

A Long-range Intramolecular Functionalization by Alkoxy Radicals: a Long-range Intramolecular Oxygenation of C(15) of the Androstane Skeleton¹

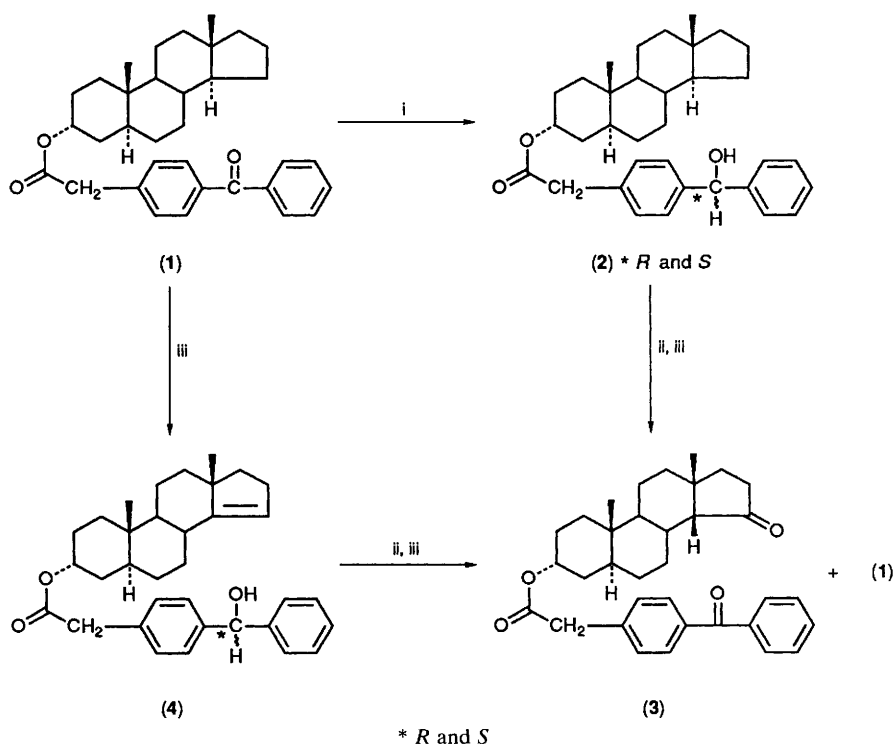
Kazuhiko Orito, Masaru Ohto, and Hiroshi Suginome*

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

The first example of a one-step introduction of a carbonyl group to C(15) of the 5 α -androstane skeleton, based on a long-range intramolecular hydrogen abstraction by alkoxy radicals, generated by irradiation of 5 α -androstane esters carrying a benzhydryl group in carbon tetrachloride containing mercury(II) oxide and iodine, is described.

In an earlier paper,² we reported a two-step long-range intramolecular hydroxylation of C(25) of the cholestane side-chain, based on a long-range intramolecular hydrogen

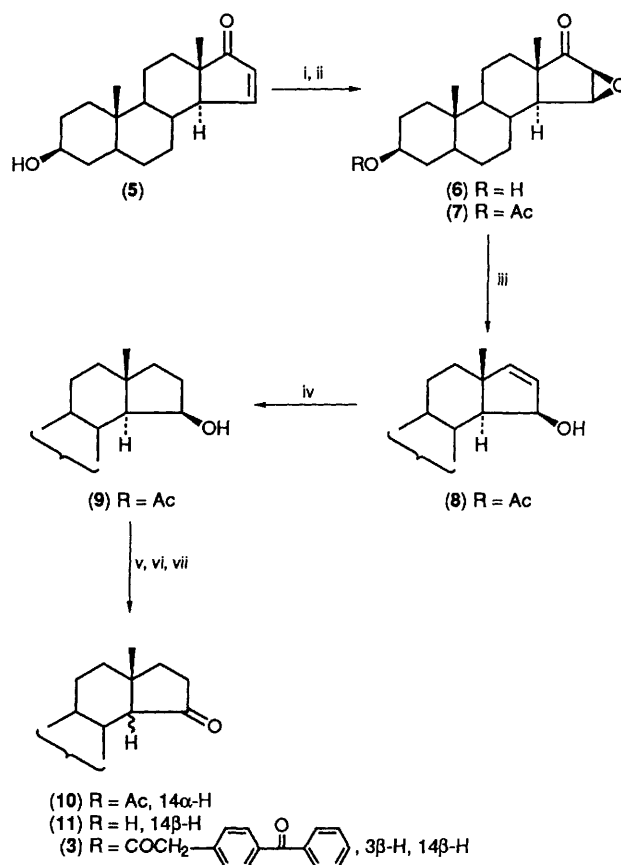
abstraction by alkoxy radicals generated by the irradiation of hypiodites of esters carrying a benzhydryl group. In this communication we report the one-step introduction of a



