Note

Stereoselective reduction of (R)-(-)-carvone with sodium dithionite in the presence of cyclomaltoheptaose (β -cyclodextrin) and its heptakis(2,6-di-O-methyl) derivative

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Regio- and stereo-selective reduction of the double bonds in conjugated ketones with numerous reducing agents under various conditions have been studied¹. The reactions usually afford mixtures of products, the compositions of which depend on the reagent, the catalyst, the solvent, the pH of the medium, and the structure of, and steric hindrance associated with, the substrate.

In principle, the reduction of unsaturated ketones in aqueous alkaline solutions by sodium dithionite may afford a mixture of isomeric dihydroketones and saturated alcohols, depending on the experimental conditions. The reduction of unsaturated conjugated ketones in polar solvents² or under phase-transfer conditions³ results in different yields (25–90%) and selectivities. We have studied the competition between 1,4- and 1,2-reduction of the conjugated enone (R)-(-)-carvone (1) in the presence of cyclomaltoheptaose (4, β -cyclodextrin, β CD) and its heptakis(2,6-di-O-methyl) derivative (5, DM- β CD), using sodium dithionite (Na₂S₂O₄) as reducing agent in aqueous sodium hydrogen carbonate with or without benzene⁴. The spectrum of products, namely, the ketones **2a,b** and the alcohols **3a-d**, expected from the non-selective reduction of 1, is shown in the annexed formulae. For purposes of comparison, the reduction of 1 was also carried out in the absence of 4 or 5. The results are summarised in Table I.

The reduction of 1 under homogeneous conditions (Table I, entry 1) yielded a mixture of the epimers 2a and 2b (*trans,cis*-ratio 2:1) and $\sim 40\%$ of a mixture of the diastereoisomers 3a-d, as determined by g.l.c.-m.s.

Under phase-transfer conditions with trimethyltetradecylammonium bromide (6) as catalyst, 98% of a mixture of 2a and 2b was obtained with a *trans,cis*-ratio of 2:1; 3a-d were absent. Camps *et al.*⁴ obtained a *trans,cis*-ratio of 96:4 using similar experi-

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Eury	Unreacted 1	Reaction	Catalyst	Solvent	Products ^b			
		(mu) əmit			Rutio 2a/2b	æ	3d	3a + 3c
1		120	I	Н,О	2 (63)	24	10	ę
~		120	6	H,O/C,H,	2 (98)"	ſ		
E.	8.4	5	4	H,O	8.6 (83.7)	6.9	0.9	traces
4	ļ	30	4	H,O	4.6 (51.9)	32.6	13.1	2.3
5	I	120	4	H,O	3.2 (21)	56.4	17.8	3.8
6	16	360	ŝ	H,O/C,H	7.1 (81.8)	1		

Reduction^{*a*} of (*R*)-(-)-carvone (1) with sodium dithionite at 80^{*a*}

TABLEI

Na,S₂O, 9 mol; NaHCO,, 18 mol; 1, 1 mol; CD, 1.1 mol; 6, 0.3 mol. " Yields determined by g.I.c. ' trans.cis-Ratio; yield in parenthesis." Isolated yield.



mental conditions, but the catalyst was a commercial mixture of ammonium salts (Adogen) and not pure 6.

The reduction of 1 in the presence of β CD for 5 min (entry 3, Table I) gave a mixture that contained 1 (~8%), 2a,b (84%, *trans,cis*-ratio ~9:1), and 3a-d (~8%). After 30 min (entry 4), no 1 remained and the mixture of products contained 2a,b (52%, *trans,cis*-ratio 4:1) and 3a-d (48%). After 120 min (entry 5), the mixture of products contained 78% of 3a-d and 21% of 2a,b (*trans,cis*-ratio 3:1).

Entry 6 (Table I) involved the use of DM- β CD in water-benzene with the purpose of allowing both complexation and reduction to occur mainly in the organic phase, and to minimise the formation of sulfinates, a major side-reaction in water⁵. The reduction was slow and only ~22% of 1 had been reduced after 120 min. After 360 min, 16% of 1 remained and **2a,b** were the only products isolated (*trans,cis*-ratio 7:1).

From the data in Table I, it is inferred that 1 is reduced in two steps, namely $1 \rightarrow 2a, b \rightarrow 3a-d$. The products 2a and 2b were isolated and characterised, but the mixture 3a-d was only partially fractionated. However, the final mixture 3a-d contained four products each having mol. wt. 154, with analytical and spectroscopic properties in agreement with those expected. The absolute configurations at C-1 and C-2 of the two isolated alcohols 3b and 3d were assigned on the basis of the ¹H-n.m.r. data, according to the Karplus relation (see Experimental).

The first step in the reduction of 1 is well separated from the second step under the appropriate experimental conditions. The diastereoselectivity is good if the reaction is stopped at an early stage. With longer reaction times, the *trans,cis*-ratio of the initial products 2a and 2b decreases, 3b is formed from the *trans* isomer 2a, and 3d from the *cis* isomer 2b. The use of β CD and DM- β CD leads to better results than those obtained by the phase-transfer method, probably because, in the presence of β CD, the solubilisation

of 1 in water and of the reducing agent in the organic phase⁶ involves the formation of tight inclusion complexes⁷ and reflects the steric requirements for inclusion⁸.

