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Microbiological Synthesis of Optically Active (2R,3S)-2,3-Deuteriocyclohexan-1-ones and (2R,3S)-2-Methyl-3-deuteriocyclohexan-1-one. Enantiospecific *Anti*-Addition of Hydrogen to the Double Bond of Cyclohex-2-en-1-ones.

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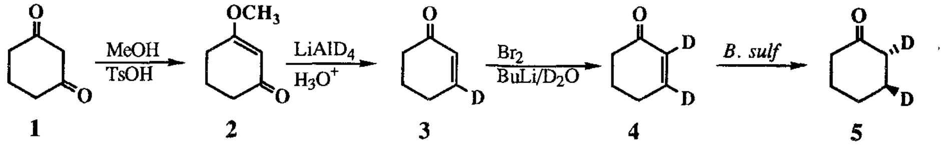
Abstract : Addition of hydrogen to the double bond of cyclohexenones during microbiological reduction by *Beauveria sulfurescens* gives the *trans* product in high yield (90%) resulting from *anti*-addition to the *si* face on C-2 and the *re* face on C-3.

We have shown that α,β-ethylenic ketones are reduced to saturated ketones by *Beauveria sulfurescens*, and that with an α-alkyl substituent the saturated ketone is optically pure[1,2]. However, cyclic α,β-unsaturated ketones having α and β-alkyl substituents are not reduced with *B. sulfurescens*. Replacement of the α- or β-alkyl substituent by deuterium in cyclohex-2-en-1-one leads to optically active 2- or 3-deuteriocyclohexanones. The optical activity is due solely to the presence of the deuterium atom. By comparison with previous work of Djerassi[9a], and using circular dichroism, we have assigned absolute configuration (2R) and (3S) to the 2-deuterio and 3-deuteriocyclohexan-1-ones obtained[3,4]. These assignments were confirmed by Djerassi[9b] from chemical synthesis. The absolute configurations of the asymmetric carbon created in the two different experiments, *i.e.* carbon 2R (α) and carbon 3S (β), implies that the reduction of α,β-unsaturated cyclic ketones with *B. sulfurescens* corresponds to an *anti*-addition of hydrogen to the double bond[3,4].

To test this hypothesis and in order to obtain additional experimental support for this *anti*-addition mechanism we have studied the microbiological reduction of cyclohexenones bearing deuterium atoms in both positions α and β : 2,3-dideuteriocyclohex-2-en-1-one and 2,3,4,4,6,6-hexadeuteriocyclohex-2-en-1-one by *B. sulfurescens* . In order to determine also if the *anti*-addition mechanism occurs during the microbiological reduction of the double bond of 2-substitued cyclohex-2-en-1-one, we have performed the same experiment on 2-methyl-3-deuteriocyclohex-2-en-1-one.

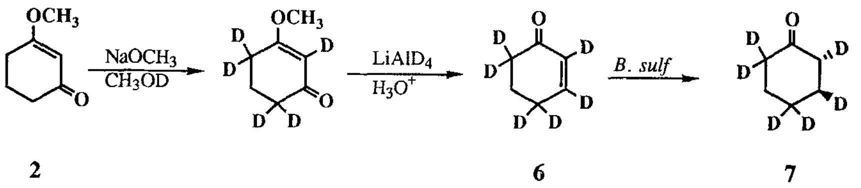
The synthesis of 2,3-dideuteriocyclohex-2-en-1-one[13] **4** (Scheme I) started with cyclohexane-1,3-dione **1** which was treated with MeOH/TsOH to give enol ether **2**. Reduction of **2** by $LiAlD_4$ gave 3-deuteriocyclohex-2-en-1-one **3** as described by Gannon and House[5]. The 2,3-dideuteriocyclohex-2-en-1-one **4** was obtained from **3** according to the method of Guaciaro[6].



