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ENANTIOSELECTIVE MICROBIAL HYDROXYLATION OF BICYCLO[2.2.1]HEPTANE CARBON SKELETON

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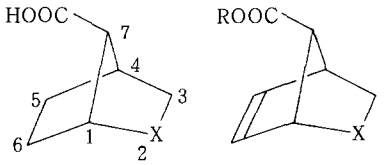
Summary: Bicyclo[2.2.1]heptane-7-carboxylic acid (1) and methyl bicyclo[2.2.1]hept-2-ene-7-*syn*-carboxylate (5) were microbiologically hydroxylated to give (1*R*)-2-hydroxy derivatives.

The bridged keto acid, 2-oxobicyclo[2.2.1]heptane-7-carboxylic acid (3), is chemically converted to methyl jasmonate.[1] The unsaturated keto acid 6 is an equivalent synthon to the bicycloheptenone precursors for prostaglandins.[2] Synthesis of natural (-)-methyl jasmonate and natural prostaglandins from 3 or 6 requires the precursors to be 1*R* in the absolute configuration. These chiral keto acids, (1*R*)-3 and (1*R*)-6, are obtained by chemical oxidation of the corresponding hydroxy acids, which will be microbiologically formed from the prochiral acids 1 and 4 (or their esters) if the microorganisms (and enzymes contained therein) can differentiate two chemically equal sites C-2 and C-3 and only C-2 is hydroxylated by the biocatalysts.



1: X = CH_2 4: X = CH_2, R = H
2: X = CHOH (*endo*) 5: X = CH_2, R = Me
3: X = CO 6: X = CO, R = H

We have screened a large number of microorganisms and found that *Aspergillus awamori* FERM P-8052 and *Bacillus thuringiensis* IFO 3951 asymmetrically hydroxylated the acid 1 and the unsaturated ester 5, respectively, in considerably high enantiomeric purity. Most of the screened microorganisms showed only low regio- and low enantioselectivity in the hydroxylation, yielding not only racemates of the *endo* and/or *exo* *anti* alcohols but also, in the case of substrate 1 and its methyl ester, the undesired *syn* alcohols (by hydroxylation at C-5 or C-6).

The mycelia of *A. awamori* (150 ml X 12 shaken cultures,[3] 31 hr old) were suspended in 0.05 M phosphate buffers (pH 7.5, 100 ml X 12) containing 3 % glycerol and 1 mM Mo^{2+}. To each suspension was added 20 mg of 1 and the mixtures were shaken at 30 °C for 64 hr. The mycelia were filtered off. The filtrate was concentrated, acidified, saturated with NaCl, and extracted with EtOAc. The extract was purified by silica gel column chromatography (EtOAc/benzene) and crystallized from EtOAc/hexane to give 161 mg (57 % yield) of (1*R*)-(-)-2-*endo*-hydroxybicyclo-[2.2.1]heptane-7-*anti*-carboxylic acid (2)[4] as needles, mp 140~141 °C, $[\alpha]_D^{25}$ = -13.4° (c=0.97, MeOH). Enantiomeric purity was 84.7 % e.e. as determined by gas chromatography for the diastereomeric (*R*)-(-)-1-(1-naphthyl)ethyl urethanes. The hydroxy acid was oxidized with Jones reagent to yield the keto acid (1*R*)-(+)-3 in 69 % yield, mp 136~141 °C, $[\alpha]_D^{25}$ = + 16° (c=0.89, MeOH).

