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LONG-RANGE INTRAMOLECULAR FUNCTIONALIZATION BY ALKOXYL RADICALS; LONG-RANGE INTRAMOLECULAR DOUBLE FUNCTIONALIZATION OF RING C OF CHOLESTANE AND ANDROSTANE SKELETONS[1]

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Abstract : A one-step double introduction of a carbon-carbon double bond and oxygen functions to ring C of 5α-steroid skeletons, based on a long-range intramolecular hydrogen abstraction by alkoxyl radicals generated from the esters of 5α-cholestan-3α-ol carrying a benzhydryl group, is described.

In previous papers[1, 2] we reported on a two-step long-range intramolecular hydroxylation of C(25) in cholestane side chain and a one-step introduction of a carbonyl group to C(15) of the 5α-androstane skeleton. These oxygenations were based on a long-range intramolecular hydrogen abstraction by alkoxyl radicals generated by irradiation of 5α-cholestane and 5α-androstane esters carrying a benzhydryl group in carbon tetrachloride which contains mercury(II) oxide and iodine.

In this communication we wish to report on a one-step double introduction of a carbon-carbon double bond and the oxygen functions regarding the C-ring(s) of steroidal skeletons. The process is based on a strategy for intramolecular functionalizations, which has been reported in the previous papers.[1,2]

The long-range functionalization of the C-ring of a steroidal skeleton has previously been achieved by Breslow and colleagues[3,4] in their well-known series of studies concerning the biomimetic control of chemical selectivity;[5] a free radical chain chlorination or a radical-relay chlorination using esters of 3α-hydroxy-5α-cholestane with *m*-iodobenzoic acid, thus, resulted respectively in the introduction of chlorine at C-9 of the skeleton; elimination of the chlorine with a base gave 3α-hydroxy-5α-cholest-9-ene.

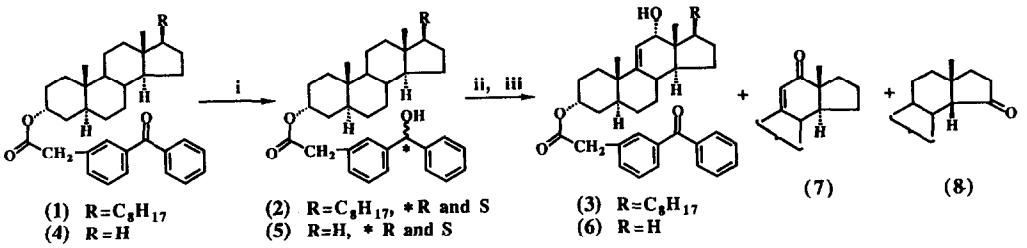
Our selective functionalization of the C-rings of the 5α-cholestane and 5α-androstane skeletons has been achieved by using esters (2) or (5) derived from esters (1) or (4) of benzophenone-3-acetic acid with 5α-cholestan-3α-ol or 5α-androstan-3α-ol. Thus, 5α-cholestan-3α-yl-3(hydroxyphenylmethyl)phenyl acetate (2) and its androstane homologue (5) were prepared by reducing the corresponding esters, (1) or (4), with $NaBH_4$. Each ester was a mixture of epimers with regard to a carbon atom carrying a hydroxyl group. Irradiation of the hypoiodite of the epimeric ester (2) in carbon tetrachloride (prepared *in situ* with 3 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 an allylic alcohol (3),[6] arising from long-range hydrogen abstraction, and the parent esters (1) were isolated in 15 and 43% yields by means of preparative TLC. Similar irradiation of the hypoiodites of the epimeric ester (5) gave an allylic alcohol (6)[7] (3.7%), an α,β-unsaturated ketone (7)[8] (6.6%), a 15-ketone (8)[9] (5.8%), and the parent ketone (4) (68.6%). The structure of the allylic alcohol (3) was established to be 12α-hydroxyandrost-9(11)-en-3α-yl(3-benzoyl) phenylacetate (3) by means of IR, MS, and ^{1}H NMR spectroscopy as well as by its conversion to steroids with unambiguous structures; the oxidation of the allylic alcohol with pyridinium chlorochromate (PCC) (87% yield), followed by hydrolysis of the resulting α,β-unsaturated ketone with potassium hydroxide, gave the corresponding 3α-ol(11) (66% yield). It was identical to the 3α-hydroxy-5α-cholest-9(11)-en-12-one (11) prepared by the oxidation of 3α-hydroxy-5α-cholest-9(11)-ene acetate (12)[10] with di-*t*-butylchromate, followed by the hydrolysis of the resulting acetate (10). The direct hydrolysis of allylic alcohol (3) with potassium hydroxide, on the other hand, gave a diol (14)[11] which was identical with 3α, 12α-dihydroxy-5α-cholest-9 (11)-ene (14) (*vide infra*). The structures of allylic alcohol (6), α,β-unsaturated ketone (7) and 15-ketone (8) were confirmed by means of spectroscopy as well as by removing their nonsteroidal portion to give the corresponding 3α-ols.

