A diastereocontrolled synthesis of perseitol using a dioxabicyclo[3.2.1]octane chiral building block

Kohei Kadota, Kunio Ogasawara,* and Yoshiharu Iwabuchi*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan
E-mail: iwabuchi@mail.pharm.tohoku.ac.jp

Dedicated to Professor Keiichiro Fukumoto on his 70th birthday

(received 30 May 03; accepted 14 Aug 03; published on the web 20 Aug 03)

Abstract

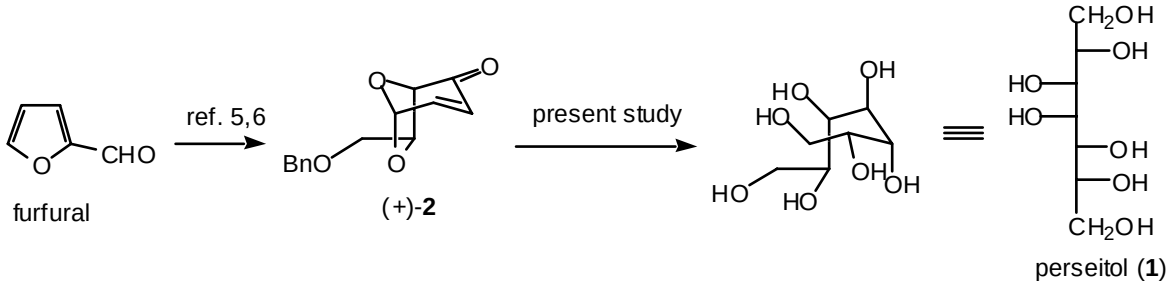
A diastereocontrolled route to the naturally occurring heptiol, perseitol (D-glycero-D-galacto-heptiol) isolated as a complex with K^+ ion from leaves of *Scurrula fusca* (Loranthaceae), has been developed starting from a chiral building block containing a 7,8-dioxabicyclo[3.2.1]octane framework.

Keywords: Perseitol, D-glycero-D-galacto-heptiol, 7,8-dioxabicyclo[3.2.1]octane framework, chiral building block, diastereocontrolled synthesis

Introduction

The leaves of a parasitic plant *Scurrula fusca* (BL.) G. Don. (Loranthaceae), whose host-plant is *Ficus riedelli* MIQ. (Moraceae), are used as the traditional folk medicine for the treatment of cancer in Sumatra and the Sulawesi Islands, Indonesia.[1] From the methanol extract of the dried leaves, perseitol (D-glycero-D-galacto-heptiol) (**1**) has been isolated as a complex with K^+ ions, and this complex has recently been shown to exhibit a potent inhibitory effect on [^{3}H]-leucine incorporation for protein synthesis on Ehrlich ascites tumor cells in mice.[2] Intriguingly, it was found that complexation of **1** with K^+ ion in a molar ratio of 20:1 is essential for expression of the anti-tumor activity.[2c] Although perseitol is known as a naturally occurring heptitol, first isolated from avocado,[3] and several preparative methods for perseitol have been developed,[4] no stereocontrolled synthesis capable of producing **1** in complete enantio- and diastereo-controlled manner has yet been reported. Since we have developed an efficient preparation from furfural of the highly functionalized bicyclic enone **2** having the 7,8-dioxabicyclo[3.2.1]octane framework, in both enantiomeric forms, by employing either chemical[5] or enzymatic procedures,[6] and since we have demonstrated its potential[7] as a versatile chiral building block,[8] especially for

carbohydrates,[9] we decided to attempt the diastereo-controlled construction of perseitol in its naturally occurring form, utilizing **2** to extend its versatility (Scheme 1).

