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Hypervalent Iodine Reagents: Synthesis of a Steroidal Orthoacetate by a Radical Reaction

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Abstract: *The reaction of steroidal alcohols (1) and (8) with (diacetoxyiodo)benzene and iodine under irradiation with visible light afforded, in addition to the expected β-fragmentation diene (2), the orthoacetate (4) in moderate yield.*

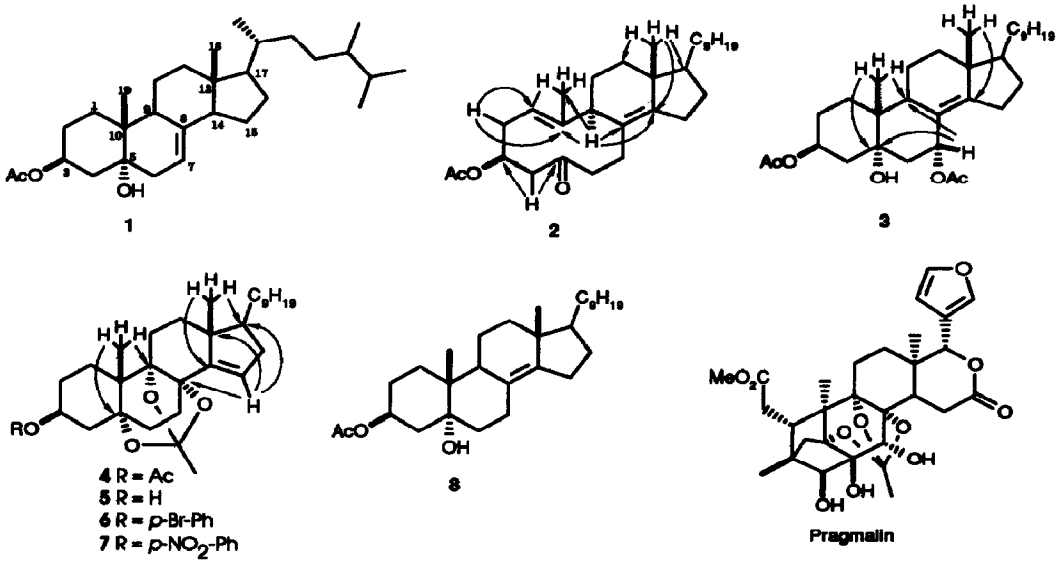
We have previously reported that photolysis of tertiary alcohols with (diacetoxyiodo)benzene (DIB)-iodine generates alkoxy radicals which undergo β-fragmentation to give medium-sized rings.[1] In the course of our studies we synthesized steroidal model (1) (Scheme 1) from ergosterol in four steps.[2] The photolysis of (1) with DIB-iodine in cyclohexane (Table, entry 1) gave not only ring expansion product (2)[3] but also diacetate (3)[4] and orthoacetate (4)[5] (Scheme 1). A reasonable yield of orthoacetate can be obtained only when the reaction is carried out to low conversion, since the products undergo further transformation and a complex mixture is obtained. When the reaction was conducted with AcOEt as solvent (entry 2), diacetate (3) was obtained in 44% yield. Other reagents were assayed (entries 3-5), with poorer results.

The unexpected formation of (4) seems interesting to us, not only from a mechanistic point of view but also because the orthoacetate group exists in many natural products such as limonoids,[6a] steroidal alkaloids,[6b] and the phorbol-related daphnetoxin.[6c] In particular, the structure of (4) closely resembles those of phragmalin[6a] and the chukrasins,[6d] (Scheme 1) with the orthoacetate group in ring B of the skeleton and on the same carbons.

The structures of compounds (2), (3) and (4) were determined on the basis of their spectroscopic data.[3-5] The diene (2) did not show any absorption in its UV spectrum. A summary of selected heteronuclear ^{1}H-^{13}C correlations determined by HMBC experiments for compounds (2) and (3) is shown in Scheme 1.