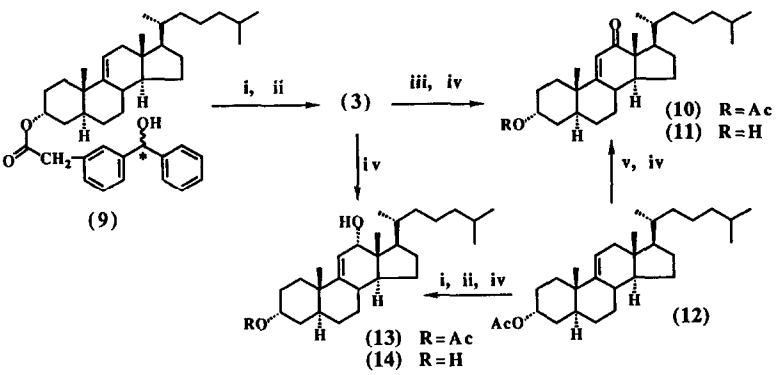
Allylic alcohols (3) and (6) are formed *via* an intermediate olefin, such as (9). This is because the irradiation of cholest-9(11)-en-3α–yl 3(hydroxyphenylmethyl) phenyl acetate (9)[12] in carbon tetrachloride containing mercury(II) oxide and iodine under the conditions mentioned above gave allylic alcohol (3) in 36 % yield. It has also been found that the irradiation of 3α-hydroxy-5α-cholest-9-ene acetate (12) in carbon tetrachloride containing mercury(II) oxide and iodine gave 3α,12α-dihydroxy-5α-cholest-9-ene 3-acetate (13)[13] (40%), the hydrolysis of which with potassium hydroxide gave the corresponding 3α-ol (14), identical to the specimen obtained by the hydrolysis of product (3) arising from a long-range reaction (*vide supra*).

The pathways of the formation of allylic alcohols (3) and (6) and α,β-unsaturated ketone (7) are summarized in Scheme 3. The alkoxyl radical (A) generated from ester (2) or (5), thus, intramolecularly abstracts the C(9) hydrogen to give olefin (9) or (15) *via* intermediate species (B) and (C). The abstraction of a hydrogen from the C(12) of olefin (9) or (15) by the iodoxyl radicals followed by a one-electron oxidation of the resulting allylic radical (D) generates an allylic cation (E). The reaction of the cation (E) with iodine oxide gives 12α-ol hypoiodite (F), from which products (3) and (6) were formed. A loss of 12β-hydrogen from the alkoxyl radical (G) leading to enone (7) may take place by either a β-scission or a hydrogen abstraction by the iodoxyl radicals.

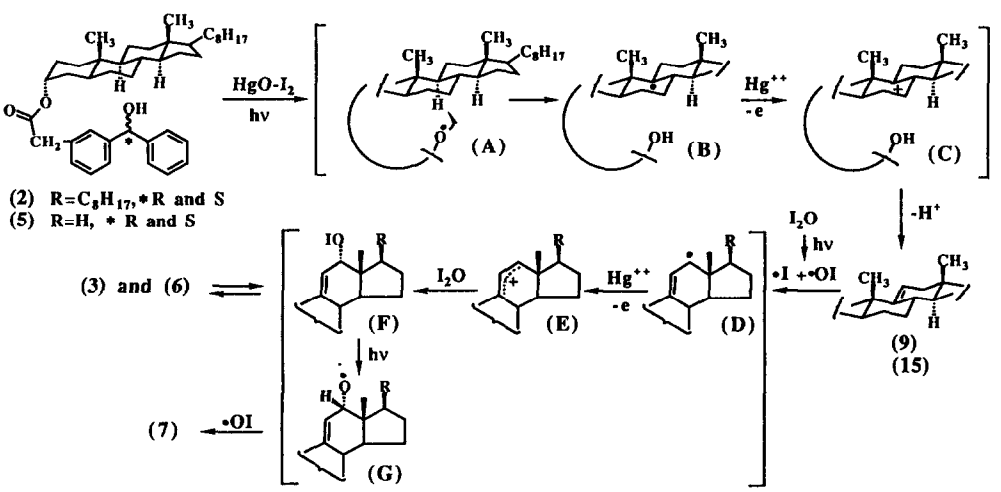
The present long-range intramolecular functionalization is the first example in which an α-oxygenated carbon-carbon double bond is introduced into a remote position in one-step as the result of a long-range intramolecular hydrogen abstraction by alkoxyl radicals which involves a 1,13 hydrogen transfer.



Scheme 1. *Reagents and conditions:* **i**, $NaBH_4$-MeOH, 25°C; **ii**, $HgO\text{-}I_2\text{-}CCl_4$; **iii**, hν.



Scheme 2. *Reagents and conditions:* **i**, $HgO\text{-}I_2\text{-}CCl_4$; **ii**, hν; **iii**, $PCC\text{-}CH_2Cl_2$, r.t.; **iv**, KOH-MeOH, reflux, 1.5-2.0 h; **v**, $CrO_2(O^tBu)_2\text{-}Ac_2O\text{-}AcOH$, reflux, 3 h.