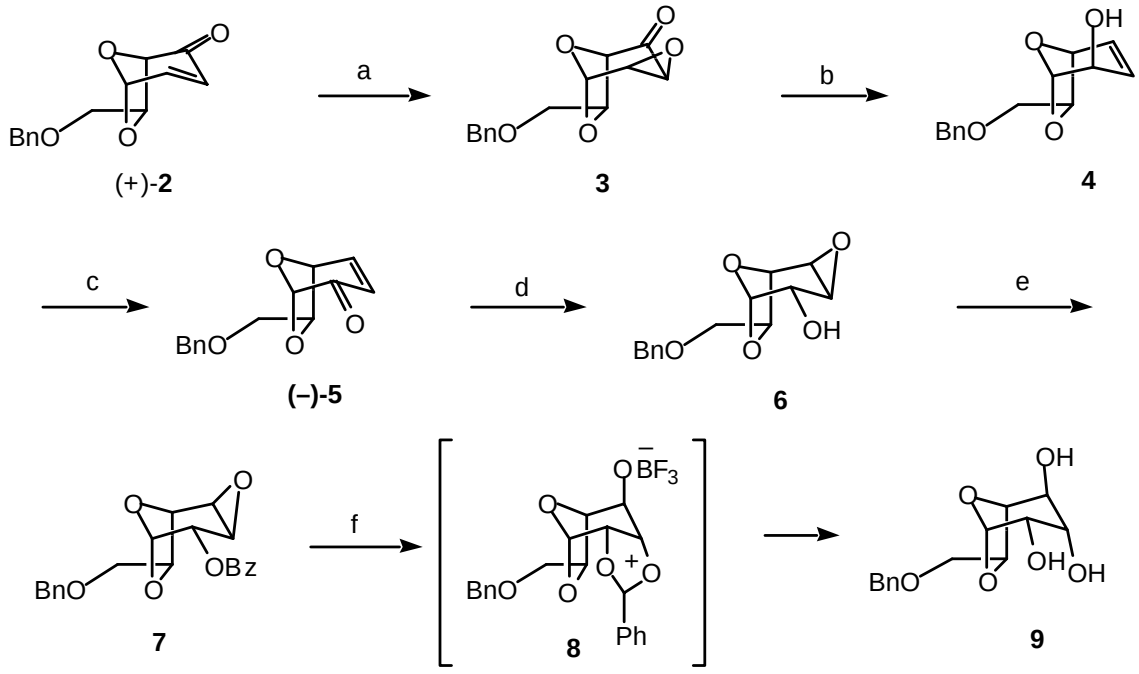


Scheme 1

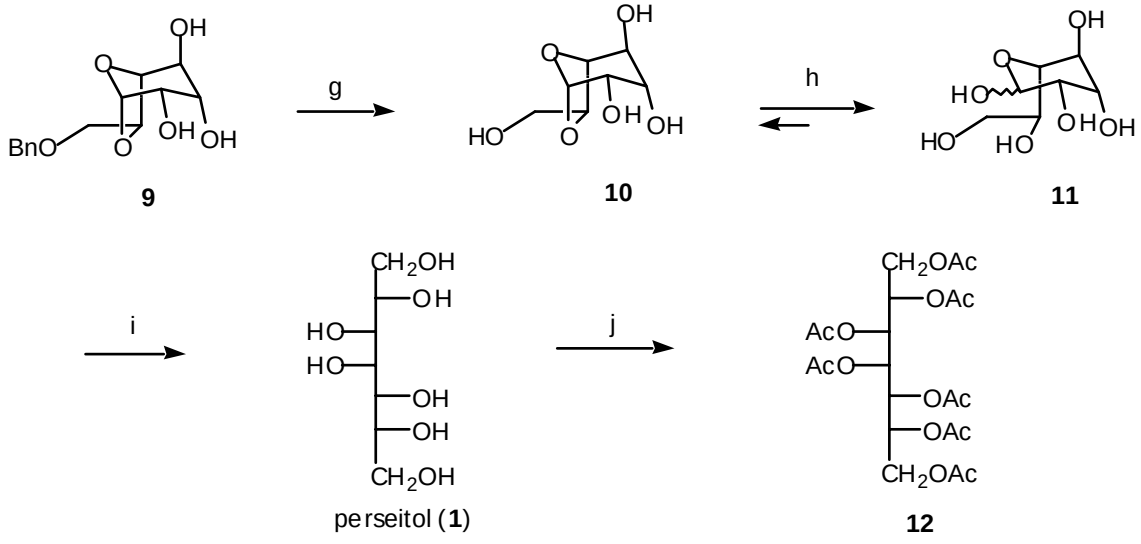
Results and Discussion

The synthesis commenced with the reaction of the (+)-enone (+)-**2**[9] with alkaline hydrogen peroxide. The reaction proceeded diastereoselectively from the convex face to give the *exo*-epoxide **3** in 75% yield. The epoxide **3** was next exposed to hydrazine hydrate in the presence of acetic acid[10] to give the allylic alcohol **4** in 60% yield, which furnished the enone **5** in 72% yield after PCC oxidation.[5] The enone **5** was treated with sodium hypochlorite in pyridine to give the *exo*-epoxide **6**, again in a completely diastereoselective fashion, which was sequentially reduced to the *endo*-alcohol by employing Luche's protocol,[11] and benzoylated to give the *endo*-benzoate **7** in 52% yield from **5**. Upon exposure of **7** to boron trifluoride etherate, the benzoate-assisted regio- and diastereo-selective epoxide cleavage[12] occurred, presumably through the transient oxonium intermediate **8**, to afford the single triol **9** in 65% yield after alkaline methanolysis of the mono-benzoate mixture (Scheme 2).

Having constructed the required five contiguous stereocenters for perseitol on the seven-carbon backbone of the building block, the only remaining tasks were the removal of the protecting group and reductive cleavage of the cyclic acetal moiety to unfold the bicyclo[3.2.1]octane structure. The benzyl group of **9** was smoothly cleaved hydrogenolytically on a Pd-C catalyst to give the tetraol, **10**. Although hydrolysis of the acetal moiety buried in the 7,8-dioxabicyclo[3.2.1]octane framework of **10** was quite sluggish under conventional conditions, *i.e.*, 90% CF_3CO_2H, or reflux in 1M HCl, heating of an aqueous solution of **10** in the presence of the cationic ion-exchange resin Dowex-50W (H^+ form) in a sealed tube at 150 °C allowed smooth reaction to afford the hemiacetal **11** in 63% yield at best, together with 31% of recovered, unchanged **10**. Finally, reduction of **11** with $NaBH_4$ furnished perseitol (**1**), which was fully characterized as the hepta-acetate **12**.



