Stereoselective Synthesis of (1*R*,3*R*,5*S*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane

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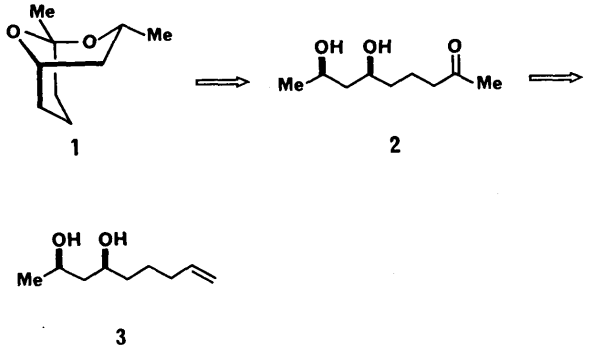
(1*R*,3*R*,5*S*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (1), a host-specific substance of ambrosia beetle, has been synthesized stereoselectively based on a highly *syn*-selective 1,3-asymmetric reduction of the β-alkoxy ketone (5) using lithium aluminum hydride–lithium iodide.

Keywords (1*R*,3*R*,5*S*)-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane; *syn*-1,3-diol; asymmetric reduction; β-alkoxy ketone; lithium aluminum hydride–lithium iodide

endo-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**1**) is a biologically active host-specific substance isolated from Norway spruce infested by the ambrosia beetle (*Trypodendron lineatum* OLIV.) and has shown to play an important role in the host selection of this beetle.[1] The relative stereochemistry of the natural product was established by comparison of the nuclear magnetic resonance (NMR) data of racemic synthetic **1** with those of the natural product. Although the absolute configuration of natural **1** had been unknown,[2] several syntheses of both racemic and optically active forms have been published.[3] In the synthesis of the bicyclic acetal (**1**), the crucial step is construction of the 1,3-diol unit in **1**. In this context the intermediate (**2**) or its equivalent (**3**) is a good target for testing new methods for the preparation of *syn*-1,3-diols.

Recently, we have developed a 1,3-asymmetric reduction of β-alkoxy and β-alkoxy-β′-hydroxy ketones using lithium aluminum hydride–lithium iodide for the synthesis of *syn*-1,3-diols and polyols; this system showed excellent *syn*-selectivity (*syn*:*anti*=95:5).[4] We report here a short and efficient synthesis of optically active **1** employing lithium aluminum hydride–lithium iodide reduction as a key step in the synthesis.



1 2 3

Chart 1

The starting optically active ketone (**5**) was prepared from the aldehyde (**4**), which was obtained from (*S*)-(−)-malic acid (95% ee).[5] Thus, reaction of **4** with 4-pentenylmagnesium bromide, giving a mixture of the adducts (*syn*:*anti*=4:6), followed by oxidation with pyridinium chlorochromate afforded the ketone (**4**) in 70% overall yield. A highly *syn*-stereoselective reduction of the β-alkoxy ketone (**5**) with lithium aluminum hydride in the presence of lithium iodide was carried out in ether at −78 °C to provide the desired *syn*-alcohol (**6**) in 88% yield. The selectivity of the reduction was *syn*:*anti*=95:5 and the *syn*- and *anti*-

