Synthesis of (±)-8,9:13,14-Diseco-18-Norestradiol: a Large-ring Hormone Analogue

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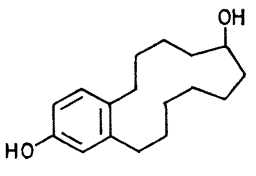
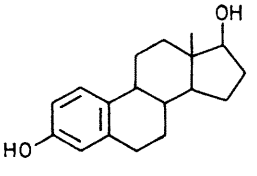
Summary The first large-ring analogue of estradiol has been prepared in nine steps by a ring-expansion route starting from 6-methoxycyclodecanone.

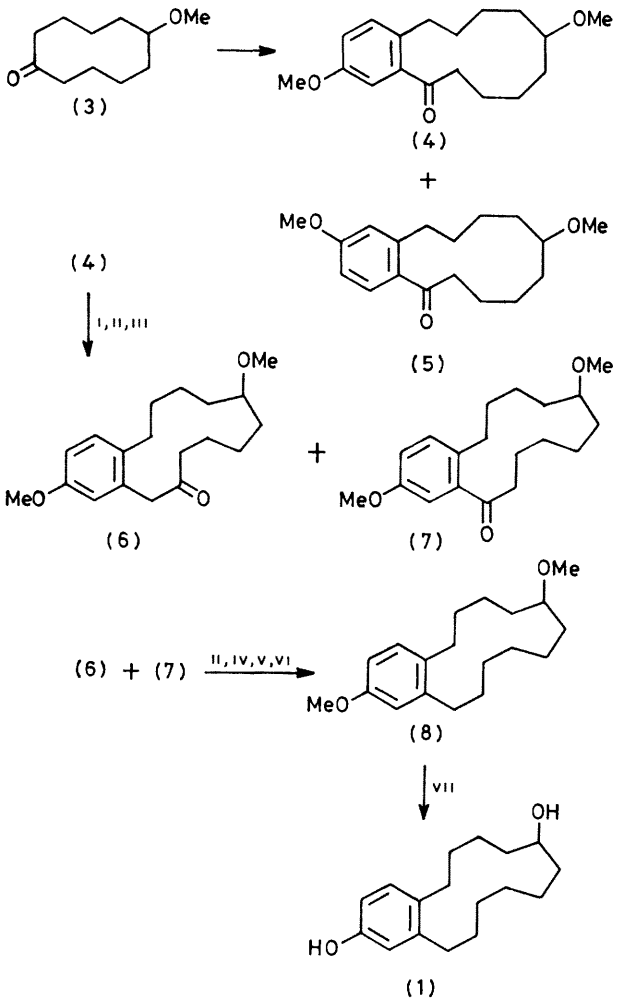
WE now report the synthesis of 8,9:13,14-diseco-18-norestradiol (**1**), the first analogue of the human sex hormones wherein the B, C and D rings are replaced by a single large ring. One model of hormone action[1] theorizes that the shape and placement of oxygen groups of the steroid, *e.g.*, estradiol (**2**), allows it to fit and interact with a particular receptor which is then deformed to fit the rigid steroid structure. The deformation then dictates the further biological activity of the complex. Compounds like (**1**) are of interest because they can adopt a shape and placement of oxygen groups like the steroid but they are flexible and thus should not deform the receptor. Several monoseco-steroid analogues with a lesser degree of flexibility have shown activity and have led to the above theory being questioned.[2]



(1)



(2)



Reagents: i, Me_3SiCN, KCN, 18-crown-6; ii, $LiAlH_4$; iii, HONO; iv, $MeSO_2Cl$; v, Bu^tOK, Me_2SO; vi, H_2, Pd; vii, $AlCl_3$, HSC_2H_4SH.

The key step in this synthesis of (**1**) generates a large-ring benzo-compound with the oxygens in the correct positions in one step. Thus, 6-methoxycyclodecanone (**3**), which is readily prepared on a large scale from decalin,[3] reacts with *p*-bromoanisole and sodamide to give approximately equal amounts of (**4**) and (**5**) along with minor amounts of 2-aryl-6-methoxycyclodecanones. The two major isomers (**4**) and (**5**), which were expected, based on the earlier unsubstituted examples,[4] were readily distinguished by the ^1H n.m.r. spectra of their aromatic protons [(**4**): 7·15 (1H, d, *J* 8 Hz) and 6·75—6·9 (2H, m); (**5**): 7·34 (1H, d, *J* 8 Hz), 6·74 (1H, d, *J* 2·5 Hz), and 6·64 (1H, dd, *J* 2·5, 8 Hz)] when compared with the related tetralones[5] and 1,2-benzocyclonon-1-en-3-ones.[6] The desired product (**4**) was isolated in 11% yield by preparative-scale, medium-pressure liquid chromatography. While the yield is not high, this one step simultaneously expands the ring, introduces the benzo-moiety with the methoxy group in place, and leaves a keto-group where it can be utilised specifically to expand the ring to (**1**). The ring-expansion proved more difficult than anticipated however. Of eight methods tried, only the expansion using trimethylsilyl cyanide with potassium cyanide–18-crown-6 catalyst[7] was successful and even there a substantial portion was converted into the trimethylsilyl enol ether. Acid catalysts apparently cause transannular rearrangements, but basic species tend to cause enolate formation rather than addition to the carbonyl group. Using nonpolar media at low temperature eventually gave a mixture of (**6**) and (**7**) in 61% yield. The sequence of steps shown for conversion into (**8**) gave a very clean product and a better yield (36%) than several more direct methods. The final unblocking of the two methoxy groups also proved to be a troublesome step. Of six methods tried, only the Fujita method[8] gave consistently reasonable yields (40%) of clean products.†

Other members of this class of hormone are under investigation; the biological results will be reported elsewhere.

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† All new compounds shown gave satisfactory high-resolution mass spectra as well as supporting i.r., ^1H n.m.r., and ^{13}C n.m.r data.

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