A Long-range Intramolecular Functionalization by Alkoxyl Radicals: a Long-range Intramolecular Hydroxylation of C(25) of Cholestane Side Chain[1]

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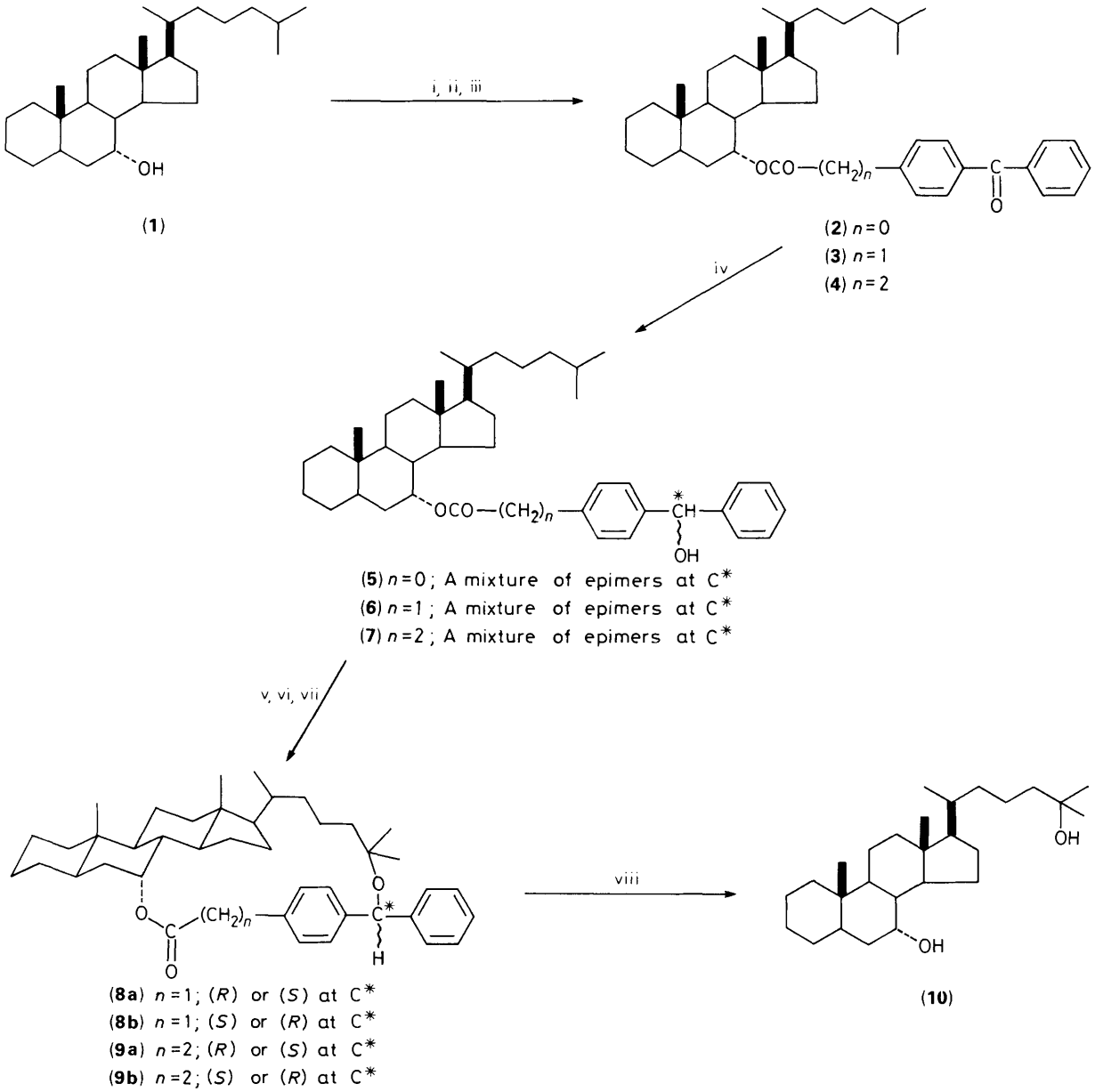
Alkoxyl radicals generated by the irradiation of hypoiodites of 5α-chlolestan-7α-yl-4-(hydroxyphenylmethyl)-phenylacetates and 5α-cholestan-7α-yl-3-[4-(hydroxyphenylmethyl)phenyl] propionates, respectively, abstracted a hydrogen from the remote C(25) of their cholestane side chain to give novel macrocyclic ether lactones which gave 5α-cholestane-7α, 25-diol by reduction with Na and liquid ammonia in good yields.