The spectroscopic data for the orthoacetate unit of (4) agree with those described in the literature for chukrasins[6d] and other orthoacetates.[6e-g] Three derivatives of product (4), compounds (5-7),[7] were synthesized in order to obtain crystals suitable for X-ray analysis. However, none of the crystals proved useful for this purpose. Nevertheless, the structure of derivative (7) has been solved by extensive spectroscopic analysis. The ^{1}H NMR and ^{13}C NMR spectra show that the steroidal skeleton remains unchanged after the photolysis. The HMBC correlations, shown in Scheme 1, supported the proposed structure.

A reasonable mechanism for the formation of compounds (2), (3) and (4) is shown in Scheme 2. Compound (1) may isomerize to alkene (8) under reaction conditions. The generation of an alkoxy radical in (8) followed by a β-fragmentation reaction (path a) would give rise to radical (9) which could stabilize by



Scheme 1.

loss of one of the hydrogens on C-1 or by trapping an iodine atom and subsequent elimination to give diene (2). Alternatively, (1) may undergo allylic hydrogen abstraction[8] from C-14 (path b), producing radical (10) which could be trapped by an acetoxy radical or by other intermediate species such us AcOI[9] to give diacetate (3). Although acetoxy radicals decarboxylate readily their detection and identification by ESR spectroscopy has proved possible.[10] A radical mechanism has been suggested for the synthesis of allylic esters from alkenes using peroxyesters and catalytic amounts of copper salts.[11] Nevertheless, in the formation of (3) we cannot exclude that radical (10) may be oxidized by an excess of reagent to an allylic carbocation, which may then react with an acetate ion.

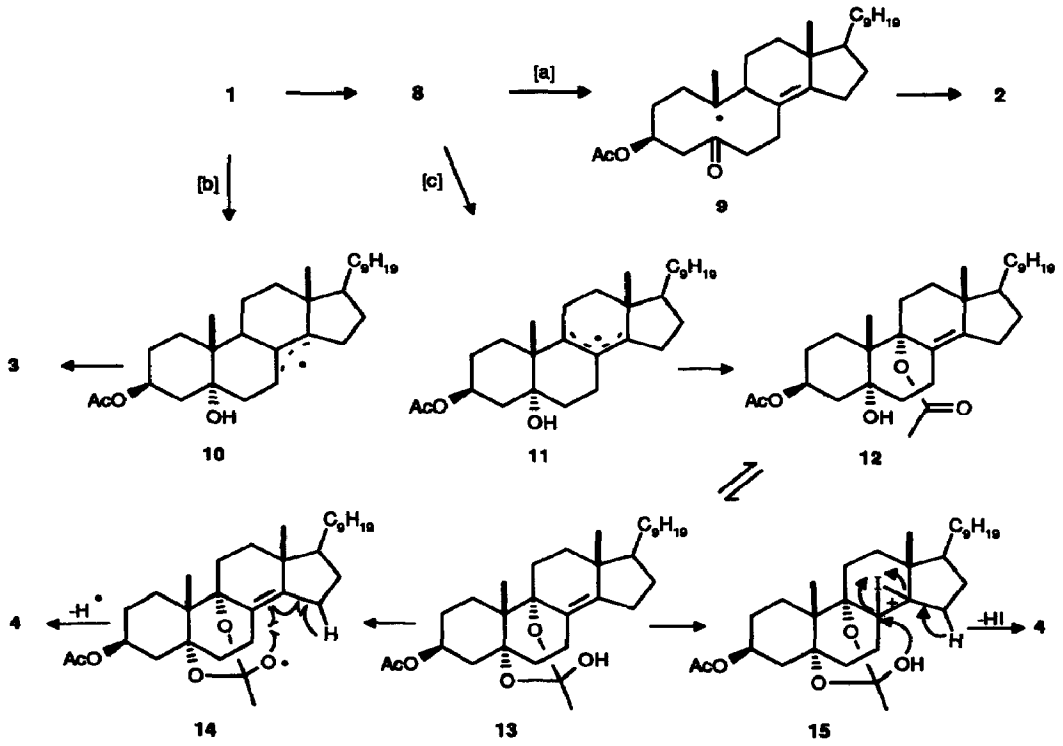
Alkene (8) may also undergo hydrogen abstraction from C-9 (path c) to give allylic radical (11). The selective radical abstraction of 9-H and 14-H in steroidal skeletons by hypervalent iodine reagents (e.g. $C_6H_6ICl_2$) has been previously reported.[8] Intermediate (11), analogously to (10), evolves, in radical or cationic form, to give acetate (12), which may be in equilibrium with the hemi-orthoester form (13). Then with an excess of reagent an alkoxy radical (14) is generated. This electrophilic radical is conveniently positioned to interact with the nucleophilic 8(14) double bond to give a C-14 radical, which is stabilized by the loss of the 15-H yielding (4). The formation of orthoester (4) from (13) could also be explained by an iodine catalysed cyclization, via iodonium ion (15) followed by hydriodic acid elimination from (15).

