A Long-range Intramolecular Functionalization by Alkoxyl Radicals: a Long-range Intramolecular Oxygenation of C(15) of the Androstane Skeleton[1]

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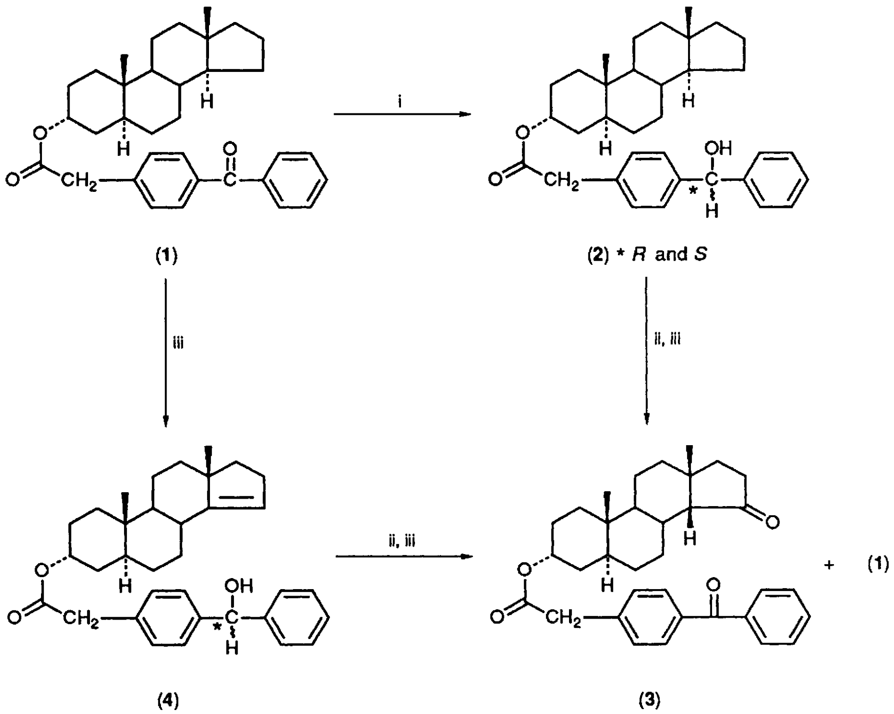
The first example of a one-step introduction of a carbonyl group to C(15) of the 5α-androstane skeleton, based on a long-range intramolecular hydrogen abstraction by alkoxyl radicals, generated by irradiation of 5α-androstane esters carrying a benzhydryl group in carbon tetrachloride containing mercury(II) 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 alkoxyl radicals generated by the irradiation of hypoiodites of esters carrying a benzhydryl group. In this communication we report the one-step introduction of a

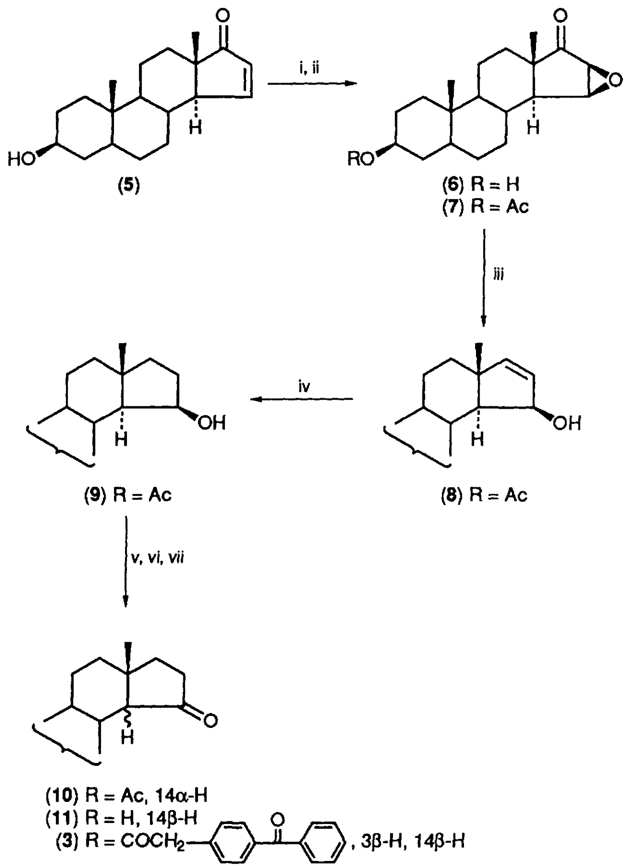


* *R* and *S*

Scheme 1. *Reagents and conditions*: i, $NaBH_4$–MeOH, 25 °C; ii, $HgO–I_2–CCl_4$; iii, *h*ν.

