A new approach to steroid ring construction based on a novel radical cascade sequence

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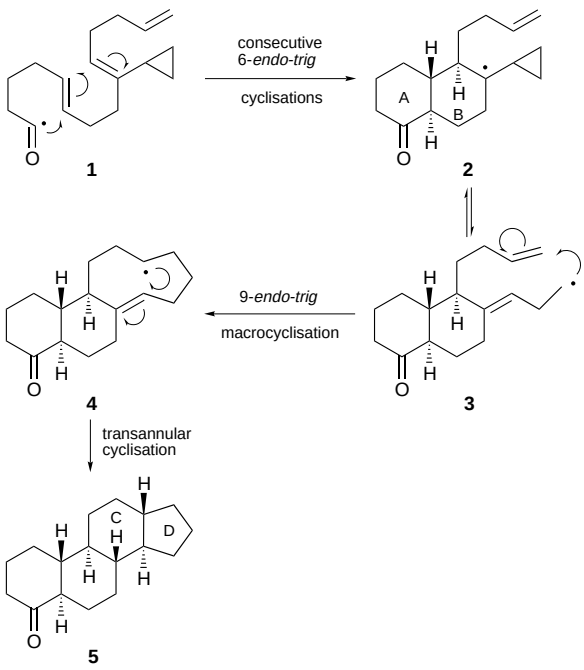
A new approach to steroid ring construction based on sequential cascade 6-*endo-trig* cyclisation/macrocyclisation/ transannulation reactions and exemplified in the synthesis of the *cis, anti, cis, anti, cis* tetracycle 17 from 15, is presented.

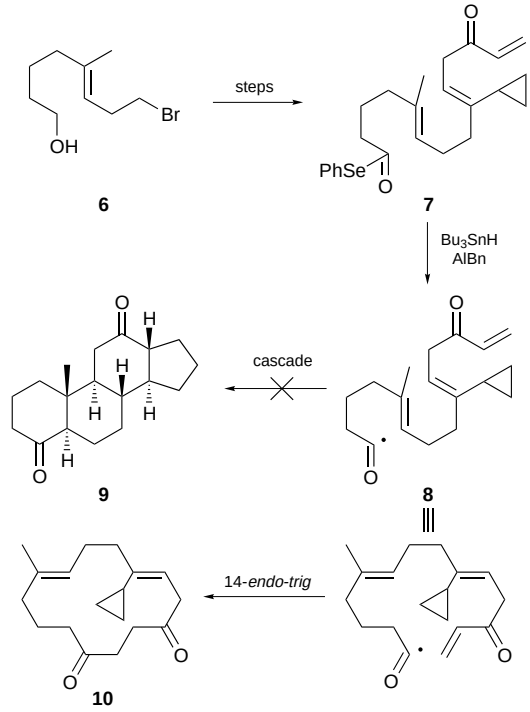
Since their structures were firmly established some fifty years ago, there have been a wide range of imaginative approaches to the total synthesis of natural steroids and to steroidal ring systems. Perhaps paramount amongst the methods that have been developed are those based on either Diels–Alder reactions (inter- and intra-molecular, including transannular based)[1] or biomimetic-type electrophilic cyclisations of polyene precursor compounds.[2] In recent years our own research group has been examining the scope for a range of cascade radical processes in the synthesis of steroids, including those based on consecutive 6-*endo-trig* cyclisations from appropriate polyene acyl radical precursors,[3] and those based on radical macrocyclisations in tandem with radical transannulations.[4] Indeed, these approaches have led to some highly efficient routes to steroids, including aza-steroids[5] and some natural products.[6] We have now conceived a new approach to steroid constructions, based on these earlier studies, whereby the A/B ring system is elaborated by consecutive 6-*endo-trig* cyclisations (**1** → **2**), *in concert with* formation of the C/D ring system *via* a macrocyclisation/ transannulation sequence (**3** → **4** → **5**), from an appropriately functionalised cyclopropyl-based polyene precursor **1** (Scheme 1).

