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HORSE LIVER ALCOHOL DEHYDROGENASE (HLADH) MEDIATED CHEMICOENZYMATIC ASYMMETRIC SYNTHESIS OF (+)-TWISTANE FROM *cis*-DECALIN-2,7-DIONE[1]

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HLADH mediated reduction differentiated between the enantiotopic carbonyl groups in *cis*-decalin-2,7-dione (**1**) to provide (-)-(7*S*,9*S*,10*R*)-7-hydroxy-*cis*-decalin-2-one (**3**) which was converted, via (+)-**4** and (+)-**6**, into (+)-twistane (**8**) of high optical purity.

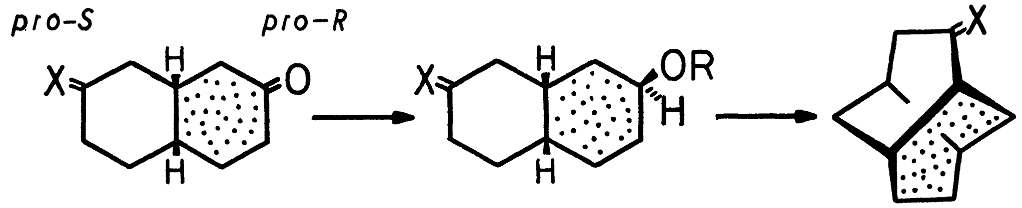
Asymmetric syntheses involving a step which effectively differentiates the enantiotopic groups in prochiral starting materials have an advantage in that the undesired stereoisomers could be converted back to the starting material. Among a variety of combinations[2] of biological systems and prochiral starting materials so far reported, few have been concerned with stereo-differentiation in *meso*-diketones.[3]

As an extension of our study[4] on the stereochemistry in microbial reduction of *meso*-2,10-dioxo[2.2]metacyclophane (C_s symmetry) with *Rhodotorula rubra*, we have been interested in biological stereo-differentiation in *meso*-diketones. In this communication we wish to report HLADH mediated reduction[5] of *cis*-decalin-2,7-dione (**1**)[6] (C_s symmetry) which eventually provides a convenient synthetic route to (+)-twistane (**8**) of high optical purity.

Since a preliminary experiment indicated a rather sluggish reduction[7] of the diketone **1** by HLADH, 4.0 g (24 mmol) of **1** was incubated for 123 h at 25°C with 2-L of 1/15 M Sørensen phosphate buffer (pH 7.0) containing NAD$^+$ (1.8 g, 2.5 mmol), ethanol (7.2 mL), and HLADH[8] (0.16 g).

Extraction with chloroform afforded an oily product (3.8 g) whose GLC revealed the presence of the recovered **1** and a ketol in a 2:3 ratio. Column chromatography yielded the recovered diketone **1** (0.75 g) and crude (-)-7-hydroxy-*cis*-decalin-2-one (**3**) (1.68 g, 42% yield) which was recrystallized from hexane, mp 68-69°C, $[\alpha]^{29}$D -16.4° (*c* 0.67, $CHCl_3$), $[\theta]_{290\ nm}$ $+9.67 \times 10^2$.

Although the positive Cotton effect of (-)-**3** when combined with the NMR data which indicated the equatorial conformation of the hydroxy group, suggested the (7*S*,9*S*,10*R*)configuration to (-)-**3**, the convincing evidence of its stereochemistry and optical purity were provided from its eventual conversion into (+)-4-twistanone (**6**) and (+)-twistane (**8**). Mesylation in pyridine converted the crude (-)-ketol **3** into the keto-mesylate **4**, mp 133-134°C, $[\alpha]^{25}$D +5.6° (*c* 1.1, $CHCl_3$) whose IR and NMR spectra were found indistinguishable from those of the racemic modification[9] (mp 109-111°C)



1 X=O
2 X=H_2

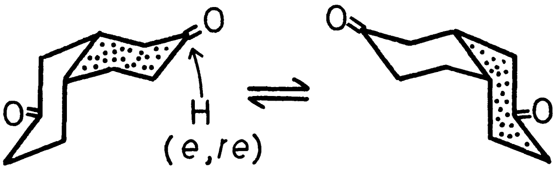
(-)-3 X=O,R=H
(+)-4 X=O,R=Ms
5 X=H_2,R=H

(+)-6 X=O
(+)-7 X=$<^{H}_{OH}$
(+)-8 X=H_2

Following Deslongchamps' procedure[9] for the racemate, the crude (+)-keto-mesylate **4** was refluxed with sodium hydride in dioxane to give crude (+)-4-twistanone (**6**) (55% yield) which was sublimed in vacuo to melt at 153-157°C, $[\alpha]^{23}$D +269.9° (*c* 1.38, EtOH). Since the IR spectrum of the (+)-**6** suggested contamination (~6%) from a ketone responsible for νC=O at 1690 cm^{-1}, this specimen was purified via (+)-*exo*-4-twistanol (**7**). $LiAlH_4$ reduction followed by purification by chromatography and sublimation in vacuo afforded (+)-*exo*-alcohol **7**, mp 193-194°C, $[\alpha]^{23}$D +383° (*c* 0.54, $CHCl_3$) whose Jones oxidation gave (+)-4-twistanone (**6**), mp 167-170°C, $[\alpha]^{24}$D +324.5° (*c* 0.82, EtOH). Finally, the Wolff-Kishner reduction of this (+)-**6** gave a 77% yield of (+)-twistane (**8**), mp 162-163°C, $[\alpha]^{25}$D +446° (*c* 0.50, EtOH) after purification through chromatography and sublimation in vacuo.

The information on the absolute configuration[10] and absolute rotation[11] of (+)-**6** and (+)-**8** clearly indicates that the HLADH mediated reduction strictly discriminates between *pro*-*R* and *pro*-*S* carbonyl groups in *cis*-decalin-2,7-dione (**1**) giving exclusively (-)-(7S,9S,10R)-ketol 3 of almost 100% optical purity.

Because of expected facile conformational mobility,[12] cis-decalin-2,7-dione (1) should be a racemic equilibrium mixture composed of the enantiomeric conformers



P-1 M-1

P-1 and M-1. Among the eight quadrant orientations possible for four carbonyl moieties in P-1 and M-1 conformers, the proposed HLADH quadrant rule[13] predicts that the orientation corresponding to equatorial and re-face attack of hydrogen on the pro-R carbonyl group in P-1 conformer is most favored giving rise to (-)-(7S, 9S,10R)-ketol 3. It seems pertinent to note that our result is in accord with ETH group's finding[14] that HLADH when incubated with (±)-cis-2-decalone (2) afforded the (2S,9R,10S)-2-decalol (5) as a sole reduction product.

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