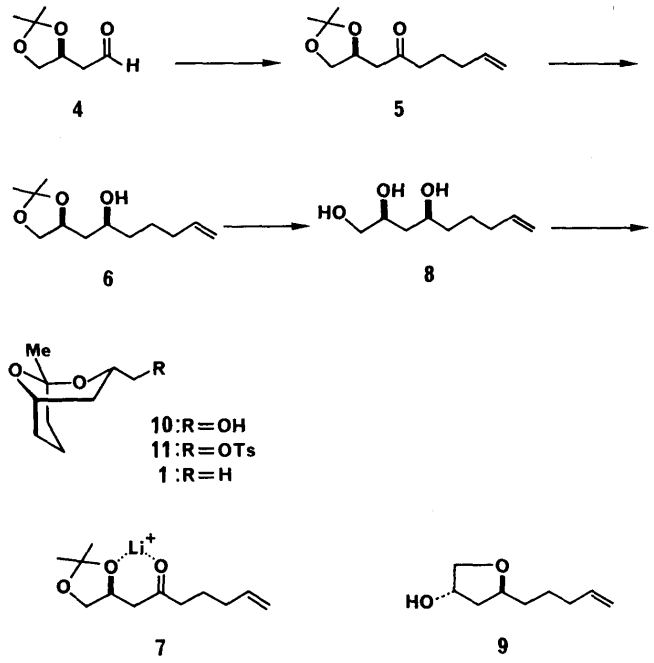


Chart 2

isomers were easily separated by flash chromatography on silica gel. The high *syn*-selectivity arises from β-chelation of lithium cation with the ketone and an ether oxygen of the 1,3-dioxolane ring to form an intermediate complex (**7**) and hydride then attacks from the less hindered α-side resulting in the formation of the *syn*-product (**6**).

Deprotection of the acetonide group of **6** with pyridinium *p*-toluenesulfonate in methanol gave the triol (**8**) in 95% yield. Removal of the primary hydroxy group and oxidation of the terminal olefin to ketone would be expected to give the intermediate (**2**). To this end, we attempted to convert **8** into a sulfonate using 2,4,6-triisopropylbenzenesulfonyl chloride in pyridine, but the compound obtained was a tetrahydrofuran derivative (**9**) in 73% yield with a small amount of the sulfonate.

Direct bicyclic acetal formation was achieved by palladium(II)-catalyzed oxidation.[6] Thus, cyclization of **8** using palladium chloride catalyst with cupric chloride as a reoxidant in 95% aqueous dimethylformamide under oxygen gave the bicyclic acetal (**10**) in 60% yield. Finally, tosylation of **10** followed by lithium aluminum hydride reduction of **11** yielded the bicyclic acetal (**1**) in 84% overall yield. The spectroscopic data were identical with the reported values.[3a,g]

Experimental

Optical rotations were measured on a JASCO DIP-181 digital polarimeter. Infrared (IR) spectra were taken on a Hitachi 215 spectrometer. ^{1}H-NMR spectra were measured on a JEOL GX-400 spectrometer; chemical shifts are given in ppm with tetramethylsilane as an internal standard. Mass spectra were taken on Shimadzu GCMS QP-1000 and Hitachi M-80 mass spectrometers. Flash chromatography was performed with Nakarai silica gel 60 (230—400 mesh).

(2*S*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-8-nonen-4-one (5) A solution of **4** (450 mg) in dry ether (10 ml) was treated with excess 4-pentenylmagnesium bromide in ether at 0 °C and the reaction mixture was stirred for 1.5 h at room temperature. The mixture was quenched with aqueous NH_4Cl, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated. The residual oil was dissolved in CH_2Cl_2, and pyridinium chlorochromate (2.87 g) and sodium acetate (302 mg) were added to the stirred solution. The reaction mixture was stirred for 6 h at room temperature and then diluted with ether. After filtration of the mixture through a Florisil column the filtrate was concentrated. Flash chromatography (20% ether–hexane) of the residue give **5** (470 mg, 70% yield). $[\alpha]_D^{23}$ −18.8° (*c*=0.5, $CHCl_3$). IR ($CHCl_3$): 1710, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, s), 1.40 (3H, s), 1.69 (2H, quintet, *J*=7.3 Hz), 2.06 (2H, q, *J*=7.1 Hz), 2.45 (2H, t, *J*=7.8 Hz), 2.56 (1H, dd, *J*=16.6, 7.1 Hz), 2.88 (1H, dd, *J*=16.6, 5.9 Hz), 3.53 (1H, dd, *J*=8.3, 6.8 Hz), 4.19 (1H, dd, *J*=8.3, 6.1 Hz), 4.46 (1H, quintet, *J*=6.6 Hz), 4.96—5.04 (2H, m), 5.76 (1H, ddt, *J*=17.1, 10.3, 6.6 Hz). CIMS (iso-C_4H_{10}) *m/z*: 213 (MH^+), 155 (base peak).