Scheme 3

References and Notes

1 Previous paper in this series. K. Orito, M. Ohto, and H. Suginome, *J. Chem. Soc., Chem. Commun.*, in press.

2 K. Orito, S. Satoh, and H. Suginome, *J. Chem. Soc. Chem. Commun.*, 1989, 1829.

3 R. Breslow, R. J. Corcoran, J. A. Dale, S. Liu and P. Kalicky, *J. Amer. Chem. Soc.*, 1974, *96*, 1973.

4 R. Breslow, R. J. Corcoran, and B. B. Snider, *J. Amer. Chem. Soc.*, 1974, *96*, 6791.

5 E. g., R. Breslow, in "Design and Synthesis of Organic Molecules based on Molecular Recognition", ed. B. van Birst, Springer-Verlag, Berlin/Heidelberg, 1986, pp. 185-197.

6 A glass; vmax (neat) 3448 (OH), 1732 (C=O), 1659 (C=O), 1600 (C=C), and 1580 cm^{-1} (C=C); δ (270 MHz), 0.61 (3H, s, 18-H), 0.89 (3H, s, 19-H), 3.64, and 3.73 (each 1H AB type *J* 14.8 Hz, $COCH_2$), 3.77(1H, d, *J* 5.5 Hz, 12β-H), 5.02 (1H, quintet, *J* 2.6 Hz, 3β-H), and 5.56 (1H, d, *J* 5.5 Hz, 11-H); FD-MS: *m/z* 513 $[(M+H)^+$, 15], 512 (M^+, 100).

7 A glass; vmax (neat) 3494 (OH), 1733 (C=O), 1657 (C=O), 1599 (C=C), and 1580 cm^{-1} (C=C); δ (270 MHz), 0.53 (3H, s, 18-H), 0.89 (3H, s, 19-H), 1.01 (3H, d, *J* 6.6 Hz, 21-H), 3.64 and 3.72 (each 1H, AB q. *J* 14.7 Hz, $COCH_2$), 3.91 (1H, d, *J* 4.4 Hz, 12β-H), 5.01 (1H, br s, 3β-H), and 5.48 (1H, d, *J* 4.4 Hz, 11-H); FD-MS: *m/z* 624 (M^+, 100).

8 A glass; vmax (neat) 1732 (C=O), 1664 (C=O), 1600 (C=C), and 1580 cm^{-1} (C=C); δ (270 MHz) 0.90 (3H, s, 18-H), 1.02 (3H, s, 19-H), 3.68 (2H, s, $COCH_2$), 5.05 (1H, quintet, *J* 2.6 Hz, 3β-H), and 5.68 (1H, d, *J* 1.8 Hz, 11-H); FD-MS: *m/z* 512 $[(M+2H)^+$, 6], 511 $[(M+H)^+$, 16], 510 (M^+, 36%).

9 13A glass; 1733 (C=O), 1662 (C=O), 1600 (C=C), and 1580 cm^{-1}, (C=C); δ (90 MHz) 0.73 (3H, s, 19-H), 1.15 (3H, s, 18-H), 2.10-2.65 (3H, m, 14β-, 16α, and 16β-H), 3.69 (2H, s, $COCH_2$), and 5.00 (1H, br s, 3β-H); FD-MS *m/z* 514 $[(M+2H)^+$, 19], 513 $[(M+H)^+$, 53], and 512 (M^+, 100%).

10 R. Breslow, R. J. Corcoran, B. B. Snider, R. J. Doll, P. L. Khanna, and R. Kaleya, 1977, 99, 905.

11 An oil; vmax 3404 cm^{-1} (OH); δ (270 MHz) 0.56 (3H, s, 18-H), 0.93 (3H, s, 19-H), 0.98 (3H, d, *J* 6.6 Hz, 21-H), 3.94 (1H, *d J* 5.1 Hz, 12β-H), 4.05 (1H, br s, 3β-H), and 5.56 (1H, d, *J* 5.1 Hz, 11-H); FD-MS: *m/z* 403 $[(M+H)^+$, 29], 402 (M^+, 100).

12 A glass; vmax 3435 (OH) and 1730 cm^{-1} (C=O); δ (270 MHz) 0.59 (3H, s, 18-H), 0.90 (3H, s, 19-H), 3.60 (2H, s, $COCH_2$), 5.01 (1H, br s, 3β-H), 5.22 (1H, d, *J* 4.8 Hz, 11-H), 5.82 (1H, d, *J* 3.3 Hz, *CH*OH); EI-MS: *m/z* 610 (M^+, 3).

13 An oil; vmax 3398 (OH) and 1736 cm^{-1} (C=O); δ (90 MHz) 0.57 (3H, s, 19-H), 0.95 (3H, s, 19-H), 0.99 (3H, d, *J* 6.6 Hz, 21-H), 2.02 (3H, s, $COCH_3$), 3.97 (1H, d, *J* 5.1 Hz, 12β-H), 5.02 (1H, br s, 3β-H), and 5.54 (1H, d, *J* 5.1 Hz, 11-H); EI-MS: *m/z* 444 (M^+, 16).

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