carbonyl group to C(15) of the androstane skeleton, based on the same strategy for intramolecular hydroxylation.[2] Thus, 5α-androstan-3α-yl-4-(hydroxyphenylmethyl)phenyl acetate (**2**)† was prepared by reducing the corresponding esters (**1**),† derived from benzophenone-4-carboxylic acid and 5α-androstan-3β-ol, with $NaBH_4$ (Scheme 1). Compound (**2**) was a mixture of epimers of the carbon carrying the hydroxy group. Irradiation of the hypoiodite 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-5α,-14β-androstan-3α-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-5α-androst-15-en-3β-ol (**5**),[3] obtained from epiandrosterone, was transformed into 15β,16β-epoxide (**6**)† with 30% hydrogen peroxide and sodium hydroxide (4 M) at room temperature. The epoxide (**6**) was converted to acetate (**7**),† which gave 3β-acetoxy-5α-androst-16-en-15β-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 3β,15β-dihydroxy-5α-androstane 3-acetate (**9**)† in 75% yield. Oxidation of 15β-ol (**9**) in dichloromethane with pyridinium chlorochromate (PCC) gave 3β-acetoxy-5α-androstan-15-one (**10**)† in 99% yield. Heating a solution of ketone (**10**) in benzene containing 5% KOH–methanol under reflux gave 15-oxo-5α,14β-androstan-3β-ol (**11**)† in 73% yield. Its reaction with 4-benzoylphenyl acetic acid in the presence of triphenylphosphine and diethylazodicarboxylate[5] in dry tetrahydrofuran (THF) gave 15-oxo-5α,14β-androstan-3α-yl 4-benzoylphenyl acetate as a glass, identical with ketone (**3**) obtained in the long-range reaction (*vide supra*).



Scheme 2. *Reagents and conditions*: i, 30% H_2O_2–NaOH (4 M)–Bu^tOH, 17 h; ii, Ac_2O–pyridine, 25 °C; iii, 90% NH_2NH_2–MeOH–AcOH, room temp.; iv, Pd/C–EtOH–H_2, room temp.; v, PCC–CH_2Cl_2, room temp.; vi, 5% KOH–MeOH, reflux, 1 h; vii, $PhCOC_6H_4CH_2CO_2H$–PPh_3–$EtO_2CN{=}NCO_2Et$–THF, room temp., 20 h.

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 iodoxyl 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.§

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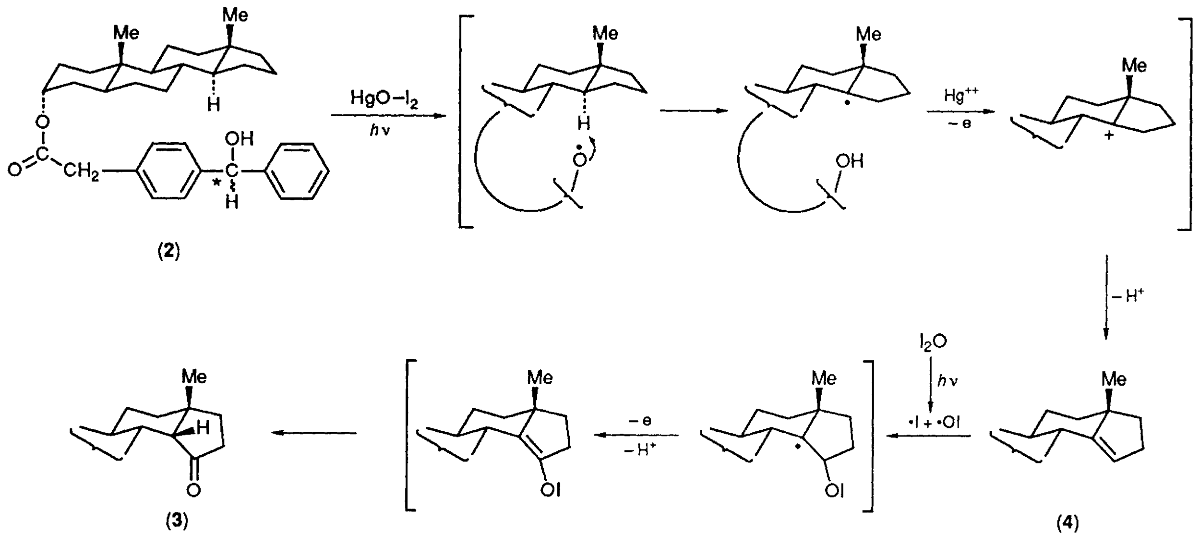
† *Selected data* for (**2**): a glass; $\nu_{max.}$ (neat) 3450 (OH), 1740 (C=O), and 1250 cm^{-1} (C–O); δ_H (270 MHz) 0.69 (3H, s, 19-H), 0.77 (3H, s, 18-H), 3.59 (2H, s, $COCH_2$), 5.00 (1H, quint., *J* 2.6 Hz, 3β-H), and 5.83 (1H, d, *J* 3.3 Hz, C*H*OH); *m/z* (FD MS used throughout) 500 (M^+, 100%) and 483 [$(M-OH)^+$, 93]. For (**1**): m.p. 135—137 °C (light petroleum); $\nu_{max.}$ (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, $COCH_2$), and 5.04 (1H, quint., *J* 2.6 Hz, 3β-H); *m/z* 498 (M^+, 100%). For (**3**): a glass; $\nu_{max.}$ (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, $COCH_2$), and 5.04 (1H, quint., *J* 2.6 Hz, 3β-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; $\nu_{max.}$ (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); $\nu_{max.}$ (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, 15α-H), 4.70 (1H, br. s, 3α-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); $\nu_{max.}$ (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, 15α-H), and 4.70 (1H, br. s, 3α-H). For (**10**): m.p. 149—154 °C (light petroleum); $\nu_{max.}$ (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, 3α-H). For (**11**): m.p. 166—167.5 °C (hexane–acetone); $\nu_{max.}$ (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, 3α-H). For (**4**): a glass; $\nu_{max.}$ (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, $COCH_2$), and 5.03 (1H, br. s, 3β-H).

‡ The yields are based on the converted starting materials.

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



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Scheme 3

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