(2*S*,4*S*)-1,2-*O*-Isopropylidene-8-nonen-1,2,4-triol (6) A solution of **5** (128 mg) and LiI (400 mg) in dry ether (20 ml) was cooled to −78 °C and $LiAlH_4$ (114 mg) was added. The reaction mixture was stirred for 1 h at the same temperature under nitrogen and quenched with 2 N KOH (1 ml). After stirring for 30 min at room temperature the mixture was filtered and the filtrate was concentrated. The residue was flash-chromatographed (40% ether–hexane) to give **6** (112 mg, 88% yield) and the *anti*-isomer of **6** (5 mg, 4% yield). **6**: $[\alpha]_D^{22}$ +3.35° (*c*=1.0, $CHCl_3$). IR ($CHCl_3$): 3530, 1635 cm^{-1}. ^{1}H-NMR (C_6D_6) δ: 1.24 (3H, s), 1.31 (3H, s), 2.03 (2H, m), 3.26 (1H, dd, *J*=8.1, 7.3 Hz), 3.65 (1H, m), 3.73 (1H, dd, *J*=8.1, 6.1 Hz), 3.93 (1H, m), 5.00 (1H, m), 5.06 (1H, dq, *J*=17.1, 1.7 Hz), 5.80 (1H, ddt, *J*=17.1, 10.3, 6.8 Hz). CIMS (iso-C_4H_{10}) *m/z*: 215 (MH^+), 157 (base peak).

anti-Isomer of **6**: $[\alpha]_D^{23}$ −0.67° (*c*=0.66, $CHCl_3$). IR ($CHCl_3$): 3500, 1638 cm^{-1}. ^{1}H-NMR (C_6D_6) δ: 1.32 (3H, s), 1.39 (3H, s), 1.94 (2H, m), 3.40 (1H, t, *J*=7.8 Hz), 3.64 (1H, m), 3.84 (1H, dd, *J*=8.1, 6.1 Hz), 4.16 (1H, m), 4.97—5.05 (2H, m), 5.75 (1H, ddt, *J*=17.1, 10.3, 6.6 Hz). CIMS (iso-C_4H_{10}) *m/z*: 215 (MH^+), 157 (base peak).

(2*S*,4*S*)-8-Nonen-1,2,4-triol (8) A solution of **6** (18.8 mg) and pyridinium *p*-toluenesulfonate (2 mg) in MeOH (4 ml) was heated at 50 °C for 4 h. After evaporation of the solvent the residue was flash-chromatographed (EtOAc) to give **8** (14.4 mg, 95% yield). $[\alpha]_D^{22}$ +7.84° (*c*=0.5, $CHCl_3$). IR ($CHCl_3$): 3400, 1638 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.60 (6H, m), 2.07 (2H, m), 3.47 (1H, dd, *J*=11.2, 6.6 Hz), 3.63 (1H, dd, *J*=11.2, 2.9 Hz), 3.89 (1H, m), 3.96 (1H, m), 4.96 (1H, dd, *J*=10.3, 1.2 Hz), 5.02 (1H, dd, *J*=17.1, 1.5 Hz), 5.80 (1H, ddt, *J*=17.1, 10.3, 6.6 Hz). HRMS *m/z*: Calcd for $C_9H_{18}O_3$: 174.1311. Found: 174.1306.

