Synthesis of (±)-2-Acetyl-8-methoxy-5,6,7,8,9,10,11,12-octahydrobenzocyclodecene: a Medium-sized Ring, Ring-C Aromatic Hormone Analogue

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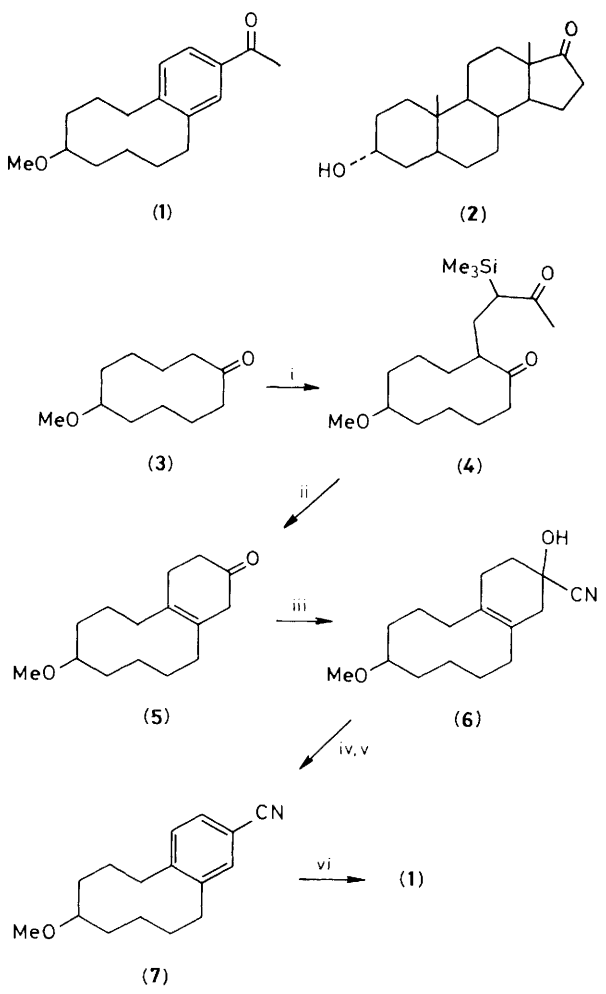
The title compound has been prepared in six steps from 6-methoxycyclodecanone.

Relatively few methods have been reported for the preparation of benzo-substituted, medium- or large-ring systems with substituents in specified positions.[1] We now report the synthesis of such a system (**1**) by a method which fuses the substituted benzo component on to an appropriately substituted medium-ring system (**3**). System (**1**) which is structurally similar to androsterone (**2**) has been prepared primarily to enable biological testing of the need of the rigid steroid backbone for



Reagents: i, $LiNPr^i_2$, $CH_2CH(SiMe_3)COCH_3$, H_2O; ii, NaOMe C_6H_6; iii, Me_3SiCN, KCN–18-crown-6, Et_2O, H^+, H_2O; iv, $POCl_3$, pyridine; v, DDQ; vi, MeLi, H^+, H_2O.

biological activity,[2] but it also of interest in comparison with the ring-C aromatic steroids[3] such as viridin.

The methoxy ketone (**3**) is well suited for the synthesis since it is readily available by the method of Criegee[4] and is symmetrical so that annelation on either side of the carbonyl group gives the same product. Earlier work had noted that traditional annelation procedures on medium- and large-ring ketones tend to give [*n*.4.1]-bicyclic products rather than the desired fused ring systems.[5] The Stork method[6] which allows the reaction to be done in two stages provides an effective condensation to give to the adduct (**4**) which can then be closed to give the fused ring system (**5**)† using conditions which have been shown to favour that pathway [58% yield of (**5**) from (**3**)]. It is interesting that the double bond strongly prefers the ring juncture position in preference to that α,β to the ketone. Treatment of the ketone with trimethylsilyl cyanide followed by aqueous acidic work-up gave the cyanohydrin (**6**) which was dehydrated by heating in pyridine–phosphorus oxychloride at 70–80 °C for 12 h [*ca.* 60% yield from (**5**)]. Refluxing the dehydration product for 20 h in a benzene solution of dichlorodicyanobenzoquinone (DDQ) gave the aromatized product (**7**) (*ca.* 43% yield). The remaining conversion of the cyano-group into an acetyl unit was accomplished by treatment with methyl-lithium in refluxing ether for 24 h followed by aqueous acid work-up. Purification by medium pressure liquid chromatography gave (**1**) in a 45% yield. Thus, a new pathway to such benzo-substituted systems has been demonstrated by preparation of (**1**); biological testing will be reported in due course.

Received, 2nd October 1981; Com. 1157

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† New compounds (**5**), (**7**), and (**1**) gave satisfactory high resolution mass spectra as well as supporting i.r., ^1H n.m.r., and ^{13}C n.m.r. data.