Scheme 1. Reagents and conditions: i, NaBH₄-MeOH, 25 °C; ii, HgO-I₂-CCl₄; iii, *hν*.

carbonyl group to C(15) of the androstane skeleton, based on the same strategy for intramolecular hydroxylation.² Thus, 5 α -androstane-3 α -yl-4-(hydroxyphenylmethyl)phenyl acetate (**2**)[†] was prepared by reducing the corresponding esters (**1**),[†] derived from benzophenone-4-carboxylic acid and 5 α -androstane-3 β -ol, with NaBH₄ (Scheme 1). Compound (**2**) was a mixture of epimers of the carbon carrying the hydroxy group. Irradiation of the hypiodite of (**2**) in carbon tetrachloride [prepared *in situ* with three equivalents of mercury(II) oxide and iodine] with a 450-W high-pressure Hg arc in a nitrogen atmosphere gave a mixture of products from which the 15-ketone (**3**)[†] arising from a long-range hydrogen abstraction and the parent ester (**1**) were isolated in 20 and 51% yields[‡] by means of preparative TLC.

The structure of ketone (**3**) was established as 15-oxo-5 α ,14 β -androstane-3 α -yl(4-benzoyl)phenylacetate by means of IR, MS, and ¹H NMR spectroscopy as well as by its independent synthesis, as outlined in Scheme 2. 17-Oxo-5 α -androst-15-en-3 β -ol (**5**),³ obtained from epiandrosterone, was transformed into 15 β ,16 β -epoxide (**6**)[†] with 30% hydrogen peroxide and sodium hydroxide (4 M) at room temperature. The epoxide (**6**) was converted to acetate (**7**),[†] which gave 3 β -acetoxy-5 α -androst-16-en-15 β -ol (**8**)[†] in 35% yield by treatment with 90% hydrazine and glacial acetic acid in methanol according to the procedure of Wharton.⁴ Catalytic hydrogenation of allylic alcohol (**8**) in ethanol over 5% Pd/C gave 3 β ,15 β -dihydroxy-5 α -androstane 3-acetate (**9**)[†] in 75% yield. Oxidation of 15 β -ol (**9**) in dichloromethane with pyridinium chlorochromate (PCC) gave 3 β -acetoxy-5 α -androstane-15-one (**10**)[†] in 99% yield. Heating a solution of ketone (**10**) in benzene containing 5% KOH-methanol under reflux gave 15-oxo-5 α ,14 β -androstane-3 β -ol (**11**)[†] in 73%



Scheme 2. Reagents and conditions: i, 30% H₂O₂-NaOH (4 M)-Bu^tOH, 17 h; ii, Ac₂O-pyridine, 25 °C; iii, 90% NH₂NH₂-MeOH-AcOH, room temp.; iv, Pd/C-EtOH-H₂, room temp.; v, PCC-CH₂Cl₂, room temp.; vi, 5% KOH-MeOH, reflux, 1 h; vii, PhCOC₆H₄CH₂CO₂H-PPh₃-EtO₂CN=NCO₂Et-THF, room temp., 20 h.