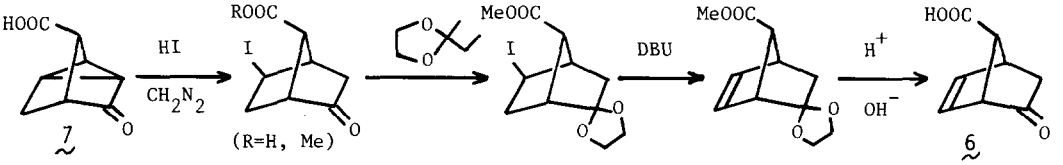
Data in GC (as methyl ester), MS, IR, and PMR were all identical to those for the authentic (1R)-(+)-specimen[6] ($[\alpha]_D^{25}$ = + 18° (c=0.87, MeOH)). Enantiomeric purity was 92.2 % e.e. as determined by gas chromatography for the diastereomeric (R)-(+)-α-methylbenzylamides.

The unsaturated ester 5 (132 mg) was treated with B. thuringiensis in the fermenting cultures (100 ml X 12)[3] for 44 hr at 28 °C. The product in the broth was extracted with EtOAc, purified by column chromatography, hydrolyzed with NaOH, and finally oxidized with Jones reagent. Crystallization from benzene/hexane gave 11 mg (8 % yield) of (1R)-(-)-6, mp 144~148 °C, $[\alpha]_D^{25}$ = -481° (c=0.09, MeOH).[8] Enantiomeric purity was 81.9 % e.e. as determined by the gas chromatographic method.

Thus, the two species of microorganisms were found to hydroxylate the prochiral bridged compound (1 or 5) in a manner of enantiotopos differentiation, although the substrates are artificial compounds. Microbial hydroxylation of bridged compounds has been studied,[9] but conversion of achiral precursors to optically active products has been reported only in the case of azabicyclo[3.3.1]nonanes.[9b] This communication will provide useful information for developing the application of microorganisms in the field of asymmetric synthesis.

References and Notes

1. S. Torii, H. Tanaka, and T. Mandai, J. Org. Chem., 40, 2221 (1975).
2. E. J. Corey, T. Ravindranathan, and S. Terashima, J. Am. Chem. Soc., 93, 4326 (1971); E. D. Brown, R. Clarkson, T. J. Leeney, and G. E. Robinson, J. C. S. Chem. Comm., 1974, 642.
3. The main nutrients of the mediums were: 1 % glucose, 0.3 % yeast and malt extract, and 0.5 % peptone for fungi; and 0.3 % glucose and glycerol, 0.2 % yeast, meat, and malt extract, and 0.5 % peptone for bacteria.
4. The endo configuration was determined by gas chromatographic comparison with the authentic specimen (methyl ester) for (±)-2, which was obtained as the major product in the sodium borohydride reduction of methyl ester of (±)-3.[5]
5. N. R. A. Beeley, R. Peel, J. K. Sutherland, J. J. Holohan, K. B. Mallion, and G. J. Sependa, Tetrahedron, 37, Suppl. No. 1, 411 (1981).
6. Prepared from (+)-anti-5-oxotricyclo[2.2.1.0^{2,6}]heptane-3-carboxylic acid (7)[7] by the method of Beeley et al.[5]
7. J.S. Bindra, A. Grodski, T.K. Schaaf, and E. J. Corey, J. Am. Chem. Soc., 95, 7522 (1973).
8. $[\alpha]_D^{25}$ = - 644° (c=0.30, MeOH) for the authentic 1R acid, which was synthesized from (+)-7[7] as shown in the following scheme:



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9. (a) K. Kieslich, "Microbial Transformations of Non-steroid Cyclic Compounds," Georg Thieme, Stuttgart, 1976. (b) R. A. Johnson, H. C. Murray, and L. M. Reineke, J. Org. Chem., 34, 3834 (1969). (c) H. Lipavská, L. Vodička, J. Burda, J. Triska, V. Krumphanzl, Z. Vaněk, and M. Podojil, Biotechnol. Lett., 4, 563 (1982). (d) A. Archelas and C. Morin, Tetrahedron Lett., 25, 1277 (1984). (e) A. Archelas, R. Furstoss, B. Waegell, J. Le Petit, and L. Deveze, Tetrahedron, 40, 355 (1984).

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