Enantiomerically Pure 4-Methyl- and 1,4-Dimethyl-bicyclo[3.2.0]hept-3-en-6-ols and Ones by Microbial Redox

Giancarlo Fantin, Marco Fogagnolo, Emanuela Marotta,† Alessandro Medici,* Paola Pedrini, and Paolo Righi†
Dipartimento di Chimica, Università di Ferrara, Via Borsari 46, I-44100 Ferrara, Italy
†*Dipartimento di Chimica Organica "A. Mangini", Università di Bologna, Viale Risorgimento 4, I-40136 Bologna, Italy*

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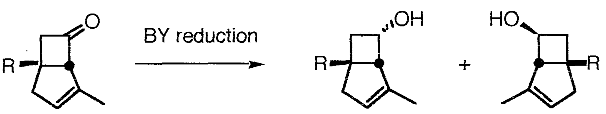
The reduction of bicyclo[3.2.0]hept-3-en-6-ones **1a,b** with Baker's yeast to a mixture of enantiomerically pure (6*S*)-*endo*- and (6*S*)-*exo*-alcohols **2a,b** and **3a,b** respectively is described. Furthermore the oxidation of the racemic *endo*-alcohols **2a,b** with *Bacillus stearothermophilus* afforded the corresponding ketones with high enantiomeric excesses resolving the *endo*-enantiomer. In the same conditions the *exo*-alcohols **3a,b** are not oxidized.

Bicyclo[3.2.0]hept-3-en-6-ones, recently prepared by efficient cyclization of 3-hydroxy-6-alkenoic acids with potassium acetate in acetic anhydride,[1] are interesting building blocks in the synthesis of natural products such as grandisol,[1] lineatin,[1] filifolone,[2] and some lactones, important intermediates for the synthesis of triquinane sesquiterpenes.[2] The synthetic potential of bicyclo[3.2.0]hept-3-en-6-ones makes the synthesis of the enantiomerically pure ketones and/or the corresponding alcohols very interesting. Since the EPC preparation of the bicyclo-[3.2.0]hept-3-en-6-ones starting from the enantiomerically pure 3-hydroxy-6-alkenoic acids was unsuccessful,[3] we have recently investigated the microbial reduction of methyl-substituted bicyclo[3.2.0]hept-3-en-6-ones which afforded the corresponding *endo*- and *exo*-alcohols.[4] Since the yields of the *exo*-alcohols are generally very low and in only one case the reduction leaves an enantiomerically pure unreacted ketone, in this paper we studied the reduction of bicycloheptenones **1a,b** with baker's yeast and the kinetic resolution *via* microbial oxidation of the corresponding racemic *endo*-alcohols **2a,b**.

The choice of the baker's yeast has been made on the basis of the reported reduction of the commercially available bicyclo[3.2.0]-hept-2-en-6-one[5] which produces good yields of the *exo*-alcohol, while the kinetic resolution *via* oxidation with *Bacillus stearothermophilus* has been supported with the excellent results on 1-arylethanols[6] and *endo*-bicycloheptenols and octenol,[7] respectively.

Reduction reactions of bicyclic compounds **1a,b** are carried out on preparative scale (0.5 g of the substrate in 0.5 mL of DMF) by preparing a suspension of baker's yeast (100 g) in tap water (500 mL) containing glucose (12.5 g) (Scheme 1).

Scheme 1.



1 6S-endo-2 6S-exo-3

a; R = H **b**; R = Me

After 48 h under stirring at 28 °C, the reaction mixture was extracted with diethyl ether (250 mL) with a continous liquid-liquid extractor. The products were purified by a short column (silica gel, petroleum ether/diethyl ether 80/20) to give the unreacted ketones and the mixture of the *endo*- and *exo* alcohols (total yields 90%). GLC analyses on chiral column[8] of the crude reaction mixture give the yields and the enantiomeric excesses. The enantiomerically pure compounds were separated by flash chromatography (silica gel, n-pentane/diethyl ether 80/20).

4-Methyl-bicyclo[3.2.0]hept-3-en-6-one (**1a**) produces the (-)-*1R,5S,6S-endo*-heptenol **2a** (30%) and the (+)-*1S,5R,6S-exo*-derivative **3a** (17%) with very high enantiomeric excesses (96% and 100%, respectively). The absolute configuration of (-)- **2a** is determined by single crystal X-ray diffraction of the compound obtained by esterification with (-)-(*1S,4R*)-camphanic acid chloride.[9] On the other hand the configuration of (+)-**3a** is assigned by chemical oxidation[10] to the corresponding ketone (+)-**1a** ($[\alpha]_D$ = 797.3) which is the same obtained from the oxidation of pure (+)-**2a**.[9] This reaction assignes also the *1S,5R* absolute configuration to the ketone (+)-**1a**.

