Use of Camphor in Steroid Synthesis: a New Approach to Optically Active *trans*-Hydrindane Derivatives

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Ring cleavage of 9,10-dibromocamphor leads to the construction of an optically active hydrindenone derivative which has potential as an intermediate in steroid synthesis.

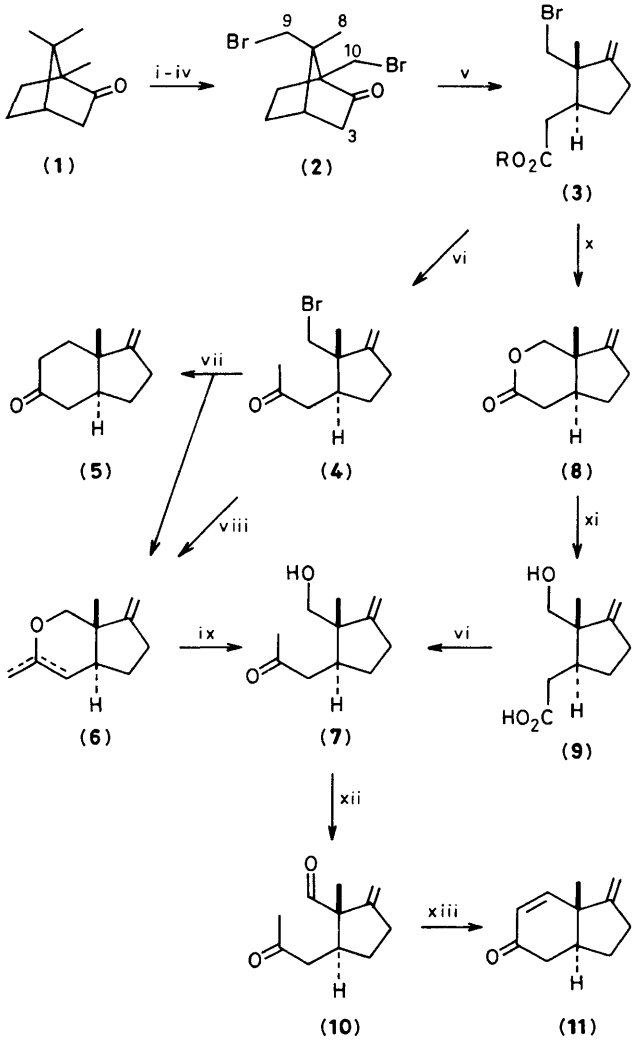
As part of our general investigations on the the use of camphor as a chiral starting material in terpenoid synthesis[1] we have recently investigated various synthetic routes from (+)- or (−)-camphor (**1**) to optically active steroid systems. The importance of *trans*, angularly-methylated hydrindane derivatives as intermediates in steroid synthesis[2] prompted us to select compounds of this type as one of our initial synthetic targets. For this purpose we developed[1] a convenient procedure for the preparation of optically active 9,10-dibromocamphor (**2**)† and in this report we describe one way‡ in which this compound can be converted into a *trans*-hydrindenone derivative (**11**) which has considerable potential as a synthetic precursor of estrogens.

Thus we have recently discovered that treatment of 9,10-dibromocamphor (**2**) with aqueous KOH–tetrahydrofuran (THF) or NaOMe–MeOH for 4 h at room temperature results in efficient conversion into unsaturated bromoacid (**3**; R = H) or methyl ester (**3**; R = Me) in 90—95% yield (Scheme 1). The spectroscopic (i.r., n.m.r.) properties of these compounds clearly established that the double bond was in the synthetically useful, less stable[3] exocyclic position and this was confirmed by oxidative cleavage (i, O_3, MeOH; ii, Me_2S)[4] to the corresponding cyclopentanone derivatives. 3,9,10-Tribromocamphor[1] and 8,10-dibromocamphor[1] also undergo facile ring cleavage with base at room temperature to provide respectively the α-bromo derivatives and *cis*-isomers of (**3**; R = H and Me) and the use of these compounds in terpenoid synthesis is being investigated. The C(1)–C(2) cleavage processes described above are examples of a reaction which is generally characteristic of blocked β-bromoketones.[5–8] However the special feature of reactions involving dibromocamphor derivatives is the ease, efficiency, and regioselectivity with which they occur. By contrast ring cleavage of 10-bromocamphor requires refluxing KOH–EtOH and provides an endocyclic cyclopentene carboxylic acid (α-campholenic acid).[5,6]