(2*S*,4*S*)-4-Hydroxy-2-(4-pentenyl)tetrahydrofuran (9) A mixture of **8** (2.5 mg) and 2,4,6-triisopropylbenzenesulfonyl chloride (43.5 mg) in pyridine (0.5 ml) was stirred for 24 h at room temperature. The reaction mixture was acidified with 10% HCl, extracted with EtOAc, dried ($MgSO_4$), and concentrated. Flash chromatography (20% acetone–$CHCl_3$) of the residue gave **9** (1.6 mg, 73% yield). IR ($CHCl_3$): 3600, 3400, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.00—2.15 (2H, m), 3.77 (1H, br d, *J*=14.4 Hz), 4.01 (1H, dd, *J*=14.4, 6.7 Hz), 4.12 (1H, m), 4.50 (1H, m), 4.90—5.05 (2H, m), 5.79 (1H, ddt, *J*=17.1, 10.3, 6.6 Hz). CIMS (iso-C_4H_{10}) *m/z*: 157 (MH^+).

(1*S*,3*S*,5*S*)-3-Hydroxymethyl-1-methyl-2,9-dioxabicyclo[3.3.1]nonane (10) A mixture of $PdCl_2$ (12 mg) and $CuCl_2 \cdot H_2O$ (71 mg) in 95% aqueous *N*,*N*-dimethylformamide (DMF) (2 ml) was stirred for 10 min under oxygen and a solution of **8** (60 mg) in DMF (1 ml) was added. The reaction mixture was stirred for 32 h at room temperature under oxygen. After removal of the solvent *in vacuo*, the residue was flash-chromatographed (EtOAc) to yield **10** (36 mg, 60% yield). $[\alpha]_D^{24}$ −17.35° (*c*=1.0, $CHCl_3$). IR ($CHCl_3$): 3450 cm^{-1}. ^{1}H-NMR ($CDCl_3+D_2O$) δ: 1.30—1.68 (5H, m), 1.79 (1H, tt, *J*=13.2, 4.4 Hz), 1.99 (1H, ddd, *J*=13.2, 11.0, 3.9 Hz), 2.07 (1H, m), 3.52 (1H, dd, *J*=11.5, 6.3 Hz), 3.69 (1H, dd, *J*=11.5, 2.9 Hz), 3.91 (1H, dddd, *J*=11.7, 6.3, 3.9, 2.9 Hz), 4.32 (1H, m). HRMS *m/z*: Calcd for $C_9H_{16}O_3$: 172.1134. Found: 172.1131.

(1*R*,3*R*,5*S*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (1) A mixture of **10** (32.2 mg) and *p*-toluenesulfonyl chloride (103 mg) in pyridine (1 ml) was stirred for 19 h at room temperature. After removal of the solvent *in vacuo* the residue was flash-chromatographed (20% EtOAc–hexane) to give **11** (60.4 mg, 98% yield). The tosylate (**11**) (55 mg) was dissolved in dry ether (2 ml) and $LiAlH_4$ (20 mg) was added to the solution. The reaction mixture was stirred for 1.5 h at room temperature and then refluxed for 15 min. After dilution with pentane the reaction mixture was quenched with 6 drops of 2 N KOH and stirred for 20 min at room temperature. Precipitates were filtered off through a short column of Celite and the filtrate was concentrated carefully. Flash chromatography (5% ether–pentane) of the residue gave **1** (22.6 mg) in 86% yield. IR ($CHCl_3$): 2940, 1455, 1440, 1378, 1238, 1159, 1145, 1078, 890 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, *J*=6.1 Hz), 1.27 (3H, s), 1.76 (1H, tt, *J*=13.4, 4.6 Hz), 2.09 (1H, ddd, *J*=13.2, 11.0, 3.9 Hz), 3.94 (1H, dqd, *J*=11.2, 6.1, 3.9 Hz), 4.26 (1H, m). EIMS *m/z*: 156 (M^+), 114, 87, 81, 71, 58. $[\alpha]_D^{24}$ −35.9° (*c*=0.5, pentane) (lit.[3f] $[\alpha]_D^{22}$ −37.3° (*c*=0.9, pentane)).

References and Notes

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