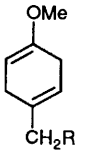
Total Synthesis of A-Ring Aromatic Steroids: A Formal Synthesis of Estrone

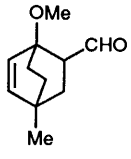
G. S. R. Subba Rao,* L. Uma Devi and Uma Javed Sheriff
Department of Organic Chemistry, Indian Institute of Science, Bangalore-560012, India

A new synthesis of estrone and its analogues is reported, intramolecular Michael reaction is the key step.

The synthesis of aromatic steroids such as estrone is still of interest since such compounds have well defined stereochemistry and wide chemotherapeutic usage. We report here a new strategy for making such compounds which allows greater flexibility for the preparation of steroid hormone analogues. The methodology is general and, with appropriate manipulation, can lead to chiral intermediates which can be transformed into optically active steroid and triterpenoid precursors.



1a; R = H
b; R = Me



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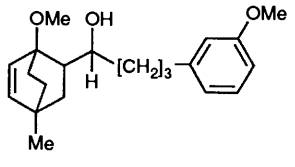

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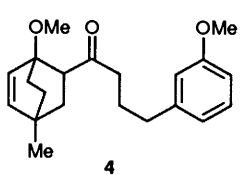
Reaction of the adduct **2**, obtained from 1-methoxy-4-methylcyclohexa-1,4-diene **1a** and acrolein, with 3-(*m*-methoxyphenyl)propylmagnesium bromide yielded the alcohol **3** (80%) which was oxidised with pyridinium chlorochromate to the ketone **4** (75%). Compound **4**, on treatment with 2% perchloric acid in acetic acid, undergoes an acid-catalysed C–C bond cleavage[2,3] assisted by the methoxy group to give the keto enone **5** (80%); ν_{max}/cm^{-1} 1710, 1680, 1600 and 1500; δ_H 1.03 (s, 3 H, Me), 1.3–2.7 (m, 14 H) 3.7 (s, 3 H, OMe), 5.65 (d, *J* 11, 1 H), 6.3–7.2 (m, 4 H, ArH) and 7.0 (d, *J* 11, 1 H). Reaction of **5** with KO^{t}Bu in *tert*-butyl alcohol afforded exclusively the *cis*-dione **6** (85%); ν_{max}/cm^{-1} 1700, 1600 and 1500; δ_H 1.3 (s, 3 H, CH_3), 1.5–2.8 (m, 16 H), 3.8 (s, 3 H, OCH_3) and 6.6–7.3 (m, 4 H). The bicyclic dione **6**, on acid catalysed cyclisation with pTSA in refluxing benzene, gave the *cis*-tetracyclic ketone **7a** (80%); m.p. 92–93 °C; λ_{max}/nm 276 (ε 16 000); ν_{max}/cm^{-1} 1700, 1600 and 1500; δ_H 1.0 (s, 3 H, Me), 1.5–2.6 (m, 15 H), 3.94 (s, 3 H, OCH_3) and 6.6–7.3 (m, 3 H).



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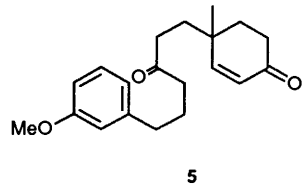

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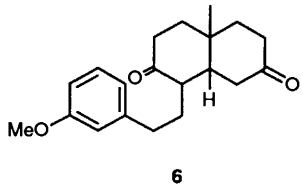

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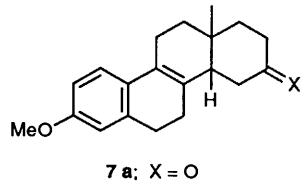
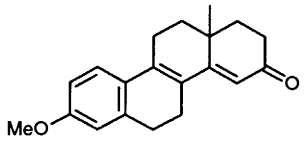


7a; X = O
b; X = H_2



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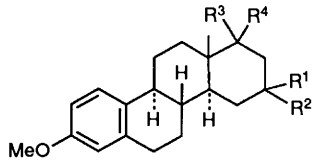
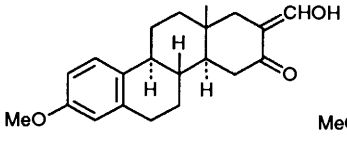


