A Simple and Stereoselective Synthesis of Des-A-B-aromatic Corticoids *via* Intramolecular Cycloaddition: Potential Intermediates for the Synthesis of Corticoids

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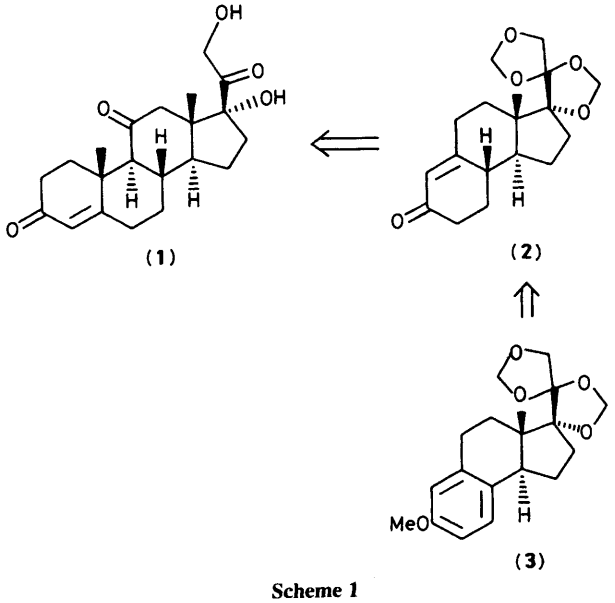
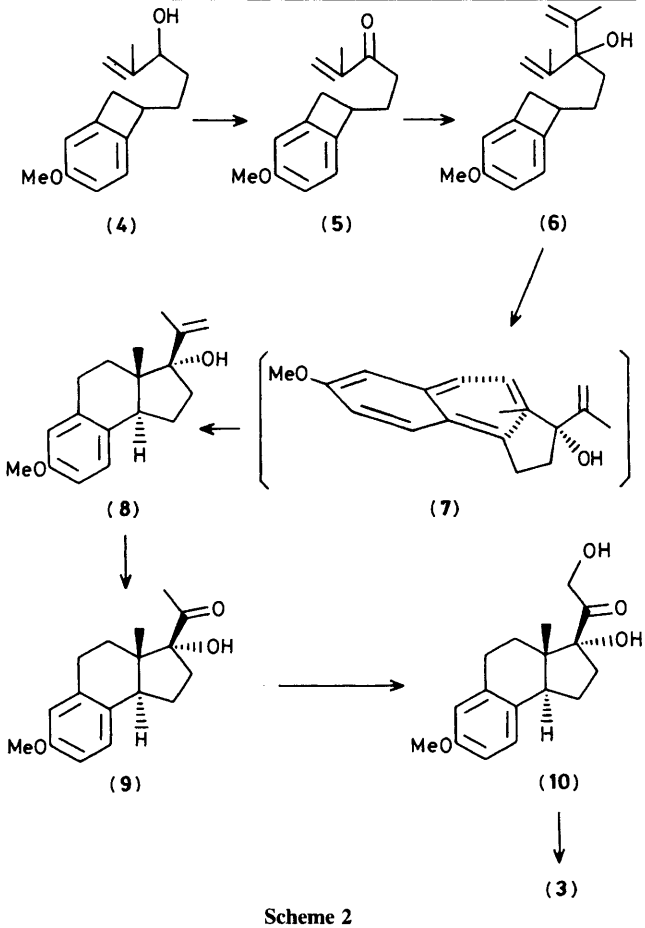
Intramolecular cycloaddition reaction of the *o*-quinodimethane (**7**) derived from thermolysis of 3-isopropenyl-1-(4-methoxybenzocyclobuten-1-yl)-4-methylpent-4-en-3-ol (**6**) gave stereoselectively *trans*-3α-hydroxy-3β-isopropenyl-7-methoxy-3aβ-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indene (**8**), which was efficiently converted into the bismethylenedioxy derivative (**3**) of the des-A-B-aromatic corticoid (**10**) *via* (**9**).

During our studies[1] on the total synthesis of steroids *via* intramolecular cycloaddition, we have become interested in the total synthesis of des-A-B-aromatic steroids[2] because of the flexibility for constructing the A-ring and introducing functional groups at the C-9 and C-11 positions. Retrosynthetic analysis for the total synthesis of corticoids, *e.g.* cortisone (**1**), from the tricyclic compound (**3**) *via* (**2**) is shown in Scheme 1, and we report a simple and stereoselective synthesis of the des-A-B-aromatic steroid (**3**) having a suitable substituent at C-17 (steroid numbering) for the generation of the dihydroxyacetone moiety in cortisone (**1**).



Scheme 1



Scheme 2

Thus, the enone (**5**) [*m/z* 230 (M^+)], prepared in 94% yield by oxidation [pyridinium chlorochromate (PCC); CH_2Cl_2; room temp.; 1 h] of the pentenol (**4**),[2a] was treated with isopropenyl-lithium[3] to give the di-isopropenyl alcohol (**6**) [*m/z* 272 (M^+)] in 88% yield. Thermolysis of (**6**) in boiling *o*-dichlorobenzene afforded the tricyclic compound (**8**)† [*m/z* 272 (M^+)] in 60% yield. The stereoselectivity in the thermolysis of (**6**) could be explained by the intermediacy of the least sterically hindered olefinic *o*-quinodimethane (**7**). Compound (**8**) thus obtained was then ozonolysed in CH_2Cl_2–MeOH at −78 °C to yield the hydroxy ketone (**9**) [m.p. 97—98 °C, *m/z* 274 (M^+)] in 76% yield. Finally, the dihydroxy ketone (**10**) [m.p. 139—140 °C, *m/z* 290 (M^+)], obtained in 47% yield by oxidation [MoO_5 · hexamethylphosphoramide · pyridine; Pr^i_2NLi (2 equiv.); THF; −78 °C; 1 h][4] of (**9**), was protected (37% HCHO; conc. HCl; CH_2Cl_2; 46 h) to furnish the initial target compound (**3**) [*m/z* 332 (M^+)] in 26% yield, which is a potential intermediate for the synthesis of corticoids.

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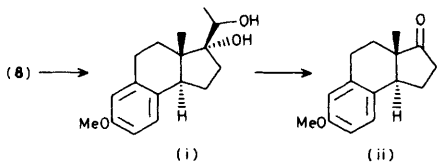
† Compound (**8**) was converted into (ii) *via* (i) by treatment with O_3 followed by $NaBH_4$ to give (i). Treatment of (i) with $Pb(OAc)_4$ gave (ii), which was identical with an authentic sample[2a] showing that the ring junction was *trans*. The angular methyl group of (**8**) resonated at δ 0.45 in its n.m.r. ($CDCl_3$) spectrum suggesting that the angular methyl and hydroxy groups are *trans*; *i.e.* the angular methyl and isopropenyl are *cis*.



References

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