SCHEME I

The microbiological reduction of **4** by *B. sulfurescens* leads to optically active 2,3-dideuteriocyclohexan-1-one[14] **5** ([α] = + 3.2). ^{1}H, ^{2}H and ^{13}C NMR allows the determination of the stucture of **5** . The ^{2}H NMR spectrum of **5** in C_6H_6 consisted of resonances at δ 1.92 and 1.28 for ^{2}H-2 and ^{2}H-3, respectively, the width at half-height being 2.8 Hz after proton irradiation. The absolute configuration of **5** is proved by the value of the coupling constant $J_{H2\text{-}H3}$= 7 Hz which corresponds to the conformational equilibrium between the two chair forms of **4**, H-2 and H-3 being *trans* and, respectively, in axial-axial or equatorial-equatorial positions (50/50). If H-2 and H-3 were *cis* to each other the calculated value for $J_{H2\text{-}H3}$ would be of 3 Hz. It follows, then, that the absolute configuration of **5** is (2R,3S). This result confirms our previous work[3,4], which showed that the reduction of cyclohex-2-en-1-ones with *B. sulfurescens* gives mainly the *trans* product resulting from *anti*-addition of hydrogen to the double bond.

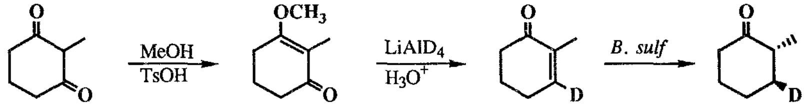
Additional support for this mechanism comes from the microbiological reduction of 2,3,4,4,6,6-hexadeuteriocyclohex-2-en-1-one[13] **6** which was synthetized from enol ether **2** according the method of Lambert and Clikeman[7] (Scheme 2).



SCHEME II

Optically active 2,3,4,4,6,6-hexadeuteriocyclohexan-1-one[14] **7** ($[\alpha]$ = + 3.8) is obtained by microbial reduction of **6** by *B. sulfurescens*. The very simple ^{1}H NMR spectrum of **7** shows a doublet ($J_{H2\text{-}H3}$= 7 Hz) for H-2 at 1.97 ppm (characteristic of *trans* coupling H-2 - H-3).

Finally we have studied the microbial reduction of 2-methyl-3-deuteriocyclohex-2-en-1-one[13] **10** which was prepared from 2-methylcyclohexane-1,3-dione **8**. Treatment by MeOH/TsOH gives enol ether **9** which was reduced[5] by $LiAlD_4$ to **10** (Scheme III).



8 **9** **10** **11**

SCHEME III

Microbiological reduction of **10** gives a 90/10 mixture of (2R,3S)- and (2R,3R)-2-methyl-3-deuteriocyclohexan-1-one[14] **11** ($[\alpha]$ = - 8). This ratio was determined from ^{1}H and ^{2}H NMR spectra. The ^{1}H NMR spectrum of **11** shows two doublets (J = 7 Hz) for the methyl, at 0.85 ppm (90.5 %) and 0.80 ppm (9.5 %) in CCl_4-C_6D_6 (9/1) and a signal at 1.22 ppm corresponding to H-3. The chemical shift of H-3 is characteristic of a hydrogen *cis* to a methyl group at C-2. ^{2}H NMR in C_6H_6 shows two singlets at δ = 1.55 (91 %) and 0.93 (9 %) characteristic, respectively, of *trans* and *cis* positions of ^{2}H-3 to the methyl group in C-2 as indicated by Campbell *et al.* for the 2-methyl-3-deuteriocyclopentan-1-one[8]. The corresponding NMR spectra of racemic 2-methyl-3-deuteriocyclohexan-1-one[14] show 50/50 signals for the methyl and for ^{2}H-3. These results show that the addition of hydrogen to the double bond of cyclohex-2-en-1-ones, during microbiological reduction by *B. sulfurescens*, occurs in an *anti* mode in high yield, through the *si* face on C-2 and the *re* face on C-3. The presence of a product in which the ^{2}H-3 and the methyl group in C-2 are in *cis* position (10 %) can be explained by a subsequent non-enzymatic epimerisation on C-2 as it is the case for 2-methylcyclohexan-1-one[10] (ee ≈ 90 %).

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10) - Enantiomeric excess of 2-methylcyclohexan-1-one[1] obtained by microbiological reduction is ≈ 90% (comparison with litterature data[11]).

