

A Wagner–Meerwein Rearrangement of the Cholestane Skeleton induced by a Long-range Intramolecular Hydrogen Abstraction by Alkoxy Radicals; the First Example of Long-range Intramolecular Addition of an Alkoxy Radical to a Carbon–Carbon Double Bond

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The formation of a novel macrocyclic ether lactone, induced by a series of long-range intramolecular reactions involving the first example of a long-range intramolecular addition of an alkoxy radical to a remote carbon–carbon double bond, accompanies the long-range intramolecular oxygenation of C(15) of the cholestane skeleton.

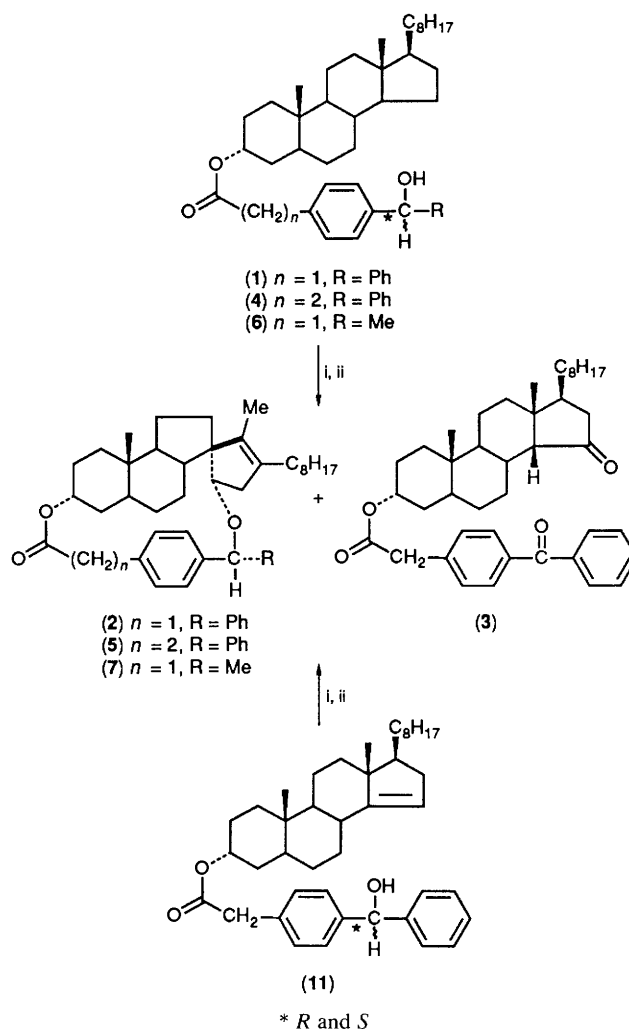
The preceding communication¹ described the one-step introduction of a carbonyl group to C(15) of the androstane skeleton based on a long-range intramolecular hydrogen

abstraction by alkoxy radicals generated by the irradiation of hypoiodites of androstane esters carrying a benzhydryl group. We have recently found that when cholestane ester (**1**) is

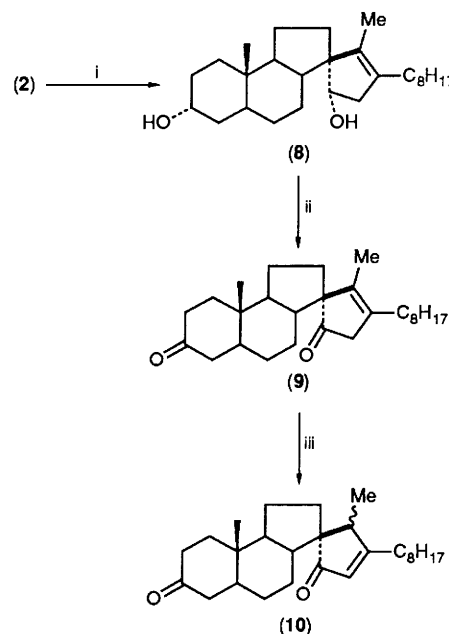
subjected to long-range oxygenation, a second product (2)[†] is obtained in 8% yield, together with the expected 15-one (3)[†] in 12% yield. This communication deals with its structure determination and genesis. We have proved that it is a novel macrocyclic ether lactone (2) and that its genesis involves the first example of a long-range intramolecular addition of an alkoxy radical to a remote carbon-carbon double bond of an alkene, arising from a long-range hydrogen abstraction by the alkoxy radical.

