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STEREOSELECTIVE SYNTHESIS OF (1R,3R,5S)-1,3-DIMETHYL-2,9-DIOXABICYCLO[3.3.1]NONANE

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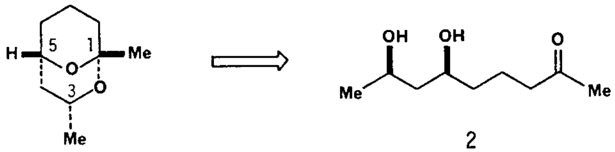
Summary: (1R,3R,5S)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**1**) has been stereoselectively synthesized based on a highly stereoselective method for the synthesis of 1,3-*syn*-polyol.

Endo-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**1**) is a host-specific substance isolated from Norway spruce infested by the ambrosia beetle (*Trypodendron lineatum* Oliv.).[1] Several groups have already synthesized the racemic and optically active **1**.[2,3] The bicyclic compound **1** corresponds to the ketone having 1,3-*syn*-diol moiety (see **2**). We have recently developed a highly stereoselective method for the synthesis of 1,3-*syn*-polyol based on the stereoselective reduction of a six-membered β-keto acetal and successive transthioacetalization.[4] We now report the stereoselective synthesis of (1R,3R,5S)-**1** using this new method.



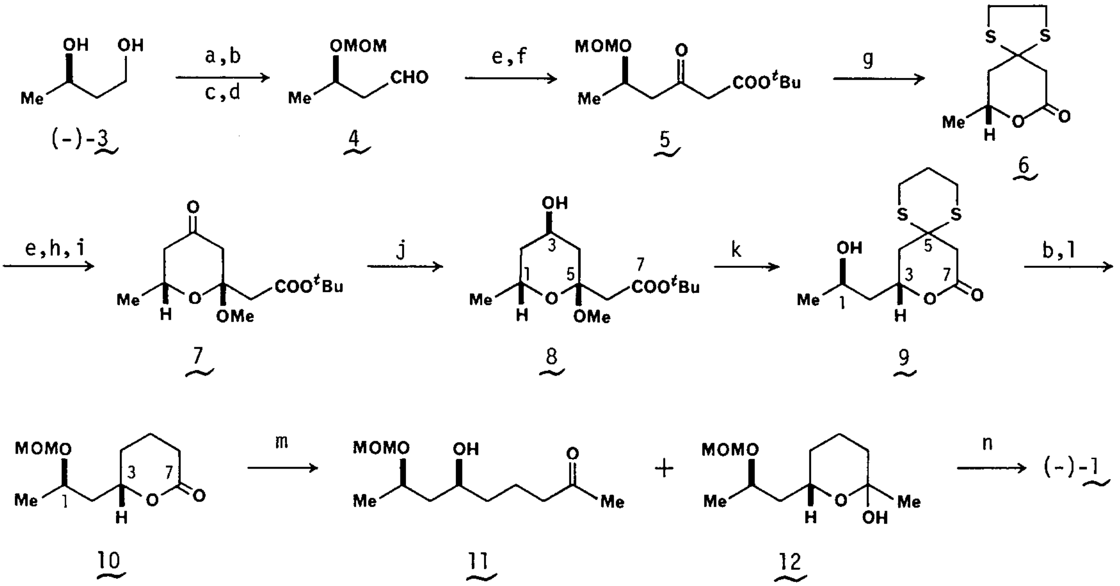
1

2

Lactone **9** used in the synthesis of 1,3-*all*-*syn*-tetraol[4] was chosen as a key intermediate. In the present synthesis, however, the optically active **9** should be synthesized. Thus, commercially available (R)-(-)-1,3-butanediol (**3**; 80% e.e.) was used as a starting material and was converted to the optically active **9** by the route shown in scheme 1. In the previous report,[4] the details up to the intermediate **6** were not shown. Therefore, in the present paper, synthesis of the optically active **6** from **3** was described. (R)-(-)-**3** was converted to aldehyde **4**[5] in 4 steps (1. *t*-BuMe$_2$SiCl, 2. MeOCH$_2$Cl, 3. *n*-Bu$_4$NF, 4. PCC; 68% overall yield), which was treated with LDA and MeCOO-*t*-Bu and then with Jones reagent giving β-keto ester **5**, $[\alpha]_D^{24}$ -13.9° (*c*=2.22, CHCl$_3$), in 75% yield. Treatment of **5** with 1,2-ethanedithiol and BF$_3$·Et$_2$O in CH$_2$Cl$_2$ afforded δ-lactone **6**, mp 92.5-93°C; $[\alpha]_D^{24}$ +30.4° (*c*=1.72, CHCl$_3$; after recrystallization), in 95% yield. Crude **6** was converted to δ-lactone **9**, $[\alpha]_D^{25}$ +2.8° (*c*=2.28, CHCl$_3$), in the same way as described in the previous paper.[4] The optical purity of **9** was found to be 80% e.e.,[6] which shows that no racemization took place during a series of reactions.[7]