Many studies have been carried out on functionalization of unactivated C–H bonds *via* an intramolecular abstraction of hydrogen attached to a carbon atom by an alkoxyl radical[2] since the importance of the process in organic synthesis has been shown by Barton and his colleagues.[3] The intramolecular hydrogen abstraction by an alkoxyl radical that demands a



(1)

(2) *n* = 0
(3) *n* = 1
(4) *n* = 2

(5) *n* = 0; A mixture of epimers at C*
(6) *n* = 1; A mixture of epimers at C*
(7) *n* = 2; A mixture of epimers at C*

(8a) *n* = 1; (*R*) or (*S*) at C*
(8b) *n* = 1; (*S*) or (*R*) at C*
(9a) *n* = 2; (*R*) or (*S*) at C*
(9b) *n* = 2; (*S*) or (*R*) at C*

(10)

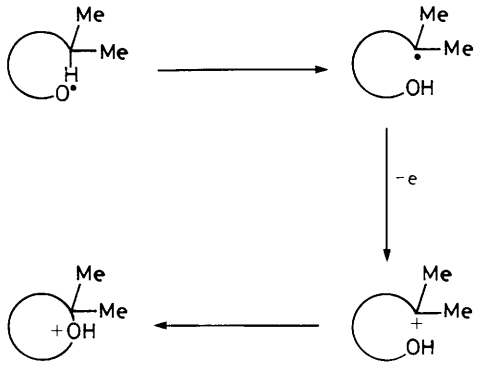
Scheme 1. *Reagents and conditions*: i, $PhCOC_6H_4COCl$–pyridine, 50—60 °C; ii, $PhCOC_6H_4CH_2COCl$–pyridine, 50—60 °C; iii, $PhCOC_6H_4(CH_2)_2COCl$–pyridine, 50—60 °C; iv, $NaBH_4$–tetrahydrofuran (THF), 25 °C; v, HgO–I_2–benzene; vi, *hν*; vii, $Pb(OAc)_4$–*hν*–benzene; viii, NH_3–Na.

6-membered cyclic transition state has been repeatedly demonstrated ever since by numerous examples with a variety of substrates.[2] There have been, however, few examples of successful intramolecular hydrogen abstraction *via* a many-membered cyclic transition state by alkoxyl radicals which are generated by the photolysis of nitrites[2,3] or hypohalites.[2,4]

On the other hand, Breslow and his colleagues have devised an ingenious extension of intramolecular abstraction of a hydrogen through a 6-membered cyclic transition state by an excited carbonyl group to a functionalization of remote unactivated methylene groups, as part of their model study of biomimetic control of chemical reactivity.[5,6] They used a series of esters derived from benzophenone-3- or -4-carboxylic acid and steroidal alcohols.

In this communication, we wish to report on a two-step long-range hydroxylation of a steroidal skeleton, based on a long-range intramolecular hydrogen abstraction by alkoxyl radicals generated by the irradiation of hypoiodites of esters carrying a benzhydryl group, derived simply by reducing Breslow-type esters with $NaBH_4$. Steroidal-25-ols are of importance since there are several biologically-active steroids belonging to this group.[7]

Thus three esters, 5α-cholestan-7α-yl-4-(hydroxyphenylmethyl)benzoates (**5**), 5α-cholestan-7α-yl-4-(hydroxyphenylmethyl)phenylacetates (**6**), and 5α-cholestan-7α-yl-3-[4-(hydroxyphenylmethyl)phenyl]propionates (**7**) were prepared by the reduction of the corresponding esters (**2**), (**3**), and (**4**), derived from appropriate benzophenone-4-carboxylic acids and 5α-cholestan-7α-ol (**1**), with $NaBH_4$.† Each ester was a mixture of epimers with regard to the carbon atom carrying the hydroxy group. The epimeric esters (**6**) in CCl_4 were first transformed into the corresponding hypoiodites with 3 equiv. of both mercury(II) oxide and iodine. The solution was then irradiated with a 450W high pressure Hg arc for 7 h in a nitrogen atmosphere to give a mixture of products from which (**8a**) (4.3%), (**8b**) (3.8%), the benzophenone esters (**3**) (29%), as well as unreacted starting alcohol (**6**) (31%) were isolated by means of preparative TLC.



