Substrate Non-enantiospecific and Product Enantioselective Reduction of Bicyclo[3.2.0]hept-2-en-6-one using Yeast

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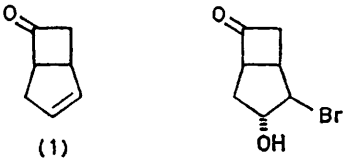
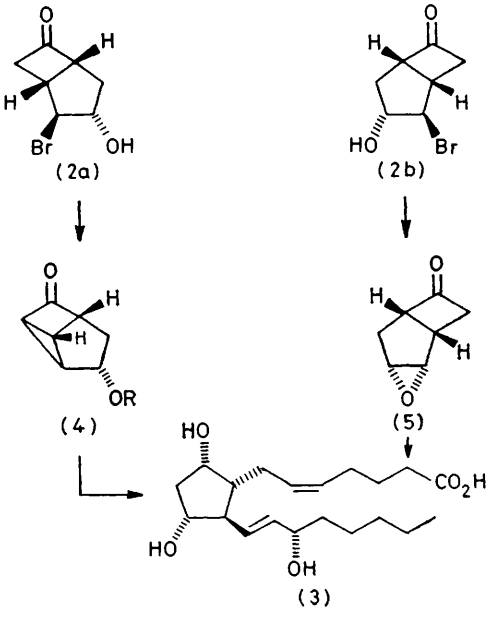
Summary The enantiomeric bromohydrins (**2a**) and (**2b**) have been obtained from (±)-bicyclo[3.2.0]hept-2-en-6-one *via* a yeast reduction.

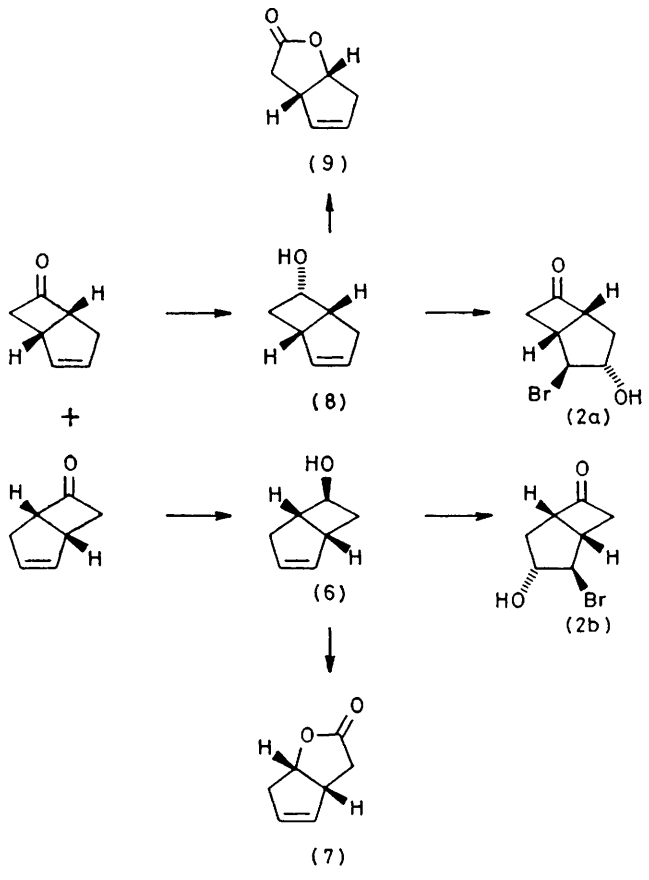
WE have previously reported[1,2] two syntheses of (±)-prostaglandins which started from (±)-bicyclo[3.2.0]-hept-2-en-6-one (**1**) and proceeded *via* the corresponding (±)-bromohydrin (**2**).



In order to accomplish stereospecific syntheses of, for instance, prostaglandin $F_{2\alpha}$ (**3**) using these routes it was necessary to obtain the enantiomeric bromohydrins (**2a**) and (**2b**). The enantiomer (**2a**) could then be converted into natural $PGF_{2\alpha}$ *via* the tricyclic ketone (**4**)[1] whereas the enantiomer (**2b**) would also yield natural $PGF_{2\alpha}$ but *via* the epoxide (**5**).[2]



