Tetrahedron 69 (2013) 7931–7935

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A new route toward 2-acetamido-4-*O*-methyl-2-deoxy-D-mannopyranose from a Ferrier derivative of tri-*O*-acetyl-D-glucal, which contributes to aldolase-catalyzed synthesis of laninamivir (CS-8958)

Hayato Okazaki, Kengo Hanaya, Mitsuru Shoji, Noriyasu Hada, Takeshi Sugai *

Department of Pharmaceutical Science, Keio University, 1-5-30, Shibakoen, Minato-ku, Tokyo 105-8512, Japan

ARTICLE INFO

Article history:
Received 31 May 2013
Received in revised form 5 July 2013
Accepted 7 July 2013
Available online 12 July 2013

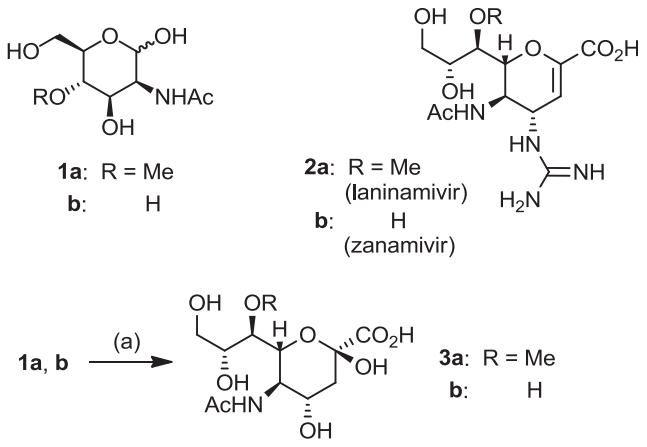
ABSTRACT

A new route toward 2-acetamido-4-*O*-methyl-2-deoxy-D-mannopyranose (4-*O*-methylManNAc), the chemo-enzymatic precursor of 7-*O*-methylsialic acid and laninamivir, was established. Known *p*-methoxyphenyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside was the starting material, and it was derived via Ferrier reaction from tri-*O*-acetyl-D-glucal. The total yield was 43% over six steps from the starting material. As the key steps, Payne oxidation provided a *syn*-epoxy alcohol, and the inversion from an aziridine to an oxazoline proceeded stereoselectively. Although the ring opening reaction of the epoxide with an azide gave both the 2- and 3-azido regioisomers, they could be merged into the desired aziridine via independent routes.

1. Introduction

2-Acetamido-4-*O*-methyl-2-deoxy-D-mannopyranose (**1a**, Scheme 1) is a simple derivative of *N*-acetyl-D-mannosamine (ManNAc, **1b**) and a very important aminosugar. Honda and co-workers reported **1a** as the starting material for the chemo-enzymatic synthesis of laninamivir (CS-8958, **2a**), whose corresponding octanoate (inavir) is a potent neuraminidase inhibitor used as a flu medicine similar to zanamivir (**2b**) as shown in Scheme 1.[1] Sialic acid aldolase has been known to transform **1a** into **3a**,[2,3] which was the synthetic precursor of **2a**, in 88% yield. In the original report, the preparation of **1a** required 17 steps from D-glucose.[2] Therefore, the starting material was later changed to ManNAc (**1b**), via regioselective ring opening of an epoxide in a 1,6-anhydrosugar intermediate[1] or methylation after regioselective protection of alcohols at C-4 and C-6,[3] respectively. Since the availability of ManNAc is scarce from natural resources, the conversion of GlcNAc to ManNAc has been developed.[4]

We have so far exploited the chemo-enzymatic route from tri-*O*-acetyl-D-glucal as shown in Scheme 2. The regio- and stereoselective introduction of a nitrogen functional group on C-2 with the desired *manno*-configuration was the key transformation to convert **4** into **5**. However, a large molar excess of very expensive rhodium acetate was required.[5] In order to overcome this low cost-efficiency, we propose a new route via oxazoline **6**, based on the double regioselective ring opening of three-membered ring intermediates involving aziridine **7** and epoxide **8a** as illustrated in Scheme 2.



Scheme 1. Aldolase-catalyzed synthesis of sialic acid derivative **3**, which are precursors for laninamivir **2a** and zanamivir **2b**; (a) sialic acid aldolase, CH_3COCO_2Na.

2. Results and discussion

Substrate **9a**[6] for the epoxidation was prepared by Ferrier reaction[7] of tri-*O*-acetyl-D-glucal with *p*-methoxyphenol, solvolysis of

* Corresponding author. Tel./fax: +81 3 5400 2695; e-mail address: sugai-tk@pha.keio.ac.jp (T. Sugai).