High-resolution MS indicated that the product (2) had the molecular formula C₄₂H₅₆O₃. The IR spectrum exhibited a lactone carbonyl at 1710 cm⁻¹, but showed no band assignable to the hydroxy group. The ¹H NMR spectrum (400 MHz) exhibited a singlet (1H) at δ 5.36 and a triplet (1H) at δ 4.17 (*J* 7.6 Hz), assignable to a proton of the ArCH(OR)C₆H₄ type and a proton attached to a carbon carrying an alkoxy group. There was also a singlet (3H) at δ 1.41, assignable to a methyl group attached to the trigonal carbon. These results indicated that the product is a macrocyclic ether lactone.

Treatment of lactone (2) with sodium-liquid ammonia cleanly removed the non-steroidal portion of the molecule and gave a crystalline diol (8)[†] (60%). The ¹H NMR spectrum (400 MHz) exhibited a 1H double doublet at δ 4.03 (*J* 6.0 and 3.1 Hz) and a 3H triplet (*J* 2.0 Hz, a homoallylic coupling) at δ 1.50, assignable to a proton attached to a carbon carrying a hydroxy group and a methyl group attached to the trigonal carbon, respectively. The diol (4) was then converted to diketone (9)[†] with pyridinium chlorochromate (PCC) in dichloromethane. The IR spectrum of diketone (9) exhibited two bands, at 1738 and 1712 cm⁻¹, assignable to the 3-one and