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12) - All compounds were characterized by NMR spectroscopy ^1H, ^2H and ^{13}C NMR at respectively 400.13 MHz, 61.4 MHz and 100.13 MHz. For ^2H NMR, C_6D_6 $\delta = 7.15$.

13) - 2,3-dideuteriocyclohex-2-en-1-one **4** : colorless liquid, NMR ^1H ($CDCl_3$) δ : 1.7 to 2.6 (m, 6H, ring methylene).

2,3,4,4,6,6,-hexadeuteriocyclohex-2-en-1-one **6** : colorless liquid, NMR ^1H ($CDCl_3$) δ : 1.92 (s, 2H, methylene)

2-methyl-3-deuteriocyclohex-2-en-1-one **10**, colorless liquid, NMR ^1H ($CDCl_3$) δ : 1.8 (s, 3H, methyl); 1.8 to 2.6 (m, 6H, ring methylene).

14) - **(+)-(2R,3S)-2,3-dideuteriocyclohexan-1-one 5**, colorless liquid, $[\alpha]_J^{25^\circ} = +3.2$ ($CHCl_3$, c = 0.1); NMR ^1H (C_6D_6) δ : 1.99 (t, 2H-6); 1.96 (d , J = 7 Hz, $W_{1/2}$= 5 Hz, H-2); 1.37 (m, 2H-5); 1.34 (m, H-3); 1.20 (m, 2H-4). NMR ^2H (C_6H_6/C_6D_6, 90/10), δ : 1.92 (s, 2H-2); 1.28 (s, 2H-3). NMR ^{13}C ($CDCl_3$), δ : 211.9 (C-1); 41.5 (t, $^1J_{^{13}C\text{-}^2H}$ = 19.5 Hz, C-2) ; 26.7 (t, $^1J_{^{13}C\text{-}^2H}$ = 19.5 Hz, C-3); 24.8 (C-4); 27.02 (C-5); 42.0 (C-6).

- **(+)-(2R,3S)-2,3,4,4,6,6-hexadeuteriocyclohexan-1-one 7**, colorless liquid, $[\alpha]_J^{25^\circ} = +3.8$ ($CHCl_3$, c = 0.12); NMR ^1H (C_6D_6), δ : 1.97 (d, J = 7 Hz, $W_{1/2}$= 5 Hz, H-2); 1.35 (s, $W_{1/2}$= 12 Hz , 2H-5, H-3). NMR ^2H (C_6H_6/C_6D_6, 90/10), δ : 1.92 (s, ^{2}H-2, 2 ^{2}H-6); 1.32 (s, ^{2}H-3), 1.12 (s, 2 ^{2}H-4).

- **(±)-2-methyl-3-deuteriocyclohexan-1-one**, NMR ^1H (CCl_4/C_6D_6 90/10), δ : 2.15 - 1.22 (m, 2x8H), 0.85 and 0.80 (d, J = 7 Hz, CH_3). NMR ^2H (C_6H_6/C_6D_6, 90/10), δ : 1.55 (d, J = 1.2 Hz), 0.93 (pseudo q, J = 1.6 Hz), ^{2}H-3 (we obtain singlets with proton irradiation).

- **(-)-(2R,3S)-2-methyl-3-deuteriocyclohexan-1-one 11**, colorless liquid; $[\alpha]_J^{25^\circ} = -8$ ($CHCl_3$, c = 0.2); NMR ^1H (CCl_4/C_6D_6 90/10), δ : 2.15 (m, 3H, H-2, 2H-6), 1.90 (m, 1H), 1.69 (m, 1H), 1.49 (m, 2H), 1.22 (m,1H, H-3); 0.85 (d, J = 7 Hz, CH_3, 90.5 %), 0.80 (d, J = 7 Hz, CH_3, 9.5 %). NMR ^2H (C_6H_6/C_6D_6, 90/10), δ : 1.55 (d, J = 1.2 Hz, 91 %)), 0.93 (pseudo q, J = 1.6 Hz, 9 %), ^{2}H-3 (we obtain singlets with proton irradiation).