Thus we chose the cyclopropyl substituted trienone selenyl ester **7** as the starting point for our cyclisation studies. The selenyl ester group was chosen as the radical precursor because of the known propensity for hex-5-enoyl radicals to undergo 6-*endo* cyclisations,[3,7] and the conjugated enone group was incorporated in the substrate **7** to facilitate the 9-*endo-trig* cyclisation[8] following ring-opening of the cyclopropylcarbinyl radical intermediate (*cf.* **2** → **3** → **4**, Scheme 1). The synthesis of **7** was achieved in fifteen steps from the known bromo alcohol **6** (Scheme 2).[9,10] When a solution of the selenyl ester **7** in dry degassed benzene (4 mM), at reflux, was treated with Bu_3SnH (syringe pump addition over 4 h) in the presence of AIBN, one major product was isolated in *ca*. 40% yield. Analysis of the spectroscopic data for the compound showed that, instead of generating the steroid dione structure **9** resulting from the predicted cascade highlighted in Scheme 1, the acyl radical intermediate **8** had undergone a single 14-*endo-trig* cyclisation producing the macrocyclic 1,4-dione **10**.[11]

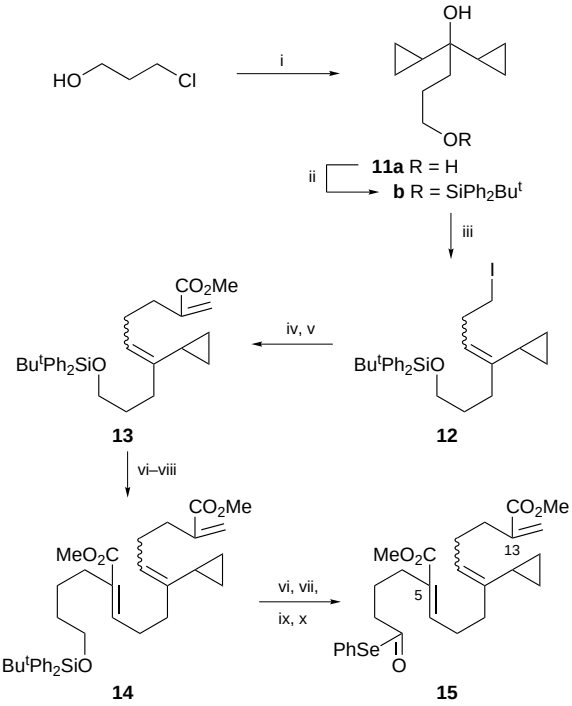
The efficient 14-*endo-trig* macrocyclisation of the nucleophilic acyl radical **8**, leading to **10**, over the competing 6-*endo-trig* cascade is no doubt a consequence of the electrophilicity of the terminal enone in **8**. In light of this we designed a new cyclisation precursor to avoid the competing pathway. The designed polyene selenyl ester **15** incorporates two carboxylate ester moieties, the first of which [at C(5)] was introduced in order to increase the rate of 6-*endo-trig* cyclisation of the acyl radical precursor and the second [at C(13)] was incorporated to lower the electrophilicity of the terminal olefin (with respect to **7**). The new precursor **15** was prepared as shown in Scheme 3. Thus formation of the Normant Grignard reagent from 3-chloro-



Scheme 1



Scheme 2



Scheme 3 *Reagents and conditions*: i, MeMgBr, THF, −30 °C, Mg, 70 °C, then dicyclopropyl ketone, 68%; ii, Bu^tPh_2SiCl, imidazole, 97%; iii, NIS, PPh_3, CH_2Cl_2 −30 °C, 64%; iv, NaH, trimethyl phosphonoacetate, DMSO, 73%; v, NaH, $(CH_2O)_3$, 85%; vi, TBAF, 91–95%; vii, Dess–Martin periodinane, 90–92%; viii, NaH, $Bu^tPh_2SiO(CH_2)_4CH(CO_2Me)PO(OMe)_2$ **16**, 0 °C, 87%; ix, KH_2PO_4, Bu^tOH, H_2O, $NaClO_2$, 2-methylbut-2-ene, 95%; x, *N*-(phenylseleno)phthalimide, PBu_3, −30 °C, 72%

