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AN ENANTIOSPECIFIC SYNTHESIS OF ESTRONE

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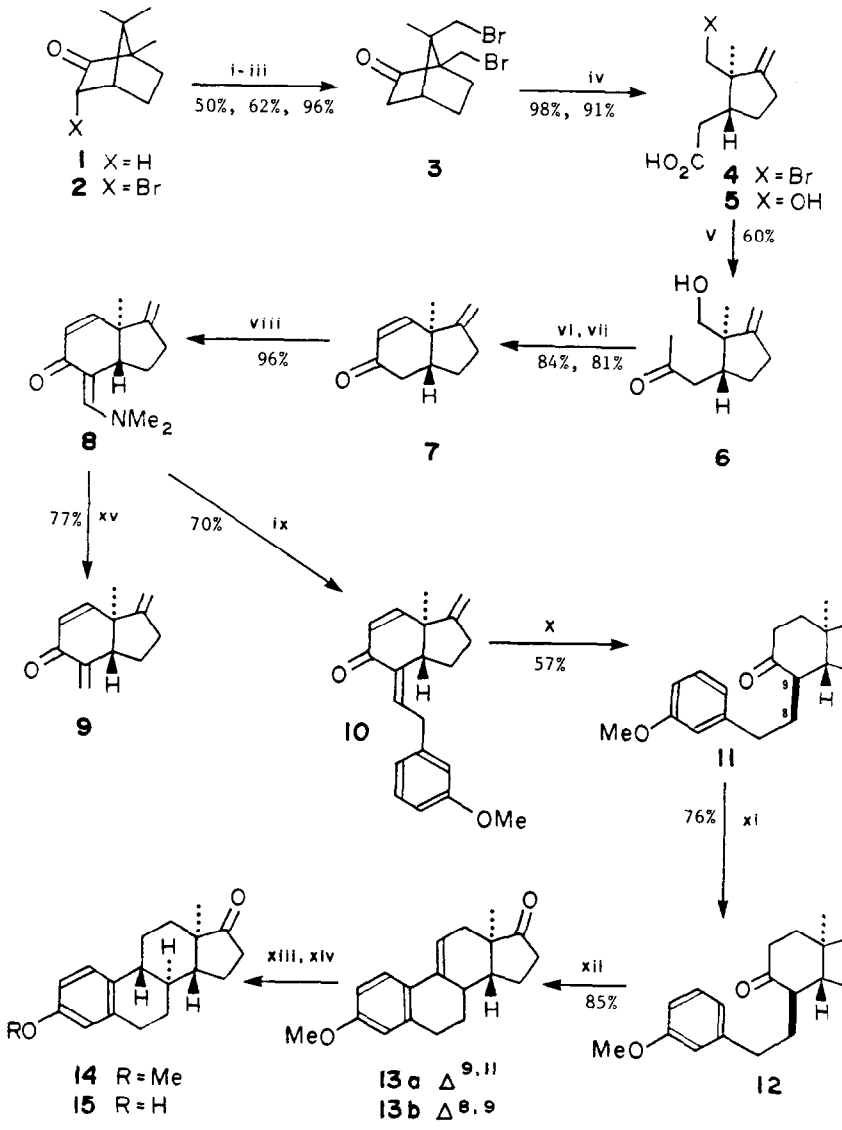
Abstract: Efficient ring cleavage of 9,10-dibromocamphor (3) provides a monocyclic hydroxyacid (5) which can serve as an intermediate in a new enantiospecific synthesis of estrone.

As part of our general investigations[1,2] on the use of (+)-camphor (1) or (-)- camphor as chiral starting materials in terpenoid synthesis we have recently evaluated various synthetic routes to optically active steroid systems. For this purpose we developed[2] a convenient synthesis of (+)-9,10-dibromocamphor (3) from (+)-3-bromocamphor (2) and subsequently discovered[3] that this compound underwent facile, efficient ring cleavage to provide bromoacid (4). More recent investigations have shown that simple amendment of the ring cleavage conditions (cf. Scheme 1) results in the direct conversion of 9,10-dibromocamphor to hydroxy-acid (5) in 90% yield. The subsequent conversion of this acid (5) to hydroxyketone (6) and hydrindenone (7) (Scheme 1) was described previously[3] and this report demonstrates that the latter compound can serve as an intermediate in the overall conversion of (+)-camphor (1; R=H) to (-)-estrone (15).

Our initial attempt to construct the tetracyclic estrone framework from the bicyclic hydrindenone (7) by alkylation at the C(4) position with 2-(m-methoxyphenyl)ethyl iodide, was unsatisfactory. This difficulty has been encountered previously[4-6] in synthetic approaches to estrone and is presumably due to the tendency of this alkyl iodide to undergo elimination rather than substitution. We decided, therefore, to adopt an approach which involved regiospecific conjugate addition of a m-methoxybenzyl group[7] to the cross-conjugated trienone (9). The latter compound was synthesized by treating hydrindenone (7) with Brederick's reagent [$(Me_2N)_2CHOBu^t$][8-12] followed by reduction of the intermediate vinylogous amide (8) with Dibal[9].

In spite of reasonable analogy[7], however, the addition of m-methoxybenzylmagnesium chloride to trienone (9) in the presence of copper(I) iodide was inefficient and a mixture of 1,2- and 1,4- addition products was obtained. However, when the vinylogous amide (8) was treated with this Grignard reagent the tricyclic cross conjugated ketone (10) was obtained in ~70% yield.[13] Subsequent reduction of (10)[14] with $Li/NH_3(l)$/ ether followed by ozonolysis (O_3/CH_2Cl_2; Me_2S) provided diketone (12) which was converted, by cyclodehydration (c. HCl/ HOAc/0°C)[15,16] and reduction (H_2/Pd)[17], to (-)-estrone methyl ether (14) [m.p. 168-170°C, lit.[7b] mp 164-167°C; $[\alpha]_D$ -149.2° (c 0.126, dioxane), lit.[18a] $[\alpha]_D$ +153.98° (c, 1.0, dioxane); i.r. and n.m.r. (400 MHz) identical to authentic (+)-estrone methyl ether. Subsequent demethylation (BBr_3)[20] provided (-)-estrone (15) with i.r., mass, and n.m.r. (400 MHz) spectra identical to those of authentic (+)-estrone[21].

The simple and comparatively efficient sequence of reactions outlined in Scheme 1 provides a further illustration of the versatility of camphor as a chiral starting material in natural product synthesis[22]. To



i $Br_2/ClSO_3H/1$ h ii $Br_2/ClSO_3H/5$ days iii $Zn/HOAc/Et_2O/0°$ iv $KOH/DMSO/H_2O/24$ h v MeLi/THF; Me_3SiCl; 1N HCl vi $PDC/CH_2Cl_2/20°/24$ h vii 2N NaOH/MeOH/0°/5 min; $MsCl/Et_3N$/DMAP; DBU viii $(Me_2N)_2CHOBut$/heat ix $m\text{-}CH_3OC_6H_4CH_2MgCl/Et_2O$ x $Li/NH_3/Et_2O$ xi O_3/CH_2Cl_2; Me_2S xii HCl/HOAc xiii H_2/Pd xiv BBr_3/CH_2Cl_2 xv DIBAL/THF

Scheme 1

obtain natural (+)-estrone would of course require the use of (-)-3-bromocamphor in the reaction sequence. This can be obtained inexpensively by oxidizing (-)-borneol to (-)-camphor[23] followed by bromination in acetic acid[24]. The commercial availability of (+)-3-bromocamphor (2), however, prompted us to conduct our preliminary investigations in the ent-series[25].

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