In order to confirm this mechanism, alkene (8)[12] was synthesized in 80% yield from ergosteryl peroxide by hydrogenation with platinum oxide hydrate Merck in AcOH. Under these conditions, the initially formed alkene (1) easily isomerizes to alkene (8), which is not reduced.[13] Photolysis of (8) with DIB-iodine in cyclohexane (Table, entry 6) gave better yields of diene (2) (39%) and orthoacetate (4) (40%), but not diacetate (3), which therefore only comes from alkene (1) (path b). Yields of compound (4) are remarkable (50% based on conversion), taking into account that several steps are involved in its formation. Besides, the reaction proceeds with excellent stereoselectivity, the acetate group entering from the α-side of the molecule. This radical reaction may thus constitute an interesting approach to the synthesis of the orthoacetate group in pragmalin and other steroidal compounds.

Table. Reactions of alcohols **1** and **8**[a]

Entry	Compound	Reagents[b]	Solvent	Conditions		Products
				T (°C)	time (h)	(yield %)
1	**1**	DIB/I_2 (2.3/1.3)	Cy	40	1.75	**1** (53), **2** (5), **3** (18), **4** (16)
2	**1**	DIB/I_2 (5/3)	AcOEt	40	3	**3** (44)
3	**1**	LTA (2)	Be	60	1.5	**1** (20), **2** (10)
4	**1**	$Hg(OAc)_2/I_2$ (4/4)	Cy	rt	2	complex mixture
5	**1**	$Ph_2Se(OH)OAc/I_2$ (4/2)	Cy	80	2	complex mixture
6	**8**	DIB/I_2 (2.5/2)	Cy	40	1	**2** (39), **4** (40), **8** (21)

a) All reactions were performed under argon by irradiation with two 100 W tungsten-filament lamps. b) Per mol of substrate. DIB = (diacetoxyiodo)benzene; Cy = cyclohexane; LTA = lead tetraacetate.



