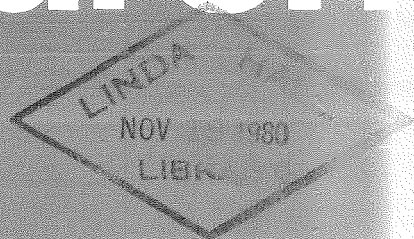


Tetrahedron Letters



The International Journal for the Rapid Publication of Preliminary Communications in Organic Chemistry

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MICROBIOLOGICAL SYNTHESIS AND CIRCULAR DICHROISM OF OPTICALLY ACTIVE 2-DEUTERIO-CYCLOALKANONES

By G. Dauphin, J.C. Gramain, A. Kergomard, M.F. Renard and H. Veschambre

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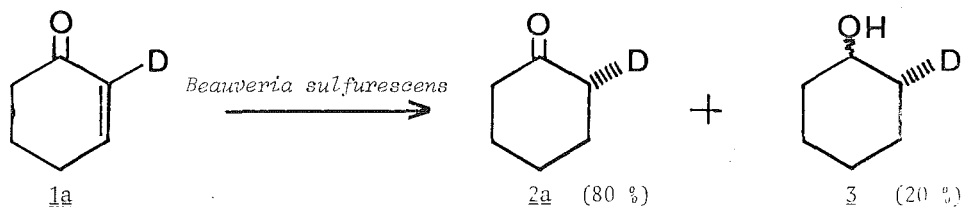
Summary : Optically active 2-deuterio-cyclopentanone and 2-deuterio-cyclohexanone have been prepared by microbiological reduction of 2-deuterio α,β -unsaturated cyclic ketones by *Beauveria sulfurescens*.

We recently described (1) the synthesis of optically active 3-deuterio cycloalkanones by microbiological reduction of the corresponding 3-deuterio-2-cycloalkanones with *Beauveria sulfurescens* (ATCC 7159). The same method is now used to prepare the optically active 2-deuterio-cycloalkanones 2a and 2b. Hitherto, the only reported 2-deuterio-cyclohexanones had been substituted in position 4, giving them a blocked conformation (2,3). The study of the optical properties of 2-deuterio-cyclohexanone can give us the confirmation of the contribution of the deuterium atom as determined by C. Djerassi (2) and S.G. Levine (3).

No 2-deuterio-cyclopentanones had hitherto been described. The optical properties of 2-deuterio-cyclopentanone enable the contribution of the deuterium atom in a five membered ring to be evaluated.

The 2-deuterio-cycloalkanones 1a and 1b (4) were prepared by the method of M.A. Guaciaro and al. (5) from the corresponding cycloalkanones in four steps.

(R)-(+)-2-DEUTERIO-CYCLOHEXANONE 2a

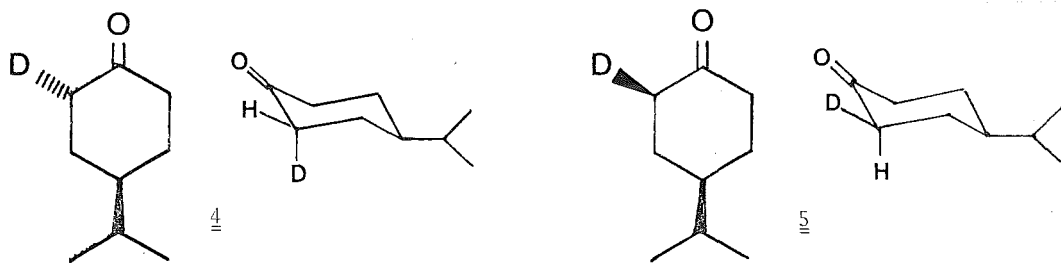


Reduction of 2-deuterio-2-cyclohexenone 1a by *Beauveria sulfurescens* (ATCC 7159) under previously described conditions (6) took 48 hours (yield 85%), giving a mixture of (R)-(+)-2-deuterio-cyclohexanone 2a (80%) (4) and the two diastereoisomers of (2R)-(+)-2-deuterio-cyclohexanol 3 (20%). 2a and 3 were separated by chromatography on silicagel.