In a typical experiment the reduction of bicyclo[3.2.0]-hept-2-en-6-one (30 g) was carried out using actively fermenting bakers' yeast in water containing riboflavin, commercial yeast nutrient, and glucose. The mixture



was stirred at 23 °C and additional glucose was added at intervals to maintain a steady fermentation. Steam distillation and ether extraction of the distillate yielded a mixture containing unchanged ketone (8·8 g) and two alcohols (16·8 g, 55%) which were separated by column chromatography. The more polar alcohol, $[\alpha]_D^{20}$ −91° (5·3 g), was identical (n.m.r., i.r., and t.l.c.) with the minor product obtained by sodium borohydride reduction of the ketone (**1**)[3] and was assigned an *exo*-hydroxy-group. This assignment was supported by the small shift of the signal due to the H–4 *endo*-proton when the ^{1}H n.m.r. spectrum was measured in the presence of tris(3-trifluoroacetyl-α-camphorato)europium(III).[4] No estimation of the optical purity was possible on the basis of the latter experiment. The less polar alcohol $[\alpha]_D^{23}$ +61° (11·5 g), was identical with the major product obtained by sodium borohydride reduction of the ketone (**1**)[3] and was assigned an *endo*-hydroxy-group. The very large downfield shift of the signal due to the H–4 *endo*-proton when the ^{1}H n.m.r. spectrum was determined in the presence of the chiral shift reagent described above provided additional proof of structure. The optical purity was estimated to be *ca.* 90%. The expected[5] *S*-configuration of the alcohols at C-6 was proven by Jones oxidation to the corresponding ketones and subsequent Baeyer–Villiger oxidation using aqueous hydrogen peroxide in acetic acid. In this way the *exo*-alcohol (**6**) afforded the known lactone (**7**) as white needles, m.p. 44 °C, $[\alpha]_D^{19\cdot5}$ −110° (lit.,[6] m.p. 46 °C, $[\alpha]_D^{20}$ −106°) after two crystallisations from ether–petrol. The *endo*-alcohol (**8**) gave the lactone (**9**), m.p. 44 °C, $[\alpha]_D^{20}$ +110°.

The required bromohydrins (**2a**) and (**2b**) were obtained in *ca.* 50% yield by treatment of the corresponding alcohols (**8**) and (**6**) respectively with *N*-bromosuccinimide in aqueous acetone containing a few drops of acetic acid for 24 h at ambient temperature. G.l.c. analysis of the L-menthol carbonate derivatives of the crude bromohydrins showed that the optical purities of (**2a**) and (**2b**), and by inference the alcohols (**8**) and (**6**), were 88 and 84% respectively.

One crystallisation gave (**2a**) as a white crystalline solid, m.p. 87—89 °C, $[\alpha]_D^{20}$ −60° (100% optically pure by g.l.c.). Similarly (**2b**) was obtained as a white crystalline solid, m.p. 89—90 °C, $[\alpha]_D^{20\cdot5}$ +63° (98% optically pure by g.l.c.).

These results represent one of the few examples of the reduction of a cyclic ketone using yeast and the only reported reduction of a cyclobutanone. In addition whereas previous examples[7] were highly substrate-enantioselective[8] we have obtained good chemical yields of alcohols from both enantiomeric ketones in excellent optical yields. We are presently using this methodology to complete the enantiospecific syntheses of natural prostaglandins and other naturally occurring compounds and analogues.

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[1] M. J. Dimsdale, R. F. Newton, D. K. Rainey, C. F. Webb, T. V. Lee, and S. M. Roberts, *J.C.S. Chem. Comm.*, 1977, 716.
[2] R. F. Newton, C. C. Howard, D. P. Reynolds, A. H. Wadsworth, N. M. Crossland, and S. M. Roberts, *J.C.S. Chem. Comm.*, 1978, 662.
[3] J. A. Berson and J. W. Patton, *J. Amer. Chem. Soc.*, 1962, **84**, 3406.
[4] M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, *J. Amer. Chem. Soc.*, 1974, **96**, 1038.
[5] K. Kieslich, 'Microbial Transformations of Chemical Compounds Excluding Steroids and Non-Cyclic Structures,' G. Thieme, Stuttgart, 1976.
[6] J. J. Partridge, N. K. Chedha, and M. R. Uskokovic, *J. Amer. Chem. Soc.*, 1973, **95**, 7171.
[7] R. L. Crumbie, D. M. Ridley, and G. W. Simpson, *J.C.S. Chem. Comm.*, 1977, 315.
[8] For an explanation of this terminology see J. B. Jones, C. J. Sih, and D. Perlman, 'Applications of Biochemical Systems in Organic Chemistry,' Part 1, Wiley–Interscience, New York, 1976, p. 73.