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Note

A facile synthesis of (1*S*,5*R*,6*S*)-5-azido-6-benzyloxycyclohex-2-en-1-ol

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This paper is dedicated to the memory of the late Professor Mugio Nishizawa

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ABSTRACT

A facile and short synthesis of (1*S*,5*R*,6*S*)-5-azido-6-benzyloxycyclohex-2-en-1-ol (**1**) has been achieved in high yield starting from 4,5-epoxycyclohex-1-ene by using a catalytic asymmetric allylic oxidation reaction.

Aminocyclitols and their analogs such as (1*S*,5*R*,6*S*)-5-azido-6-benzyloxycyclohex-2-en-1-ol (**1**) have been recognized for their importance as glycosidase inhibitors.[1–4] Recently, Pelyvás, Sztaricskai and co-workers reported the synthesis of **1** and structurally related compounds starting from D-glucose.[5] Here, we report the facile synthesis of **1** based on a catalytic asymmetric allylic oxidation reaction.

We recently reported the efficient synthesis of enantiopure (1*S*,5*S*,6*R*)-5,6-epoxycyclohex-2-en-1-ol (**2**) based on the enantioselective allylic oxidation of 4,5-epoxycyclohex-1-ene as shown in Scheme 1.[6]

The hydroxy group of enantiomerically pure **2** was protected by a MOM group (94%), followed by the ring opening with NaN_3/NH_4Cl that proceeded regioselectively to afford the MOM-protected azido alcohol **4** (80%) (Scheme 2). The remaining hydroxyl group was then benzylated to give **5** (91%). Finally, the MOM group was deprotected by CF_3CO_2H to give the desired (1*S*,5*R*,6*S*)-5-azido-6-benzyloxycyclohex-2-en-1-ol (**1**) (94%) ($[\alpha]_D^{22}$ 110.5 (*c* 1.0, $CHCl_3$)). Pelyvás, Sztaricskai and co-workers synthesized **1** in 13 steps from D-glucose ($[\alpha]_D$ 106.2 (*c* 1.0, $CHCl_3$)). Therefore, compared with the reported method starting from D-glucose,[5] the present method is clearly superior from the viewpoint of a shorter number of steps, total yield and operational simplicity (4 steps in 64% yield from **2**).

1. Experimental

1.1. General

All reactions were performed under an argon atmosphere using Schlenk tube techniques and freshly distilled solvents. All melting points were measured on a Yanaco MP-500D apparatus and are uncorrected. ^1H and ^{13}C NMR spectra (400 and 100.6 MHz, respectively) were recorded on a JEOL JNM-LA 400 using Me_4Si as the internal standard (0 ppm). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Elemental analyses were performed with a Yanaco CHN Corder MT-5. Mass spectra were measured on a Thermo Quest LCQ DECA plus. Optical rotations were measured on a HORIBA SEPA-300 polarimeter for solutions in a 1-dm cell. Preparative column chromatography was carried out on Fuji Silysia BW-820MH or YMC* GEL silica gel (6 nm I-40–63 μm). Thin-layer chromatography (TLC) was carried out on E. Merck 25 TLC aluminum sheets coated with Silica Gel 60 F_{254}. Chiral HPLC was performed on a HITACHI L-2000 series instrument equipped with an L-2455 diode array detector.

1.2. (1*S*,5*S*,6*R*)-5,6-Epoxycyclohex-2-en-1-ol (2)

To a solution of the *p*-nitrobenzoate of 5,6-epoxycyclohex-2-en-1-ol (2.09 g, 8.0 mmol) in MeOH (20 mL) was added a 0.5 M NaOMe solution (0.8 mL, 0.4 mmol). After 2 h stirring at rt, TLC showed the disappearance of starting material, and AcOH (24 mL, 0.4 mmol) was added to quench the reaction. MeOH was removed by rotary evaporator and the residue was purified by chromatography (4:1–2:1 hexane–EtOAc) to give compound **2**[6] as a colorless