The best selective 1,2-reduction of conjugated enones so far reported involved the use of complex Li–Cu hydrides⁹ or iron carbonyls¹⁰ with prolonged reaction times and 1,4-reduction required different and more complex systems¹. Sodium dithionite in the presence of β CD or DM- β CD is a versatile reducing system for conjugated enones, since good selectivity can be achieved by choosing the proper experimental conditions, the work-up of the products is easy, and the reagent is not expensive.

EXPERIMENTAL

¹H-N.m.r. spectra were recorded on solutions in CDCl₃ (internal Me₄Si) with a Bruker WP 200 SY instrument. G.l.c.-m.s. was performed with a Hewlett-Packard 5970 instrument, equipped with a polydimethylsiloxane column (15 m \times 0.25 mm i.d.; Alltech) at 60°. The retention times (*T*) are given in min. I.r. spectra were recorded on a Perkin-Elmer 580 B spectrophotometer.

Reduction reactions. — A typical procedure was as follows. Water or a waterbenzene mixture (100 mL) that contained NaHCO₃/Na₂S₂O₄/substrate in molar ratios 18:9:1 and the appropriate catalyst (1.1 mol for β CD and DM- β CD, 0.3 mol for 6) was heated at 80° under nitrogen and stirred vigorously. The mixture was cooled, then extracted with ether, the extract was dried (Na₂SO₄) and concentrated, and the ratios of the products in the residue were determined by g.l.c.. The epimers **2a** and **2b** and the isomers **3b** and **3d** were separated by column chromatography on silica gel, using hexane–ether (7:3) and light petroleum–ether (9:1), respectively.

The following compounds were characterized (see Table I).

(5R,2R)-(+)-5-Isopropenyl-2-methylcyclohexanone (**2a**), $[\alpha]_D$ + 18⁵ (*c* 4.2, chloroform); ν_{max}^{KBr} 3083 (w, = CH), 2970, 2935, 2861, and 1450 (m, CH), 1713 (vs, C=O), 1644 cm⁻¹ (w, C=C). N.m.r. data: δ 4.71–4.78 (m, 2 H, H-8.8), 2.38, 2.15, 1.94, 1.61, and 1.37 (5 m, 8 H, H-2,3,3,4,4,5,6,6), 1.74 (s, 3 H, Me-2), 1.03 (d, 3 H, *J* 6.4 Hz, Me-2). Mass spectrum (70 eV, *T* 9.7 min): m/z 152 (M[±]), 137 (10), 109 (30), 95 (55), 82 (37), 67 (100), 55 (35), 41 (78).

Anal. Calc. for C₁₀H₁₆O: C, 78.9; H, 10.5. Found: C, 78.7; H, 10.4.

(5R,2S)-(+)-5-Isopropenyl-2-methylcyclohexanone (**2b**), $[\alpha]_D$ + 36° (*c* 4.2, chloroform); ν_{max}^{KBr} 3089 (w, = CH), 2969, 2935, 2868, and 1456 (s, CH), 1710 (vs, C = O), 1643 cm⁻¹ (m, C = C). N.m.r. data: δ 4.83 and 4.69 (2 bs, 2 H, H-8,8), 2.58, 2.40, 1.86, and 1.61 (4 m, 8 H, H-2,3,3,4,4,5,6,6), 1.73 (~t, 3 H, Me-7), 1.09 (d, 3 H, J7.2 Hz. Me-2). Mass spectrum (70 eV, T 9.9 min): m/z 152 (M[±]), 137 (10), 109 (15), 95 (55), 82 (32), 67 (100), 55 (35), 41 (83).

Anal. Calc. for C₁₀H₁₆O: C, 78.9; H, 10.5. Found C, 78.8; H, 10.4.

(1R,2R,5R)-5-Isopropenyl-2-methylcyclohexanol (**3b**). N.m.r. data: δ 4.69 (s, 2 H, H-8,8), 3.18 (ddd, 1 H, $J_{1.6eq}$ 3.8, $J_{1.2}$ 9.3, $J_{1.6ax}$ 10.8 Hz, H-1), 1.98, 1.72, and 1.22 (3 m, 12 H, H-2,3,3,4,4,5,6,6, Me-7, and OH), 1.02 (d, 3 H, $J_{2.Me}$ 6.4 Hz, Me-2). Mass spectrum (70 eV, *T* 10.6 min): m/z 154 (M[±]), 136 (28), 121 (40), 107 (48), 93 (65), 81 (50), 79 (55), 67 (55), 55 (61), 43 (73), 41 (100).

Anal. Calc. for C₁₀H₁₈O: C, 77.9; H, 11.7. Found: C, 77.8; H, 11.6.

(1R,2S,5R)-5-Isopropenyl-2-methylcyclohexanol (**3d**). N.m.r. data: δ 4.61 (s, 2 H, H-8,8), 10.0 [ddd, 1 H, $J_{1,6ax}$ 11.3, $J_{1.6eq}$ 4.3 (or 4.8), $J_{1.2eq}$ 4.8 (or 4.3) Hz, H-1], 1.96, 1.73, 1.65, and 1.42 (4 m, 12 H, H-2,3,3,4,4,5,6,6, Me-7, and OH), 0.94 (d, 3 H, J 7.3 Hz, Me-2). Mass spectrum (70 eV, T 13.1 min): m/z 136 (M⁺ – H₂O), 121 (37), 107 (52), 93 (68), 81 (50), 77 (52), 67 (57), 55 (56), 43 (72), 41 (100).

Anal. Calc. for C₁₀H₁₈O: C, 77.9; H, 11.7, Found: C, 77.6; H, 11.5.

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