

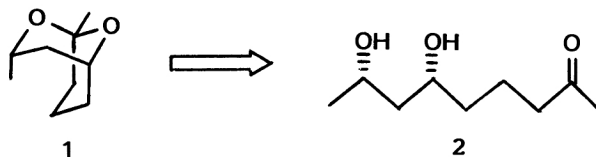
Asymmetric Synthesis of (1*S*,3*S*,5*R*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane
Mediated by Fermenting Bakers' Yeast

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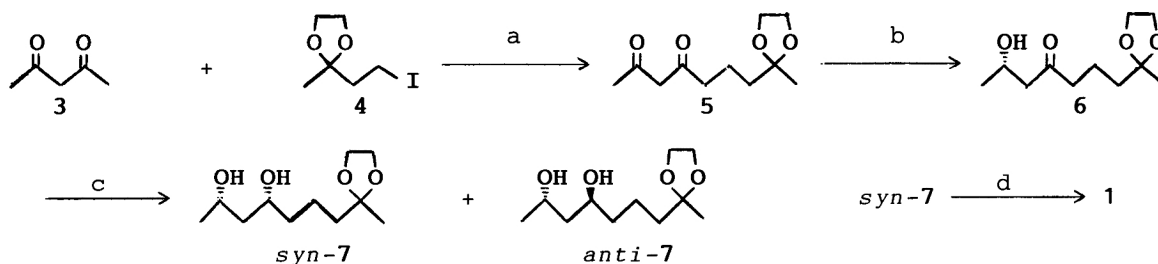
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Optically active (1*S*,3*S*,5*R*)-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane has been synthesized in short steps including regio- and enantioselective reduction of 1,3-diketones by actively fermenting bakers' yeast.

Among variety types of reactions mediated by actively fermenting bakers' yeast (*Saccharomyces cerevisiae*), reduction of 2,4-alkanediones to afford (*S*)-2-hydroxy-4-alkanones is unique, because of the high regio- and enantioselectivity.¹⁾ Recently, methods for diastereoselective reduction of β -hydroxyketones have been developed, which make it possible to obtain both *syn*-²⁾ or *anti*-³⁾ 1,3-diols. Combination of these enzymatic and chemical technique is expected to provide an elegant tool for the synthesis of optically active compounds. In this letter, we wish to report a new approach to the title compound **1**, which has been isolated from Norway spruce infested by a timber pest, the ambrosia beetle (*Trypodendron lineatum* Oliv.), and has proved to exhibit an important role for the beetle in selection of the host.⁴⁾ The synthesis of **1** can be convertible to the synthesis of **2**, because **2** spontaneously cyclizes to afford **1**. Several syntheses of **1** have been reported in racemic⁵⁾ or optically active⁶⁾ form. The present route is rather simpler than the previous methods, including 4 steps starting from acetylacetone (**3**).



Coupling of dianion of acetylacetone (**3**), generated by NaH and *n*-BuLi in the presence of 0.1 equiv. CuLi_2Cl_4 in HMPA, with 3,3-ethylenedioxy-1-iodobutane,⁷⁾ afforded the key intermediate, 8,8-ethylenedioxy-2,4-nonanedione (**5**) in 51% yield. Biochemical reduction of **5** was carried out as described before.^{1a)} Dry bakers' yeast (Oriental Yeast Co., 10 g) and 5 g of glucose were mixed in 50 ml of tap water and stirred for 10 min at room temperature. Then, 0.1 g of **5** was added and the mixture was continued to stir at the same temperature for 2 days. The ordinary work-up and purification with preparative TLC afforded (*S*)-8,8-ethylenedioxy-4-oxo-2-nonanol (**6**) in 65% yield.⁸⁾ The assignment of *S* configuration for **6** was tentative at this stage, but verified later by the specific rotation of final product **1**. The optical purity was revealed to be 97.5% by the HPLC analysis of the (*R*)-(+)-MTPA ester of **6** (Zorbax Sil, 30 cm, hexane/AcOEt 6:1, retention time 66.6 and 75.5 min). Diastereoselective reduction of ketol **6** to *syn*-diol **7** was achieved by the combination of NaBH_4 - Et_2BOME demonstrated by K.-M. Chen *et al.*^{2a)}



- a) 1. NaH/HMPA 2. *n*-BuLi/CuLi₂Cl₄ (0.1 eq), -30 °C 3. addition of 4
 b) bakers' yeast c) NaBH₄-Et₂BOMe/THF-MeOH d) 2 M H₂SO₄/C₆H₁₄

(yield 70%, *syn:anti* >99:<1).⁹⁾ Deprotection of 7 with 2 M sulfuric acid followed by spontaneous ring formation afforded bicyclic product 1 in a yield of 51%; $[\alpha]_{\text{D}}^{22} +36.8^\circ$ (c 1.3, C₅H₁₂),¹⁰⁾ lit. $[\alpha]_{\text{D}}^{27} -37.3^\circ$ for (1*R*,3*R*,5*S*)-one.^{6b)}

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- 7) The iodide 4 is readily available starting from ethyl 3-oxobutanoate by the sequence of acetalization with ethylene glycol, reduction with LiAlH₄, tosylation and substitution of the resulting tosyloxy group with NaI.
- 8) $[\alpha]_{\text{D}}^{23} +34.1^\circ$ (c 1.28, CHCl₃); IR ν_{max} 3425, 2950, 1700, 1440, 1400, 1370, 1250, 1220, 1120, 1040, 940, 860 cm⁻¹; ¹H NMR (CCl₄) δ 1.08 (d, 3H, J=6.0 Hz), 1.20 (s, 3H), 1.42 1.76 (m, 4H), 2.20 2.55 (m, 4H), 3.81 (s, 4H), 4.06 (sext, 1H, J=6.0 Hz).
- 9) The ratio of *syn/anti* of diol 7 was determined by ¹H NMR. The signal due to the C-1 protons of *syn*-7 appeared at δ 1.207 (d, J=6.35 Hz), while that of *anti*-7 at δ 1.240 (d, J=6.34 Hz).
- 10) IR ν_{max} (NaCl) 3400, 2925, 1720, 1460, 1370, 1260, 1110, 1070, 970, 850 cm⁻¹; ¹H NMR (CCl₄) δ 1.20 (d, 3H, J=6.11 Hz), 1.27 (s, 3H), 1.20-2.55 (m, 8H), 3.89-3.99 (m, 1H), 4.23-4.32 (m, 1H).

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