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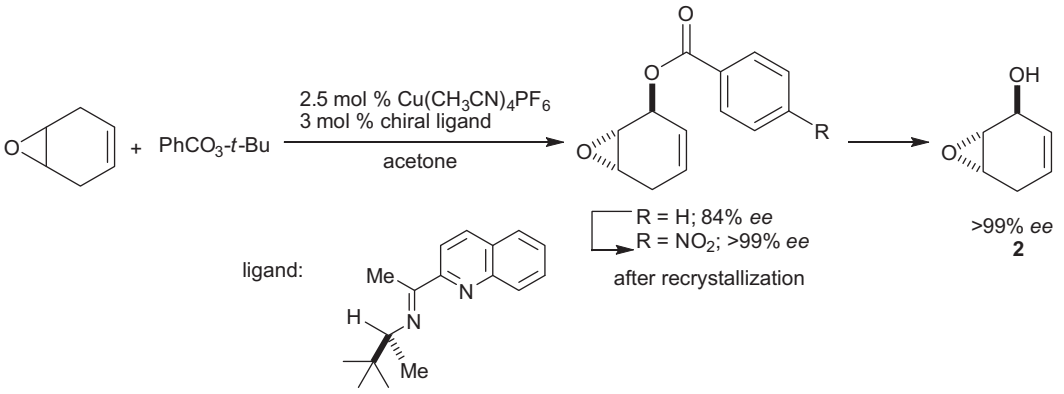
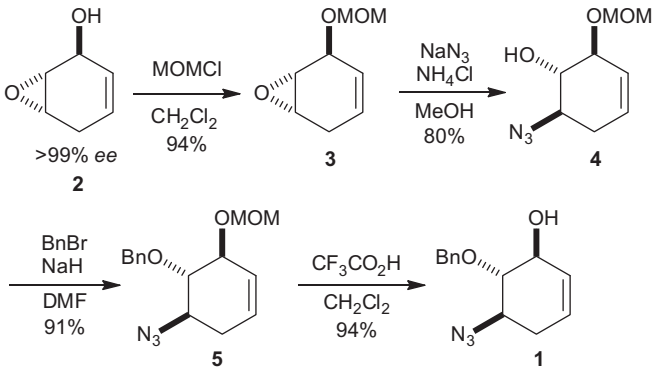


Scheme 1.



Scheme 2.

liquid (0.89 g, 99%). R_f 0.18 (1:1 hexane–EtOAc); $[\alpha]_D^{20}$ +119 (*c* 0.5, $CHCl_3$); 99% ee (determined by GC: β-DEX-225 (Supelco®), oven temp. 150 °C, t_R of major isomer = 7.17 min (1*S*,5*S*,6*R*), t_R of minor isomer = 8.57 min (1*R*, 5*R*, 6*S*)); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71–5.67 (m, 1 H), 5.62–5.58 (m, 1H), 4.5 (br s, 1H), 3.3 (br s, 1H), 3.3 (br s, 1H), 2.59–2.50 (m, 2H), 2.0 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 124.7, 124.6, 62.8, 53.6, 50.2, 25.0; ESIMS: *m*/*z* 113.0 $(M+H)^+$.

1.3. (1*S*,5*S*,6*S*)-1-Methoxymethoxy-5,6-epoxycyclohex-2-ene (3)

To a solution of the deprotected compound **2** (0.64 g, 5.7 mmol) in CH_2Cl_2 (30 mL) was added diisopropylethylamine (DIPEA, 2.9 mL, 17.3 mmol), followed by the addition of MOMCl (1.3 mL, 17.3 mmol). The mixture was stirred for 10 h and H_2O (30 μL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography (5:1 hexane–EtOAc) to give the MOM-protected compound **3** as a colorless oil (0.88 g, 99%). R_f 0.28 (3:1 hexane–EtOAc); $[\alpha]_D^{17}$ +118.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.6 (br s, 2H), 4.78 (d, *J* = 7.2 Hz, 1H), 4.75 (d, *J* = 7.2 Hz, 1H), 4.4 (br s, 1H), 3.40 (s, 3H), 3.2 (br s, 1H), 3.3 (br s, 1H), 2.63–2.51 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 125.3, 122.8, 95.9, 68.7, 55.5, 52.4, 50.3, 25.1; ESIMS: *m*/*z* 157 $(M+H)^+$. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.25; H, 7.81.

1.4. (1*S*,5*R*,6*S*)-5-Azido-1-methoxymethoxy-cyclohex-2-ene-6-ol (4)

To a solution of **3** (1.0 g, 6.4 mmol) in MeOH (48 mL) and H_2O (6 mL) were added NH_4Cl (0.68 g, 12.8 mmol) and NaN_3 (1.25 g, 19.2 mmol). The mixture was heated at 80 °C for 16 h. After cooling to rt, additional H_2O (30 mL) was added to dissolve the solid, and the MeOH was removed by an evaporator. The aqueous solution was extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (20 mL × 3) and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by chromatography (5:1 hexane–EtOAc) to give compound **4** as a colorless liquid (1.04 g, 82%). R_f 0.26 (3:1 hexane–EtOAc); $[\alpha]_D^{18}$ +165 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71–5.66 (m, 1H), 5.60–5.55 (m, 1H), 4.79 (s, 2H), 4.4 (br s, 1H), 4.0 (br s, 1H), 3.66–3.57 (m, 2H), 3.47 (s, 3H), 2.50–2.43 (m, 1H), 2.13–2.06 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 127.2, 125.9, 97.6, 83.3, 75.6, 60.6, 55.8, 30.7; ESIMS: *m*/*z* 222.3 $(M+Na)^+$. Anal. Calcd for $C_8H_{13}N_3O_3$: C, 48.23; H, 6.58; N, 21.09. Found: C, 48.55; H, 6.61; N, 20.95.

