A Simple Stereoselective Steroid Synthesis: Cyclization of an Epoxystannane

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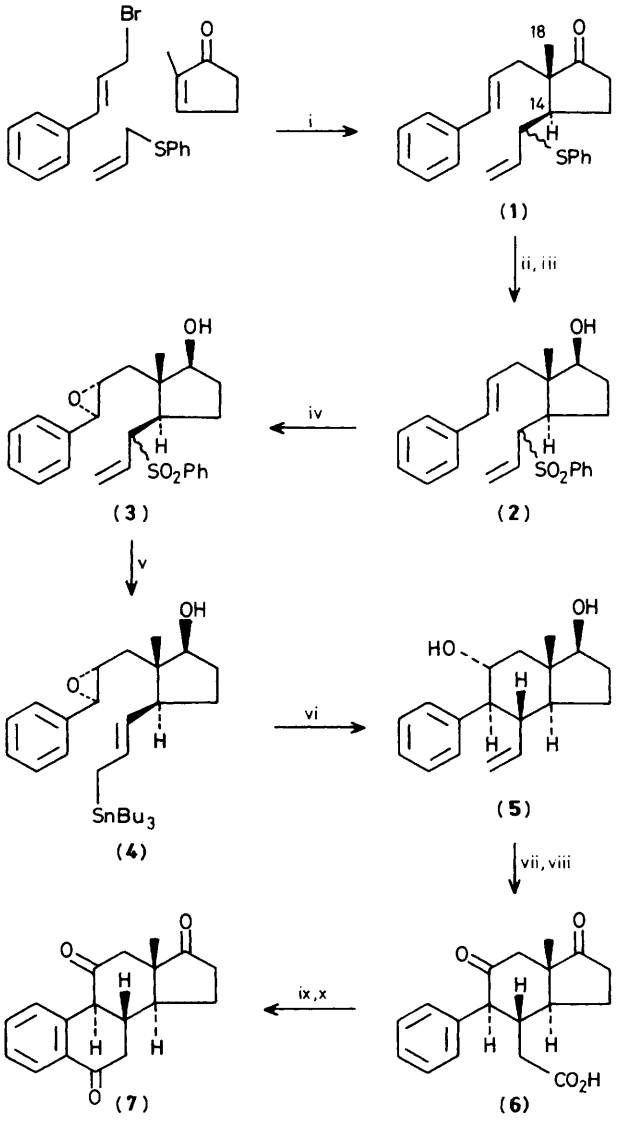
The highly stereoselective acid-catalysed cyclization of an epoxystannane, together with the stereoselective alkylation by cinnamyl bromide of the enolate derived by conjugate addition of the anion of allyl phenyl sulphide to 2-methylcyclopent-2-enone, are the key steps in a simple synthesis of an aromatic steroid.

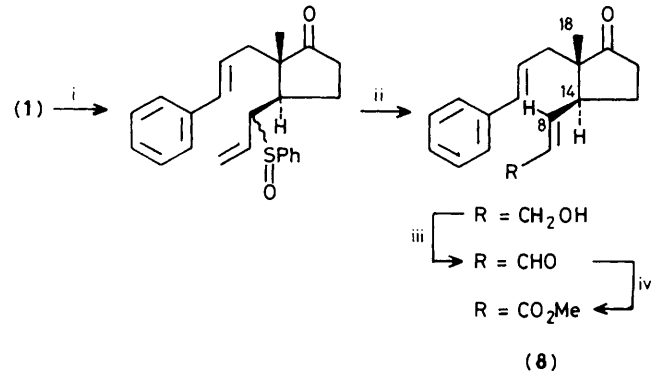
The continuing quest for improved steroid syntheses[1] has culminated in recent concise approaches to ring-A aromatic steroids,[2] most of which employ intramolecular cycloadditions of quinodimethanes to construct rings B and C with the correct stereochemistry. We now report an alternative strategy based on a highly stereoselective intramolecular attack of an allyl stannane upon an epoxide, which leads ultimately to a 6,11,17-triketosteroid. Substituents at these positions confer important physiological properties upon steroid molecules,[3] and the location of the three chemically distinguishable keto groups potentially permits access to a wide variety of substituted steroids.

The adduct derived by conjugate addition[4] of the lithio-anion of allyl phenyl sulphide to 2-methylcyclopent-2-enone was trapped by cinnamyl bromide to give the product (**1**) (53%), which contains all the carbon atoms of the estrane skeleton (Scheme 1). The stereochemical consequences of related reactions involving cyclopent-2-enone[4] and 2-methylcyclopent-2-enone[5] led us to anticipate that the product with the *trans*-orientation of 18-Me and 14-H (steroid numbering) would predominate. That the sole product isolated had this required *trans*-orientation was confirmed by the n.m.r. spectrum† of the unsaturated ester (**8**, R = CO_2Me) derived from (**1**) according to Scheme 2. The n.m.r. spectrum of (**1**) was complicated by the presence of phenylthio epimers at C-8.