Scheme 2

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2. Curry, D.J.; Midgley, J. M.; Leung, S.L.; Watt, R.; Whalley, W.B. *J. Chem. Soc., Perkin Trans. 1* **1977**, 822.
3. Compound (2): m.p. 101.6-102.6 °C (MeOH), $[\alpha]_D$ -106° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 1732, 1700, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.79 (3H, d, *J* 6.8 Hz, 28-H_3), 0.80 (3H, d, *J* 6.8 Hz, 27-H_3), 0.87 (3H, d, *J* 6.8 Hz, 26-H_3), 0.89 (3H, s, 18-H_3), 0.93 (3H, d, *J* 6.5 Hz, 21-H_3), 1.59 (3H, s, 19-H_3), 2.05 (3H, s, AcO), 2.69 (1H, ddd, *J* 14.9, 12.0, 3.1 Hz, 2-H), 2.96 (1H, m, 9-H), 3.20 (1H, dd, *J* 16.2, 11.1 Hz, 4-H), 5.36 (1H, dd, *J* 4.8, 12 Hz, 1-H), 5.43 (1H, m, 3-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 211.81 (5-C), 170.27 (AcO), 147.14 (14-C), 143.04 (10-C), 126.52 (8-C), 120.52 (1-C), 70.41 (3-C), 56.31 (17-C), 43.03 (13-C), 39.52 (9-C), 18.70 (19-C); MS *m/z* 456.36048 (M^+, 39%).
4. Compound (3): m.p. 145-147 °C (MeOH), $[\alpha]_D$ +9° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 3582, 1723 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ_H 0.79 (3H, s, 19-H_3), 0.96 (3H, d, *J* 6.6 Hz, 27-H_3), 0.96 (3H, s, 18-H_3), 0.98 (3H, d, *J* 6.6 Hz, 28-H_3), 1.04 (3H, d, *J* 7.2 Hz, 26-H_3), 1.08 (3H, d, *J* 6.7 Hz, 21-H_3), 1.67 (3H, s, AcO), 1.92 (3H, s, AcO), 3.32 (1H, OH), 5.8 (1H, m, 3-H), 6.01 (1H, m, 7-H); ^{13}C NMR (100.6 MHz, C_6D_6) δ_C *inter alia* 169.54 (CO), 168.62 (CO), 152.20 (14-C), 124.14 (8-C), 74.76 (5-C), 70.73 (3-C or 7-C), 70.51 (3-C or 7-C), 37.98 (9-C); MS *m/z* 438.34752 (M^+-H_2O-AcOH, 40%).
5. Compound (4): Amorphous, $[\alpha]_D$ -66.6° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 1726 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.79 (6H, d, *J* 6.7 Hz, 28-H_3, 27-H_3), 0.87 (3H, d, *J* 6.8 Hz, 26-H_3), 0.93 (3H, s, 18-H_3), 0.95 (3H, d, *J* 5.6 Hz, 21-H_3), 1.18 (3H, s, 19-H_3), 1.53 (3H, s, $MeCO_3$), 2.02 (3H, s, AcO), 2.35 (1H, ddd, *J* 7.2, 15.6, 3.4 Hz, 16-H), 2.54 (1H, dt, *J* 4.1, 14.5 Hz, 1-H), 4.95 (1H, m, 3-H), 5.7 (1H, m, 15-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 170.4 (CO), 152.7 (14-C), 124.26 (15-C), 116.50 (CO_3), 82.11 (s), 82.03 (s), 79.92 (s), 70.23 (3-C); MS *m/z* 454.34499 (M^+, 62%).
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7. Compound (7): m.p. 209.1-209.8 °C (*n*-hexane), $[\alpha]_D$ -66° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 1727, 1531, 1270 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.79 (6H, d, *J* 6.7 Hz, 27-H_3, 28-H_3), 0.86 (3H, d, *J* 6.8 Hz, 26-H_3), 0.94 (3H, s, 18-H_3), 0.95 (3H, d, *J* 4.5 Hz, 21-H_3), 1.25 (3H, s, 19-H_3), 1.57 (3H, s, $MeCO_3$), 2.36 (1H, ddd, *J* 15.7, 3.4, 7.0 Hz, 16-H), 2.64 (1H, dt, *J* 4.1, 14.5 Hz, 1-H), 5.26 (1H, m, 3-H), 5.71 (1H, m, 15-H), 8.19 (2H, d, *J* 8.9 Hz, arom.), 8.28 (2H, d, *J* 8.9 Hz, arom.); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 164.0 (CO_2), 152.58 (14-C), 150.41 (arom.), 136.19 (arom.), 130.61 (arom.), 124.39 (15-C), 123.44 (arom.), 116.56 (CO_3), 82.17 (s), 82.06 (s), 80.01 (s), 72.26 (3-C), 56.91 (17-C), 46.28 (13-C), 38.84 (10-C), 35.13 (16-C), 28.70 (1-C), 18.28 (19-C) ; MS *m/z* 561.34589 (M^+-AcOH, 9%).
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12. Compound (8): m.p. 155-156 °C (*n*-hexane), $[\alpha]_D$ +6° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 3599, 1724 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.78 (6H, d, *J* 6.7 Hz, 28-H_3, 27-H_3), 0.85 (3H, d, *J* 7.3 Hz, 26-H_3), 0.84 (3H, s, 18-H_3), 0.88 (3H, s, 19-H_3), 0.93 (3H, d, *J* 6.4 Hz, 21-H_3), 2.02 (3H, s, AcO); 5.16 (1H, m, 3-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 170.63 (CO), 143.01 (14-C), 125.33 (8-C), 74.75 (5-C), 70.97 (3-C); MS *m/z* 458 (M^+, 1%), 440 (45).
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