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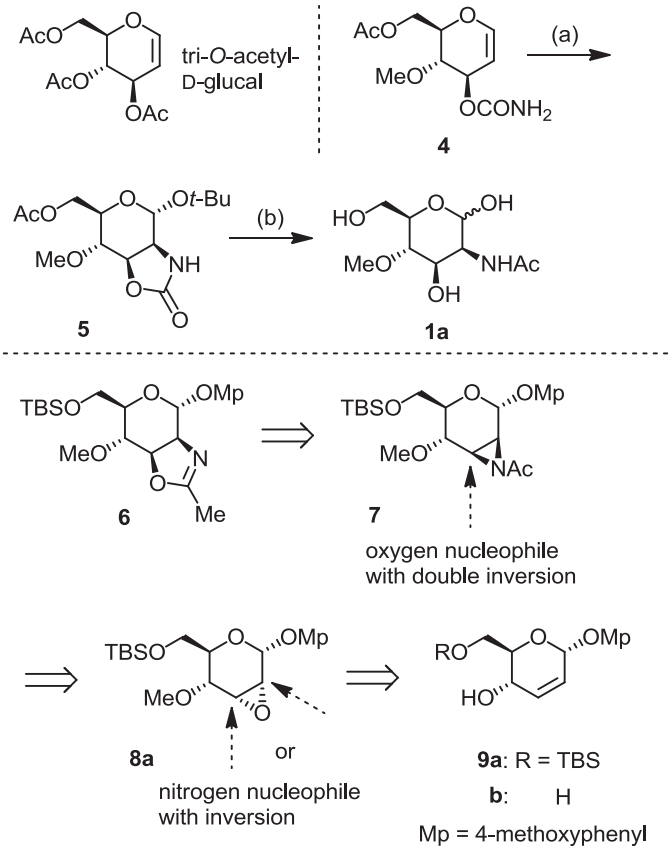
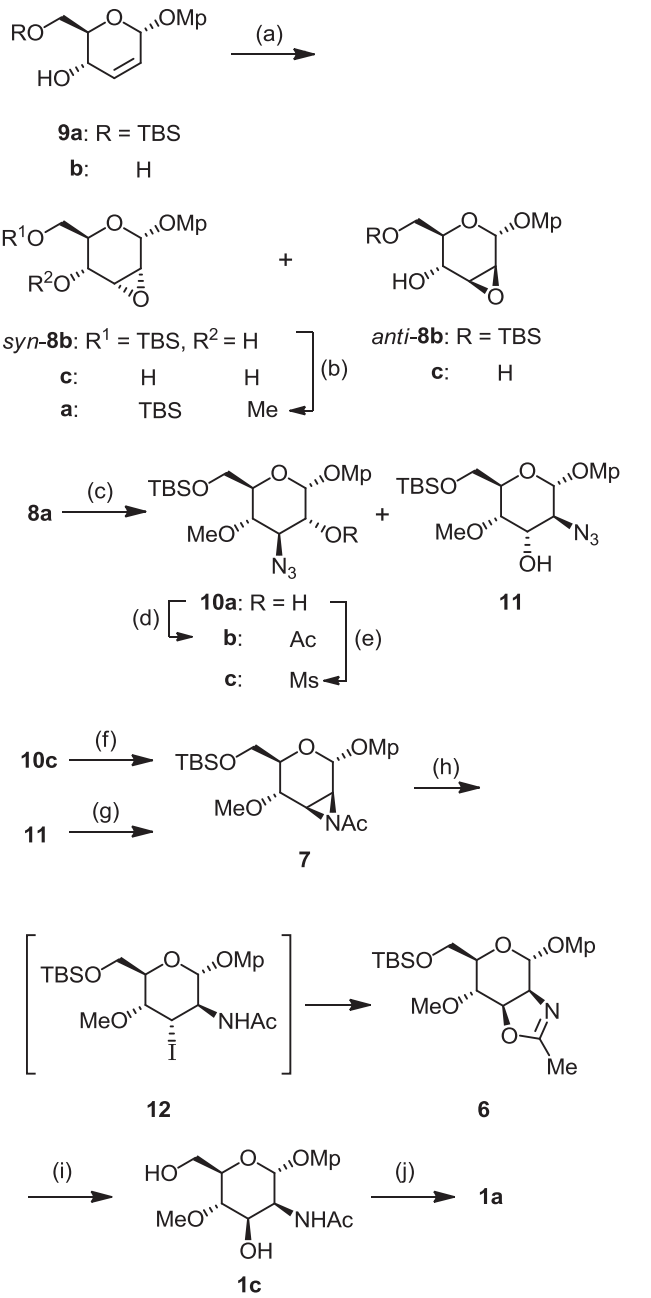
http://dx.doi.org/10.1016/j.tet.2013.07.018



Scheme 2. Our previous synthesis of 2-acetamido-4-*O*-methyl-2-deoxy-D-mannopyranose (**1a**) and the proposed new transformation; (a) $PhI(OCOt\text{-}Bu)_2$, $Rh_2(OAc)_4$, *t*-BuOH, $ClCH_2CH_2Cl$; (b) Ref. 5 (three steps).



Scheme 3. Synthesis of **6** from **9** via regio- and stereoselective ring opening of the aziridine **7**; (a) urea–hydrogen peroxide complex (UHP), $KHCO_3$, CH_3CN; (b) CH_3I, Ag_2O, DMF; (c) NaN_3, NH_4Cl, aq MeOH; (d) Ac_2O, pyridine, CH_2Cl_2; (e) MsCl, Et_3N, CH_2Cl_2; (f) Ph_3P, $(i\text{-}Pr)_2NEt$, aq CH_3CN; then Ac_2O, pyridine; (g) PPh_3, toluene; then Ac_2O, pyridine; (h) NaI, *N*,*N*-dimethylacetamide (DMA); (i) 2 M HCl, THF; (j) $(NH_4)_2[Ce(NO_3)_6]$, $NaHCO_3$, aq CH_3CN.

