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MICROBIAL STEREODIFFERENTIATING REDUCTION OF (±)-4-METHYL-1-OXO[2.2]METACYCLOPHANE AND REVISION OF THE ABSOLUTE CONFIGURATION OF 4-SUBSTITUTED [2.2]METACYCLOPHANES

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The (-)-Cotton effect indicates (pS)-configuration to (-)-4-methyl-1-oxo[2.2]metacyclophane (17) which was isolated from a culture solution of (±)-14 with Rhodotorula rubra, and the conversion of (-)-17 to (+)-4-methyl[2.2]metacyclophane (21) via 19 assigns (pR)-configuration to (+)-21, contrary to Schlögl's proposal.

In the preceding paper,[1] we described the microbial reduction of (±)-[2.2]metacyclophane-4-aldehyde (15) with R. rubra to afford 4-hydroxymethyl derivative 20 enriched in the (+)-enantiomer. Application of the quadrant rule[2] assigned (pR)-configuration to (+)-20 opposite to Schlögl's proposal,[3] and this prompted us to reinvestigate the absolute configuration of 4-substituted [2.2]metacyclophanes.

In our strategy, the key intermediate is optically active 4-methyl-1-oxo[2.2]-metacyclophane (17), whose absolute configuration could be deduced from CD analysis and whose conversion into 21 via 19 in turn should provide informations on the configuration of 20 and 21.

Our unambiguous synthesis of (±)-14 (Scheme) started from bromination of 2,5-dimethylbenzoic acid which yielded a mixture of the mono-bromides 1 and 2. Alkaline hydrolysis of the mono-bromides followed by lactonization converted the resulting 4 into lactone leaving 3 as free acid. Conversion of 3 into the bromide 8 was rather straightforward; esterification to 5, methylation to 6, $LiAlH_4$ reduction to 7, and PBr_3 bromination to 8 successively (75% total yield from 3).

Coupling the bromide 8 with lithio-derivative[3] of m-methoxymethylbenzaldehyde trimethylenedithioacetal in THF gave 9, the dithioacetal group of which was removed by NBS oxidation to afford the ketone 10. Heating with aq HBr converted 10 into the dibromide 11 whose dithioacetal 12 was treated with BuLi[4] to yield the [2.2]metacyclophane 13. Removal of the protecting group by oxidation with NBS in acetone finally gave (±)-14, mp 82-84°C (11% total yield from 8).

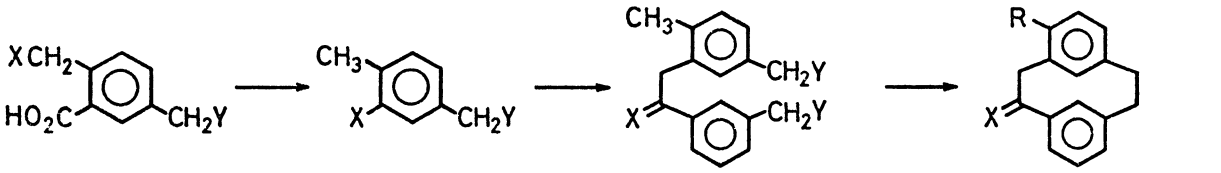
The metabolite distribution in a 24 h culture solution of (±)-14 with R. rubra exhibited a similar spectrum[1] reported for the parent ketone (±)-16; the recovered (-)-(pS)-ketone 17, mp 120°C, $[\alpha]_D^{20}$-420° ($CHCl_3$), $[\theta]_{321}$-2.74x10^4 (isooctane) (29% yield), the (-)-(pR,1S)-axial alcohol 22, mp 94°C, $[\alpha]_D^{25}$-2.5° ($CHCl_3$) (39% yield), and the (-)-(pS,1S)-equatorial alcohol 23, mp 129°C, $[\alpha]_D^{25}$-98.3° ($CHCl_3$) (10% yield).

Comparison of CD spectra with the parent (-)-(pS)-ketone 18[5] of known absolute configuration established (pS)-configuration[6] to the recovered (-)-ketone 17, and

characteristic NMR spectra[2] combined with oxidation to the enantiomeric ketones assigned respective (pR,1S)- and (pS,1S)-configuration[6] to the metabolite alcohols 22 and 23.

Finally, the (-)-ketone 17 (optical purity ~90%)[7] was converted into the (+)-dithioacetal 19, mp 130°C, $[\alpha]_D^{20}$+45° ($CHCl_3$) which was stirred with Raney Ni in an ethanol-ethyl acetate solution at room temperature for 2 h to give an 84% yield of (+)-4-methyl[2.2]metacyclophane (21), mp 86°C, $[\alpha]_D^{24}$+23.0° ($CHCl_3$).

This correlation assigns the (pR)-configuration to (+)-4-methyl 21 as well as (+)-4-hydroxymethyl 20 derivatives, to be opposite to Schlögl's proposal.[3]

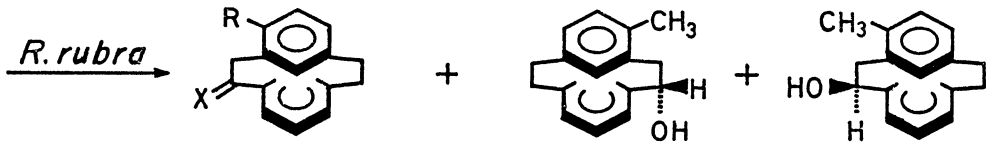


(1) X=H, Y=Br
(2) X=Br, Y=H
(3) X=H, Y=OH
(4) X=OH, Y=H

(5) X=CO_2CH_3, Y=OH
(6) X=CO_2CH_3, Y=OCH_3
(7) X=CH_2OH, Y=OCH_3
(8) X=CH_2Br, Y=OCH_3

(9) X=$S(CH_2)_3S$, Y=OCH_3
(10) X=O, Y=OCH_3
(11) X=O, Y=Br
(12) X=$S(CH_2)_3S$, Y=Br

(13) R=CH_3, X=$S(CH_2)_3S$
(14) R=CH_3, X=O
(15) R=CHO, X=H_2
(16) R=H, X=O



(-)-(pS)-(17) R=CH_3, X=O
(-)-(pS)-(18) R=H, X=O
(+)-(pS)-(19) R=CH_3, X=$S(CH_2)_3S$
(+)-(pR)-(20) R=CH_2OH, X=H_2
(+)-(pR)-(21) R=CH_3, X=H_2

(-)-(pR,1S)-(22)

(-)-(pS,1S)-(23)

References and Notes

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3) B.Kainradl, E.Langer, H.Lehner, and K.Schlögl, Justus Liebigs Ann. Chem., 766, 16(1972).
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5) K.Mislow, M.Brzechffa, H.W.Gschwend, and R.T.Puckett, J. Am. Chem. Soc., 95, 621 (1973).
6) To avoid ambiguity, the (pR),(pS)-specification for these 1-oxygenated 4-methyl-[2.2]metacyclophanes refers to their parent 1-oxygenated [2.2]metacyclophanes. R.S.Cahn, C.K.Ingold, and V.Prelog, Angew. Chem. Int. Ed., 5, 385(1966).
7) Based on the reported $[\theta]_{321}$-3.30x10^4 (isooctane)[1] for (-)-(pS,10S)-10-hydroxy-1-oxo[2.2]metacyclophane (optical purity 100%).

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