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# ENANTIOSELECTIVE MICROBIAL ASYMMETRIC REDUCTION OF PENTACYCLO[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]UNDECANE-8,11-DIONE

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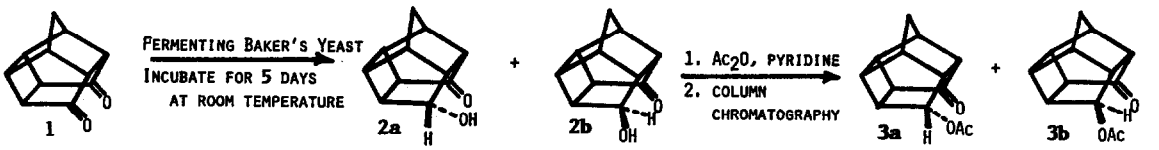
Summary: Baker's yeast promotes moderately enantioselective but diastereorandom reduction of the title compound (1) via preferential hydrogen transfer to the exo-Si and endo-Re faces of one of the two C=O groups.

Asymmetric reduction of prochiral ketones has proved to be a convenient and general method for synthesizing optically active secondary alcohols.[1,2] Recently, Japanese investigators[3] have utilized horse liver alcohol dehydrogenase (HLADH) to reduce pentacyclo[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecane-8,11-dione (PCUD-8,11-dione, **1**).[4] The optically active cage keto alcohol thereby obtained was converted subsequently into optically active derivatives of $D_3$-trishomocubane.[3]

As part of a program that is involved with the synthesis and chemistry of novel cage compounds,[5] we have investigated microbial reduction of **1**. For this reaction, we employed baker's yeast (Saccharomyces cerevisiae), an inexpensive and readily available enzymic catalyst system that lends itself to relatively large scale (i.e., multigram) reduction of carbonyl-containing compounds.[1]

Asymmetric reduction of meso diketone **1** was performed via incubation with a fermenting yeast solution for five days at room temperature. The metabolites were extracted with chloroform and then purified by elution chromatography on silica gel (25% ethyl acetate-hexane mixed solvent as eluent). An intractable mixture of optically active endo and exo keto alcohols, **2a** and **2b**, was thereby obtained. The mixture of **2a** and **2b** was acetylated by using acetic anhydride-pyridine reagent. The resulting ca. 1:1 mixture of acetate esters [(+)-**3a** and (+)-**3b**, respectively] then could be separated conveniently by careful column chromatography on silica gel (10% ethyl acetate-hexane eluent). In this way, (+)-**3a** (43.5%, $[\alpha]_D$ +10.75°, c 3.7, $CHCl_3$) and (+)-**3b** (40%, $[\alpha]_D$ +39.66°, c 1.93, $CHCl_3$) were obtained.



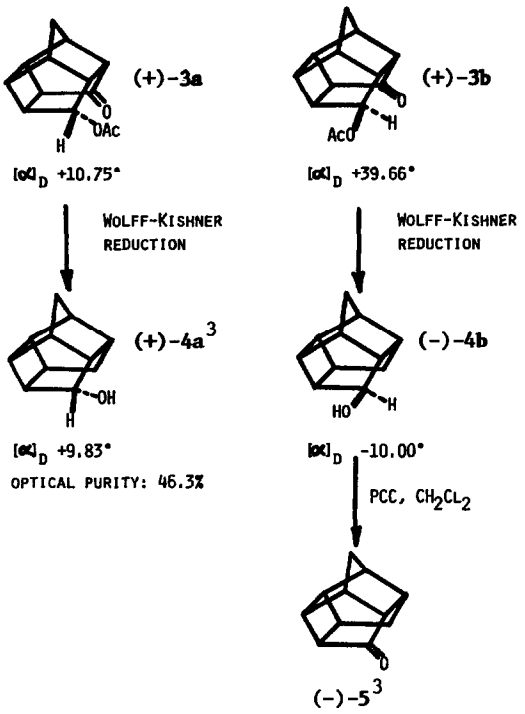

The structures of (+)-**3a** and **3b** were assigned by analyzing their respective proton NMR spectra. In earlier work on a number of 8-substituted and 8,11-disubstituted PCUDs, we noted that the $^1$H NMR spectral signals that correspond to the exo-8,11 protons generally display triplet splitting, whereas little or no fine structure is observed in the corresponding signals for the endo-8,11 protons.[6] In the present study, application of this criterion to the CHOH signals at $\delta$ 4.75 (t, $J$ = 4.3 Hz) and 4.80 (s) enabled us to make exo,endo assigments and thereby to assign the structures of (+)-**3a** and (+)-**3b**, respectively, with confidence. In addition, the carbon-13 NMR spectrum obtained for (+)-**3b** is essentially identical with the corresponding NMR spectrum reported previously for racemic **3b**.[7]