$\underline{2a}$: $E_b = 155^\circ$; $\{\alpha\}_{578}^{25} = +2.5$ ($c = 0.05$, $CHCl_3$) ; $c.d. \{ \theta \}_{max} = +95^\circ$ at 288 nm. ($c = 9.4$ g/l, EtOH)
 ^{13}C N.M.R. δ (p.p.m. from Me_4Si) 211.9 (C-1), 42.0 (C-6), 41.7 (t. 1J ($^{13}C - ^1H$) = 20 Hz, C-2), 27.1 (C-3 and C-5), 25.1 (C-4) ; 2H N.M.R. 38.39 MHz δ (p.p.m. from Me_4Si) 2.1.

Results obtained previously for the microbiological reduction of 2-methyl-2-cyclohexanone (6,7), showed that the asymmetric carbon atom formed always had absolute configuration R. We thus assume that the α -carbon in $\underline{2a}$ also has absolute configuration R.

C. Djerassi (2) and S.G. Levine (3) were able to show from the study of the circular dichroism of (2S) and (2R)-deuterio-(4R)-isopropylcyclohexanone $\underline{4}$ and $\underline{5}$ that the contribution of the α -axial and α -equatorial deuterium is anti-octant (dissignate).



The circular dichroism curve of $\underline{2a}$ and octant diagrams of its two conformers are shown in figure 1. We assume that no conformational preference is introduced by the presence of the deuterium atom (8). The positive sign of the circular dichroism is consistent with the presence of an axial deuterium in a negative octant. The contribution of equatorial deuterium is weak. The value of the circular dichroism observed for $\underline{2a}$ is consistent with the value calculated from the circular dichroisms of $\underline{4}$ and $\underline{5}$ (2) in which the deuterium is blocked in the axial and equatorial position respectively.

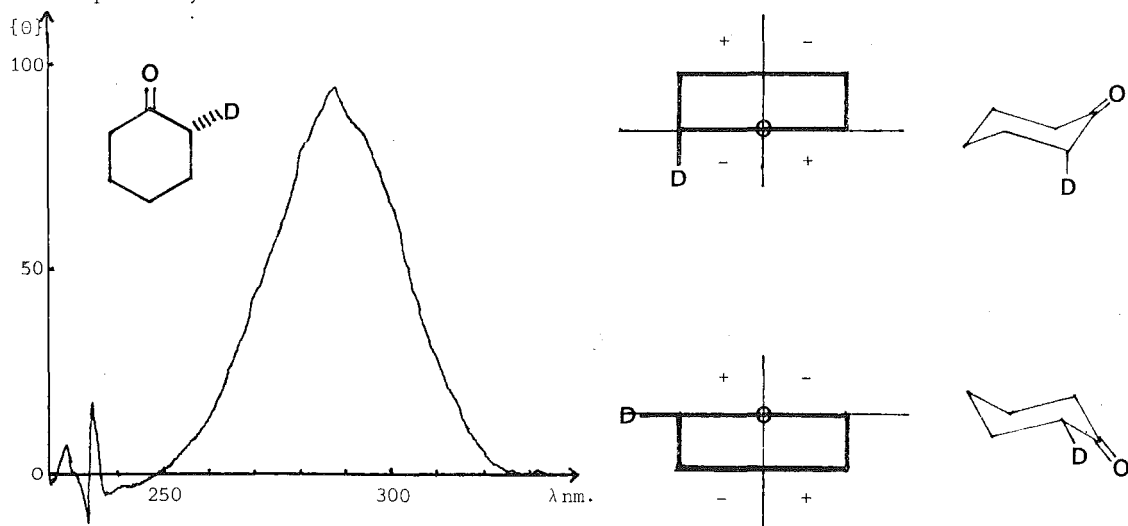
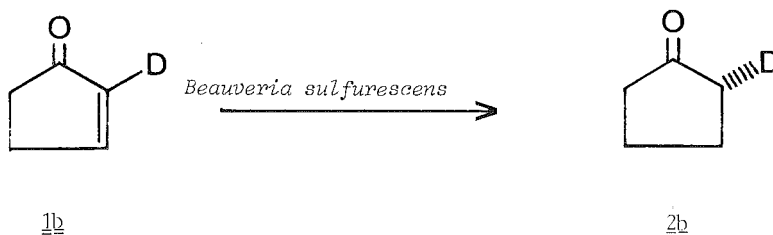


Figure 1 : Circular dichroism curve of $\underline{2a}$ and octant diagrams of its two conformers.

The unresolvable mixture of alcohols 3 consists of a 50/50 mixture of *cis* and *trans* isomers (^2H N.M.R. analysis).