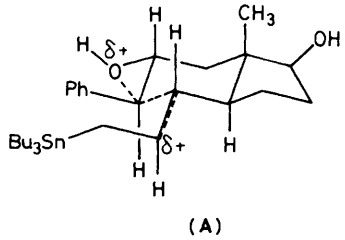
Straightforward conversion of the keto-sulphide (**1**) into the hydroxysulphone (**2**) (64%) (Scheme 1) was followed by chemoselective and stereoselective epoxidation of the styryl



Scheme 1. *Reagents:* i, Allyl phenyl sulphide, Bu^sLi (1 equiv.), tetrahydrofuran (THF), hexamethylphosphoric acid triamide, hexane (16:1:3), −78 °C, 15 min; then 2-methylcyclopent-2-enone (1 equiv.), −78 °C, 15 min; then cinnamyl bromide (1.5 equiv.), THF, −78 to 0 °C, 2 h; ii, *m*-chloroperbenzoic acid (*m*CPBA), CH_2Cl_2, 0 °C, 1 h; iii, $NaBH_4$, MeOH, 0 °C, 30 min; iv, *m*CPBA, CH_2Cl_2, 0 °C, 12 h; v, Bu_3SnH, 2,2-azobis-2-methylpropionitrile, C_6H_6, 80 °C, 2 h; vi, CF_3CO_2H, CH_2Cl_2, −78 to 0 °C, 3 h, or $SnCl_4$, CH_2Cl_2, −78 to 0 °C, 2 h; vii, BF_3·THF, 50 °C, 30 min, then H_2O_2–OH^-; viii, Jones reagent, acetone, 0 °C, 30 min; ix, $(COCl)_2$, 40 °C, 1 h; x, $AlCl_3$, CS_2, 46 °C, 2 h.



Scheme 2. *Reagents:* i, *m*CPBA, EtOAc, −40 °C; ii, $(MeO)_3P$, MeOH, 20 °C; iii, $BaMnO_4$, CH_2Cl_2; iv, MnO_2, NaCN, MeOH, AcOH.



† Nuclear Overhauser effect (n.O.e.) difference ^1H n.m.r. spectroscopy ($CDCl_3$, 400 MHz); irradiation of the 18-Me singlet at δ 0.95 produced an 8.8% enhancement of the 8-H vinyl dd at δ 6.96, and no enhancement of the 14-H ddd at δ 2.95.

double bond to give the 9α,11α-epoxide (**3**) (76%). The apparently complete stereoselectivity of this reaction, which was predicted from models, is considered to be a consequence of the steric shielding of the β-face of the styryl double bond by the allyl sulphone group at C-14. Treatment of the allyl sulphone with tri-n-butyltin hydride gave the (*E*)-allyl stannane (**4**) (67%):[6] this complete stereoselectivity is unusual, mixtures of (*E*) and (*Z*) isomers are obtained in related cases.[6,7]

Reactions of allyl stannanes with epoxides have not been reported, although reactions with other electrophiles are known.[6—8] The related, but less reactive[8] allyl silanes cleave epoxides both intermolecularly and intramolecularly with formation of carbon–carbon bonds.[9] We therefore expected the allyl stannane (**4**) to react intramolecularly with the epoxide under acid catalysis, and to do so regiospecifically at the benzylic C-9 position. Furthermore, models indicated that the preferred conformation (A) of the putative transition state for the reaction would lead to the desired 8β,9α,14α-configuration. Other transition state conformations are much more sterically compressed.

Accordingly, the epoxy allyl stannane (**4**) readily underwent acid-catalysed ring closure to give the tricyclic compound (**5**) (62%) in a highly stereoselective manner, as determined by the n.m.r. spectrum‡ which indicated an all *trans*-diaxial configuration of the 11β, 9α, 8β, and 14α protons. The dihydroxyalkene (**5**) was oxidised in two steps to the diketo acid (**6**) (69%), and ring B was closed by intramolecular Friedel–Crafts acylation *via* the corresponding acid chloride to give estra-1,3,5(10)-triene-6,11,17-trione (**7**) (53%).

This convergent synthesis of an aromatic steroid from readily available starting materials introduces each ring junction with apparent complete stereoselectivity, and involves no protection–deprotection sequences.

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‡ ^{1}H N.m.r. ($CDCl_3$, 400 MHz), decoupling difference spectroscopy, δ 4.02 (1 H, ddd, 11-H), 2.34 (1 H, dt, 8-H), 2.25 (1 H, t, 9-H), 1.39 (1 H, dt, 14-H), 0.96 (3 H, s, 18-Me), $J^{11,9} = J^{9,8} = J^{8,14} = 10$ Hz; n.O.e. difference spectroscopy, irradiation of the 8-H signal produced a 6.5 and 10.4% enhancement of the 11-H and 18-Me signals respectively.

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