Scheme 2. Reagents and conditions: (a) H_2O_2, 0.5*M* NaOH, THF (75%); (b) $NH_2NH_2.H_2O$, AcOH (cat.), MeOH, (60%); (c) PCC, NaOAc, CH_2Cl_2, (72%); (d) NaOCl, pyridine, then $NaBH_4$, $CeCl_3.7H_2O$, MeOH (65% 2 steps); (e) BzCl, pyridine, CH_2Cl_2, (80%); (f) $BF_3.OEt_2$, toluene, then NaOMe, MeOH (65%).



Scheme 3. Reagents and conditions: (g) H_2, 10% Pd-C, MeOH, (83%); (h) Dowex 50W(H^+), H_2O, sealed tube, 150°C, (63% of **11**; 31% of **10** recovered); (i) $NaBH_4$, H_2O; (j) Ac_2O, pyridine, (40%, 2 steps).

Conclusions

We have established a diastereocontrolled synthesis of perseitol (D-glycero-D-galacto-heptiol) (**1**) starting from the (+)-enone, **2**, on the basis of its inherent diastereoselectivity and high functionality. Although only the synthesis of perseitol is shown in this report, the antipodal perseitol (L-glycero-L-galactoheptiol) has been synthesized in the formal sense.

Experimental Section

General Procedures. Unless otherwise mentioned, all reactions were performed in oven-dried glassware under an atmosphere of argon. Anhydrous THF and CH_2Cl_2 were purchased from Kanto Chemical Co., Inc. Organic extracts were dried by stirring over anhydrous $MgSO_4$, filtered through a pad of Celite, and concentrated under reduced pressure using a rotary evaporator. Column chromatography was carried out using Merck 60 (230–400 mesh) silica gel. Reactions were analyzed on pre-coated silica gel 60 F_{254} plates (Merck) and visualizing compounds with a UV lamp (254 nm) and/or staining by *p*-anisaldehyde in EtOH, or phosphomolybdic acid (in EtOH). Melting points (mp) are uncorrected. IR spectra were recorded on a JASCO IR-700 spectrometer. ^{1}H- and ^{13}C- NMR spectra were recorded on Gemini 2000 (300MHz) or JEOL AL-400 (400 MHz) spectrometers. Mass spectra were recorded on a JEOL JMS-DX303 instrument. Optical rotations were measured with a JASCO DIP-370 digital polarimeter.

