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

Kazuhiko Orito, Masaru Ohto, and Hiroshi Suginome*

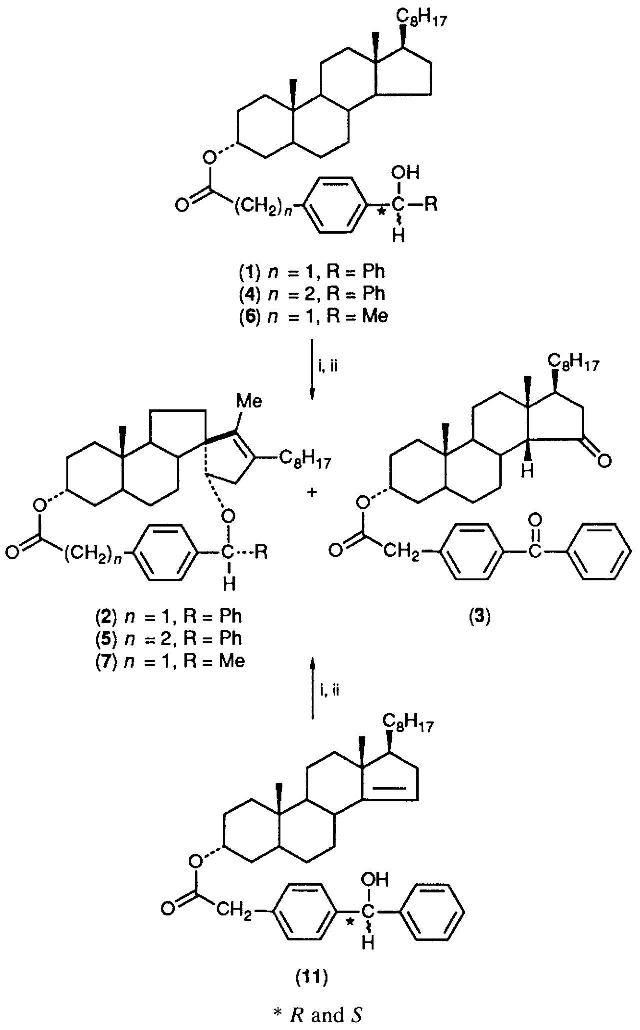
Organic Synthesis Division, Faculty of Engineering, Hokkaido University, Sapporo 060, Japan

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 alkoxyl radical to a remote carbon–carbon double bond, accompanies the long-range intramolecular oxygenation of C(15) of the cholestane skeleton.

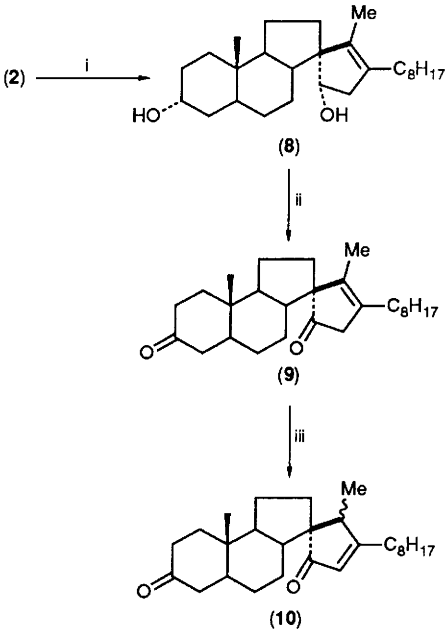
The preceding communication[1] described the one-step introduction of a carbonyl group to C(15) of the androstane skeleton based on a long-range intramolecular hydrogen abstraction by alkoxyl radicals generated by the irradiation of hypoiodites of androstane esters carrying a benzhydryl group. We have 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 alkoxyl radical to a remote carbon–carbon double bond of an alkene, arising from a long-range hydrogen abstraction by the alkoxyl radical.

High-resolution MS indicated that the product (**2**) had the molecular formula $C_{42}H_{56}O_3$. 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 $ArC\mathit{H}(OR)C_6H_4$ type and a proton attached to a carbon carrying an alkoxyl 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

