α-substituents is important for stereocontrol of the benzoxylamino 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 benzoxylamino group on product 7 via favorable conformers minimizing A1,3-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-α-glucose 8 was treated with p-TolSH in the presence of BF3·OEt2 to give 9. Decacetylation of 9 followed by selective protection of 4,6-hydroxyl groups using p-anisaldehyde dimethylacetal gave 10 in 96% yield.12) Benzylolation of 10 using benzyl bromide and NaN3 followed by treatment with NaBH4CN 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-benzhydroxyamine 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-isomers.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 benzoxylamino group on product 7 was highly controlled in the radical cyclization of 6 as a result of A1,3-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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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 1H-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 benzoylxyamino group of trans-7 with LiAlH₄ 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 A₁,₃-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. ¹H- and ¹³C-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 60F₂₅₄). Medium-pressure column chromatography was
performing used Lobar größe B (E. Merck 310-25, Lichroprep S60).

4-Methylphenyl (5)-4,6-O-[(4-Methoxyphenyl)methylene]-1-thio-D-gluco-pyranoside (10) To a solution of 9 g (50.1 g, 0.1 mol) in MeOH (600 ml) was added NaOMe (28% in MeOH, 2.57 ml) under a nitrogen atmosphere. Purification by flash chromatography (Hexane/ EtOAc 1:2) afforded 13 (87 mg, 98%) as a colorless oil (a mixture of α-/β-isomer). 1H-NMR of major isomer (CDCl3): 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 (CHCl3) cm−1: 3554, 1725. HR-MS (EI) m/z: 522.2233 (Calcd 522.2254).

6-[(4-Methoxyphenyl)methyl-2,3-bis-O-(phenylmethyl)-D-gluco-pyranoside (11) To a solution of 13 (2 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 to afford 400 mesh.

1H-NMR (CDCl3) δ: 2.24 (3H, s), 2.68 (1H, br s), 2.83 (1H, br s), 3.39—3.53 (3H, m), 3.70—3.90 (2H, m), 4.35 (1H, dd, J=10, 3.5 Hz), 3.79 (1H, d, J=4.6 Hz, J=9.5 Hz), 5.48 (1H, s, 6.86—7.45 (8H, m). 13C-NMR (CDCl3), δ: 21.0, 55.1, 68.3, 70.2, 72.4, 83.0, 88.5, 100.1, 113.6, 127.5, 129.3, 129.7, 133.8, 138.4. Some carbon peaks were missing due to their overlapping. IR (CHCl3) cm−1: 3592. High resolution (HR)-MS ion (electro impact (EI)) m/z: 404.1289 (Calcd for C19H18O6S: M+ 404.1294).

Anal. Calcd for C19H18O6S: 3/2ZnO: C, 58.45; H, 6.31. Found: C, 58.34; H, 6.05.

4-Methylphenyl (5)-6-O-[(4-Methoxyphenyl)methyl]-2,3-bis-O-(phenylmethyl)-1-thio-D-gluco-pyranoside (111) 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 water and then the organic phase was washed with water, saturated NaHCO3, water, and saturated NaCl. The extract was dried over MgSO4 and concentrated at reduced pressure. Purification by recrystallization (hexane/AcOEt 3:1) afforded 111 (42.8 g, 96%) as colorless crystals. mp 152—157°C. [α]D22: −36° (c=1.00, CHCl3). 1H-NMR (CDCl3) δ: 2.36 (3H, s), 2.68 (1H, br s), 2.83 (1H, br s), 3.39—3.53 (3H, m), 3.70—3.90 (2H, m), 4.35 (1H, dd, J=10, 3.5 Hz), 3.79 (1H, d, J=4.6 Hz, J=9.5 Hz), 5.48 (1H, s, 6.86—7.45 (8H, m). 13C-NMR (CDCl3), δ: 21.0, 55.1, 68.3, 70.2, 72.4, 83.0, 88.5, 100.1, 113.6, 127.5, 129.3, 129.7, 133.8, 138.4. Some carbon peaks were missing due to their overlapping. IR (CHCl3) cm−1: 3592. High resolution (HR)-MS ion (electro impact (EI)) m/z: 404.1289 (Calcd for C19H18O6S: M+ 404.1294).

Anal. Calcd for C19H18O6S: 3/2ZnO: C, 58.45; H, 6.31. Found: C, 58.34; H, 6.05.
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 CH2Cl2 (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 EtO2 and filtered through a pad of Celite, the filtrate was concentrated at reduced pressure. Purification by flash column chromatography (AcOEt/hexane 1:2) afforded cis- and trans-7 (207 mg, 22%) as a colorless oil.

**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 Bu3SnH (1.0 ml, 3.72 mmol) in (CDCl3) solution of Bu3SnH (1.0 ml, 3.72 mmol) and AIBN (61 mg, 0.37 mmol) in cis- and trans-7 (202 mg, 59%) as colorless crystals.

**5-Deoxy-1,2-O-(1-methylthiophenyl)-D-myo-inositol (cis-7)** 

<table>
<thead>
<tr>
<th>Compound</th>
<th>mp</th>
<th>Infrared (cm−1)</th>
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<tbody>
<tr>
<td>cis-7</td>
<td>157°C</td>
<td>3429, 1773.</td>
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**4-Deoxy-1,2-O-(1-methylthiophenyl)-D-myo-inositol (trans-7)** mp 112—114°C (Hexane). [α]D25 8.0° (c = 2.14, CHCl3). H-NMR (CDCl3) δ: 1.39 (3H, s), 1.47 (3H, s), 2.77 (3H, brd), 2.94 (1H, t, J = 10.0 Hz), 3.63 (1H, brd, J = 10.5 Hz), 3.71 (1H, brd, J = 10.0 Hz), 3.76 (1H, brd, J = 10.5 Hz), 3.97 (1H, t, J = 10.0 Hz), 4.18 (1H, td, J = 6.5, 5.5 Hz), 4.48 (1H, dd, J = 5.5, 4.5 Hz), 4.62 (1H, dd, J = 10.0 Hz), 4.68, 4.71 (2H, ABq, J = 12.7 Hz), 4.72, 4.91 (2H, ABq, J = 12.7 Hz), 6.27 (1H, brs), 7.26—7.38 (15H, m). 13C-NMR (CDCl3) δ: 26.0, 27.7, 62.4, 65.7, 73.4, 75.2, 75.5, 75.9, 79.4, 84.1, 109.0, 127.7, 127.7, 127.7, 132.8, 132.8, 132.8, 132.8, 133.3, 138.3, 138.3, 139.5. Some carbon peaks were missing due to their overlapping. IR (CHCl3) cm−1: 3536, 3429, 1773. HR-MS (EI) m/z: 585.1527 (Calcd for C30H35NO6 (M+): 585.1525).

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**References and Notes**

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