(1*R*,3*S*,4*R*,5*R*,7*S*)-7-Benzyloxymethyl-3,4-epoxy-6,8-dioxabicyclo[3.2.1]octan-2-one (3). To a stirred solution of the enone **2** (300 mg, 1.22 mmol) in THF (10 ml) and 0.5 *M* NaOH (1.22 ml. 0.61 mmol) was added 30% H_2O_2 (0.21 ml, 1.83 mmol) at 0°C. After stirring for 5 min, the mixture was diluted with EtOAc (10 ml) and the organic layer was washed with 10% aq. $Na_2S_2O_3$ (2 ml), H_2O (2 ml) and brine (2 ml), and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was chromatographed (silica gel 15 g, elution with EtOAc–hexane, 1:4 v/v) to give the *exo*- epoxide **3** (240 mg, 75%) as a colorless solid. mp 58.5–59.5°C; $[\alpha]_D^{26}$ +3.2°(*c* 1.0, $CHCl_3$); IR (neat): 1733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.39–7.26 (5H, m), 5.84 (1H, s), 4.54 (2H, s), 4.48 (1H, s), 4.09 (1H, t, *J* = 6.3 Hz), 3.31–3.35 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$), δ 198.2, 137.6, 128.7, 128.1, 127.9, 98.3, 81.3, 76,6, 73.6, 69.6, 52.6, 49.5; MS *m/z*: 262 (M^+), 91 (100%) ; HRMS Calcd. $C_{14}H_{14}O_5$: 262.0840. Found: 262.0840.

(1S,2R,5S,6S)-6-Benzyloxymethyl-7,8-dioxabicyclo[3.2.1]oct-3-en-2-ol (4). To a stirred solution of **3** (200 mg, 0.76 mmol) in MeOH (8 ml) containing HOAc (0.005 ml) was added hydrazine hydrate (0.11 ml, 2.3 mmol) at 0°C, and stirring was continued for 4 h at r.t. The mixture was diluted with Et_2O and treated with sat. aq. $NaHCO_3$. The mixture was extracted with EtOAc (15 ml) and washed with H_2O (2 ml) and brine (2 ml), and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was chromatographed (silica gel,

10 g, elution with EtOAc–hexane, 1:1 v/v) to give the alcohol **4** (113 mg, 60%) as a colorless oil. $[\alpha]_D^{29}$ -108.5° (*c* 1.0, $CHCl_3$); IR (neat), 3414 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (5H, m), 6.22 (1H, dd, *J* = 9.8, 4.7 Hz), 5.82 (1H, ddd, *J* = 9.8, 3.8, 1.9 Hz), 5.50 (1H, t, *J* = 1.4 Hz), 4.55 (1H, d, *J* = 4.7 Hz), 4.54 (2H, s), 3.99 (1H, dd, *J* = 8.5, 5.2 Hz), 3.62 (1H, dddd, *J* = 10.7, 3.8, 1.4, 1.1 Hz), 3.47 (1H, dd, *J* = 9.3, 5.2 Hz), 3.36 (1H, dd, *J* = 9.3, 8.5 Hz), 1.78 (1H, br d, *J* = 10.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 131.0, 128.5, 127.9, 127.8, 126.6, 102.9, 78.2, 73.4, 71.9, 70.2, 65.5; MS m/z 248 (M^+), 91 (100%); HRMS Calcd. $C_{14}H_{16}O_4$: 248.1049. Found: 248.1022.