the acetates,[8] and selective protection of the resulting primary alcohol at C-6 with a TBS group in good overall yield up to 88%. In our first trials, the epoxidation did not proceed with conventional reagents, such as *m*-chloroperoxybenzoic acid (*m*-CPBA) or magnesium monoperoxyphthalate (MMPP). The desired reaction could only be performed by applying a less sterically hindered iminohydroperoxide, which was generated in situ under Payne oxidation conditions[9] with alkaline H_2O_2 in acetonitrile (Scheme 3). The ratio between *syn*-**8b** (*syn*-epoxy alcohol) and diastereomeric *anti*-**8b** (*anti*-epoxy alcohol) was estimated to be 64:36 (see Experimental, Section 4.3). Undesired β-epoxidation occurred to a certain extent, although α-epoxidation was expected by hydrogen bond formation between the oxidant and the α-oriented allylic alcohol. It was supposed that the α-oriented *p*-methoxyphenyl group at C-1, and hydrogen bond formation between the allylic hydroxy group and surrounding water under the aqueous Payne oxidation conditions interfered with the access of the oxidant from the α-orientation. In order to avoid the influence of the latter effect, aqueous hydrogen peroxide was replaced with urea–hydrogen peroxide complex (UHP),[10] which improved the ratio to 87:13. The major *syn*-**8b** was recovered by silica gel column chromatographic separation of the diastereomers (72% yield, 82% based on the consumed starting material). An attempt at reagent-based control of stereochemistry in the epoxidation of **9a** under Sharpless' asymmetric epoxidation conditions [*t*-BuOOH, $Ti(O^iPr)_4$, and diethyl D-(−)-tartrate][11] resulted in no reaction.

At this stage, we compared another substrate for epoxidation, **9b** with a free hydroxy group at C-6. The selectivity between *syn*-**8c** and *anti*-**8c** was 64:36 under aqueous Payne oxidation conditions and 83:17 with UHP, which was similar to that using TBS ether **9a**. Since the handling of epoxy alcohol **8b** was easier than that of **8c**, TBS ether **9a** was chosen as the substrate for epoxidation.

After the methylation of the resulting free hydroxy group in *syn*-**8b** to form **8a** (96%), the opening of the epoxide ring in **8a** with nitrogen-containing nucleophiles, such as azide, acetamide, and isocyanate was attempted. Among them, only the azide could open the epoxide ring, giving a regioisomeric mixture of **10a** and **11** in a ratio of 74:26 in 82% combined yield. The regio- and stereochemistry of **10a** was determined after conversion to the corresponding acetate **10b**, whose downfield chemical shift of H-2 and coupling constants ($J_{1,2}$=3.4 Hz, $J_{2,3}$=10.7 Hz) indicated a free hydroxy group at C-2 with α-configuration. With this assignment, the stereochemistry in *syn*-**8b** was also unambiguously confirmed as depicted in Scheme 3. The free hydroxy group at C-2 in **10a** was mesylated to **10c**, and the product was cyclized by the action of

triphenylphosphine by Staudinger reaction. Subsequent acetylation furnished aziridine **7** in 75% yield. The regioisomer **11**, which had been produced at the stage of the epoxide opening reaction was effectively merged into the same **7** in 81% yield.

The regio- and stereoselective transformation at C-3 was inspired by the work of El Shafei and Guthrie.[12] Aziridine **7**, which was activated by the introduction of an electron-withdrawing acetyl group, was treated with iodide to give intermediate **12**, which has an α-oriented iodine atom at C-3 with inversion of stereochemistry. The reaction mixture was further heated to allow recyclization by the oxygen atom of *N*-acetamide to give oxazoline **6** in 87% yield. Formation of the oxazoline functionality was confirmed by the ^{13}C NMR chemical shift of the oxazoline sp^2 carbon (δ 165.68), which matched that of the reported one (168.3).[13] Through this step, the double inversion at C-3 with retention at C-2 occurred to furnish the correct stereochemistry. The stereochemical identities of **6** and mannosamine were further confirmed by spectral data in the course of its conversion to **1a** via **1c**, through deprotection and ring opening of the oxazoline.[12,13]

3. Conclusion

We accomplished a new route for 4-*O*-methylated mannosamine in its oxazoline form (**6**) in 43% yield over six steps, starting from known **9a**. The total yield of 7-*O*-methylsialic acid from commercially available tri-*O*-acetyl-D-glucal was estimated to be 15%. In the present synthesis, the α-oriented *p*-methoxyphenyl group installed by a stereoselective Ferrier reaction, effectively worked to suppress the undesired side reaction, that is, the ring opening of the aziridine from the wrong direction at C-2 in **7**. All operation could be performed at a lower cost, compared to the previous synthesis based on rhodium nitrenoid-mediated regio- and stereoselective cyclization to introduce the key mannosamine functionality.

4. Experimental

4.1. Material and methods

Merck silica gel 60 F_{254} thin-layer plates (1.05744, 0.5 mm thickness) and silica gel 60 (spherical and neutral; 100–210 μm, 37558–79) from Kanto Chemical Co. were used for preparative thin-layer chromatography and column chromatography, respectively.

4.2. Analytical methods

All mps are uncorrected. IR spectra were measured by ATR on a Jeol FT-IR SPX60 spectrometer. ^{1}H and ^{13}C NMR spectra were measured at 400 or 100 MHz on an Agilent 400-MR, or at 500 or 125 MHz on an INOVA-500 spectrometer, respectively. High resolution mass spectra were recorded on a Jeol JMS-700 MStation spectrometer at 70 eV. Optical rotation values were recorded on a Jasco P-1010 polarimeter.

