Enantiospecific Route to C,D Ring System of Steroids

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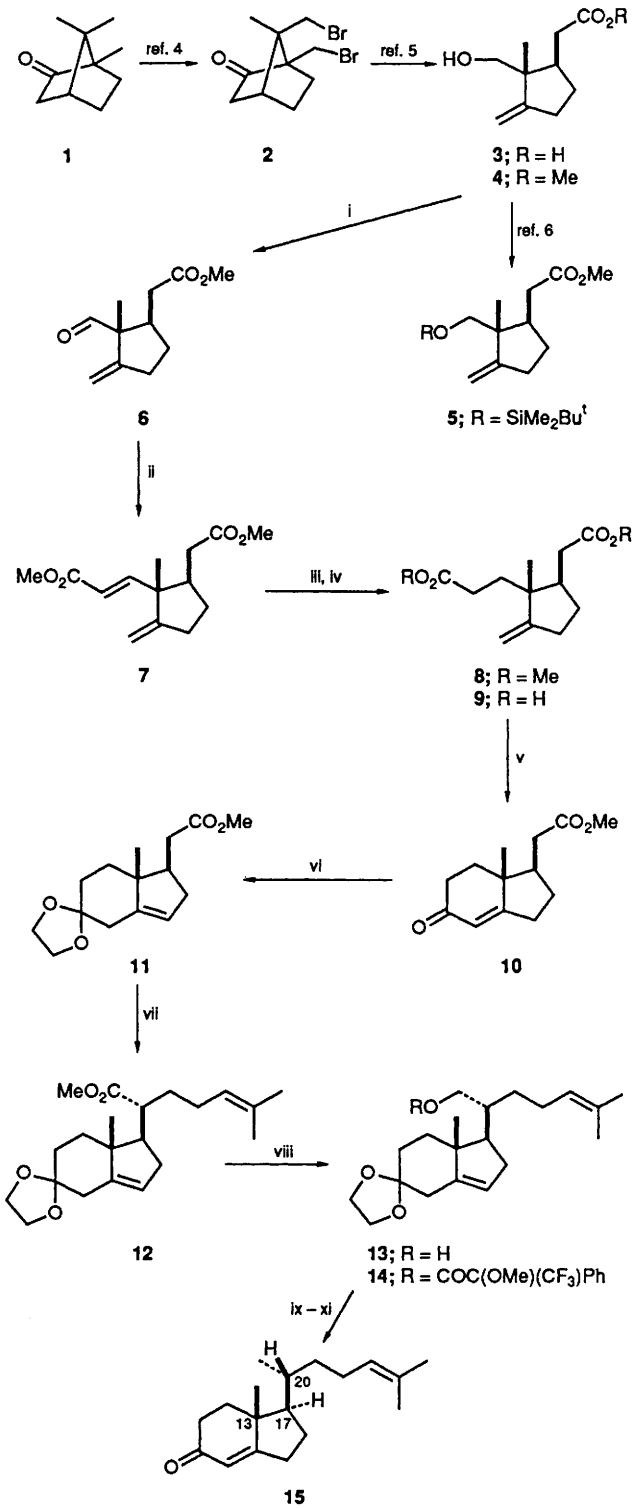
A simple versatile enantiospecific synthetic route from camphor to the C,D ring system and side-chain unit of steroids has been developed.

The resurgence of interest in steroid synthesis[1] has been characterised by the development of imaginative new ways of synthesising hydrindanone and hydrindenone derivatives which represent the C,D ring system and side-chain unit of the steroids; for recent examples see refs. 2 and 3.

Our recent efforts in this area (Scheme 1) are an extension of our previous investigations which showed that (+)-9,10-dibromocamphor **2**[4,5] undergoes efficient ring cleavage to provide hydroxy acid **3**[5] and that the derived ester **5** undergoes stereoselective alkylation.[6] In our investigations hydroxy ester **4** was converted to unsaturated diester **7** which was then reduced (Mg–MeOH)[7] and hydrolysed to provide the monocyclic diacid **9**.

Cyclisation of **9** with trifluoroacetic anhydride[8] followed by methanol work-up produced hydrindenone ester **10** directly in *ca.* 80% yield. By analogy with acyclic,[9] monocyclic,[6,10,11] bicyclic[2] and steroidal esters[12,13] in which the ester group is flanked by a chiral centre containing hydrogen, we expected that alkylation of ketal ester **11** would be stereoselective. In the event, alkylation of **11** with 5-iodo-2-methylpent-2-ene followed by reduction with $LiAlH_4$ provided hydroxy ketal **13** in ~85% yield. The optical purity of this compound was determined to be *ca.* 100% by ^1H NMR (400 MHz) and ^{19}F NMR(254 MHz) spectra of the corresponding Mosher ester **14**. The relative configuration of the C(20) position in hydroxy ketal **13** was confirmed by X-ray crystallographic analysis.[14] Finally, conversion of hydroxy ketal **13** to the corresponding tosylate followed by reduction with lithium triethylborohydride[15] and subsequent acid hydrolysis, yielded the required hydrindenone **15** in *ca.* 85% yield.

The synthetic route described above can provide intermediates (*cf.* **15**) with the correct absolute configuration at



Scheme 1. *Reagents and conditions*: i, $(COCl)_2$, Me_2SO, CH_2Cl_2, −60 °C; Et_3N, −60 °C → 25 °C (95%); ii, NaH, tetrahydrofuran (THF), $(MeO)_2P(O)CH_2CO_2Me$, (86%); iii, Mg, MeOH (98%); iv, KOH, MeOH, H_2O (77%); v, $(CF_3CO_2)O$; CH_2Cl_2; *p*-$MeC_6H_4SO_3H$, MeOH (82%); vi, pyridinium toluene-*p*-sulphonate, $HOCH_2CH_2OH$, C_6H_6 (75%); vii, $LiPr^i_2N$, THF, −78 °C; $Me_2C{=}CHCH_2CH_2I$, THF, −78 °C → 25 °C (95%) viii, $LiAlH_4$, THF (87%); ix, $PhC(OMe)(CF_3)COCl$, C_5H_5N, CH_2Cl_2 (80%); x, $MeSO_2Cl$, 4-dimethylaminopyridine, Et_3N, CH_2Cl_2; $LiBHEt_3$, THF, 0 °C (84%); xi, HCl, H_2O, acetone, reflux (91%).

C(13), C(17) and C(20)† (steroid numbering) and in which the nature of the steroid side-chain unit is predetermined by the choice of an appropriate electrophilic reagent in the alkylation of ester **11**. In addition, the subsequent annulation of **15** to provide tetracyclic steroid structures should be relatively straightforward using literature methods.[16]

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† Alternatively the 20(*S*) configuration could be obtained by methylation of ketal ester **11** followed by homologation of the ester group (*cf.* ref. 13).