(1*S*,5*S*,6*S*)-6-Benzyloxymethyl-7,8-dioxabicyclo[3.2.1]oct-3-en-2-one (5). A stirred mixture of the alcohol **4** (2.7 g 10.9 mmol), NaOAc (3.13 g, 38.2 mmol) and MS 4A (1.3g) in CH_2Cl_2 (50 ml) was added pyridinium chlorochromate (PCC) (5.87 g, 27.3 mmol) at r.t., and stirred for 2 h. After filtration through a Celite pad, the filtrate was concentrated under reduced pressure and chromatographed (silica gel 150 g, elution with EtOAc–hexane, 1:3 v/v) to give the enone **5** (1.96 g, 72%) as a colorless oil. $[\alpha]_D^{31}$ -275°(*c* 1.3, $CHCl_3$); IR (neat), 1701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.25 (6H, m), 6.12 (1H, ddd, *J* = 10.2, 1.7, 0.8 Hz), 5.33 (1H, m), 4.87 (1H, d, *J* = 4.7 Hz), 4.56 (2H, s), 4.05 (1H, dd, *J* = 9.1, 4.7 Hz), 3.63 (1H, ddd, *J* = 9.3, 4.7, 0.8 Hz), 3.40 (1H, ddd, *J* = 9.3, 9.1, 0.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 188.7, 148.3, 137.5, 128.5, 128.0, 127.8, 126.9, 101.9, 76.2, 73.5, 73.3, 70.0; MS m/z, 218 (M^+-CO), 91 (100%); HRMS Calcd. $C_{13}H_{14}O_3$: 218.0942. Found: 218.0948.

(1*R*,2*S*,3*R*,4*R*,5*R*,6*S*)-6-Benzyloxymethyl-3,4-epoxy-2-hydroxy-7,8-dioxabicyclo[3.2.1]octane (6). To a stirred solution of the enone **5** (1.6 g, 6.5 mmol) in pyridine (12 ml) was added aq. NaOCl (available chlorine, *ca*. 6%, 6.24 ml) at 0°C and stirring was continued for 1 h at r.t. The mixture was diluted with EtOAc (50 ml), washed with H_2O (5 ml) and brine (5 ml), and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was chromatographed (silica gel 80 g, elution with EtOAc–hexane, 1:1 v/v) to give the corresponding epoxy ketone. To a stirred solution of epoxide and $CeCl_3.7H_2O$ (2.9 g, 7.8 mmol) in MeOH (12 ml) was added $NaBH_4$ (295 mg, 7.8 mmol) at 0°C. After stirring for 30 min at the same temperature, the mixture was diluted with EtOAc (80 ml), washed with H_2O (8 ml) and brine (8 ml), and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was chromatographed (silica gel, 80 g, elution with EtOAc–hexane, 1:2 v/v) to give the epoxy-alcohol **6** (1.12 g, 65%) as a colorless oil. $[\alpha]_D^{30}$-42.5°(*c* 1.0, $CHCl_3$); IR (neat): 3454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (5H, m), 5.32 (1H, dd, *J* = 3.0, 2.5 Hz), 4.58 (1H, s), 4.56 (2H, s), 4.31 (1H, dd, *J* = 7.7, 6.0 Hz), 3.81 (1H, dd, *J* = 11.2, 3.0 Hz), 3.51 (1H, ddd, *J* = 9.3, 6.0, 1.4 Hz) 3.41 (1H, ddd, *J* = 9.3, 7.7, 1.4 Hz), 3.13 (1H, dd, *J* = 2.7, 1.1 Hz), 3.01 (1H, dd, *J* = 2.7, 2.2 Hz), 2.32 (1H, br. d, *J* = 11.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 128.7, 128.1, 128.0, 99.7, 77.5, 73.7, 71.6, 70.0, 64.8, 51.0, 49.7; MS m/z: 264 (M^+), 91 (100%) ; HRMS Calcd. $C_{14}H_{16}O_5$, 264.0998. Found, 264.0990.