4.3. *p*-Methoxyphenyl 2,3-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-α-D-allopyranoside (*syn*-8b) and *p*-methoxyphenyl 2,3-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-α-D-mannopyranoside (*anti*-8b)

To a solution of **9a** (3.10 g, 8.45 mmol) in CH_3CN/MeOH (1:1, 8.5 mL) were added $KHCO_3$ (4.20 g, 42.0 mmol) and 30% H_2O_2 (7.0 mL). The mixture was stirred for 13 h at room temperature. To the reaction mixture were added another portion of CH_3CN (2.0 mL) and 30% H_2O_2 (3.5 mL), and the mixture was further stirred for 5 h. To the reaction mixture were added still another portion of CH_3CN (2.0 mL) and 30% H_2O_2 (3.5 mL), and the mixture was still further stirred for 20 h. The progress of the reaction was checked by silica gel TLC, developed with hexane/EtOAc (2:1), R_f for *syn*-**8b**: 0.33; *anti*-**8b**: 0.65. The reaction was quenched with $Na_2S_2O_3$ aq solution and organic materials were extracted with EtOAc three times. The combined extract was washed with brine and dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was charged on a silica gel column (100 mL). Elution with hexane/EtOAc (5:1) furnished *syn*-**8b** (1.13 g, 35%) as a colorless solid, along with an inseparable mixture of *anti*-**8b** and the unreacted starting material, **9a** (1.98 g, 63%; *anti*-**8b**:**9a**=33:67, judged by its ^{1}H NMR spectrum). The ratio between *syn*-**8b** (*syn*-epoxy alcohol) and diastereomeric *anti*-**8b** (*anti*-epoxy alcohol) was estimated to be 64:36 by the comparison of ^{1}H NMR spectrum of the crude mixture.

syn-**8b**: mp 77 °C; $[\alpha]_D^{22}$ +89.6 (*c* 0.60, $CHCl_3$); IR ν_{max} 3473, 2951, 2927, 2856, 1506, 1464, 1250, 1217, 1146, 1099, 1003, 922, 829, 773, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.04 (dd, *J*=3.1, 9.2 Hz, 1H), 7.03 (dd, *J*=3.1, 9.2 Hz, 1H), 6.80 (dd, *J*=3.1, 9.1 Hz, 1H), 6.79 (dd, *J*=3.1, 9.1 Hz, 1H), 5.50 (d, *J*=2.9 Hz, 1H), 4.02 (ddd, *J*= 1.8, 6.0, 10.6 Hz, 1H), 3.75 (s, 3H), 3.78–3.90 (m, 2H), 3.72 (dd, *J*=5.0, 10.3 Hz, 1H), 3.68 (dd, *J*=2.9, 4.1 Hz, 1H), 3.54 (dd, *J*=1.8, 4.1 Hz, 1H), 2.68 (d, *J*=6.0 Hz, 1H), 0.86 (s, 9H), 0.05 (d, *J*=2.7 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ: 155.13, 150.96, 118.76 (×2), 114.44 (×2), 93.40, 68.77, 67.56, 63.93, 55.60, 55.12, 53.97, 25.81 (×3), 18.25, −5.50, −5.56. Anal. Calcd for $C_{19}H_{30}O_6Si$: C, 59.66; H, 7.90. Found: C, 59.44; H, 7.88.

anti-**8b**: ^{1}H NMR ($CDCl_3$) δ: 6.99 (dd, *J*=3.0, 9.0 Hz, 1H), 6.98 (dd, *J*=3.0, 9.0 Hz, 1H), 6.82 (dd, *J*=3.0, 9.0 Hz, 1H), 6.81 (dd, *J*=3.0, 9.0 Hz, 1H), 5.51 (s, 1H), 3.85 (d, *J*=8.6 Hz, 1H), 3.76 (s, 3H), 3.68–3.80 (m, 2H), 3.60 (dd, *J*=8.6, 8.0 Hz, 1H), 3.37 (d, *J*=3.7 Hz, 1H), 3.30 (d, *J*=3.7 Hz, 1H), 3.19 (d, *J*=2.0 Hz, 1H), 0.86 (s, 9H), 0.05 (s, 6H).

Alternative procedure by applying UHP is as follows. To a solution of **9a** (1.53 g, 4.17 mmol) in CH_3CN (21 mL) were added $KHCO_3$ (5.84 g, 58.3 mmol) and UHP (4.21 g, 44.8 mmol). The mixture was stirred at 40 °C. After 17.5, 45.5, 65.5 h, $KHCO_3$ and UHP were supplemented. First portion: 2.92 g (29.2 mmol) and 2.10 g (22.3 mmol); second portion: 2.92 g (29.2 mmol) and 2.10 g (22.3 mmol); third portion: 2.92 g (29.2 mmol) and 2.10 g (22.3 mmol), and after the final addition, the mixture was further stirred for 5.0 h. The workup and purification were performed in the same manner as above, to give *syn*-**8b** (1.15 g, 72%) and the mixture of *anti*-**8b** and **9a** (351 mg, 23%; *anti*-**8b**:**9a**=48:52).

