Enantiospecific Synthetic Approach to C,D-Ring System of Steroids with Functionalized Side-chains

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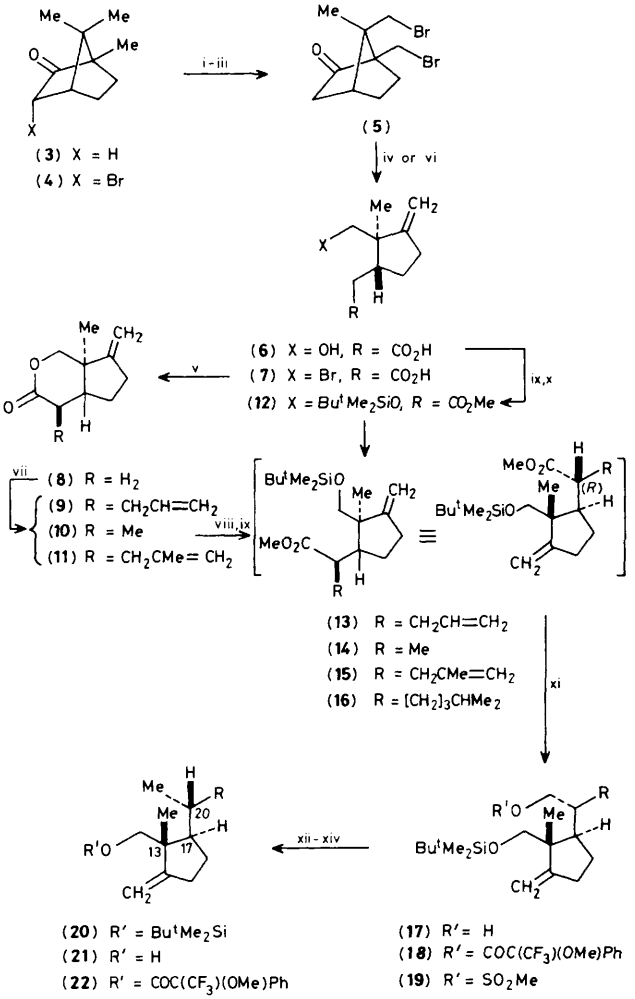
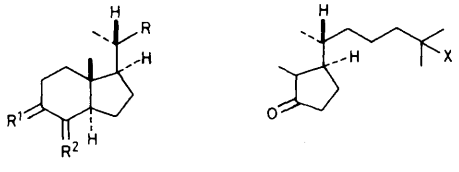
Diastereoselective alkylation of a chiral ester derived from camphor provides potentially useful intermediates for the synthesis of steroids with functionalized side-chains.

The important biological activity of steroids containing functionalized side-chains (*e.g.* clinically important vitamin D_3 metabolites such as 1,25-dihydroxycholecalciferol, plant growth-promoting steroids, insect moulting hormones, anti-tumour steroids, marine steroids) has stimulated considerable interest in their total synthesis.[1] Hydrindanone derivatives [*cf.* (**1a,b**)] or chiral cyclopentanoid intermediates [*cf.* (**2a,b**)] are recognized as important intermediates in the synthesis of steroids with functionalized side-chains and several elegant routes to intermediates of this type have recently been developed.[1] Recent reports by Finini,[2] Takano,[3] and their respective co-workers, describing the synthesis of chiral monocyclic intermediates (**2a,b**) prompt us to report our preliminary results in this area.

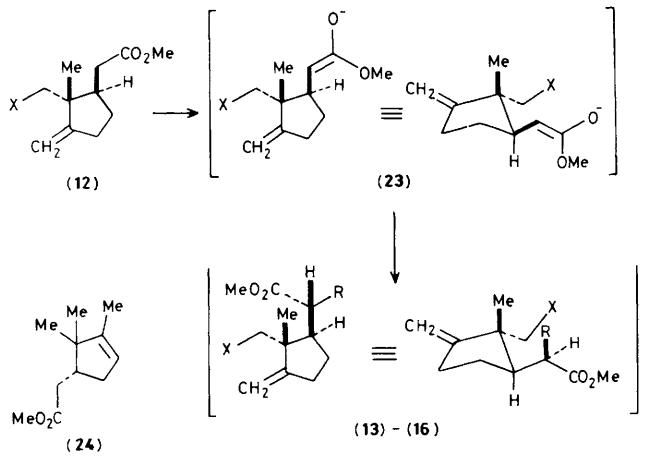
As part of our investigations on the use of camphor as a chiral starting material in natural product synthesis[4] we have recently shown[4d] that (+)-9,10-dibromocamphor (**5**)[4b] can be converted, in high yield into hydroxyacid (**6**), bromoacid (**7**), or lactone (**8**) (Scheme 1) and that these compounds [or their enantiomers derived from (−)-camphor] have considerable potential as chiral synthons in natural product synthesis.[4] Our recent investigations in this area have now established that alkylation of lactone (**8**) with allyl bromide, methyl iodide, or 2-methylallyl iodide provides alkylated lactones (**9**)—(**11**) (Scheme 1) in excellent yield (>80%). The 400 MHz n.m.r. spectra and capillary g.l.c. characteristics of (**9**)—(**11**) indicated that the alkylation processes had occurred with complete diastereoselectivity and this was supported by the following transformations. Methanolysis of (**9**)—(**11**) followed by protection of the hydroxy group as the t-butyldimethylsilyl ether, provided monocyclic esters (**13**)—(**16**). Reduction of ester (**13**) followed by acylation of alcohol (**17**; R = $CH_2CH{=}CH_2$) with (+)-α-methoxy-α-trifluoromethylphenylacetyl (MTPA) chloride[5] provided the MTPA ester (**18**; R = $CH_2CH{=}CH_2$) whose stereochemical purity was established by the presence of single resonances for the CMe and CCF_3 groups in the ^1H n.m.r. (400 MHz) and ^{19}F n.m.r. (254 MHz) spectra respectively and also by the presence of single resonances in the proton decoupled ^{13}C n.m.r. spectrum. Mesylation of monocyclic alcohol (**17**; R = $CH_2CH{=}CH_2$), followed by hydrogenolysis ($LiBHEt_3$) and removal of the silyl protective group, yielded a chiral synthon (**21**; R = $CH_2CH{=}CH_2$) whose stereochemical purity was again established by capillary g.l.c. and the n.m.r. spectra of the corresponding MTPA ester (**22**; R = $CH_2CH{=}CH_2$). The stereochemical purity of (**10**) and (**11**) (Scheme 1) was established in similar fashion and, in the case of (**10**), independently confirmed by *X*-ray crystallographic analysis.[6]



