Synthetic Route to 8-Substituted Camphor Derivatives

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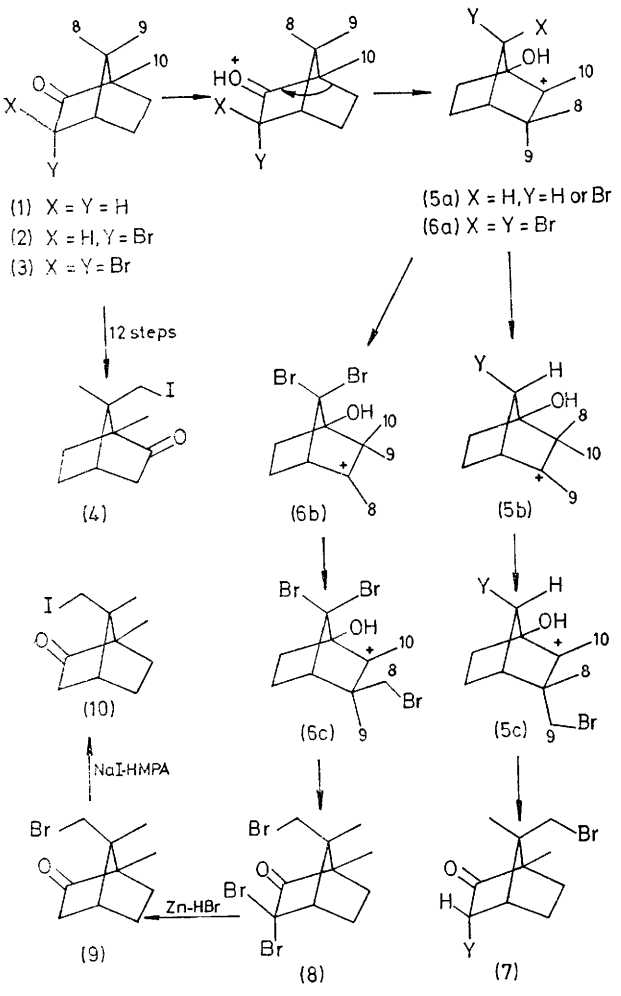
Summary Bromination of 3,3-dibromocamphor followed by selective debromination provides a new stereospecific route to 8-bromocamphor.

THE importance of 8-substituted camphor derivatives as intermediates in organic synthesis[1] and as mechanistic probes in rearrangement studies[2] has been widely recognised. However, no simple synthetic route to these compounds exists. The well-known bromination and sulphonation reactions on camphor provide only 9- and 10-substituted compounds[1a,2a] and indirect methods have been necessary to achieve synthetic entry into the 8-substituted series. A combination of a reaction sequence devised by Corey *et al.*[1a] and some appropriate transformations reported by Rodig *et al.*[1c] enabled us recently to obtain (−)-8-iodocamphor (**4**) in 12 steps from (+)-camphor (**1**).[1b] Attempts to shorten this reaction sequence have failed[3a,b] and our own efforts to take advantage of the proximate relationship between the C-8 Me and C-2 OH group in isoborneol were also unsuccessful.[3a,c]

The ease of 9-bromination of camphor and the absence of 8-bromination can be explained in terms of the accepted



mechanism for this reaction since 9-bromination involves *exo*-methyl migration in the bicyclic intermediate, (**5a**) → (**5c**), while 8-bromination may require a rare *endo*-methyl migration, (**6a**) → (**6c**).[4] Thus, we considered the possibility of reversing this preference for *exo*- over *endo*-methyl migration by placing a bulky group in the 7-*syn* position of the bicyclic intermediate, *e.g.* (**6a**). This required the use of a 3-*exo*-substituted camphor as starting material and since the group had to be capable of subsequent removal in the event of success we synthesised 3,3-dibromocamphor (**3**)† from commercially available (+)-3-bromocamphor (**2**) in 95% yield and subjected it to the usual bromination conditions (Br_2–$ClSO_3H$). The crude reaction product (**8**) was treated with Zn–HBr and provided (+)-8-bromocamphor (**9**); m.p. 83—85° {$[\alpha]_D$ +76·7° (*c* 4·08, 95% EtOH), $[\alpha]_D$ +59° (*c* 1·42, $CHCl_3$), ν_{max} (CCl_4) 1740 cm^{-1}, τ(CCl_4) 9·09 (3H, s), 8·85 (3H, s), and 6·87 (2H, s)} in 77% overall yield. Although the physical constants of our reaction product differed from those previously reported[1a] for 8-bromocamphor they are in complete agreement with values recently obtained by Meyer and his co-workers.‡ Moreover, our structural assignment was confirmed by conversion of (**9**) into (+)-8-iodocamphor (**10**)§ and by *X*-ray crystallographic analysis.[5]

A solution to the long-standing problem of direct 8-substitution of camphor has therefore been found and the implication of this result in terms of our general synthetic route to sesquiterpenes[6] will be described in a future report. The mechanism of our 8-halogenation reaction is unknown: as an alternative to the unusual *endo*-methyl migration considered above one could envisage a rearrangement mechanism involving 2,6-hydride shifts and more favourable 2,3-*exo*-methyl shifts.[4a]

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† Treatment of 3-*endo*-bromocamphor (**2**) with Br_2–$ClSO_3H$ provides (+)-3,9-dibromocamphor (**7**; X = H, Y = Br) with retention of configuration.

‡ We thank Prof. Walter Meyer (University of Arkansas) for providing us with the spectral data and physical constants of a sample of (−)-8-bromocamphor prepared by the twelve-step sequence previously used for the synthesis of optically active 8-substituted camphor derivatives.[1]

§ Spectroscopic data in complete agreement (except for sign of rotation) with (−)-8-iodocamphor (**4**) synthesised previously.[1b]

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