4.4. *p*-Methoxyphenyl 2,3-anhydro-α-D-allopyranoside (*syn*-8c) and *p*-methoxyphenyl 2,3-anhydro-α-D-mannopyranoside (*anti*-8c)

To a solution of **9b** (300 mg, 1.19 mmol) in CH_3CN (6.0 mL) were added $KHCO_3$ (596 mg, 5.95 mmol) and 30% H_2O_2 (1.96 mL). The mixture was stirred for 4 h at room temperature. The progress of the reaction was checked by silica gel TLC, developed with EtOAc, R_f for *syn*-**8c**: 0.37; *anti*-**8c**: 0.63. The reaction was quenched by adding catalytic amount of PtO_2 and the mixture was filtered through a short column of Celite®. Organic materials were extracted with EtOAc five times from the solid residue. The combined extract was washed with brine and dried over anhydrous Na_2SO_4, and concentrated in vacuo. The ratio of the products was as follows: *syn*-**8c**:*anti*-**8c**:**9b**=1:0.57:0.69, judged from ^{1}H NMR of the mixture [δ: 3.56 (dd, H-3 for *syn*-**8c**), 3.43 (d, H-3 for *anti*-**8c**), 3.34 (d, H-2 for *anti*-**8c**), 5.93 (ddd, H-3 for **9b**), 6.10 (ddd, H-2 for **9b**)]. This residue was charged on a silica gel column (15 mL). Elution with $CHCl_3$ furnished *syn*-**8c** (75 mg, 24%) as a colorless solid.

syn-**8c**: Mp 126 °C; $[\alpha]_D^{26}$ +181.6 (*c* 0.44, CH_3OH); IR ν_{max} 3367, 3005, 2933, 2837, 1799, 1639, 1502, 1464, 1443, 1213, 993, 918, 829, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.04 (dd, *J*=3.1, 9.2 Hz, 1H), 7.03 (dd, *J*=3.1, 9.2 Hz, 1H), 6.80 (dd, *J*=3.1, 9.1 Hz, 1H), 6.79 (dd, *J*=3.1, 9.1 Hz,

1H), 5.55 (d, *J*=3.1 Hz, 1H), 4.00–4.07 (br, 1H), 3.76–3.90 (m, 3H), 3.75 (s, 3H), 3.73 (dd, *J*=3.1, 4.1 Hz, 1H), 3.56 (dd, *J*=1.8, 4.1 Hz, 1H). HRMS (FAB): calcd for $C_{13}H_{16}O_6$: $[M]^+$: 268.0947; found: 268.0958.

Further purification of the small amount of less polar fractions by preparative TLC provided an analytical sample of *anti*-**8c**: ^{1}H NMR ($CDCl_3$) δ: 7.00 (dd, *J*=3.1, 9.0 Hz, 1H), 6.99 (dd, *J*=3.1, 9.0 Hz, 1H), 6.83 (dd, *J*=3.1, 9.0 Hz, 1H), 6.82 (dd, *J*=3.1, 9.0 Hz, 1H), 5.57 (s, 1H), 3.96 (dd, *J*=5.2, 8.4 Hz, 1H), 3.68–3.76 (m, 3H), 3.76 (s, 3H), 3.41 (d, *J*=3.6, 1H), 3.33 (d, *J*=3.6 Hz, 1H), 2.38 (d, *J*=5.2, 1H), 1.71 (s, 1H).

The epoxidation of **9b** (70 mg, 0.28 mmol) with UHP was carried out in the similar manner as described for **9a**. The ratio between *syn*-**8c**:*anti*-**8c**:**9b** was 22:4:74. Chromatographic purification provided pure *syn*-**8c** (9.8 mg, 13%).

4.5. *p*-Methoxyphenyl 2,3-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-α-D-allopyranoside (*syn*-8b)

To a solution of *syn*-**8c** (10 mg, 0.037 mmol) in CH_2Cl_2 (186 μL) were added imidazole (3.0 mg, 0.044 mmol) and TBSCl (5.6 mg, 0.037 mmol). The solution was stirred for 4 h at 0 °C. The progress of the reaction was checked by silica gel TLC, developed with hexane/EtOAc (2:1), R_f for *syn*-**8b**: 0.33. After consumption of starting material, the reaction was diluted H_2O and organic materials were extracted with EtOAc three times. The combined extract was washed with brine and dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was charged on a silica gel column (2.0 mL). Elution with hexane/EtOAc (5:1) furnished *syn*-**8b** (13 mg, 93%) as a colorless solid. The physicochemical properties and the spectral data of the present *syn*-**8b** were identical with those reported in Section 4.3.

4.6. *p*-Methoxyphenyl 2,3-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-4-*O*-methyl-α-D-allopyranoside (8a)

