

## Microbiological Synthesis of Optically Active 3-Deuterio-cycloalkanones

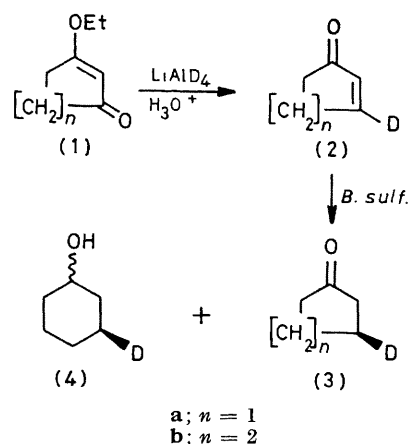
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**Summary** Optically active 3-deuterio-cyclopentanone and 3-deuterio-cyclohexanone have been prepared by microbiological reduction of 3-deuterio  $\alpha\beta$ -unsaturated cyclic ketones by *Beauveria sulfurescens*.

MANY synthetic problems, in particular the production of an asymmetric centre may be solved by use of highly stereospecific microbiological reactions. Micro-organisms are useful sources of chiral reagents<sup>1</sup> and have led, for many syntheses, to optical yields of 100%.<sup>2</sup> The synthesis of optically active deuterio-cycloalkanones, the optical activity of which is due to the presence of deuterium, has been described in detail.<sup>3-5</sup> Starting from optically active material and using classical transformations, deuterium is introduced through a stereospecific reaction (reduction of a mesylate with LiAlD<sub>4</sub>). The overall yield of this multi-step transformation is low and the optical purity of the product depends on the stereospecificity of the deuterium introduction. The optical purity of the products must be checked after each step since some of them can lead to partial racemization.

We have shown<sup>6</sup> that  $\alpha\beta$ -ethylenic ketones are reduced to saturated ketones with *Beauveria sulfurescens* (ATCC 7159). Provided there is an  $\alpha$ -alkyl substituent on the double bond, the saturated ketone is optically active and its optical purity is equal to 100%. However, cyclic  $\alpha\beta$ -unsaturated ketones having a  $\beta$ -alkyl substituent are not reduced with *B. sulfurescens*. Replacement of the  $\alpha$ - or  $\beta$ -alkyl substituent by deuterium should then lead, because of the asymmetric disturbance by the latter, to optically active cycloalkanones.

Reduction (LiAlD<sub>4</sub>, then H<sub>3</sub>O<sup>+</sup>) of the enol ethers (1a) and (1b) yields the deuterio-derivatives (2a) and (2b), respectively.<sup>†</sup> Reduction of (2a) with *B. sulfurescens*, under the



conditions described elsewhere,<sup>6</sup> is complete within 48 h (90% yield) and yields only (S)-(+)-3-deuteriocyclopentanone (3a),  $[\alpha]_{578}^{25} + 2.1^\circ$  (c 0.1 CHCl<sub>3</sub>); c.d.,  $[\theta]_{\text{max}} + 62^\circ$  at 297 nm (c 8.7 mg/ml, EtOH); <sup>13</sup>C n.m.r. (p.p.m. from Me<sub>4</sub>Si) 212.2 (C-1), 38.4 (C-2 + C-5), 23.2 (C-4), and 23.0 [t, <sup>1</sup>J(<sup>13</sup>C-<sup>2</sup>H) 20 Hz, C-3].<sup>‡</sup> This ketone is thus the enantiomer of that reported by Djerassi *et al.* (same optical purity,  $[\theta]_{\text{max}} - 63^\circ$ ).<sup>3</sup>

The similar reduction of (2b) is complete within 96 h (85% yield) and yields a 50:50 mixture (g.l.c.) of (S)-(+)-3-deuteriocyclohexanone<sup>†</sup> (3b) and a mixture of the stereoisomeric deuteriated alcohols (4), which was separated by silica gel column chromatography; (3b):  $[\alpha]_{578}^{25} + 2.7^\circ$  (c 0.07, CHCl<sub>3</sub>); c.d.  $[\theta]_{\text{max}} + 122^\circ$  at 291 nm (c 14 mg/ml, EtOH); <sup>13</sup>C n.m.r. (p.p.m. from Me<sub>4</sub>Si) 212.1 (C-1), 41.2

<sup>†</sup> The isotopic purity of the deuterio compounds is >98% (mass and <sup>1</sup>H n.m.r. spectroscopy).

<sup>‡</sup> Other spectral parameters of these compounds accord with the proposed structures (i.r., mass, and <sup>1</sup>H n.m.r. spectroscopy).

(C-2 + C-6), 27 (C-5), 26.7 [t,  $^1J(^{13}\text{C}-^2\text{H})$  20 Hz, C-3], and 25 (C-4).<sup>‡</sup> This deuterium-substituted chiral ketone thus has the same absolute configuration as that reported by Djerassi *et al.*,<sup>4</sup> but is of much higher optical purity (lit.,<sup>4</sup>  $[\theta]_{\text{max}}$  47°). The unresolvable mixture of alcohols (**4**) [probably arising from the reduction of (**3b**) with *B. sulfurescens*] comprises a 50:50 mixture of *cis*- and *trans*-isomers ( $^2\text{H}$  n.m.r. analysis).

Microbiological reduction of the cyclic  $\alpha\beta$ -unsaturated ketones (**2a**) and (**2b**) with *B. sulfurescens* thus yields the optically active deuterium substituted ketones (**3a**) and (**3b**) with the *S* absolute configuration. Both yield and stereospecificity are very high and only three steps are necessary starting from the 1,3-dione. Previous results<sup>6</sup> on substituted

cyclic ketones lead us to believe that (**3a**) and (**3b**) are in fact optically pure. Furthermore, after the reduction with *B. sulfurescens* of 2-alkyl  $\alpha\beta$ -unsaturated cyclic ketones, C-2 has the *R* absolute configuration.<sup>6</sup> Hence, we conclude that the reduction of  $\alpha\beta$ -unsaturated cyclic ketones with *B. sulfurescens* corresponds to a *trans*-addition of hydrogen to the double bond through the *si* face on C-2 and *re* face on C-3.

We thank Miss F. Gueritte (Institut de Chimie des Substances Naturelles, C.N.R.S., Gif-sur-Yvette) for c.d. curves and Dr C. Brevard (Brucker Spectrospin, Wissembourg) for  $^2\text{H}$  n.m.r. spectra.

(Received, 21st December 1979; Com. 1332.)

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