(R)-(+)-2-DEUTERIO-CYCLOPENTANONE 2b



The analogous reduction of 1b took 48 hours (80 % yield) and gave only (R)-(+)-2-deuterio cyclopentanone 2b (4), purified by chromatography on silicagel and distilled.

2b : $E_b = 130^\circ$; $\{\alpha\}_{578}^{25} = +0.6$ ($c = 0.05$, CHCl_3) ; $c.d.\{\theta\}_{\text{max}} = -55^\circ$ at 299 nm. ($c = 5.65$ g/l, EtOH)
 ^{13}C N.M.R. δ (p.p.m. from Me_4Si) 220.5 (C-1), 38.3 (C-5), 38.0 (t. $^1J(^{13}\text{C} - ^1\text{H}) = 20$ Hz C-2), 23.2 (C-3 and C-4).

The absolute configuration of the α -carbon is assumed to be R for the following two reasons :

- (i) reduction of 2-methyl-2-cyclopentenones and 2-methyl-2-cyclohexenones always produced an R configuration, (6) and (7).
- (ii) the stereochemistry of the reduction of 2-deuterio-cyclohexenones is the same as that of 2-methyl-2-cyclohexenone (as indicated previously).

The circular dichroism curve of 2b and octant diagrams of its two conformers are shown in figure 2.

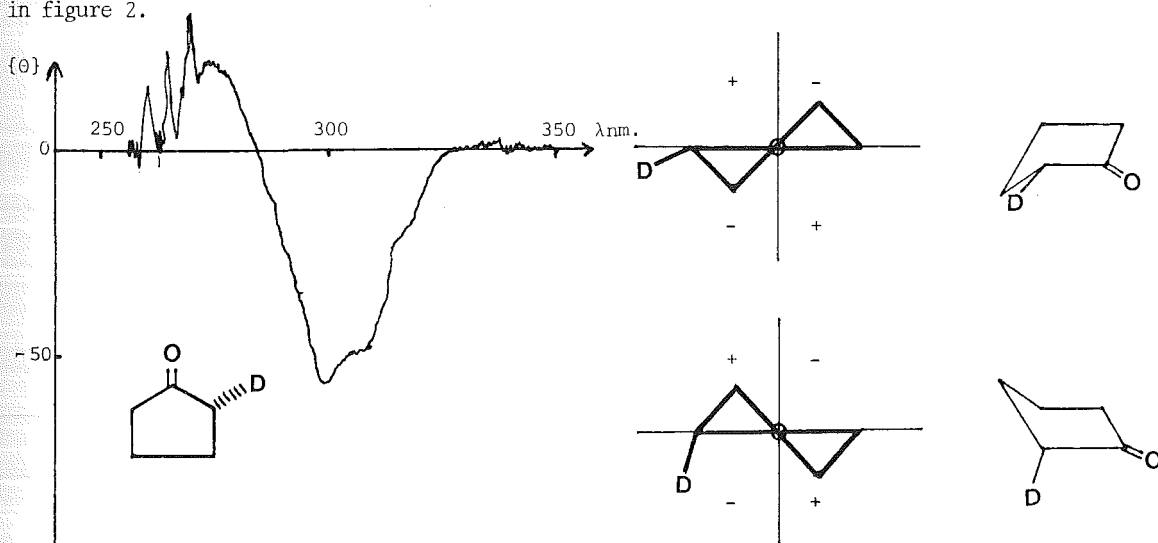


Figure 2 : Circular dichroism of 2b and octant diagrams of its two conformers.

The sign of the circular dichroism implies (assuming the deuterium has no preferred conformation and does not modify the conformations of figure 2) that in a cyclopentanone, a pseudo-equatorial or pseudo-axial deuterium makes a consignate contribution, unlike that in analogous cyclohexanones (2) and (3).

However, such an interpretation assumes that the atom of deuterium does not modify the relative populations of the two conformers to the extent that the sign of the circular dichroism is determined by the contribution of carbon atoms 3 and 4 of the ring. Further study of other homologous 2-deuterio-cyclopentanones is required to ascertain whether this assumption is a valid one.

The use of a microbiological reducing agent enables optically active 2-deuterio-cycloalkanones to be easily prepared. The optical activity of these derivatives is solely due to the presence of the deuterium atom. Previous results (6) and (7) with substituted cyclic ketones justify the assumption that 2a and 2b are optically pure.

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