9 **a**; R^1, R^2 = O, R^3 = R^4 = H
b; R^1 = R^2 = R^3 = R^4 = H
c; R^1 = R^2 = H, R^3, R^4 = O



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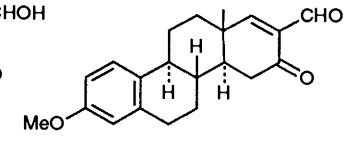

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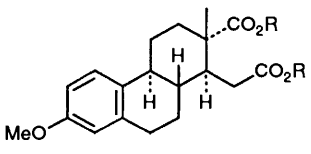
Acid-catalysed reaction of the tetracyclic ketone **7a** failed to isomerise[4] the Δ^8-double bond to the $\Delta^{9(11)}$ position



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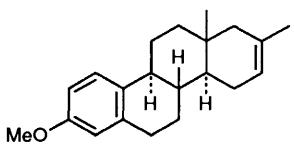

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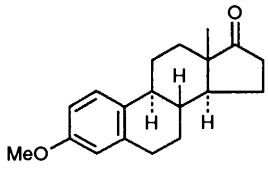

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indicating that the stereochemistry at the C/D ring junction is *cis*. This was confirmed by the Wolff–Kishner reduction of **7a** to the tetracyclic compound **7b** and comparison with an authentic sample, obtained by the Wolff–Kishner reduction of the known 3-methoxy-D-homo-14-isoestra-1,3,5(10),8-tetraen-17a-one.[5] Intramolecular Michael addition of the enedione **5** was attempted under a variety of conditions with different bases and resulted[3] only in the *cis*-compound **6**. MM2 calculations indicate that the isomeric *trans*-compound is more stable than the *cis*.

Reaction of the tetraenone **7a** with sodium tetrachloropalladate,[6] in refluxing THF afforded the pentaenone **8** (90%); m.p. 83 °C; $_{max}$/nm 370 (ε 24 220); ν_{max}/cm^{-1} 1665, 1660, 1580 and 1500; δ_H 1.15 (s, 3 H, Me), 1.6–2.75 (m, 12 H), 3.8 (s, 3 H, OMe), 5.9 (s, 1 H, vinylic H), 6.5–7.5 (m, 3 H, ArH); M$^+$, 294. Li/NH_3 reduction of **8** gave the ketone **9a** (80%); λ_{max}/nm 278 and 285 (ε 4850 and 4230); ν_{max}/cm^{-1} 1700, 1600 and 1500; δ_H 1.2 (s, 3 H, Me), 1.25–3.13 (m, 17 H), 3.76 (s, 3 H, OCH_3) and 6.72–7.24 (m, 3 H, ArH); M$^+$, 298. Wolff–Kishner reduction of **9a** yielded **9b**, identical with an authentic specimen obtained by the Wolff–Kishner reduction of the known[5] ketone **9c**, thus confirming the stereochemistry of the tetracyclic compound **9a** at the ring junctions BC and CD as *trans*, *anti*, *trans*. The formyl derivative **10**, obtained from **9a** with ethyl formate and sodium methoxide in benzene, was oxidised with SeO_2 in DMSO resulting in the unsaturated keto aldehyde **11**; δ_H 1.25 (s, 3 H, Me), 1.6–3.2 (m, 13 H), 3.8 (s, 3 H, OMe), 6.65–7.7 (m, 4 H, ArH and vinylic H) and 9.85 (s, 1 H, CHO); M$^+$, 324. Reaction of compound **11** with aqueous $KMnO_4$–Na_2CO_3, followed by oxidative work-up and esterification with ethereal diazomethane gave the dimethyl ester of marrianolic acid methyl ether[7] **12**, m.p. 93–95 °C. This compound has earlier been transformed[8] into estrone.

Alkylation of **10** with methyl iodide followed by hydrolysis, reduction with sodium borohydride and dehydration yielded the tetracyclic compound[9] **13**, m.p. 96–97 °C. This compound was earlier converted into (±)-estrone methyl ether **14**, thus completing a formal synthesis of estrone. Exploitation of this strategy to the total synthesis of biologically potent 13β-ethylgonatrienes from **1b** and to the tetracyclic triterpenes is currently under progress.

Acknowledgements

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