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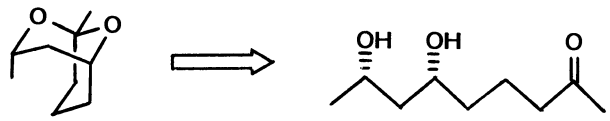
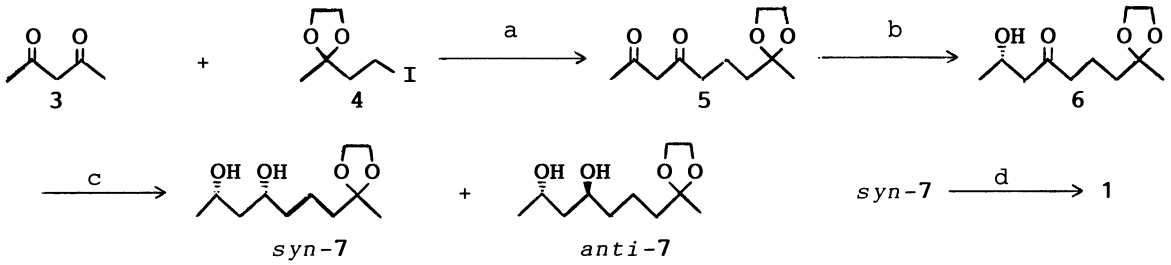
Optically active (1*S*,3*S*,5*R*)-1,3-dimethyl-2,9-dioxabicyclo-[3.3.1]nonane has been synthesized in short steps including regio- and enantioselective reduction of 1,3-diketones by actively fermenting bakers' yeast.

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 racemic[5] or optically active[6] form. The present route is rather simpler than the previous methods, including 4 steps starting from acetylacetone (**3**).



1 **2**

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/$CuLi_2Cl_4$ (0.1 eq), -30 °C 3. addition of 4
b) bakers' yeast c) $NaBH_4$-Et_2BOMe/THF-MeOH d) 2 M H_2SO_4/C_6H_{14}

(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%; $[\alpha]_D^{22}$ +36.8° (c 1.3, C_5H_{12}),[10] lit. $[\alpha]_D^{27}$ -37.3° for (1*R*,3*R*,5*S*)-one.[6b]

Referencces

1) a) H. Ohta, K. Ozaki, and G. Tsuchihashi, Agric. Biol. Chem., 50, 2499 (1986); b) J. Bolte, J.-G. Gourcy, and H. Veschambre, Tetrahedron Lett., 27, 565 (1986).

2) a) K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repic, and M. J. Shapiro, Tetrahedron Lett., 28, 155 (1987); b) S. Kiyooka, H. Kuroda, and Y. Shimasaki, *ibid.*, 27, 3009 (1986); K. Narasaka and F.-C. Pai, Tetrahedron, 40, 2233 (1984).

3) D. A. Evans and K. T. Chapman, Tetrahedron Lett., 27, 5939 (1986).

4) V. Heemann and W. Francke, Naturwissenshaften, 63, 344 (1976); Planta Med., 32, 342 (1977); [Chem. Abstr., 88, 10563h (1978).]

5) H. Gerlach and P. Kunzler, Helv. Chim. Acta, 60, 638 (1977); B. Kongkathip and N. Kongkathip, Tetrahedron Lett., 25, 2175 (1984); P. C. B. Page, C. M. Rayner, and I. O. Sutherland, *ibid.*, 27, 3535 (1986); P. Mohr and C. Tamm, *ibid.*, 28, 395 (1987).

6) a) H. Redlich, B. Schneider, and W. Franke, Tetrahedron Lett., 21, 3013 (1980); T. Sato, T. Itoh, C. Hattori, and T. Fujisawa, Chem. Lett., 1983, 1391; T. Nakata, S. Nagao, S. Takao, T. Tanaka, and T. Oishi, Tetrahedron Lett., 26, 73 (1985); b) H. Redlich, B. Schneider, R. W. Hoffmann, and K. J. Geuke, Justus Liebig's Ann. Chem., 1983, 393.

7) The iodide **4** is readily available starting from ethyl 3-oxobutanoate by the sequence of acetalization with ethylene glycol, reduction with $LiAlH_4$, tosylation and substitution of the resulting tosyloxy group with NaI.

8) $[\alpha]_D^{23}$ +34.1° (c 1.28, $CHCl_3$); IR ν_{max} 3425, 2950, 1700, 1440, 1400, 1370, 1250, 1220, 1120, 1040, 940, 860 cm^{-1}; ^1H NMR (CCl_4) 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 (CCl_4) 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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