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SELECTIVE AND STEREOSPECIFIC HORSE LIVER ALCOHOL DEHYDROGENASE-CATALYZED REDUCTION OF CAGE-SHAPED *meso*-DIKETONE. AN EFFICENT ACCESS TO OPTICALLY ACTIVE D_3-TRISHOMOCUBANE DERIVATIVE

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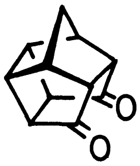
Horse liver alcohol dehydrogenase-catalyzed reduction of *meso*-diketone: pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8,11-dione gave (-)-11-hydroxypentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one which was transformed to (+)-D_3-trishomocuban-4-ol. HLADH also catalyzed the reduction of (±)-pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one (**4**) afforing (+)-**4** and (-)-pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-ol.

The ability of enzymes to catalyze enantioselective conversions of racemic substrates and stereoselective transformations of *meso*-substrates into optically active products is of considerable value in the preparation of optically active compounds.$^{1)}$ Our continuing interest in the syntheses of optically active cage-shaped compounds and in biological stereo-differentiation in *meso*-substrate$^{2)}$ prompted us to prepare optically active pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane derivatives by horse liver alcohol dehydrogenase(HLADH)-catalyzed reduction and to transfer these derivatives into optically active D_3-trishomocubane derivatives. D_3-Trishomocubane is the most stable member of the saturated set of compounds of formula $C_{11}H_{14}$ and the smallest rigid cage-shaped hydrocarbon of the point groups D_3. Rigid chiral hydrocarbons and derivatives are of special interest at test cases for chiroptic theories. In this communication, we wish to report HLADH-catalyzed reduction of *meso*-diketone: pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8,11-dione (**1**) and racemic ketone: pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one (**4**), and preparations of (+)-D_3-trishomocuban-4-ol (**6**) and (-)-1-methyl-D_3-

trishomocubane (11) from (-)-pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-ol (3) and (-)-4, respectively.

Four synthetic routes[3-6] have been reported for the preparation of optically active D$_3$-trishomocubane (7). In all cases, D$_3$-trishomocubane derivatives were optically resolved and no optically active pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane derivative has been reported.

meso-Diketone 1[7] (200 mg) was incubated for 52 h at room temperature with 800 mL of 1/15 M Sørensen phosphate buffer (pH 7.0) containing NAD$^+$ (40 mg), EtOH (1 mL) and HLADH[8] (1 mg). Silica gel chromatography of the CHCl$_3$-extracted metabolite gave the recovered diketone 1 (9%) and the *endo*-ketol (-)-2 (74%), mp 230-232.5 °C $[\alpha]_D^{26}$ -12.4° (CHCl$_3$), as a sole product. Neither the *exo*-ketol (diastereomer of 2) nor diols 5[9] were detected. The *endo*-configuration of (-)-2 was unambigously confirmed by comparison of its spectral data and GLC behavior with those of the corresponding racemate, mp 253-254 °C, prepared according to the Dekker's procedure.[10]



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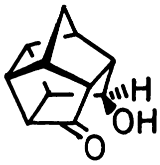

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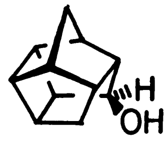

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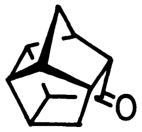

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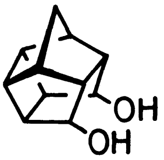

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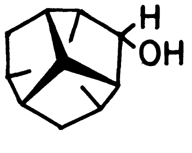

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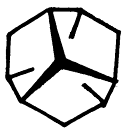


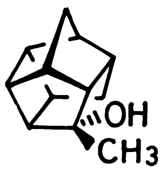
(+)-7

The Wolff-Kishner reduction of (-)-2 gave (-)-3, mp 209-211 °C $[\alpha]_D^{27}$ -15.4° (CHCl$_3$), in 68% yield after sublimation (at 100 °C, 10 mmHg). Its spectral data and GLC behavior were also in agreement with those of the corresponding racemate, mp 231-232 °C.[10] Jones oxidation of (-)-3 gave (+)-4, mp 196-197 °C (racemate[10] mp 194-195 °C) $[\alpha]_D^{27}$ +81.6° (CHCl$_3$). These compounds (-)-3 and (+)-4 serve as key intermediates in the preparation of D$_3$-trishomocubane derivative and its related cage-shaped compound in an optically active form. Skeletal rearrangement of (-)-3 to D$_3$-trishomocubanyl system was accomplished by heating under reflux for 6 h in glacial acetic acid containing a catalytic amount of 98% sulfuric acid.

