Microbial Stereo-differentiating Reduction of the Carbonyl Groups located on the C_2 Axes of Gyrochiral Molecules[1]

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Summary Stereochemistry of microbial reduction (*Curvularia lunata* and *Rhodotorula rubra*) of the gyrochiral ketones whose C_2 axes coincide with the carbonyl axes was examined to reveal a remarkable enantiomer selectivity.

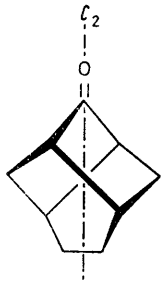
THE enantiotopic faces of carbonyl groups which are flanked by two groups with different bulkiness can be distinguished by various microbes, the most extensively studied systems so far being *C. falcata* and baker's yeast. The stereochemistry of this biological reduction has been summarized in a general rule (the 'Prelog rule'[2]): the hydrogen atom preferentially attacks the B-*re* face of the carbonyl group affording the B-*S*-alcohol.†

In gyrochiral ketones‡ whose carbonyl groups are located on the C_2 axes, the faces around these carbonyl groups are homotopic in an internal comparison, and the only stereochemical distinction is that between enantiotopic faces in each enantiomer in an external comparison. Our continuing interest in gyrochiral molecules has led us to investigate the stereochemistry of the microbial reduction of this type of ketone.

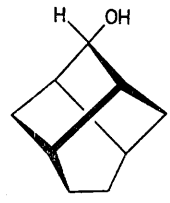
Incubation of (±)-9-twist-brendanone (**1**)[3] (200 mg) with *C. lunata* at 29 °C for 48 h gave a mixture of the recovered ketone (**1**) and the alcohol (**2**) which was chromatographed to yield (−)-(**1**)§[4] (60 mg), m.p. 170—171·5 °C, $[\alpha]_D^{27}$ −179° (MeOH) (optical purity 63·4%) and (+)-9-twist-brendanol (**2**)[4] (60 mg), m.p. 177—179 °C, $[\alpha]_D^{27}$ +222° (MeOH) (optical purity 85%).

(±)-2-Brexanone (**3**)[5] (400 mg) was treated with *C. lunata* at 30 °C for 72 h to give the recovered (+)-ketone (**3**)[6] (139 mg), b.p. 100—105 °C at 27 mmHg, $[\alpha]_D^{26}$ +65° (EtOH) (optical purity 23%) and (−)-2-brexanol (**4**)[6] (70 mg), m.p. 85—87 °C, $[\alpha]_D^{26}$ −158° (EtOH) (optical purity 100%).

Incubation of (±)-D_3-trishomocubanone (**5**)[7] (200 mg) for 3 h at 29 °C with *C. lunata* was sufficient to give a 57 : 43 mixture of the recovered ketone (**5**) and the alcohol (**6**) which was chromatographed to afford (−)-(**5**)[8] (79 mg), m.p. 162—164 °C, $[\alpha]_D^{28}$ −35° (EtOH) (optical purity 40%) and (+)-D_3-trishomocubanol (**6**)[8] (49 mg), m.p. 165—167 °C, $[\alpha]_D^{28}$ +92° (EtOH) (optical purity 61%).



(−) - (1)



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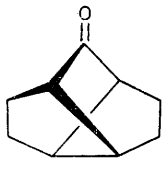

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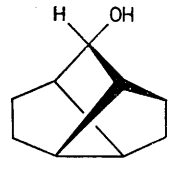
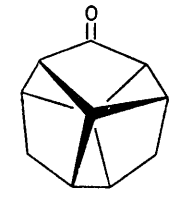
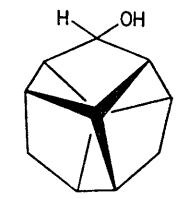


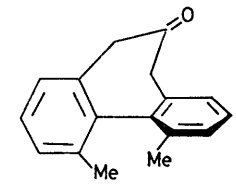
(−) - (4)



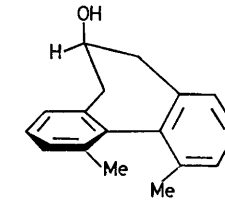
(−) - (5)



(+) - (6)



(+) - (7)



(+) - (8)

The stereochemical environment around the C_2 axes of these recovered ketones, (−)-(**1**), (+)-(**3**), and (−)-(**5**), can be schematically represented by a projection diagram (Figure) in which the ketones are viewed from the carbonyl oxygen atom along their C_2 axes. Since this diagram applies to the recovered ketones, our experiments clearly indicate that enantiomeric C_2-ketones having the larger parts of the molecules in upper right (UR) and lower left (LL) quadrants are preferentially reduced by *C. lunata*.

Although *R. rubra* demonstrated a similar enantiomer selectivity for these ketones, but only to a small extent,

† The letter 'B' is an indication of the 'bulkiness sequence subrule' (priority sequence: oxygen atom > large group > small group > hydrogen atom); this is adapted to supplement the *R–S* notation.

‡ This name is proposed to describe the symmetry of a shape which is chiral but not asymmetric; *cf.* M. Nakazaki, K. Naemura, and H. Yoshihara, *Bull. Chem. Soc. Japan*, 1975, **48**, 3278.

§ All structural formula in this communication are presented in their absolute configurations.

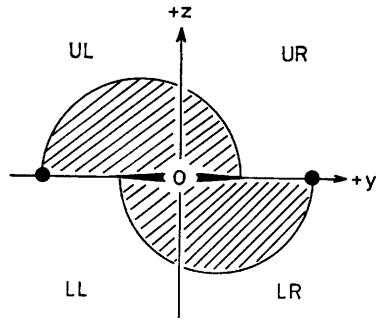


FIGURE. Schematic representation indicating the stereochemical environment around the C_2 axes of the recovered ketones (−)-(**1**), (+)-(**3**), (−)-(**5**), and (+)-(**7**).

this microbe was found to exhibit a marked enantiomer selectivity with a similar stereochemical requirement (Figure) for the (±)-ketone (**7**),[9] the axially gyrochiral C_2-ketone on which a partial asymmetric reaction has been carried out.[10]

After incubation of (±)-(**7**) for 25 h at 30 °C with *R. rubra*, (*R*)-(+)-(**7**),[9] (62% yield), m.p. 61—63 °C, $[\alpha]_D^{30}$ +629·5° (benzene) (optical purity 100%), and (*S*)-(+)-(**8**)[9] (79% yield), m.p. 78—79·5 °C, $[\alpha]_D^{30}$ +132° (benzene) (optical purity 94%) were isolated from the culture solution, while partial asymmetric Meerwein–Ponndorf reduction[10] with (*S*)-(+)-octan-2-ol was reported to afford (*S*)-(**7**) (optical purity 34·8%), and (*R*)-(**8**) (optical purity 11·7%).

(*Received*, 21*st February* 1978; *Com.* 184.)

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