propanol followed by reaction with dicyclopropyl ketone first gave the diol **11a** which was then protected selectively as its TBDPS ether **11b**. Selective ring opening of one of the cyclopropane rings in **11b** was achieved by treatment with *N*-iodosuccinimide (NIS)–PPh_3 to produce the vinyl cyclopropyl intermediate **12** as a 1 : 1 mixture of *E*- and *Z*-isomers. Nucleophilic displacement of the homoallylic iodide in **12** by the anion generated from trimethyl phosphonoacetate and subsequent Wadsworth–Emmons reaction with paraformaldehyde next installed the terminal methacrylate residue in the form of intermediate **13**. The silyl ether group in **13** was converted into the corresponding aldehyde which was then used in a further Wadsworth–Emmons olefination with the phosphate **16** giving the triene **14** as a mixture of separable isomers about the newly formed double bond. Finally, a series of functional group interconversions then led to the target selenyl ester **15**.

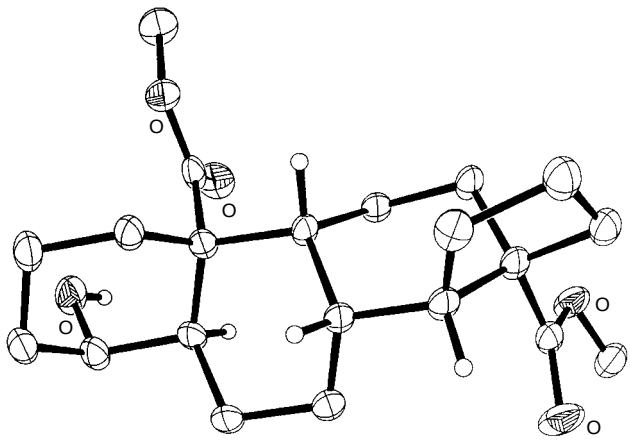
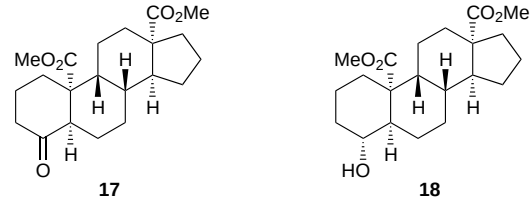


Fig. 1 X-Ray crystallographic structure of **18**

Treatment of the selenyl ester **15** with Bu_3SnH–AIBN under conditions similar to those which produced **10** from **7** led to the formation of one major product in *ca*. 45% yield, and some minor products. Detailed analysis of the NMR data for the separated major product indicated that the compound had the hoped-for tetracyclic (steroid) ring system, but the data could not define its stereochemistry unambiguously. Fortunately, the tetracyclic ketone product could be reduced selectively using $NaBH_4$ leading to the crystalline carbinol **18**, mp 126–128 °C (Et_2O–light petroleum). An X-ray crystallographic analysis of this tetracycle showed, surprisingly, that it had the very unusual *cis, anti, cis, anti, cis*-stereochemistry, *viz*. **17** and **18** (Fig. 1). Thus we had not only demonstrated the scope for the new strategy for steroid ring construction enunciated in Scheme 1, but we have also uncovered a route to the unusual all *cis*-stereochemistry for the steroid ring system produced when **15** undergoes a radical cascade cyclisation to **17**. Further studies are now in progress to develop this novel stratagem for polycycle construction in other fused ring systems.



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Notes and References

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‡ *Crystal data* for **18**: $C_{21}H_{32}O_5$, M = 364.47, triclinic, a = 7.499(6), b = 10.405(6), c = 12.297(7) Å, α = 82.70(4), β = 80.93(6), γ = 79.83(5)°, U = 927.7(11) Å^3, T = 150 K, space group $P\bar{1}$ (No. 2), Z = 2, D_c = 1.305 g cm^{-3}, μ(Mo-Kα) = 0.091 mm^{-1}, 5459 reflections measured, 3120 unique (R_{int} = 0.019), final R_1 [$F_o \geqslant 4\sigma(F_o)$] = 0.0628, wR_2 (all data) = 0.209 for 242 refined parameters. CCDC 182/715.

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