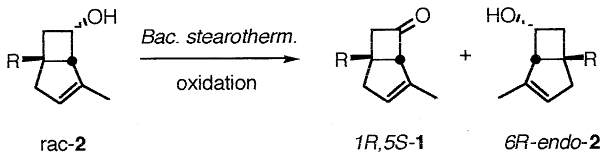
Excellent results are obtained, moreover, by the BY reduction of 1,4-dimethyl-bicyclo[3.2.0]hept-3-en-6-one (**1b**): the enantiomerically pure (-)-*1R,5S,6S-endo*-**2b** (37%, ee 100%) and (+)-*1S,5R,6S-exo*-heptenol **3b** (47%, ee 100%). The absolute configuration of **2b** is determined, as for **2a**, by single crystal X-ray diffraction.[9] The absolute configuration of (+)-**3b** is assigned oxidizing the enantiomerically pure alcohol to the corresponding ketone (+)-**1b** ($[\alpha]_D$ = 745) and comparing the optical rotation with that of the ketone *1R,5S*-**1b** ($[\alpha]_D$ = -821.3 (c 0.96, $CHCl_3$)) obtained by oxidation of the enantiomerically pure (-)-**2b**.[9]

It is worth mentioning that in all cases the BY reduction affords the S-enantiomer, i.e. *6S* configuration, not discriminating between the racemic ketones. This feature is confirmed by the enantiomeric excesses of the unreacted ketones which are always very low. On the other hand this reduction is an important route to the *exo*-alcohols which, by chemical reduction, are obtained in very low yields with respect to the *endo*-derivative.

On the basis of these results, we also studied the oxidation of the racemic bicyclic *endo*- and *exo*-alcohols **2** and **3**, respectively, with *Bacillus stearothermophilus* ATCC 2027. In any case the *exo*-derivatives are not oxidized (Scheme 2).

The microbial oxidations are carried out at 39 °C utilizing a nutrient broth prepared dissolving bactotryptone (20 g), yeast extract (10 g), K_2SO_4 (2.6 g), $Na_2HPO_4\cdot 2H_2O$ (6.4 g), and citric acid (20 g) as carbon source in 1 L of distilled water and adgjusting the pH solution to 7.1 with 6N KOH. A sterilized nutrient broth (200 mL) was inoculated with a loopful of *Bacillus steraothermophilus* ATCC (American type culture collection) 2027. The mixture was incubated for 2 days at 39 °C on a reciprocatory shaker.To the resulting suspension of grown cells the racemic *endo*-alcohol **2** (0.5 g) in DMSO (0.5 mL) was added. After 4-6 h at 39 °C the reaction mixture was extracted

Scheme 2 .



with diethyl ether (100 mL) with a continous liquid-liquid extractor. The products were purified by a short column (silica gel, petroleum ether/diethyl ether 80/20) to give the ketones **1** and the unreacted *endo*-alcohols (total yields 92%). The yields and the enantiomeric excesses were obtained by GLC analyses on chiral column[8] of the crude reaction mixture. The racemic 1-methyl- and 1,4-dimethyl-bicyclo[3.2.0]heptenols **2a** and **2b** are oxidized to the corresponding *1R,5S*-ketones (-)-**1a** and (-)-**1c** (yields 45-47%) with good enantiomeric excesses (82-86%) and the recovered *1S,5R,6R*-heptenols (+)-**2a** and (+)-**2c** (45-47%) are about enantiomerically pure (ee 95-98%). It is noteworthy that in all cases the unreacted alcohols have the opposite configuration (*6R*) than that obtained *via* BY reduction.

In conclusion matching the BY reduction of bicyclic heptenones and the oxidation with *Bacillus stearothermophilus* of the corresponding racemic *endo*-alcohols it is possible to obtain three of the four stereoisomers. The only limitation is the failure of the microbial oxidation of the racemic *exo*-alcohols which is under investigation in our laboratory.

References and Notes

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8 Enantiomer separation was obtained on Megadex 5 column (25 m X 0.25 mm) containing n-pentyl dimethyl β-cyclodextrin in OV 1701 from Mega s.n.c.: carrier gas: helium 0.8 atm; temp. 100-200°C (1.5 °C/min). Retention time in min: (-)-*1R,5S*-**1a**, 9.12; (+)-*1S,5R*-**1a**, 9.44; (-)-*1R,5S,6S-endo*-**2a** (as acetyl derivative), 14.10; (+)-*1S,5R,6R-endo*-**2a** (as acetyl derivative), 14.51; (-)-*1R,5S,6R-exo*-**3a**, 14.15; (+)-*1S,5R,6S-exo*-**3a**, 14.53; (-)-*1R,5S*-**1b**, 7.09; (+)-*1S,5R*-**1b**, 7.39; (-)-*1R,5S,6S-endo*-**2b**, 10.43; (+)-*1S,5R,6R-endo*-**2b**, 10.78; (-)-*1R,5S,6R-exo*-**3b**, 11.23; (+)-*1S,5R,6S-exo*-**3b**, 11.59.

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