(1*R*,2*S*,3*R*,4*R*,5*R*,6*S*)-2-Benzoyloxy-6-benzyloxymethyl-3,4-epoxy-7,8dioxabicyclo[3.2.1]-octane (7). To a stirred solution of the alcohol **6** (550 mg 2.08 mmol) in CH_2Cl_2 (50 ml) was added benzoyl chloride (0.72 ml, 6.24 mmol) at r.t. and stirring was continued for 8 h. The

mixture was diluted with Et_2O (50 ml) and washed with H_2O (5 ml) and brine (5 ml), and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was chromatographed (silica gel 80 g, elution with EtOAc–hexane, 1:10 v/v) to give the epoxy-benzoate **7** (612 mg, 80%) as a white solid. mp 115°C; $[\alpha]_D^{29}$ -63.6°(*c* 0.9, $CHCl_3$); IR (neat), 1721 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (2H, d, *J* = 7.4 Hz), 7.59 (1H, t, *J* = 7.4 Hz), 7.50–7.42 (2H, m), 7.37–7.28 (5H, m), 5.58 (1H, t, *J* = 2.5 Hz), 5.07 (1H, d, *J* = 3.0 Hz), 4.68 (1H, s), 4.56 (2H, s), 4.43 (1H, dd, *J* = 8.2, 5.2 Hz), 3.53 (1H, dd, *J* = 9.3, 5.2 Hz), 3.42 (1H, dd, *J* = 9.3, 8.2 Hz), 3.22 (1H, d, *J* = 3.7 Hz), 3.18(1H, dd, *J* = 3.7, 2.5 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 165.5, 137.7, 133.5, 130.0, 129.1, 128.53, 128.48, 128.0, 127.9, 97.6, 76.9, 73.5, 71.6, 69.7, 67.1, 49.5, 49.2; MS m/z 368 (M^+), 105 (100%) ; HRMS Calcd. $C_{21}H_{20}O_6$: 368.1260. Found: 368.1269.

(1*R*,2*S*,3*S*,4*R*,5*R*,6*S*)-6-Benzyloxymethyl-2,3,4-trihydroxy-7,8-dioxabicyclo[3.2.1]octane (9). To a stirred solution of the epoxybenzoate **7** (530 mg 1.44 mmol) in toluene (8 ml) was added $BF_3.OEt_2$ (0.18 ml, 1.44 mmol) at r.t. and stirring was continued for 20 min. The mixture was diluted with EtOAc (50 ml) and washed with H_2O (5 ml) and brine (5 ml), and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was chromatographed (silica gel 50 g, elution with EtOAc–hexane, 2:1 v/v) to give the diol. The crude diol was dissolved in MeOH (6 ml). The mixture had NaOMe (233 mg, 4.3 mmol) added at r.t., and was stirred for 30 min. After evaporation of the solvent under reduced pressure, the residue was chromatographed (silica gel 20 g, elution with EtOAc–hexane, 2:1 v/v) to give the triol **9** (263 mg, 65%) as a colorless oil. $[\alpha]_D^{29}$ -56.1°(*c* 1.3, $CHCl_3$); IR (neat) 3368 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (5H, m), 5.36 (1H, s), 4.55 (1H, m), 4.54 (2H, d, *J* = 3.2 Hz), 4.31 (1H, s), 3.96 (1H, br. s) 3.88 (1H, br. d, *J* = 8.3 Hz), 3.69 (1H, br. s), 3.48 (1H, dd, *J* = 9.5, 5.9 Hz), 3.39 (1H, dd, *J* = 9.5, 7.6 Hz), 2.87 (1H, br. s), 2.79 (1H, br. s), 2.35 (1H, br. s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 128.5, 128.1, 102.2, 77.8, 73.6, 73.5, 71.6, 71.1, 70.6, 65.9; MS m/z 282 (M^+), 91 (100%); HRMS Calcd. $C_{14}H_{18}O_6$: 282.1103. Found: 282.1124.