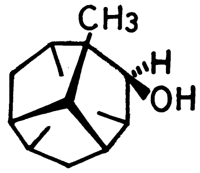
The resulting acetate was directly hydrolyzed with 10% HCl (refluxed for 6 h) to give (+)-D_3-trishomocuban-4-ol (6), mp 167.5-169 °C $[\alpha]_D^{26}$ +108° ($CHCl_3$) (72.5±1% optical purity) in 79% overall yield after purification through alumina chromatography and sublimation (at 100 °C, 10 mmHg).

As far as we know, this preparation of (+)-D_3-trishomocuban-4-ol (6) is the most facile synthesis of an optically active D_3-trishomocubane derivative. The information on the absolute configuration and absolute rotation of (+)-6 ($[\alpha]_{D\ abs.}$ 147°3) 151°4)) permitted us to assign the 1R,2R,3R,5S,6S,7S,9R,10S,11R, configuration to (-)-2 and estimate 72.5±1% enantiomer excess for the metabolite endo-ketol (-)-2.

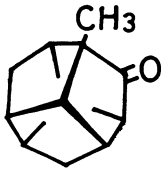
We next turned our attention to the preparation of optically active 3 and 4 by the HLADH-mediated enantioselective reduction of (±)-4. Incubation of (±)-4 (80 mg) with HLADH (1 mg), NAD^+ (40 mg), and EtOH (1 mL) in 1 L of 1/15 M Sørensen phosphate buffer (pH 7.0) at room temperature was terminated after 60 h when GLC monitoring indicated a 53:47 ratio of 3 and 4 in the $CHCl_3$-extracted metabolite. Alumina chromatography of the metabolite afforded (-)-3 (40%), mp 208-211 °C $[\alpha]_D^{26}$ -5.38° ($CHCl_3$) (25.4% e.e.), and (-)-4 (51%), mp 196-197 °C $[\alpha]_D^{26}$ -23.5° ($CHCl_3$) (20.9% e.e.). In this HLADH-mediated reduction, the exo-alcohol (diastereomer of 3) was not detected.



(+)-8



(-)-9



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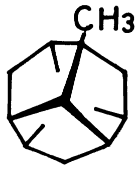

(-)-11

Following Dekker's procedure for the racemate,11) optically active 1-alkyl-D_3-trishomocubane was prepared from (-)-4. Treatment of (-)-4 with methylmagnesium iodide in dry ether (refluxed for 6 h) gave (+)-8, mp 96 °C $[\alpha]_D^{27}$ +4.73° (EtOH), in 51% yield after chromatography followed by sublimation (at 75 °C, 10 mmHg). Skeletal rearrangement of (+)-8 to D_3-trishomocubanyl system was accomplished by heating under reflux for 3 h in acetone-98% sulfuric acid (2:1) to result in the formation of (-)-9, mp 121-122 °C (racemate11) mp 113-114 °C) $[\alpha]_D^{27}$ -22.5° (EtOH), in 90% yield after alumina chromatography and sublimation (at 85 °C, 10 mmHg). Oxidation with 8 M Jones reagent in acetone at 0 °C converted (-)-9 into

(-)-**10**, $[\alpha]_D^{27}$ -13.3° ($CHCl_3$), as an oil after alumina chromatography. Finally, the Wolff-Kishner reduction of (-)-**10** furnished (-)-1-methyl-D_3-trishomocubane (at 100 °C, 30 mmHg). The structure of (-)-**11** was confirmed by comparison of its spectral data and GLC behavior with those of the corresponding racemate, mp 60-62 °C (lit.11) mp 59-62 °C). The optical purity of the precursor ketone (-)-**4** (20.9% e.e.) permitted calculation of the absolute rotation, $[\alpha]_D$ abs. -155°, of (-)-**11**. This value is close to that of D_3-trishomocubane (**7**) ($[\alpha]_D$ abs. 164°3) 165°4) 162°5)).

The results demonstrate that the HLADH-catalyzed stereoselective reduction of meso-diketone **1** is a more efficient route to optically active **3** and **4** than the HLADH-catalyzed enantioselective reduction of (±)-**4**.

References

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