[†] Selected data for (**2**): a glass; ν_{\max} (neat) 3450 (OH), 1740 (C=O), and 1250 cm⁻¹ (C-O); δ_{H} (270 MHz) 0.69 (3H, s, 19-H), 0.77 (3H, s, 18-H), 3.59 (2H, s, COCH₂), 5.00 (1H, quint., *J* 2.6 Hz, 3 β -H), and 5.83 (1H, d, *J* 3.3 Hz, CHOH); *m/z* (FD MS used throughout) 500 (*M*⁺, 100%) and 483 [(*M*-OH)⁺, 93]. For (**1**): m.p. 135–137 °C (light petroleum); ν_{\max} (Nujol) 1735 (C=O) and 1655 cm⁻¹ (PhC=O); δ_{H} (270 MHz) 0.68 (3H, s, 19-H), 0.77 (3H, s, 18-H), 3.71 (2H, s, COCH₂), and 5.04 (1H, quint., *J* 2.6 Hz, 3 β -H); *m/z* 498 (*M*⁺, 100%). For (**3**): a glass; ν_{\max} (Nujol) 1725 (C=O) and 1655 cm⁻¹ (PhC=O); δ_{H} (270 MHz) 0.73 (3H, s, 19-H), 1.15 (3H, s, 18-H), 3.71 (2H, s, COCH₂), and 5.04 (1H, quint., *J* 2.6 Hz, 3 β -H); *m/z* 512 (*M*⁺, 100%). For (**6**): an oil; δ_{H} (90 MHz) 0.86 (3H, s, 19-H), 1.15 (3H, s, 18-H), 3.27 (1H, d, *J* 2.6 Hz, 15-H), 3.57 (1H, m, 3-H), and 3.81 (1H, d, *J* 2.6 Hz, 16-H). For (**7**): an oil; ν_{\max} (neat) 1730 (C=O) and 1248 cm⁻¹ (C-O); δ_{H} (90 MHz) 0.88 (3H, s, 19-H), 1.15 (3H, s, 18-H), 2.02 (3H, s, OCOMe), 3.27 (1H, d, *J* 2.6 Hz, 15-H), and 3.81 (1H, d, *J* 2.6 Hz, 16-H); *m/z* 346 (*M*⁺, 100%), 330 [(*M*-16)⁺, 6], and 287 [(*M*-OCOMe)⁺, 16%]. For (**8**): m.p. 157–159 °C (hexane); ν_{\max} (Nujol) 3458 (OH) and 1714 cm⁻¹ (C=O); δ_{H} (90 MHz) 0.90 (3H, s, 19-H), 1.83 (3H, s, 18-H), 2.02 (3H, s, OCOMe), 4.53 (1H, br. s, 15 α -H), 4.70 (1H, br. s, 3 α -H), 5.86 (1H, dd, *J* 5.8 and 2.6 Hz, 16-H), and 6.20 (1H, d, *J* 5.8 Hz, 17-H). For (**9**): m.p. 118.5–119.5 °C (hexane); ν_{\max} (Nujol) 3514 (OH) and 718 cm⁻¹ (C=O); δ_{H} (90 MHz) 0.86 (3H, s, 19-H), 0.99 (3H, s, 18-H), 2.01 (3H, s, OCOMe), 4.30 (1H, br. s, 15 α -H), and 4.70 (1H, br. s, 3 α -H). For (**10**): m.p. 149–154 °C (light petroleum); ν_{\max} (Nujol) 1730 (C=O) and 1244 cm⁻¹ (C-O); δ_{H} (90 MHz) 0.79 (3H, s, 18-H), 0.83 (3H, s, 19-H), 2.01 (3H, s, OCOMe), and 4.68 (1H, br. s, 3 α -H). For (**11**): m.p. 166–167.5 °C (hexane-acetone); ν_{\max} (Nujol) 3280, 3178 (OH), and 1739 cm⁻¹ (C=O); δ_{H} (90 MHz) 0.76 (3H, s, 19-H), 1.15 (3H, s, 18-H), 2.0–2.8 (3H, m, 14- and 16-H), and 3.59 (1H, br. s, 3 α -H). For (**4**): a glass; ν_{\max} (neat) 1732 (C=O) and 1662 cm⁻¹ (PhC=O); 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).