Scheme 2

The molecular formulae of crystalline products (**8a**) and (**8b**) were determined to be $C_{42}H_{58}O_3$ by means of high resolution mass spectrometry and by elemental analysis. IR spectra of (**8a**) and (**8b**) showed the absorption bands at 1722 and 1720 cm^{-1} assignable to the lactone carbonyl groups, respectively. The ^1H NMR spectrum (400 MHz) of product (**8a**) exhibited a 1H singlet at δ 5.43 and two 3H singlets at δ 1.25 and 1.30 assignable to -C_6H_4-CH(OR)-C_6H_5 and the *gem* dimethyl group, besides the signals due to the H(18), H(19), and H(7β). These spectral results indicated that the structure of the product is a macrocyclic ether lactone (**8a**). The ^1H NMR of the product (**8b**) similarly exhibited a singlet at δ 5.56 (1H) and two singlets (each 3H) at δ 1.09 and 1.20 assignable to the -C_6H_4-CH(OR)-C_6H_5 and the *gem* dimethyl group. These spectral data suggested that it is a macrocyclic ether lactone (**8b**) epimeric with (**8a**).

A similar irradiation of the epimeric esters (**6**) in CCl_4, each containing 3 equiv. of lead tetra-acetate and iodine, for 4 h gave lactones (**8a**) (5.2%), (**8b**) (3.9%), benzophenone ester (**3**) (32%), and the recovered alcohol (**6**) (13%). The lactones (**8a**) and (**8b**) were not formed, however, when esters (**6**) in CCl_4, each containing 3 equiv. of iodosylbenzene diacetate,[8] were irradiated.

Reduction of the macrocyclic lactone (**8a**) or (**8b**) with Na–liquid ammonia cleanly removed the non-steroidal portion of the lactones to give 5α-cholestane-7α, 25-diol (**10**)† in 84 and 75% yields, respectively.

Irradiation of epimeric esters (**7**) having a longer spacer in CCl_4 containing 3 equiv. of mercury(II) oxide and iodine similarly gave a mixture of homologous macrocyclic ether lactones (**9a**) and (**9b**),† albeit in low yield (2%), together with homologous benzophenone ester (**4**) (46%), and the recovered starting alcohol (**7**) (14%). Reduction of ether lactones (**9a**) and (**9b**) with Na–liquid ammonia gave 5α-cholestane-7α, 25-diol (**10**) in a high yield.

A long-range intramolecular functionalization by the alkoxyl radical generated from epimeric esters (**5**), carrying a shorter spacer, failed to give any macrocyclic ether lactone corresponding to lactones (**8**) and (**9**), resulting only in the formation of the benzophenone ester (**2**).

The macrocyclic ethers (**8a**), (**8b**), (**9a**), and (**9b**) should be formed through a cyclization of a carbocation which is formed from one-electron oxidation of the C(25) tertiary radical generated by intramolecular hydrogen abstractions as outlined in Scheme 2.

The present long-range intramolecular functionalization involving 1,20 or 1,21 hydrogen transfer is the first example in which an oxygen atom is directly introduced into the remote