Preparation of bromoketone (**4**) was readily accomplished in *ca.* 70% yield by sequential treatment of bromoacid (**3**; R = H) with methyl-lithium–THF and chlorotrimethylsilane.[9] Subsequent cyclization of bromoketone (**4**) with lithium di-isopropylamide (LDA) in THF–hexamethylphosphoramide (HMPA)[10,11] resulted in the formation of two compounds in

† Our published yield (*ca.* 60%) for the conversion of 3,9,10-tribromocamphor into 9,10-dibromocamphor has been increased to 95% by conducting the selective debromination with Zn–HOAc at 5 °C for 30 min.

‡ Other synthetic routes involving the oxime of 3-*endo*-methyl-9,10-dibromocamphor and alkyl derivatives of lactone (**8**) will be described in future reports.



Scheme 1. i, Br_2–HOAc; ii, Br_2–$ClSO_3H$, 4 h; iii, Br_2–$ClSO_3H$, 5 days; iv, Zn–HOAc, 5 °C, 0.5 h; v, KOH–H_2O–THF, 20 °C, vi, MeLi–THF; Me_3SiCl; 1 M HCl, 10 min; vii, LDA–THF, −60 °C; HMPA, −60 to 80 °C, 1 h; viii, $KOBu^t$–$HOBu^t$, 70 °C, 1 h; ix, 1 M HCl–Et_2O, 20 °C, 45 min; x, KOH–Me_2SO : H_2O (99 : 1)–Ag_2O, 65 °C, 3 h; xi, 0.5 M KOH–THF, 20 °C, 30 min; xii, PDC–CH_2Cl_2, 20 °C, 24 h; xiii, 2 M KOH–MeOH, 80 °C, 1 h.

approximately equal amounts. One of the compounds was identified by spectroscopic evidence (i.r., n.m.r., high resolution mass) as the *trans*-hydrindanone derivative (**5**) while the other, more volatile component was assigned the enol ether structure (**6**) on the basis of its subsequent acid hydrolysis to hydroxyketone (**7**). A molecular model of the kinetic enolate derived from bromoketone (**4**) indicates that there is some strain in achieving the proper trajectory required for 6-(enolendo)-*exo*-tet cyclization[10] and therefore, 6-*exo*-tet cyclization (O-alkylation) becomes a viable alternative.[10–12] When bromoketone (**4**) was treated with potassium t-butoxide–t-butanol 6-*exo*-tet cyclisation of the thermodynamic enolate mixture provided, in low yield (*ca.* 30%), an enol ether which could also be hydrolysed to hydroxyketone (**7**). The last compound was prepared more efficiently (50—60% overall yield) by converting bromoacid (**3**; R = H) into lactone (**8**) (Scheme 1). Hydrolysis of (**8**) yielded hydroxyacid (**9**) which, on treatment with methyl-lithium and chlorotrimethylsilane,[11] provided hydroxyketone (**7**). Oxidation of (**7**) with pyridinium dichromate[13] (PDC) followed by intramolecular aldol condensation of the intermediate keto-aldehyde (**10**) resulted in the formation of the optically active§ *trans*-hydrindenone derivative (**11**)¶ in 55—65% yield.

It is expected that regiospecific and stereoselective alkylation of hydrindenone (**11**) at the C(4) position will result in the completion of a simple enantiospecific route from camphor to common steroid systems.

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§ Since (+)-camphor and (−)-camphor are both readily available, either enantiomer of the key intermediate (**11**) can be prepared. The sequence shown in Scheme 1 starts with (−)-camphor (**1**) and produces the (+)-enantiomer of (**11**).

¶ Satisfactory spectroscopic [i.r., n.m.r. (400 MHz), high resolution mass] data have been obtained for compounds (**3**)—(**5**), (**7**)—(**11**).