In order to determine the configuration of optically active **3a** and **3b**, it was expedient[8] to relate each structure chemically to a corresponding optically active compound whose absolute configuration is known with certainty.[3] Thus, Wolff-Kishner reduction of (+)-**3a** afforded optically active PCUD-endo-8-ol [(+)-**4a**, $[\alpha]_D$ +9.83°, $c$ 3.0, $CHCl_3$] in 90% yield. The absolute rotation of (-)-**4a** has been reported previously ($[\alpha]_D$ -21.2°).[3] Hence, on the basis of the optical rotation observed for (+)-**4a** that was obtained from this reaction, we estimate its optical purity to be 46.3%.

The configuration of (+)-**3b** was determined as follows. First, (+)-**3b** was subjected to Wolff-Kishner reduction. The resulting cage alcohol, **4b**, was oxidized subsequently with pyridinium chlorochromate (PCC), thereby affording optically active (-)-**5**, $[\alpha]_D$ -56.66°, $c$ 1.65, $CHCl_3$], in 80% chemical yield (Scheme 1). Based upon the previously estimated[3] rotation of optically pure (+)-**5**, we conclude that the rotation observed for (-)-**5** in the present study corresponds to 50.4% optical purity.

The absolute configurations of (-)-**4a** and of (+)-**5** are known with certainty.[3] Furthermore, Jones oxidation of (-)-**4a** is known to afford (+)-**5**.[3] Hence, it is possible to draw conclusions regarding the extent of diastereoselectivity and of enantioselectivity displayed by baker's yeast in microbial reduction of **1** to **2a** + **2b**. The results given above

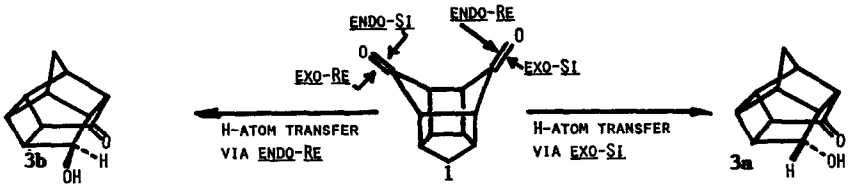
SCHEME 1




indicate that this reduction proceeds with moderate levels of asymmetric induction (i.e., ca. 50% ee). However, since (i) the two reaction products have been related chemically to (-)-**5** and (ii) the two products (that contain an exo-11-OH and and endo-11-OH group, respectively) are formed in ca. 1:1 ratio, it follows that microbial reduction of one ketone functionality in **1**, while moderately enantioselective, occurs with virtually no exo/endo diastereoselectivity.

Comparison of the above findings with the results obtained by Naemura and coworkers[3] for the corresponding HLADH catalyzed reduction of **1** is instructive. HLADH reduction of **1** afforded exclusively (-)-**2a** (74% chemical yield, 72.5±1% ee) along with recovered **1** (9% yield).[3] We conclude that microbial reduction of **1** by baker's yeast affords **2a** in an enantioselective process that is opposite of that observed for the corresponding HLADH catalyzed reduction. Furthermore, in contrast to the results obtained via baker's yeast catalyzed reduction of **1**, neither exo keto alcohol **2b** nor any of the three possible PCUD-8,11-diols was produced via HLADH catalyzed reduction of **1**.

Our results indicate that baker's yeast promotes reduction of **1** via preferential transfer of hydrogen from the exo-Si and endo-Re faces of one of the two carbonyl groups in **1**.




The corresponding HLADH-promoted reduction of **1** has been reported[3] to afford exclusively (-)-**2a**. In contrast to our results obtained by using baker's yeast, the corresponding exo keto alcohol, i.e., (+)- or (-)-**2b**, is not produced via HLADH-promoted reduction of **1**.[3] The corresponding metal hydride-promoted reductions of **1** generally result in reduction of both C=O functionalities when excess reductant is employed. Sodium borohydride (1 equivalent) reacts with **1** to afford endo keto alcohol **2a** along with a mixture of diastereoisomeric 8,11-cage diols.[9] Other than the results obtained herein for microbial reduction of **1** with baker's yeast, we know of no other example wherein exo keto alcohol **2b** is formed via reduction of one of the carbonyl groups in **1**, either enzymatically[3] or chemically.[9]

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