To a solution of *syn*-**8b** (1.09 g, 2.83 mmol) in anhydrous DMF (14 mL) was added CH_3I (1.33 mL, 21.3 mmol) and Ag_2O (3.95 g, 14.2 mmol). The solution was stirred for 23 h at room temperature under an argon atmosphere. The progress of the reaction was checked by silica gel TLC, developed with hexane/EtOAc (2:1), R_f for **8a**: 0.55. After consumption of starting material, the mixture was filtered through a short column of Celite® and the filtrate was diluted with EtOAc. The organic layer was washed sequentially with brine, H_2O four times, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was charged on a silica gel column (50 mL). Elution with hexane/EtOAc (5:1) furnished **8a** (1.08 g, 96%) as a colorless solid; mp 58 °C; $[\alpha]_D^{22}$ +135.1 (*c* 0.84, $CHCl_3$); IR ν_{max} 2953, 2931, 2856, 2833, 1506, 1462, 1248, 1217, 1146, 1109, 1092, 991, 922, 827, 775, 667 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.05 (dd, *J*=3.1, 9.0 Hz, 1H), 7.04 (dd, *J*=3.1, 9.0 Hz, 1H), 6.79 (dd, *J*=3.1, 9.0 Hz, 1H), 6.78 (dd, *J*=3.1, 9.0 Hz, 1H), 5.49 (d, *J*=3.1 Hz, 1H), 3.89 (ddd, *J*=2.2, 3.5, 9.4 Hz, 1H), 3.75 (s, 3H), 3.69–3.81 (m, 3H), 3.65 (dd, *J*=3.1, 4.1), 3.61 (dd, *J*=1.4, 4.1 Hz, 1H), 3.52 (s 3H), 0.86 (s, 9H), 0.025 (s, 6H); ^{13}C NMR ($CDCl_3$) δ: 155.09, 151.18, 118.83 (×2), 114.44 (×2), 93.60, 73.28, 68.70, 62.20, 57.25, 55.65, 54.62, 51.23, 25.92 (×3), 18.40, −5.30, −5.40. Anal. Calcd for $C_{20}H_{32}O_6Si$: C, 60.58; H, 8.13. Found: C, 60.44; H, 8.11.

4.7. *p*-Methoxyphenyl 6-*O*-(*tert*-butyldimethylsilyl)-4-*O*-methyl-3-deoxy-3-azido-α-D-glucopyranoside (10a) and *p*-methoxyphenyl 6-*O*-(*tert*-butyldimethylsilyl)-4-*O*-methyl-2-deoxy-2-azido-α-D-altropyranoside (11)

To a solution of **8a** (735 mg, 1.85 mmol) in MeOH/H_2O (8:1, 12 mL) was added NH_4Cl (198 mg, 3.70 mmol) and NaN_3 (964 mg, 14.8 mmol), and the mixture was stirred at 80 °C for 3 days. The progress of the reaction was checked by silica gel TLC, developed with hexane/EtOAc (2:1), R_f for **10a**: 0.70 and **11**: 0.51. After consumption of starting material, the reaction was diluted H_2O and organic materials were extracted with EtOAc three times. The combined extract was washed with brine and dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was charged on a silica gel column (30 mL). Elution with hexane/EtOAc (5:1) furnished **10a** (495 mg, 61%) and **11** (169 mg, 21%), respectively.

Compound **10a**: colorless oil; $[\alpha]_D^{21}$ +169.4 (*c* 0.85, $CHCl_3$); IR ν_{max} 3437, 2949, 2929, 2856, 2835, 2104, 1506, 1464, 1250, 1213, 1126, 1076, 1024, 825, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 6.97–7.03 (m, 2H), 6.78–6.84 (m, 2H), 5.35 (d, *J*=3.7 Hz, 1H), 3.76 (s, 3H), 3.64–3.83 (m, 4H), 3.57 (s, 3H), 3.52–3.62 (m, 1H), 3.24 (dd, *J*=9.5, 9.8 Hz, 1H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ: 155.41, 150.33, 118.15 (×2), 114.70 (×2), 97.49, 77.78, 72.26, 71.35, 66.97, 61.68, 60.38, 55.64, 25.85 (×3), 18.29, −5.21, −5.43. Anal. Calcd for $C_{20}H_{33}N_3O_6Si$: C, 54.65; H, 7.57; N 9.56. Found: C, 54.47; H, 7.67; N, 9.11.

The regiochemistry of **10a** was confirmed after conversion to the corresponding acetate **10b** in a conventional manner. ^{1}H NMR ($CDCl_3$) δ: 6.92–6.98 (m, 2H), 6.76–6.84 (m, 2H), 5.47 (d, *J*=3.4 Hz, 1H), 4.69 (dd, *J*=3.4, 10.7 Hz, 1H), 4.05 (dd, *J*=9.8, 10.7 Hz, 1H), 3.80 (dd *J*=3.5, 10.5 Hz, 1H) 3.75 (s, 3H), 3.66–3.77 (m, 2H), 3.58 (s, 3H), 3.31 (dd, *J*=9.8, 10.5 Hz, 1H), 2.13 (s, 3H) 0.88 (s, 9H), 0.042 (s, 6H). The enhancement of signal (5.5%) for H-2 was observed by a nuclear Overhauser effect, when H-1 was irradiated.

Compound **11**: ^{1}H NMR ($CDCl_3$) δ: 7.03 (dd, *J*=3.1, 9.2 Hz, 1H), 7.02 (dd, *J*=3.1, 9.2 Hz, 1H), 6.80 (dd, *J*=3.1, 9.2 Hz, 1H), 6.79 (dd, *J*=3.1, 9.2 Hz, 1H), 5.27 (d, *J*=4.3 Hz, 1H), 4.02–4.12 (m, 2H), 3.87 (dd, *J*=4.3, 7.0 Hz, 1H), 3.83 (dd, *J*=3.3, 11.3 Hz, 1H), 3.78 (dd, *J*=4.5, 11.3 Hz, 1H), 3.75 (s, 3H), 3.57 (dd, *J*=3.7, 6.0 Hz, 1H), 3.45 (s, 3H), 2.83 (d, *J*=8.4 Hz, 1H), 0.87 (s, 9H), 0.05 (s, 6H).

