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BRIDGED RING A STEROIDS: TOTAL SYNTHESIS OF (±)-14β-HYDROXY-1β,4β-METHANO-5β,8α,9β-ANDROSTANE-7,17-DIONE

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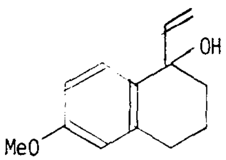
Abstract: A modification of the Torgov steroid synthesis in which a vinyl methyl ether group in ring B stabilizes the critical cationic intermediate has been used to synthesize the title compound (15), whose structure has been confirmed by X-ray crystallographic analysis.

Earlier work from these Laboratories on the synthesis of carbon-bridged ring A and ring B steroids has involved transformations of natural or pre-formed steroids.[1] We report now on the total synthesis of a carbon-bridged ring A steroid by a newly modified version of the Torgov steroid synthesis.[2] The essence of the Torgov route is the generation of a cationic species 1a from the precursor 1 and the reaction of this with 2-methyl-1,3-cyclopentanedione (2). Although it represents an elegant and rapid entry into the steroid series, particularly in some modified versions,[3] it does not provide a convenient route from non-aromatic precursors to non-aromatic ring A steroids bearing a C-19 methyl group. Valenta and co-workers[4] overcame this problem by the use of 3 as a precursor; however, such an approach cannot be readily adapted to the synthesis of bridged ring A steroids. It occurred to us that this obstacle might be overcome by generating an analogue of 1a in which formation of the cationic species is facilitated by a vinyl methyl ether group in ring B rather than an anisyl group in ring A.



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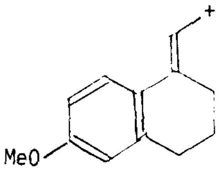
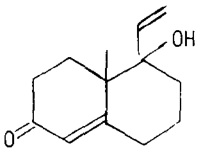


1a



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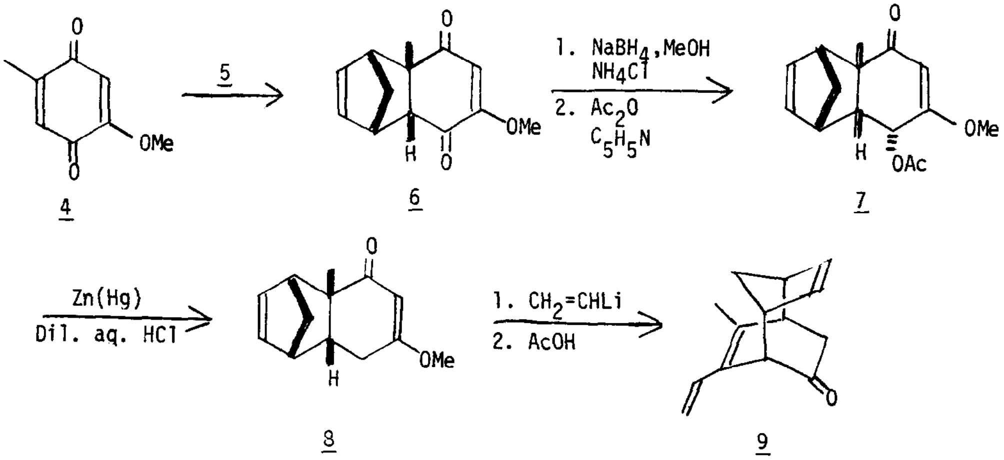
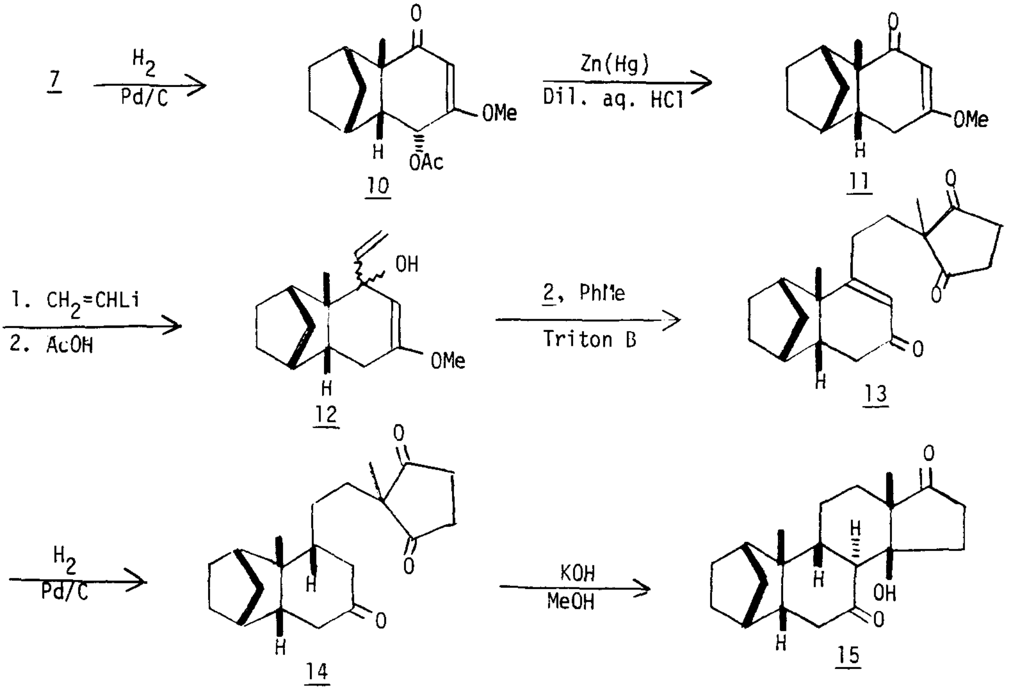
[†] Dedicated with admiration, appreciation, and affection to Harry Wasserman on the occasion of his sixty-fifth birthday.

