Stereoselective Synthesis of (*cis*-Hydrindane) Models for C-18 Radical Reactivity in Steroid C/D Rings

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The keto-acid **5** undergoes stereospecific Peterson reaction to afford the (*Z*)-α-unsaturated ester-acid **6**, and the derived phenyl selenoester cyclises also stereospecifically to the *cis*-hydrindanone **8** *via* a 5-*exo* acyl radical process: the ketone **8** is transformed through enone **11** into the diene-acids **2** and **3**, models for study of C-18 radical reactions in steroid C/D systems.

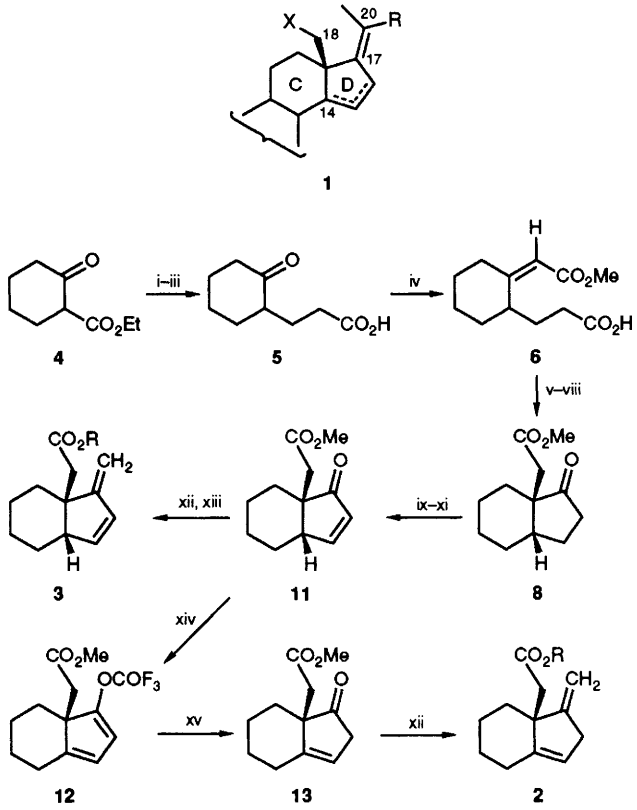
In decades of extensive investigation, many facets of the chemistry and synthesis of steroids and related model systems have been explored. However, work focused on the angular methyl groups is relatively limited, with few modes of access to functionalised alkyls at the A/B or C/D junctions, either in natural steroid transformations or in synthetic relatives. In connection with studies of biosynthesis and biomimetic reactions involving the C/D rings of plant steroids of the withanolide[1] and nicandrenoid[2] groups, we required compounds of type **1**, in which function X could be used to generate C-18 carbon radicals or carbocations. For our immediate purpose, double bonds at C-17(20) and either C-14 or C-15 were needed, while the C/D fusion could be *cis* or *trans*. In this communication we describe the syntheses of two model systems, the hydrindenes **2** and **3**, using an acyl radical cyclization strategy.

2-Ethoxycarbonylcyclohexanone **4** was reacted with ethyl 3-bromopropanoate in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol, and the product diester was hydrolysed and decarboxylated in aq. hydrochloric acid to provide the keto-acid **5** (61%). The latter was olefinated using a Peterson reaction with 3 equiv. of lithium diisopropylamide (LDA) and methyl trimethylsilylacetate at −78 °C (warmed to room temperature before quenching), to afford the unsaturated ester **6** (89%); only the (*Z*)-isomer was formed, as demonstrated by ^{1}H and ^{13}C NMR comparisons with methyl cyclohexylideneacetate.

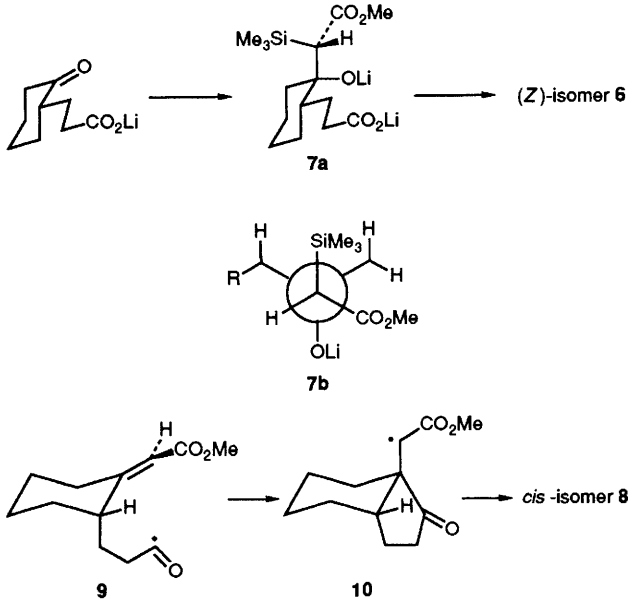
The formation of the (*Z*)-isomer may relate to the stability of the intermediate β-alkoxysilane **7a**, whose preferred geometry is likely to be as shown in **7b**, with the trimethylsilyl group occupying the least crowded site and the methoxycarbonyl and the side chain moieties staggered. *syn*-Elimination of trimethylsilyl oxide then affords the observed stereochemistry.

The acid **6** was then converted *via* treatment of the acid chloride with sodium phenyl selenide into the corresponding selenoester, which on refluxing in benzene followed by reaction with tributyltin hydride provided the *cis*-hydrindanone **8**[3] in excellent yield (91%). The stereochemistry is believed to be controlled by the conformation of the intermediates; the (*Z*)-geometry in the starting acid **6** forces the α-side chain into an *axial*-orientation and the acyl radical **9**[4] is thus ideally disposed to cyclise to the *cis*-product, *via* radical **10**.

Dehydrogenation of the hydrindanone **8** was effected by α-phenylselenylation and oxidative elimination to yield **11** (43%). Methylenation was carried out by the method of Nozaki,[5] and mild basic hydrolysis gave one of the desired dienes **3**. Access to the second target **2** was found through formation of the dienol trifluoroacetate **12** from enone **11**, using trifluoroacetic anhydride; methanolysis of the enol ester provided the deconjugated enone **13**, presumably by kinetically favoured α-protonation.[6] Finally methylenation as before yielded diene **2**. Both dienes were relatively stable, and showed no marked tendency to isomerise by double bond migration. This series of hydrindanes comprises a useful set of steroid C/D models, in which the angular methyl is replaced by methoxycarbonyl methyl unit, which might serve for chain extension, re-functionalisation, *etc.* The chemistry would also



Scheme 1 *Reagents and conditions*: i, KOBu^t, Bu^{t}OH; ii, $BrCH_2CH_2CO_2Et$; iii, aq. HCl; iv, 3 equiv, LDA, 3 equiv. Me_3Si-CH_2CO_2Me; v, $(COCl)_2$; vi, PhSeNa; vii, PhH, reflux; viii, Bu$^n{}_3$SnH, AIBN, PhH; ix, PhSeCl; x, dimethyldioxirane, −78 °C, xi, Et_3N; xii, CH_2I_2, Zn, $TiCl_4$; xiii, K_2CO_3, MeOH; xiv, $(CF_3CO)_2O$; xv, MeOH



be applicable to steroids, starting from ring-D *seco* compounds. We employed these materials to examine C-18 radical reactions; this work is discussed in the following communication.

Received, 1st September 1992; Com. 2/04664D

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