A Synthesis of (±)-Pregn-4-en-20-one

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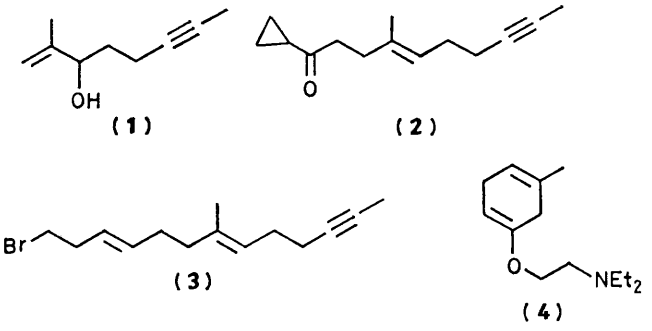
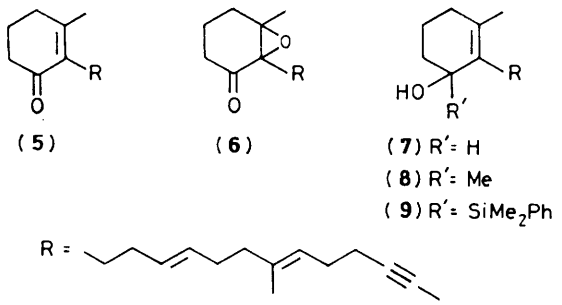
An adaptation of Johnson's polyene cyclisation method has led to the total synthesis of (±)-pregn-4-en-20-one by direct cyclisation.

In furtherance of our work on the use of derivatives of 2-substituted 3-methylcyclohex-2-enones as initiators of polyene cyclisation[1] we have synthesised the potential steroid precursor (5) containing the Johnson side-chain. The enone (5) was pre-

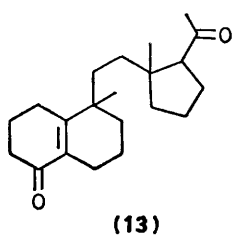


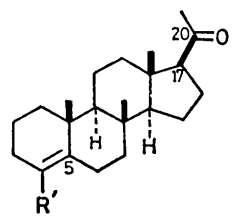


pared in an overall yield of 26% from the alcohol[2] (**1**) which was initially converted into cyclopropyl ketone (**2**) by two routes. In the first, S_Ni' reaction of (**1**) with $SOCl_2$ gave the *E*-allyl chloride which was used to alkylate ethoxycarbonylmethyl cyclopropyl ketone;[3] hydrolysis and decarboxylation then gave (**2**) which was also prepared by Claisen rearrangement of the allyl vinyl ether from (**1**) and cyclopropyl methyl ketone dimethyl acetal.[4] Reduction of (**2**) ($NaBH_4$) followed by formation of the cyclopropyl bromide (Ph_3P–Br_2) and then rearrangement[3] ($ZnBr_2$) gave the bromide (**3**). Alkylation[5] of the lithio-derivative of the ether (**4**) with bromide (**3**) gave, after hydrolysis, the cyclohexenone (**5**) which was converted into the epoxide (**6**) ($NaOH$–$MeOH$–H_2O_2).[6]

Attempts to cyclise the oxide (**6**) were disappointing; with a number of Lewis acids only partially cyclised materials were obtained. Reaction with $EtAlCl_2$–CH_2Cl_2 at −78 °C gave a mixture of crystalline tetracyclic compounds, but the reaction could not be made preparatively useful. Previously where the cyclisation of epoxides had given poor results good yields were obtained when the cyclohexenone was allowed to react with $(CF_3CO)_2O$–CF_3CO_2H.[1] When these conditions were applied to (**5**) the major products were assigned structures (**13**) [λ_{max} 247 nm (ϵ 10,500 $mol^{-1}dm^3cm^{-1}$), ν_{max} 1705, 1665 cm^{-1}, τ 7.92 (3H, s), 8.63 ($\frac{3}{2}$H, s), 8.94 ($\frac{3}{2}$H, s), and 9.00 (3H, s), *m/z* 316, 164] suggesting two independent cyclisations.† Attempts to prepare the intermediate dienol ester of the cyclohexenone (**5**) from the kinetic enolate led only to polyacylation. The *O*-trimethylsilyldienol was prepared (lithium di-isopropylamide–THF–Me_3SiCl) (THF = tetrahydrofuran) but exposure to cyclisation conditions only regenerated the ketone (**5**).

Efficient cyclisation could be achieved using an allylic cation initiator of the type developed by Johnson.[7] Reaction of the ketone (**5**) with MeLi gave the alcohol (**8**) which on treatment with CF_3CO_2H–n-C_5H_{12}–CH_2Cl_2 at 0 °C gave, after hydrolysis, a mixture of C-17 epimers (5:1 β:α) (**10**) (44%); the 17β-isomer could be obtained by crystallisation [ν_{max} 1700 cm^{-1}; τ 7.89 (3H, s), 8.40 (3H, s), 9.01 (3H, s), 9.38 (3H, s)]. Anticipating that the secondary alcohol (**7**) would cyclise at the least





alkylated terminus of the allyl cation[7] we have developed a new method to prepare cyclisation products without carbon substituents at C-4. The requirement is for a substituent which will direct cyclisation to the methylated terminus of the allyl cation and then be readily replaced by H; a silyl substituent was an obvious choice. Reaction of the ketone (**5**) with $PhMe_2SiLi$[8] in THF gave only the 1,2-addition product (**9**) which was cyclised with CF_3CO_2H–CF_3CH_2OH at −10 °C. After hydrolysis the product was chromatographed to give a tetracyclic fraction (50%) containing four products‡ (cap. g.c.). The major product was shown to be identical with the chiral pregn-4-en-20-one (**11**) by cap. g.c.–m.s. and 300 MHz ^1H n.m.r. spectroscopy. A second product was identical by cap. g.c.–m.s. with the 17α-isomer of (**11**). The two other isomers were tentatively identified as the 17α- and 17β-isomers of pregn-5-en-20-one on the basis of their formation (cap. g.c.) from the 17α- and 17β-isomers of (**11**) under the cyclisation conditions and the formation of one of them as a minor product in the desulphurisation of the 3-ethylenedithioacetal of progesterone. These reactions constitute a formal total synthesis of progesterone which has been prepared from (**11**).[9]

We assume that the allyl cation derived from (**9**) initiates cyclisation to give the enol trifluoroacetate of (**12**) which then undergoes protodesilylation and that the Δ^5-compound is produced by an isomerisation of the initial cyclisation product.

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† It would appear that the conditions necessary to generate the dienol trifluoroacetate also bring about protonation of the trisubstituted double bond.

‡ Assuming that our identification of the peaks is correct the mixture has the isomer composition Δ^4,17β (66%), Δ^4,17α (14%), Δ^5,17β (14%), Δ^5,17α (5%).