1.5. (1*S*,5*R*,6*S*)-5-Azido-6-benzyloxy-1-methoxymethoxycyclohex-2-ene (5)

To a suspension of NaH (60% dispersion in oil, 40 mg, 1.0 mmol) in DMF (1 mL) was added **4** (100 mg, 0.5 mmol) in DMF (0.5 mL). The mixture was stirred for 30 min. Then, BnBr (120 μL, 1.0 mmol) was added. The mixture was stirred for 3 h and brine (10 mL) was added to quench the reaction. The aqueous solution was extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (20 mL) and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by chromatography (20:1 hexane–EtOAc) to give compound **5** (130 mg, 90%). R_f 0.55 (2:1 hexane–EtOAc); $[\alpha]_D^{21}$ +78.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (d, *J* = 7.0 Hz, 2H), 7.36 (t, *J* = 7.0 Hz, 2H), 7.31 (d, *J* = 7.0 Hz, 1H), 4.89 (d, *J* = 10.8 Hz, 1H), 4.82 (d, *J* = 10.8 Hz, 1H), 4.80 (d, *J* = 7.0 Hz, 1H), 4.71 (d, *J* = 7.0 Hz, 1H), 4.24–4.27 (m, 1H), 3.68 (ddd, *J* = 6.0, 10.4, 10.4 Hz, 1H), 3.54 (dd, *J* = 7.2, 10.4 Hz, 1H), 3.38 (s, 3H), 2.43–2.50 (m, 1H), 2.05–2.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 138.1, 128.4, 128.2, 128.0, 127.8, 125.2, 96.9, 83.3, 78.8, 75.3, 60.8, 55.6, 31.3; ESIMS: *m*/*z* 312 $(M+Na)^+$.

1.6. Preparation of (1*S*,5*R*,6*S*)-5-azido-6-benzyloxycyclohex-2-ene-1-ol (1)

To a solution of **5** (90 mg, 0.3 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.5 mL, 3.0 mmol). The mixture was stirred at 18 °C for 1.5 h, and the TFA and CH_2Cl_2 were evaporated. EtOAc (40 mL) was added to dilute the mixture. The solution was washed with satd aq $NaHCO_3$ (10 mL × 2) and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by chromatography (10:1 hexane–EtOAc) to give compound **1** (65 mg, 86%). R_f 0.40 (2:1 hexane–EtOAc); $[\alpha]_D^{22}$ +110.5 (*c* 1.0, $CHCl_3$) (lit.[5] $[\alpha]_D$ +106.2 (*c* 1.16, $CHCl_3$)); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (d, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.33 (d, *J* = 7.4 Hz, 1H), 5.55–5.65 (m, 2H), 4.97 (d, *J* = 11.4 Hz, 1H), 4.76 (d, *J* = 11.4 Hz, 1H), 4.26 (br s, 1H), 3.69 (ddd, *J* = 5.6, 9.6, 9.6 Hz, 1H), 3.42 (dd,

J = 7.2, 9.6 Hz, 1H), 2.46–2.53 (m, 1H), 2.04–2.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 138.1, 128.8, 128.6, 128.1, 128.0, 124.9, 84.2, 74.8, 72.1, 60.5, 31.2; ESIMS: m/z 268 $(M+Na)^+$.

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References

1. Berridge, M. J. *Annu. Rev. Biochem.* **1987**, *56*, 159–193.
2. Atsumi, S.; Umezawa, K.; Iinuka, H.; Naganawa, H.; Nakamura, H.; Iitaka, Y.; Takeuchi, T. *J. Antibiot.* **1990**, *43*, 49–53.
3. Legler, G.; Bollhagen, R. *Carbohydr. Res.* **1992**, *233*, 113–123.
4. Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319–384.
5. (a) Tóth, Z. G.; Pelyvás, I. F.; Szegedi, C.; Benke, P.; Magyar, E.; Miklovicz, T.; Batta, G.; Sztaricskai, F. *Carbohydr. Res.* **1997**, *300*, 183–189; (b) Pelyvás, I. F.; Tóth, Z. G.; Vereb, G.; Balla, A.; Kovács, E.; Gorsás, A.; Sztaricskai, F.; Gergely, P. *J. Med. Chem.* **2001**, *44*, 627–632.
6. Tan, Q.; Hayashi, M. *Org. Lett.* **2009**, *11*, 3314–3317.