After protection of the C-1 hydroxyl group as MOM ether (88% yield), reductive dethioacetalization of **9** with Raney Ni in dioxane afforded lactone **10**, $[\alpha]_D^{27}$ -33.5° (*c*=1.8, CHCl$_3$); IR (neat): 1730 cm^{-1}; NMR: δ 1.24 (d, *J*=6.1 Hz; Me), 3.36 (s; OMe), 4.46 (m; C-3β H),[8] in 73% yield. Reaction of 10 with MeLi in THF-Et$_2$O produced a mixture of 11 and 12 in a ratio of 5.5 : 1 (77% yield), which, on treatment with acid, was converted to bicyclic acetal (-)-1, $[\alpha]_D^{25}$ -35.6° (c=0.71, pentane),[7] lit.[2c] $[\alpha]_D^{22}$ -37.3°; NMR: δ 1.20 (d, J=6.4 Hz; C-3 Me), 1.27 (s; C-1 Me), 3.94 (dqd, J=12.5, 6.4, 3.9 Hz; C-3 H), 4.27 (m; C-5 H),[8] in 43% yield.

Scheme 1



a) t-BuMe$_2$SiCl/imidazole/DMF, b) MeOCH$_2$Cl/i-Pr$_2$NEt/CH$_2$Cl$_2$, c) n-Bu$_4$NF·3H$_2$O/THF, d) PCC/3A molecular sieves/CH$_2$Cl$_2$, e) LDA/MeCOO-t-Bu/THF/-78°C, f) Jones reagent/acetone/0°C, g) HSCH$_2$CH$_2$SH/BF$_3$·Et$_2$O/CH$_2$Cl$_2$/rt, h) CH(OMe)$_3$/CSA/MeOH/CH$_2$Cl$_2$, i) NBS/AgNO$_3$/Na$_2$CO$_3$/aq MeCN, j) K-Selectride/THF/-78°C, k) HS(CH$_2$)$_3$SH/BF$_3$·Et$_2$O/CH$_2$Cl$_2$/-40°C, l) Raney Ni/dioxane/reflux, m) MeLi/THF/ether/-78°C, n) 15% HCl/MeOH/reflux; p-TsOH/CH$_2$Cl$_2$

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References and Notes

1. V. Heemann and W. Francke, Naturwissenschaften, 63, 344 (1976); Planta Med., 32, 342 (1977) [Chem. Abstr., 88, 101563h (1978)].
2. For the synthesis of racemic form: a) H. Gerlach and P. Künzler, Helv. Chim. Acta, 60, 638 (1977); b) B. Kongkathip and N. Kongkathip, Tetrahedron Lett., 25, 2175 (1984). For the synthesis of optically active form: c) H. Redlich, B. Schneider, and W. Francke, Tetrahedron Lett., 21, 3013 (1980); H. Redlich, B. Schneider, R. W. Hoffmann, and K.-J. Geueke, Liebigs Ann. Chem., 393 (1983); d) T. Sato, T. Itoh, C. Hattori, and T. Fujisawa, Chemistry Lett., 1391 (1983).
3. The absolute configuration of natural 1 remains unknown since its $[\alpha]_D$ value has not been measured yet.
4. T. Nakata, S. Takao, M. Fukui, T. Tanaka, and T. Oishi, Tetrahedron Lett., 24, 3873 (1983).
5. Cf. A. I. Meyers and R. A. Amos, J. Am. Chem. Soc., 102, 870 (1980).
6. The optical purity of 9 was determined from ^{1}H NMR spectra[8] of the corresponding MTPA ester.
7. If the optically pure 3 was employed, the optically pure 9 and thence 1 should be obtained.
8. ^{1}H NMR spectra were taken on a JEOL GX-400 instrument in CDCl$_3$.

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