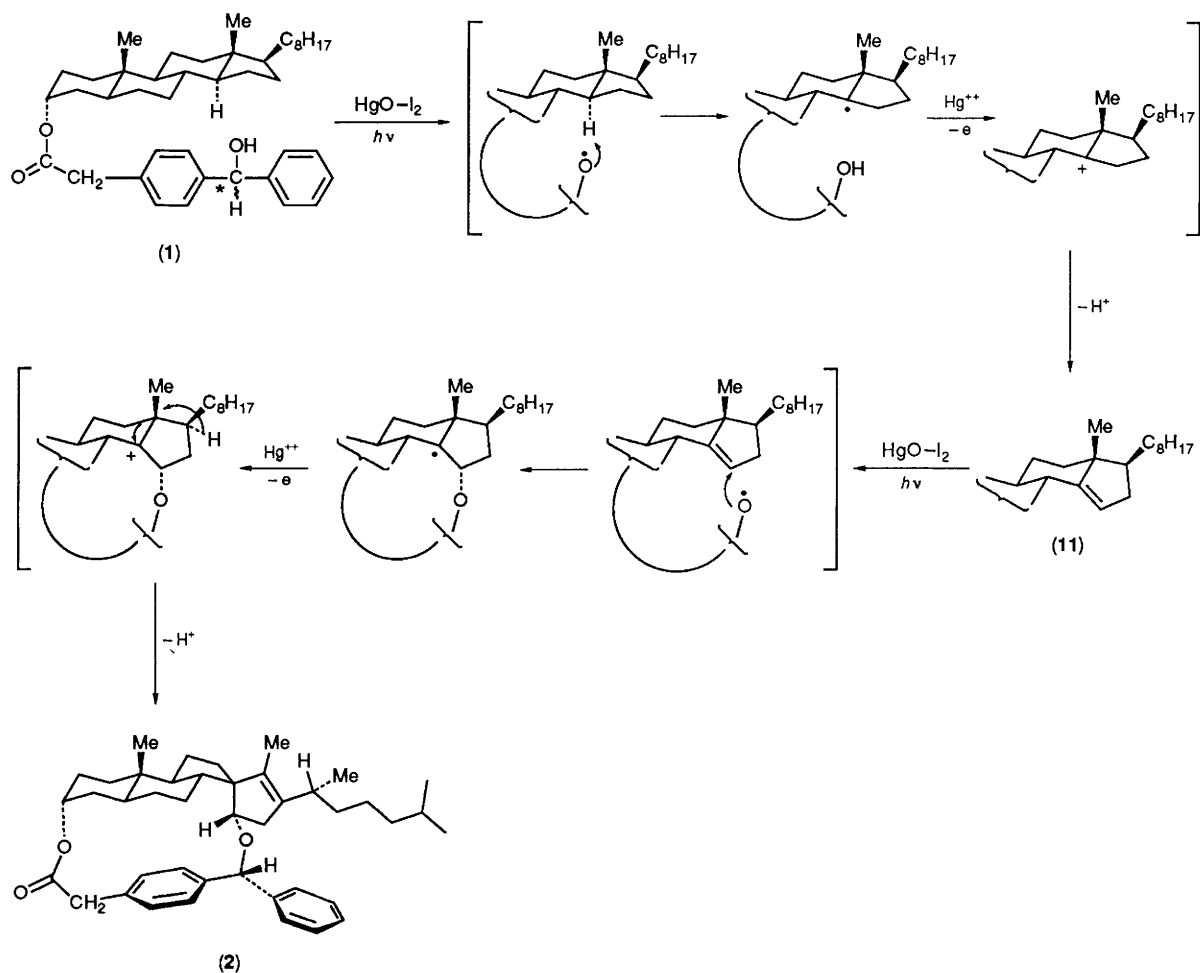


Scheme 1. Reagents and conditions: i, HgO-I₂-CCl₄; ii, hv.



Scheme 2. Reagents and conditions: i, Na-*liq.* NH₃; ii, PCC-CH₂Cl₂; iii, 5% KOH-MeOH, reflux, 40 min.

[†] Selected data for (2): a glass; ν_{\max} (neat) 1710 (C=O) cm⁻¹; δ_{H} (400 MHz) 0.60 (3H, s, 19-H), 1.42 (3H, s, 18-H), 2.12 (1H, ddq, *J* 14.9, 7.6, and 2.1 Hz, 16 α -H), 2.26 (1H, ddd, *J* 12.9, 9.5, and 4.8 Hz, 12 α -H), 2.46 (1H, ddq, *J* 14.9, 7.6, and 1.2 Hz, 16 β -H), 2.46 (1H, sextet, *J* 6.6 Hz, 20-H), 3.53 and 3.67 (each 1H, AB q, *J* 15.0 Hz, COCH₂), 4.17 (1H, t, *J* 7.6 Hz, 15 β -H), 4.81 (1H, br. s, 3 β -H), and 5.36 [1H, s, CH(O-)-Ph]. *m/z* (FD MS used throughout) 610 [(*M* + 2H)⁺ 13], 609 [*M* + H)⁺, 42], and 608 (*M*⁺, 100%). For (3): a glass, ν_{\max} (neat) 1732 (C=O), 1662 (C=O), 1610 (C=C), and 1580 cm⁻¹ (C=C); δ_{H} (270 MHz) 0.73 (3H, s, 19-H), 1.15 (3H, s, 18-H), 3.72 (2H, s, COCH₂), and 5.03 (1H, br. s, 3 β -H); *m/z* 626 [(*M* + 2H)⁺, 18], 625 [(*M* + H)⁺, 43], and 624 (*M*⁺, 100%). For (8): m.p. 147–149°C (light petroleum); ν_{\max} (Nujol) 3320 cm⁻¹ (OH); δ_{H} (400 MHz) 0.76 (3H, s, 19-H), 1.50 (3H, t, *J* 2.0 Hz, 18-H), 2.01 (1H, ddd, *J* 13.7, 8.8, and 6.5 Hz, 12 α -H), 2.07 (1H, ddq, *J* 16.0, 3.1, and 2.0 Hz, 16 α -H), 2.42 (1H, ddq, *J* 16.0, 6.0, and 2.0 Hz, 16 β -H), 2.51 (1H, sextet, *J* 6.9 Hz, 20-H), 4.03 (1H, dd, *J* 6.0 and 3.1 Hz, 15 β -H), and 4.08 (1H, br. s, 3 β -H). *m/z* 404 [(*M* + 2H)⁺, 7] and 403 [(*M* + H)⁺, 32%]. For (9): an oil; δ_{H} (400 MHz) 0.96 (3H, s, 19-H), 1.67 (3H, t, *J* 2.2 Hz, 18-H), 2.60 [2H, AB type dq, *J* 20.1 (d) and 2.4 (q) Hz, 16-H], 2.67 (1H, br. m, 20-H); *m/z* 400 [(*M* + 2H)⁺, 7], 399 [(*M* + H)⁺, 32], and 398 (*M*⁺, 100%). For (10): an oil; ν_{\max} (neat) 1710 (C=O), 1695 (C=O), and 1611 cm⁻¹ (C=C); δ_{H} (400 MHz) 0.93 (3H, s, 19-H), 1.15 (3H, d, *J* 6.7 Hz, 18-H), 2.64 (1H, q, *J* 6.7 Hz, 17-H), 2.82 (1H, sextet, *J* 7.2 Hz, 20-H), and 5.77 (1H, s, 16-H); *m/z* 400 [(*M* + 2H)⁺, 20], 399 [(*M* + H)⁺, 76], and 398 (*M*⁺, 100%). For (5): a glass; ν_{\max} (neat) 1720 cm⁻¹ (C=O); δ_{H} (270 MHz) 0.61 (3H, s, 19-H), 1.40 (3H, s, 18-H), 2.14 (1H, ddq, *J* 15.0, 6.6, and 2.6 Hz, 15 α -H), 2.25 (1H, ddd, *J* 12.5, 8.4, and 3.0 Hz, 12 α -H), 2.47 [(1H, dq, *J* 1.1 and 6.6 Hz, 16 β -H), 2.47 (1H, sextet, *J* 6.6 Hz, 20-H)], 2.7–3.1 (4H, m, COCH₂CH₂), 4.11 (1H, t, *J* 7.3 Hz, 15 β -H), 4.84 (1H, br. s, 3 β -H), and 5.32 [1H, s, CH(O-)-Ph]; *m/z* 624 [(*M* + 2H)⁺, 11], 623 [(*M* + H)⁺, 57], and 622 (*M*⁺, 100%). For (7): a glass; ν_{\max} (neat) 1725 cm⁻¹ (C=O); δ_{H} (270 MHz) 0.58 (3H, s, 19-H), 1.37 (3H, s, 18-H), 1.51 [3H, d, *J* 6.6 Hz, CH(O-)-Me], 1.97–2.12 (2H, m, 12 α -H and 15 α -H), 2.39–2.53 (2H, m, 16 β -H and 20-H), 3.52 and 3.71 (each 2H, AB q, *J* 15.2 Hz, COCH₂), 3.91 (1H, t, *J* 7.3 Hz, 15 β -H), 4.31 [1H, q, *J* 6.6 Hz, CH(O-)-Me], and 4.81 (1H, br. s, 3 β -H); *m/z* 548 [(*M* + 2H)⁺, 21], 547 [(*M* + H)⁺, 72], 546 (*M*⁺, 100%).