† *Selected spectroscopic data* for (**5**); a glass; IR ν_{max} (Nujol) 3400 (OH), 1710 (C=O), and 1275 cm^{-1} (C–O); ^1H NMR (270 MHz): δ 0.66 [3H, s, H(18)], 0.83 [3H, s, H(19)], 5.12 [1H, br. s, 7H(7β)], and 5.90 (1H, s, –C*H*OH). For (**6**); m. p. 107 °C; IR ν_{max} (Nujol) 3450 (OH), 1700 (C=O), and 1270 cm^{-1} (C–O); ^1H NMR: δ 0.59 [3H, s, H(18)], 0.74 [3H, s, H(19)], 3.59 (2H, s, –$COCH_2$–), 4.82 [1H, br. s, H(7β)], and 5.82 (1H, s, –C*H*OH–). For (**7**); a glass; IR ν_{max} (Nujol) 3450 (OH), 1700 (C=O), and 1270 cm^{-1}; ^1H NMR: δ 0.59 [3H, s, H(18)], 0.74 [3H, H(19)], 4.82 [1H, br. s, H(7β)], and 5.83 (1H, s, –C*H*OH–). For (**2**); a glass; IR ν_{max} (Nujol) 1710 (C=O), 1640 (Ph C=O), and 1270 cm^{-1} (C–O); ^1H NMR: δ 0.68 [3H, s, H(18)], 0.85 [3H, s, H(19)], and 5.18 [1H, br. s, H(7β)]. For (**3**); m. p. 129—130 °C; IR ν_{max} (Nujol) 1660 (PhC=O) and 1270 cm^{-1} (C–O); ^1H NMR: δ 0.58 [3H, s, H(18)], 0.76 [3H, s, H(19)], 3.71 (2H, s, –OCH_2–), 4.86 [1H, br. s, H(7β)]. For (**4**); m.p. 97—101 °C; IR ν_{max} (Nujol) 1725 (C=O), and 1650 (PhCO); ^1H NMR: δ 0.62 [3H, s, H(18)], 0.77 [3H, s, H(19)], 2.73 and 2.71 (each 2H, each t, *J* 7.3 Hz, –$OCOCH_2CH_2$–), and 4.90 [1H, br. s, H(7β)]. For (**8a**); m.p. 292—298 °C (light petroleum); IR ν_{max} (Nujol) 1722 (C=O) and 1265 cm^{-1} (C–O); ^1H NMR (400 MHz): δ 0.50 [3H, s, H(18)], 0.76 [3H, s, H(19)], 3.43 and 3.49 (each 1H, each d, *J* 11.72 Hz, –$COCH_2$–), 4.73 [1H, br. s, H(7β)], and 5.43 (1H, s, –CHO–); *m/z* 610 (M^+, 100) and 592 [$(M - 18)^+$, 30%]. For (**8b**); m.p. 262—270 °C (light petroleum); IR ν_{max} (Nujol) 1720 (C=O) and 1275 cm^{-1} (C–O); ^1H NMR (400 MHz): δ 0.52 [3H, s, H(18)], 0.77 [3H, s, H(19)], 0.93 [3H, d, *J* 6.8 Hz, H(21)], 1.09 and 1.20 [each 3H, each s, H(26) and/or H(27)], 3.43 and 3.57 (each 1H, each d, *J* 12.2 Hz, –$COCH_2$–), 4.81 [1H, br. d, *J* 2.73 Hz, H(7β)], and 5.56 (1H, s, –CHO–); *m/z* 610 (M^+, 100) and 592 [$(M - 18)^+$, 6%]. For (**10**); m.p. 146—148 °C (light petroleum); IR ν_{max} 3380 cm^{-1} (OH); ^1H NMR (270 MHz): δ 0.66 [3H, s, H(18)], 0.78 [3H, s, H(19)], 0.92 [3H, d, *J* 6.6 Hz, H(21)], 1.21 [6H, s, H(26) and H(27)], and 3.81 [1H, br. s, H(7β)]; *m/z* [field desorption (FD)MS], 404 (M^+, 44), 386 [$M - H_2O$, 34], 369 [$(M - H_2O - OH)^+$, 71], and 59 [$(Me_2C{=}O + H)^+$, 100%]. For (**9a** and **b**); IR ν_{max} (neat) 1720 cm^{-1} (C=O); ^1H NMR (90 MHz): δ 0.53 and 0.66 [each 3H, each s, H(18) and H(19)].

position as a result of a long-range intramolecular hydrogen abstraction.

The results of our further investigation of this long-range oxygenation of steroid skeletons will be reported in our future publications.‡

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‡ Satisfactory spectral and analytical results were obtained for all the compounds described here.