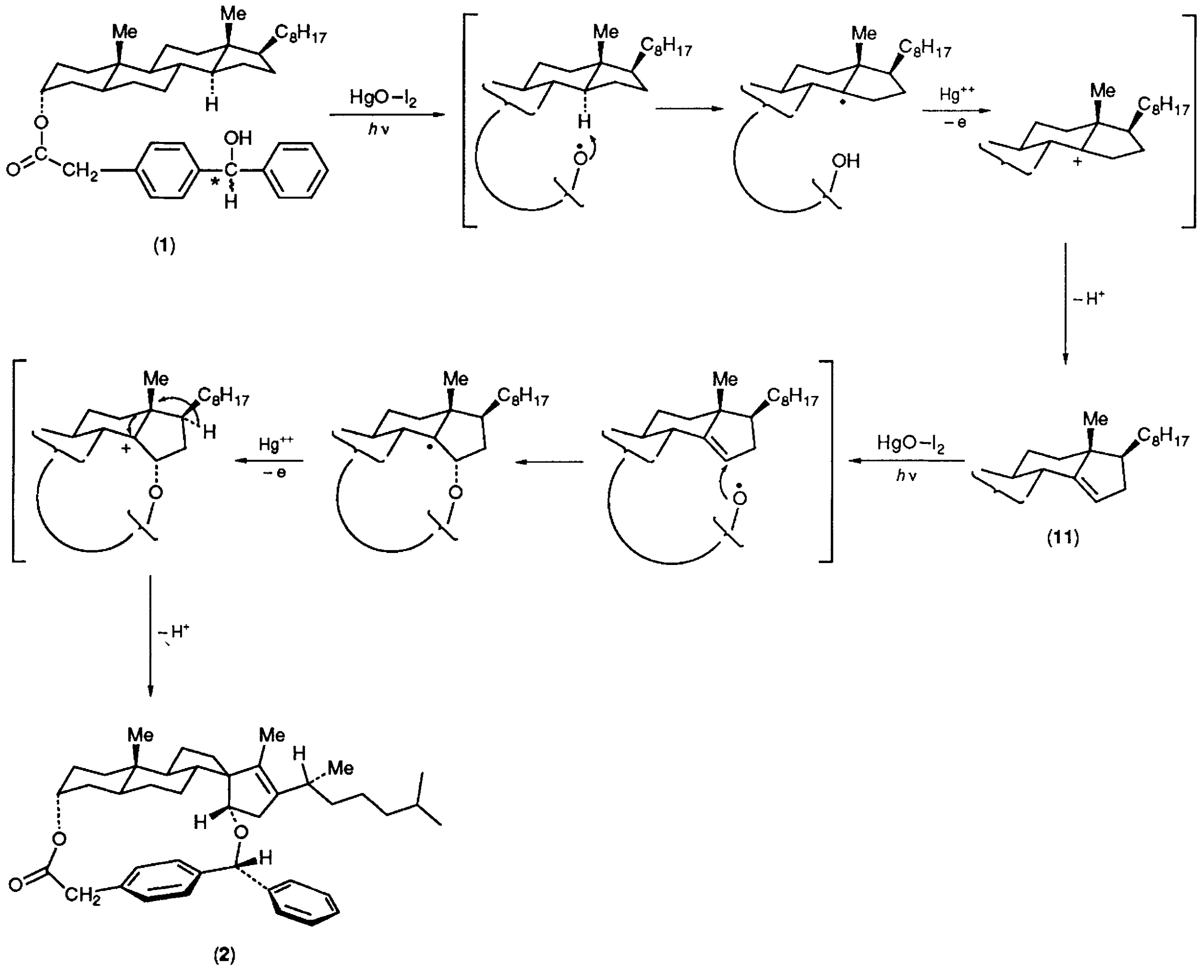


Scheme 1. *Reagents and conditions:* i, $HgO–I_2–CCl_4$; ii, *hv*.



Scheme 2. *Reagents and conditions:* i, Na–liq. NH_3; ii, $PCC–CH_2Cl_2$; iii, 5% KOH–MeOH, reflux, 40 min.

[†] *Selected data* for (**2**): a glass; $\nu_{max.}$ (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, 16α-H), 2.26 (1H, ddd, *J* 12.9, 9.5, and 4.8 Hz, 12α-H), 2.46 (1H, ddq, *J* 14.9, 7.6, and 1.2 Hz, 16β-H), 2.46 (1H, sextet, *J* 6.6 Hz, 20-H), 3.53 and 3.67 (each 1H, AB q, *J* 15.0 Hz, $COCH_2$), 4.17 (1H, t, *J* 7.6 Hz, 15β-H), 4.81 (1H, br. s, 3β-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, $\nu_{max.}$ (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, $COCH_2$), and 5.03 (1H, br. s, 3β-H); *m/z* 626 [$(M + 2H)^+$, 18], 625 [$(M + H)^+$, 43], and 624 (M^+, 100%). For (**8**): m.p. 147—149 °C (light petroleum); $\nu_{max.}$ (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, 12α-H), 2.07 (1H, ddq, *J* 16.0, 3.1, and 2.0 Hz, 16α-H), 2.42 (1H, ddq, *J* 16.0, 6.0, and 2.0 Hz, 16β-H), 2.51 (1H, sextet, *J* 6.9 Hz, 20-H), 4.03 (1H, dd, *J* 6.0 and 3.1 Hz, 15β-H), and 4.08 (1H, br. s, 3β-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; $\nu_{max.}$ (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; $\nu_{max.}$ (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, 15α-H), 2.25 (1H, ddd, *J* 12.5, 8.4, and 3.0 Hz, 12α-H), 2.47 [(1H, dq, *J* 1.1 and 6.6 Hz, 16β-H), 2.47 (1H, sextet, *J* 6.6 Hz, 20-H)], 2.7—3.1 (4H, m, $COCH_2CH_2$), 4.11 (1H, t, *J* 7.3 Hz, 15β-H), 4.84 (1H, br. s, 3β-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; $\nu_{max.}$ (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, 12α-H and 15α-H), 2.39—2.53 (2H, m, 16β-H and 20-H), 3.52 and 3.71 (each 2H, AB q, *J* 15.2 Hz, $COCH_2$), 3.91 (1H, t, *J* 7.3 Hz, 15β-H), 4.31 [1H, q, *J* 6.6 Hz, C*H*(O–)Me], and 4.81 (1H, br. s, 3β-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 dm^3 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 alkoxyl 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 alkoxyl radical to the carbon–carbon double bond, followed by one-electron oxidation, gives the carbocation. Its Wagner–Meerwein rearrangement[2] 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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