4.8. *p*-Methoxyphenyl 2,3-(acetylepimino)-6-*O*-(*tert*-butyldimethylsilyl)-4-*O*-methyl-2,3-dideoxy-α-D-glucopyranoside (7)

To the solution of **10a** (663 mg, 1.51 mmol) in anhydrous CH_2Cl_2 (7.5 mL) was added Et_3N (315 μL, 2.26 mmol) and MsCl (141 μL, 1.82 mmol), and the mixture was stirred for 40 min at 0 °C under an argon atmosphere. The reaction was quenched with phosphate buffer solution and organic materials were extracted with EtOAc three times. The combined extract was washed with brine and dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude mesylate **10c** was employed for the next step without further purification.

To the solution of the above-mentioned **10c** in CH_3CN (10 mL) was added Ph_3P (396 mg, 1.51 mmol), and the mixture was stirred 0 °C under an argon atmosphere. After 10 min, to the resultant mixture, H_2O (2.0 mL) was added and the mixture was stirred for 11 h. To the solution was added DIPEA (789 μL, 4.5 mmol) and the mixture was allowed to warm to reflux and further stirred for 4.0 h. To the resultant mixture was cooled to 0 °C and added pyridine (0.4 mL, 5.0 mmol) and Ac_2O (0.3 mL, 3.2 mmol) and the mixture was stirred for 20 min. The progress of the reaction was checked by silica gel TLC, developed with hexane/EtOAc (2:1), R_f for **7**: 0.43. After consumption of starting material, the reaction was diluted H_2O and organic materials were extracted with EtOAc three times. The combined extract was washed with brine and dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was charged on a silica gel column (20 mL). Elution with hexane/EtOAc (10:1) furnished **7** (496 mg, 75% in two steps) as a colorless oil; $[\alpha]_D^{21}$ +100.7 (*c* 0.52, $CHCl_3$); IR ν_{max} 2953, 2929, 2856, 2833, 1705, 1504, 1464, 1441, 1431, 1362, 1252, 1213, 1200, 1107, 1012, 987, 829, 775, 725, 665, 609 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.05 (dd, *J*=3.1, 9.0 Hz, 1H), 7.04 (dd, *J*=3.1, 9.0 Hz, 1H), 6.80 (dd, *J*=3.1, 9.0 Hz, 1H), 6.79 (dd, *J*=3.1, 9.0 Hz, 1H), 5.54 (s, 1H), 3.75 (s, 3H), 3.64–3.72 (m, 3H), 3.51 (s, 3H), 3.39 (d, *J*=8.4 Hz, 1H), 2.96 (d, *J*=5.7 Hz, 1H), 2.87 (d,

J=5.7 Hz, 1H), 2.18 (s, 3H), 0.83 (s, 9H), −0.004 (s, 6H); ^{13}C NMR ($CDCl_3$) δ: 181.59, 155.05, 118.27 (×2), 114.49 (×2), 94.31, 71.14, 69.31, 62.86, 57.27, 55.58, 37.53, 35.62, 25.86 (×3), 23.38, 18.34, −5.40, −5.42. Anal. Calcd for $C_{22}H_{35}NO_6Si$: C, 60.38; H, 8.06, N, 3.20. Found: C, 60.19; H, 8.08, N, 3.06.

The regioisomer **11** was merged to **7** as follows. To the solution of **11** (280 mg, 0.64 mmol) in toluene (3.2 mL) was added Ph_3P (167 mg, 0.64 mmol), and the mixture was stirred 0 °C under an argon atmosphere. After 20 min, the mixture was allowed to warm to reflux and further stirred for 12 h. After cooling to 0 °C, pyridine (154 μL, 1.91 mmol) and Ac_2O (121 μL, 1.28 mmol) were added and the mixture was stirred for 40 min. The workup and purification were performed in the same manner for the cyclization of **10c**, to give **7** (226 mg, 81%).

4.9. 2-Methyl-1′-*O*-methoxyphenyl-4′-*O*-methyl-6′-*O*-(*tert*-butyldimethylsilyl)-α-D-mannopyrano[2′,3′]-Δ2-oxazoline (6)

To a solution of **7** (354 mg, 0.81 mmol) in anhydrous DMA (4.0 mL) was added NaI (243 mg, 1.62 mmol), and the mixture was stirred at 120 °C for 46 h under an argon atmosphere. The progress of the reaction was checked by silica gel TLC, developed with $CHCl_3$/MeOH (50:1), R_f for **6**: 0.58. The reaction was diluted H_2O and organic materials were extracted with Et_2O three times. The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4, then concentrated in vacuo. The residue was charged on a silica gel column (20 mL). Elution with hexane/EtOAc (5:1) furnished **6** (307 mg, 87%) as a yellow oil; $[\alpha]_D^{23}$ +55.5 (*c* 0.33, $CHCl_3$); IR ν_{max} 2949, 2929, 2854, 2831, 1672, 1506, 1387, 1217, 1119, 1097, 1036, 997, 982, 831, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 6.99 (dd, J=3.2, 9.2 Hz, 1H), 6.98 (dd, J=3.2, 9.2 Hz, 1H), 6.79 (dd, J=3.2, 9.2 Hz, 1H), 6.78 (dd, J=3.2, 9.2 Hz, 1H), 5.72 (s, 1H), 4.77 (dd, J=6.2, 9.4 Hz, 1H), 4.26 (d, J=9.4 Hz, 1H), 3.74 (s, 3H), 3.74 (dd, J=4.1, 11.1 Hz, 1H). 3.71 (dd, J=2.3, 11.1 Hz, 1H). 3.66 (ddd, J=2.3, 4.1, 10.0 Hz, 1H), 3.48 (s, 3H), 3.27 (dd, J=6.2, 10.0 Hz, 1H), 2.02 (d, J=2.0 Hz, 3H), 0.84 (s, 9H), 0.001 (d, J=2.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ: 165.68, 154.85, 150.37, 117.86 (×2), 114.56 (×2), 97.64, 82.15, 77.25, 68.98, 68.91, 62.50, 58.66, 55.63, 25.88 (×3), 18.34, 14.17, −5.31, −5.43. Anal. Calcd for $C_{22}H_{35}NO_6Si$: C, 60.38; H, 8.06, N, 3.20. Found: C, 60.19; H, 8.14, N, 3.04.