(1*R*,2*S*,3*S*,4*R*,5*R*,6*S*)-6-Hydroxymethyl-2,3,4-trihydroxy-7,8-dioxabicyclo[3.2.1]octane (10). A mixture of the triol **9** (360 mg, 1.28 mmol) and 10% Pd-C (36 mg) in MeOH (6ml) was stirred under H_2 at r.t. for 3 h. After filtration through a Celite pad, the filtrate was evaporated under reduced pressure and chromatographed (silica gel, 30 g, elution with EtOAc–MeOH–H_2O, 7:2:1 v/v) to give the tetraol **9** (222 mg, 83%) as a colorless oil. $[\alpha]_D^{31}$ -92.1°(c 1.0, MeOH); IR (neat) 3344 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 5.32 (1H, br. s), 4.35 (1H, t, *J* = 6.3 Hz), 4.24 (1H, br. s), 3.88–3.83 (2H, m), 3.67–3.63(1H, m), 3.48–3.40, (2H, m); ^{13}C NMR (75 MHz, D_2O) δ 101.7, 77.0, 75.0, 70.9, 69.8, 65.3, 62.5; MS m/z 193 (M^+-OH), 73 (100%); HRMS Calcd. $C_7H_{13}O_6$: 193.0712. Found: 193.0716.

Perseitol hepta-acetate (12). A mixture of **10** (41 mg 0.21 mmol) and Dowex 50W ion-exchange resin (80 mg) in H_2O (2 ml) was heated at 150°C for 8 h in a sealed tube. The mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure and chromatographed (silica gel 4 g, elution with EtOAc–MeOH–H_2O, 14:2:1 v/v) to give the hexaol **11** (28 mg, 63%) and recovered **10** (12 mg, 30%). To stirred solution of **11** (27 mg, 0.13 mmol)

in H_2O (1 ml) was added $NaBH_4$ (15mg, 0.39 mmol) and stirred for 30 min at 0°C and treated with Amberlite IR-120 (H^+) ion-exchange resin (2 ml) for 10 min. The mixture was filtered through a Celite pad, concentrated under reduced pressure, chromatographed (silica gel 4 g, elution with EtOAc–MeOH–H_2O, 14:2:1 v/v) and lyophilized to give perseitol **1** (26 mg). A mixture of **1**, pyridine (2 ml) and Ac_2O (2 ml) was stirred for 8 h at r.t. and concentrated under reduced pressure, the residue was extracted with EtOAc (6 ml), washed with H_2O (1 ml) and brine (1 ml), and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was chromatographed (silica gel 4 g, elution with EtOAc–hexane, 2:3 v/v) to give perseitol hepta-acetate **12** (25 mg, 39% from **11**) as colorless needles.

Perseitol (1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.46–4.40 (2H, m), 4.34 (1H, m), 4.15–4.06 (2H, m), 4.05 (1H, d, *J* = 7.6 Hz), 3.97 (1H, d, *J* = 7.8 Hz), 3.71–3.65 (2H, m), 3.61 (1H, m), 3.55 (1H, m), 3.45–3.37 (5H, m). The ^{1}H- spectrum in DMSO-d_6 was identical with that in the literature.[1c]

Perseitol hepta-acetate (12). mp 119°C; $[\alpha]_D^{29}$ -10.4° (*c* 0.9, MeOH) [lit.[2c, 12]] mp 119–120°C; $[\alpha]_D^{25}$ -14.8° (*c* 1.2, $MeOH_)$; IR (neat) 1749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (1H, dd, *J* = 10.0, 2.0 Hz), 5.35 (1H, dd, *J* = 8.8, 2.0 Hz), 5.24 (1H, dd, *J* = 10.0, 2.0 Hz), 5.16 (1H, m), 5.00 (1H, m), 4.28 (1H, dd, *J* = 11.7, 5.1 Hz), 4.21 (1H, dd, *J* = 12.4, 2.7 Hz), 4.02 (1H, dd, *J* = 12.4, 5.1 Hz), 3.82 (1H, dd, *J* = 11.7, 7.3 Hz), 2.11 (3H, s), 2.09 (3H, s), 2.08 (3H, s), 2.06 (6H, s), 2.04 (6H, s), 2.04 (3H, s), 2.02 (3H, s) ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.3, 170.1, 169.7, 169.5, 68.0, 67.6, 67.5, 67.2, 66.6, 62.2, 61.8, 20.9, 20.8, 20.72, 20.70, 20.68, 20.6. Anal. Calcd. for $C_{21}H_{30}O_{14}$, C, 49.80; H, 5.97. Found: C, 49.60; H, 5.95. The ^{1}H- and ^{13}C-NMR spectra in $CDCl_3$ were identical with those in the literature.[2c,13]

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