The Diels-Alder adduct 6, prepared from the quinone 4 and cyclopentadiene (5),[5] was chemoselectively reduced with NaBH$_4$/NH$_4$Cl/MeOH[6] and the resulting keto alcohol was acetylated to give the keto acetate 7,[7] which on reduction with zinc amalgam gave the ketone 8. This on treatment with vinyllithium followed by mild acidic work-up gave a product that is considered to have a structure of type 9[8] and to be formed by dehydration, rearrangement, and hydrolysis of the initially formed tertiary alcohol.



In order to reduce the proclivity for rearrangement the keto acetate 7 was chemoselectively hydrogenated to give 10 and this was then reduced with zinc amalgam to 11. Treatment of the las with vinyllithium followed by mild acidic work-up gave the tertiary alcohol 12. Reaction of thi with 2-methyl-1,3-cyclopentanedione (2) under conditions similar to those used by Torgov,[2,9] followed by hydrolysis gave the tricyclic intermediate 13. This on hydrogenation gave 14, whic was converted to the bridged steroid 15 by treatment with base.[10,11] The relative stereochemistry at C-9 in 14 and C-8, 13 and 14 in 15 was originally assigned on the basis of examination of molecular models. It has subsequently been confirmed by a single crystal X-ray analysis[12] of 15 (a stereographic plot is shown in Fig. 1).

This general type of approach to ring A bridged steroids has the potential of providing other stereoisomeric forms of such steroids. Furthermore, this new variant of the Torgov synthesis holds the promise of providing a new route to unbridged non-aromatic steroids with a C-19 methyl group.



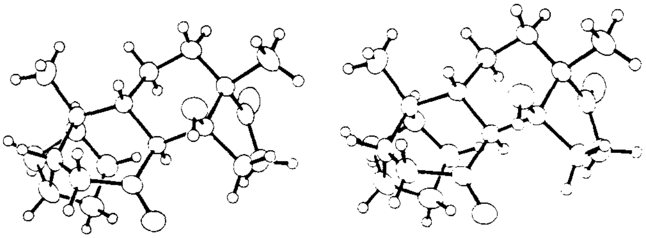


Figure 1

Acknowledgement. We thank the Natural Sciences and Engineering Research Council of Canada for support of this work.

References and Notes

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7. The relative stereochemistry at C-6 (steroid numbering) is assigned on the basis of ^{1}H nmr coupling of the proton at C-6 (dd, *J* =10, 2 Hz) and confirmed by the ready closure of the corresponding alcohol to an iodo ether on treatment with $I_2/NaHCO_3$.
8. Ir λ_{max} ($CHCl_3$): 5.80 µm; ^{1}H nmr δ ($CDCl_3$): 1.89 (s, 3H), 2.1 (m, 2H), 2.4 - 3.8 (m, 6H), 4.91 (d, *J* = 11 Hz, 1H), 5.20 (d, *J* = 17.5 Hz, 1H), 5.3 - 5.6 (m, 2H), 5.60 (dd, *J* = 11, 17.5 Hz, 1H); ^{13}C nmr δ ($CDCl_3$): 18.8 (q), 38.1 (t), 39.4 (d), 40.2 (t), 44.3 (d), 48.3 (d), 51.6 (d), 111.5 (t), 128.4 (s), 129.4 (d), 131.1 (d), 132.2 (d), 138.7 (s), 212.9 (s).
9. Use of other conditions[3] did not give the desired product.
10. M.p. 210 - 212°C; ir λ_{max} ($CHCl_3$): 3.00, 5.76, 5.90 µm; ^{1}H nmr δ ($CDCl_3$): 1.00 (s, 3H), 1.09 (s, 3H), 1.1 - 3.2 (m, 22H); ^{13}C nmr δ ($CDCl_3$): 19.7, 21.5, 24.8, 26.1, 30.1, 30.8, 31.3, 34.5, 39.2, 39.3, 41.8, 42.4, 43.8, 46.9, 47.0, 53.8, 55.0, 80.2, 216.7, 218.6.
11. The yield in each step is >85%, with the exception of the conversion of **12** to **13** where the yield was 26%; this can clearly be improved upon because **12** is accompanied by the corresponding dienol methyl ether.
12. Crystal Data: $C_{20}H_{28}O_3$, fw = 316.4, triclinic, space group $P\bar{1}$, a = 7.408(2), b = 10.758(2), c = 11.687(2) Å, α = 66.02(1), β = 86.72(2), γ = 74.85(2)°, U = 820 Å^3, D_c = 1.28 gcm^{-3} for Z = 2. Enraf-Nonius CAD4 diffractometer, Mo K$\bar{\alpha}$ radiation (λ = 0.71069 Å), h, ±k, ±ℓ quadrants with 2θ ⩽ 55°, 4158 reflections. Structure soln. by direct methods, final R(w^R) = 0.0408(0.0518) for 2800 observed (I>3σ(I)) reflections.

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