4.10. Confirmation of the regio- and stereochemistry of 6

A solution of **6** (68 mg, 0.16 mmol) in a mixture of THF (1.4 mL) and 2 M HCl (388 μL) was stirred for 1 h at 0 °C. The reaction was quenched with $NaHCO_3$ aq solution and organic materials were extracted with $CHCl_3$ five times. The combined extract was washed with brine and dried over anhydrous Na_2SO_4, and concentrated in vacuo to give crude product (126 mg). It contained partially deprotected form **1c**; ^{1}H NMR ($CDCl_3$) δ: 6.93 (dd, J=3.0, 9.0 Hz, 1H), 6.92 (dd, J=3.0, 9.0 Hz, 1H), 6.79 (dd, J=3.0, 9.0 Hz, 1H), 6.78 (dd, J=3.0, 9.0 Hz, 1H), 6.00 (d, J=7.7 Hz, 1H), 5.39 (d, J=1.7 Hz, 1H), 4.54 (ddd, J=1.5, 4.7, 7.7 Hz, 1H), 4.34 (dd, J=4.7, 9.5 Hz, 1H), 3.74–3.82 (m, 2H), 3.74 (s, 3H), 3.71 (ddd, J=3.0, 4.1, 9.7), 3.59 (s, 3H), 3.38 (dd, J=9.5, 9.7 Hz, 1H), 2.07 (s, 3H). The contamination of 2-amino-3-*O*-acetyl derivative caused by another mode of oxazoline ring opening was suggested, δ: 5.41 (dd, J=3.9, 9.0 Hz, 1H), 5.13 (d, J=1.7 Hz, 1H), 2.18 (s 3H). This byproduct was related to the less polar spot of two [$CHCl_3$/MeOH (4:1), R_f 0.67 and 0.57] on silica gel TLC analysis of the crude mixture.

Next, above-mentioned crude product was dissolved in a mixture of CH_3CN/H_2O (4:1, 15 mL). After cooling to 0 °C, to the mixture was added $NaHCO_3$ (104 mg, 1.24 mmol) and the resulting mixture was stirred for 36 h at room temperature, to remove the contaminant. During this operation, the less polar component disappeared probably by hydrolysis. Then, to the mixture, $(NH_4)_2[Ce(NO_3)_6]$ (340 mg, 0.62 mmol) was added. The mixture was stirred for 15 min at 0 °C. The progress of the reaction was checked by silica gel TLC, developed with EtOAc/EtOH (4:1), R_f for **1a**: 0.31. The reaction was quenched with 1,2,4-trimethoxybenzene (100 μL). The mixture was partitioned with toluene and water. The organic phase was extracted with H_2O twice. The combined water layer was concentrated in vacuo. The residue was charged on a silica gel column (10 mL). Elution with $CHCl_3$/MeOH (20:1) furnished **1a** (59 mg); ^{1}H NMR (D_2O, 3:2 mixture of α- and β-anomers) δ: 5.09 (d, J=1.6 Hz, 1H), 4.99 (d, J=1.6 Hz, 0.7H), 4.42 (dd, J=1.5, 4.5 Hz, 0.7H), 4.31 (dd, J=1.6, 4.5 Hz, 1H), 4.11 (dd, J=4.5, 9.8 Hz, 1H), 3.91 (dd, J=4.5, 9.8 Hz, 0.7H), 3.77–3.90 (m, 3.3H), 3.55 (s, 3H), 3.54 (s, 2H), 3.34–3.43 (m, 2.3H), 3.29 (dd, J=9.7, 9.8 Hz, 1H), 2.10 (s, 2H), 2.06 (s, 3H); ^{13}C NMR (D_2O, δ: 1.7 for CH_3CN as an internal standard) δ: 176.5, 175.5, 93.4, 93.4, 77.4, 77.0, 75.8, 72.4, 71.6 (×2), 69.3, 60.8, 60.7, 60.6, 54.8, 53.9, 22.6, 22.5. Its ^{1}H and ^{13}C NMR spectra were in good accordance with those previously reported.[5] The yield (46%) in this two-step transformation was estimated by comparing the integration of signals of in ^{1}H NMR of **1a** with those of methyl β-D-glucopyranoside, which was added as the internal standard.[4]

Acknowledgements

This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction. The authors thank Mr. Nobuyuki Chishima and Dr. Eriko Suzuki of this lab, for their help in the early phase of this study, and Mr. Sho Inomata for discussion. This work was supported both by a Grant-in-Aid for Scientific Research (No. 23580152) and MEXT-supported program for the strategic research foundation at private universities (centers of excellence for research) in 'molecular nanotechnology for green innovation', FY 2012-2016 and acknowledged with thanks.

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