Scheme 1. *Reagents and conditions:* i, Br_2, $ClSO_3H$, 1 h; ii, Br_2, $ClSO_3H$, 5 days, iii, Zn, HOAc–Et_2O, 0 °C; iv, KOH–dimethyl sulphoxide (DMSO), H_2O [affords (**7**)]; v, KOH–HMSO : H_2O (99 : 1), 65 °C, 12 h; vi, KOH–DMSO : H_2O (5 : 1), 65 °C, 24 h [affords (**6**)]; vii, lithium di-isopropylamide–tetrahydrofuran (THF), −78 °C; alkyl halide; viii, MeOH–H^+; ix, Bu^tMe_2SiCl, 4-*N*,*N*-dimethylaminopyridine, CH_2Cl_2; x, CH_2N_2–Et_2O; xi, $LiAlH_4$, THF; xii, $MeSO_2Cl \cdot C_5H_5N$; xiii, $LiBHEt_3$, THF; xiv, Bu_4NF, THF.



Stimulated by the recently reported[7] stereoselective alkylation of steroidal esters we subsequently found that monocyclic esters (**13**)—(**16**) could be prepared by diastereoselective



X = Bu^{t}Me$_2$SiO

Scheme 2

alkylation of the silyloxy ester (**12**) derived from hydroxyacid (**6**) (Scheme 1). The 95—100% stereoselectivity of these alkylation reactions was established by comparing the capillary g.l.c. characteristics, n.m.r. spectroscopic properties, and specific rotations of alkylated esters with those recorded for the same compound derived, as described above, by alkylation of lactone (**8**). Alkylation of ester (**12**) with isohexyl iodide provided ester (**16**) and its diastereoisomer in a ratio of 95 : 5. However subsequent reduction and chromatography provided pure primary alcohol (**17**; R = C_6H_{13}) whose stereochemical purity was supported by capillary g.l.c. characteristics and the presence of single resonances in the ^{13}C n.m.r. spectrum. Subsequent hydrogenolysis of the corresponding methanesulphonate (**19**; R = C_6H_{13}) with LiBHEt$_3$ followed by removal of the silyl protective group provided the monocyclic chiral synthon (**21**; R = C_6H_{13}) in ~ 50% overall yield from 9,10-dibromocamphor (**5**).

The diastereoselectivity of alkylation of lactone (**8**) can be explained by the avoidance of 1,3-diaxial repulsions present in the alternative diastereoisomer. On the other hand, the diastereoselective alkylation of ester (**12**) may be explained (Scheme 2) by postulating electrophilic attack on the less-hindered face of the preferred conformation (**23**) of the ester enolate ion. A similar explanation can be invoked to explain the diastereoselective alkylation of steroidal esters[7] and also the diastereoselective methylation of methyl α-campholenate (**24**).[8] In addition a recent report by Fleming and Lewis[9] has shown that acyclic enolates adjacent to chiral centres can also be methylated with a considerable degree of diastereoselectivity. Our results and those of other research groups[7—10] are therefore consistent with the rule proposed by Houk, Barton, and their co-workers[11] to predict the diastereoselectivity of reaction between electrophiles and double bonds flanked by a chiral centre.

In any event, the diastereoselective alkylation of lactone (**8**) or ester (**12**) coupled with their easy preparation from (+)-9,10-dibromocamphor (**5**) provides a convenient means of preparing chiral compounds which have considerable potential as intermediates in the enantiospecific† synthesis of steroids with structurally diverse side-chains. The versatility of this approach is associated with the fact that the nature of the steroid side chain can be predetermined by the choice of an appropriate electrophilic reagent. Although only alkyl halides have been used as electrophiles there is ample analogy to support the assumption that carbonyl compounds would also react with enolate (**23**) in a stereoselective fashion.

The chiral monocyclic alcohol (**21**; R = $[CH_2]_3CHMe_2$), having the correct absolute configuration at C(13), C(17), and C(20) (steroid numbering), represents ring D and the side-chain of a steroid framework and we are currently examining various synthetic sequences to convert this compound (and derivatives with different side-chains) into bicyclic intermediates [*cf.* (**1a,b**)] with the correct absolute chirality at C(14).

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† The enantiomeric series of compounds could be obtained by using the enantiomer of (**8**) or (**12**) which, of course, would be derived from commercially available (−)-camphor or (−)-borneol.

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