* R and S

Scheme 3

a cyclopentanone carbonyl. Treatment of the diketone (9) with a base resulted in isomerization, giving an isomeric diketone (10),[†] the IR and UV spectra of which showed that it had a cyclopentenone structure [IR, 1695 cm⁻¹; UV λ_{max} (EtOH) 231 nm (ε 12800 dm³ mol⁻¹ cm⁻¹)]. These results, together with consideration of the reaction pathway (*vide infra*), suggested that the product is a macrocyclic ether lactone (2). The pathway to lactone (2), discussed below, required the stereochemistry of the cyclopentane moiety of lactone (2) to be as depicted. The configuration of the benzylic proton was then confirmed by NOE spectroscopy; irradiation of the 15β-proton resulted in an enhancement of the signal area of the benzylic proton, and *vice versa*.

The pathway through which product (2) is formed is outlined in Scheme 3. Thus, the alkoxy radical generated from ester (1) abstracts the C(14) hydrogen to give a carbon radical. A one-electron oxidation and removal of the C(14) proton gives an alkene intermediate (11). A long-range intramolecular addition of the alkoxy radical to the carbon-carbon double bond, followed by one-electron oxidation, gives the carbocation. Its Wagner-Meerwein rearrangement² gives macrocyclic ether lactone (2).

The existence of the intermediate alkene (11)³ was proved by the fact that both macrocyclic lactone (2) (7%) and 15-ketone (3) (15%) were obtained when alkene (11) was exposed to the oxygenation reaction conditions (*vide supra*). Finally, we found that the reaction of the analogous epimeric ester (4) or (6) under these conditions also afforded the macrocyclic ether lactone (5) or (7) in 2.3 and 27% yields, respectively (Scheme 1).[†]

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