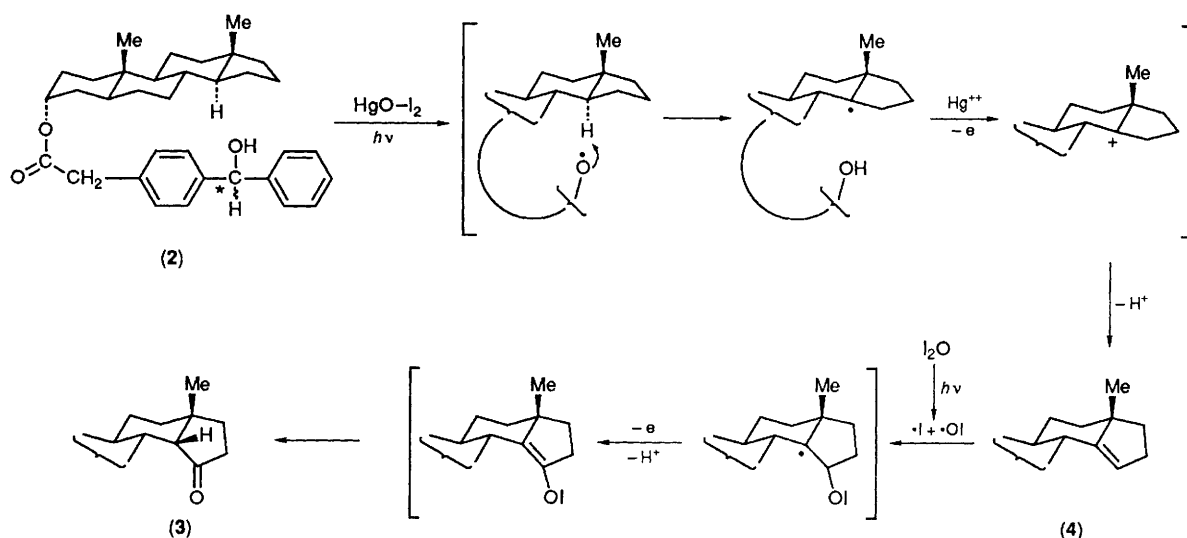
[‡] The yields are based on the converted starting materials.

yield. Its reaction with 4-benzoylphenyl acetic acid in the presence of triphenylphosphine and diethylazodicarboxylate⁵ in dry tetrahydrofuran (THF) gave 15-oxo-5 α ,14 β -androstane-3 α -yl 4-benzoylphenyl acetate as a glass, identical with ketone (**3**) obtained in the long-range reaction (*vide supra*).

The experiments described below proved that ketone (**3**) is formed *via* alkene (**4**)[†] as an intermediate. Thus, the irradiation of androstane alkene (**4**)⁶ in carbon tetrachloride containing mercury(II) oxide and iodine under the same conditions as for ester (**2**) gave *D*-ring ketone (**3**) in 32% yield. The pathway for formation of (**3**) is outlined in Scheme 3. Thus, the alkoxyl radical generated from esters (**2**) abstracts the C(14) hydrogen to give alkene (**4**) first. The addition of the iodoxy radical to (**4**), followed by a one-electron oxidation of the resulting radical, gives the *D*-ring ketone (**3**).

The long-range intramolecular functionalization reported herein is the first example in which a carbonyl group is introduced to a remote position in one step as the result of a long-range intramolecular hydrogen abstraction involving a 1,17-hydrogen transfer.[§]

[§] Satisfactory analytical and spectral results were obtained for all the compounds described in this paper.



*R and S

Scheme 3

This work was supported by a Grant-in-Aid for Special Project Research from the Japanese Ministry of Education, Science, and Culture.

Received, 27th February 1990; Com. 0/00907E

References

- 1 Previous paper in this series: K. Kobayashi, H. Shimizu, M. Itoh, and H. Suginome, *Bull. Chem. Soc. Jpn.*, in the press.
- 2 K. Orito, S. Satoh, and H. Suginome, *J. Chem. Soc., Chem. Commun.*, 1989, 1829.
- 3 P. N. Rao and A. H. Moore, Jr., *Steroids*, 1977, **29**, 171.
- 4 P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, 1961, **26**, 3615; C. Djerassi, G. von Mutzenbecher, J. Fajkos, D. H. Williams, and H. Bludzikiewicz, *J. Am. Chem. Soc.*, 1965, **87**, 817; T. Nambata, H. Hosoda, M. Usui, and L. Y. Ng, *Chem. Pharm. Bull.*, 1971, **19**, 2555.
- 5 A. K. Bose, B. Lal, W. A. Hoffman, and M. S. Manhas, *Tetrahedron Lett.*, 1973, 1619.
- 6 This alkene was prepared from ester (1) according to the reported procedure: R. Breslow, S. Baldwin, T. Flechtner, R. Kalicky, S. Liu, and W. Washburn, *J. Am. Chem. Soc.*, 1973, **95**, 3251.