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Sequential Alkoxy Radical Fragmentation. A One-step Method for Breaking Two 1,3-Positioned C-C Bonds

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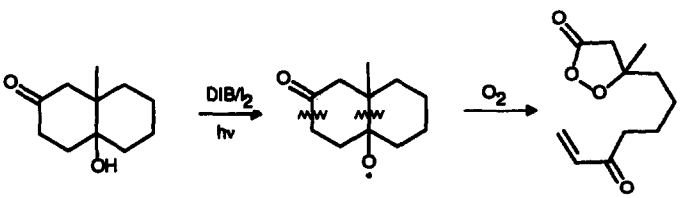
Abstract: Cyclic hydroxy-ketones (1) and (2) in the presence of (diacetoxyiodo)benzene or mercuric oxide and iodine under oxygen atmosphere and irradiation with visible light undergo a new sequential alkoxy radical fragmentation-radical peroxidation-peroxyradical cyclization-alkoxy radical fragmentation reaction. This methodology allows the cleavage of two 1,3-positioned C-C bonds in a single step and constitutes a new synthesis of β-peroxylactones.

We have recently reported that the C-radical produced during the β-fragmentation of alkoxy radicals is able to trap a molecule of oxygen, and that the peroxyradical formed can eventually react with a suitably positioned double bond.[1] Highly functionalized medium-sized ketones can be obtained by this tandem β-fragmentation-cycloperoxyiodination reaction. For instance, irradiation with visible light of 2-cholesten-5α-ol with (diacetoxyiodo)benzene (DIB) and iodine in the presence of oxygen gave a mixture of 5,10-seco-2α,10α-epidioxy-3ξ-iodocholestan-5-one. The structure and stereochemistry have been determined by X-ray crystallographic analysis of one of the isomeric iodides.

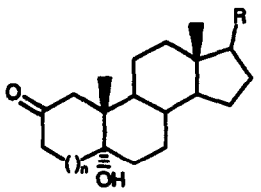
Scheme 1



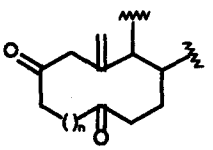
With this reaction in mind we conceive that the generation of alkoxy radicals from hydroxy-ketones of the type shown in Scheme 1 could be a convenient procedure, through sequential β-fragmentation, to promote the cleavage of two 1,3-positioned C-C bonds in a single step.

In this communication we describe our preliminary results on this reaction and its application to the steroid models (**1**)[2] and (**2**).[3] In order to generate the alkoxy radicals the hydroxy-ketones (**1**) and (**2**) were treated with DIB and iodine or mercuric oxide and iodine under irradiation with two 100 W tungsten-filament lamps under the conditions summarized in the Table. When the reaction is performed under argon (entries 1, 2 and 8) the expected ring expansion occurs[4] and a mixture of C-10 olefins, compounds (**3**) to (**7**),[5] is formed.

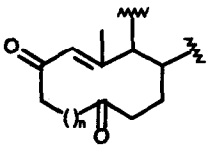
In the case of compound (**1**) when the reaction was conducted under oxygen (entries 3-7) it proceeded to give the β-peroxylactone (**8**)[6] in moderate yield. When DIB/I_2 was used with increasing oxygen pressure the reaction led to clearly inferior results (compare entries 3-5). Similar yields were observed with the system HgO/I_2 (entries 6-7).



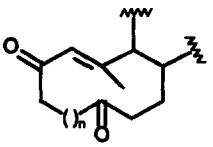
1 n = 1, R = C_8H_{17}
2 n = 0, R = OAc



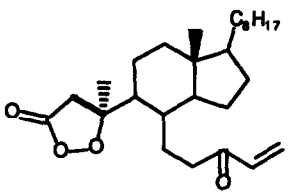
3 n = 1, R = C_8H_{17}
4 n = 0, R = OAc



5 n = 1, R = C_8H_{17}
6 n = 0, R = OAc



7 n = 1, R = C_8H_{17}



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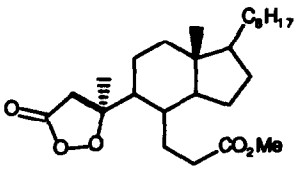

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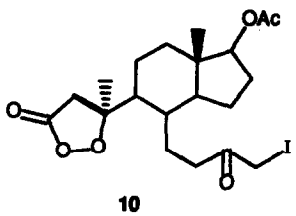

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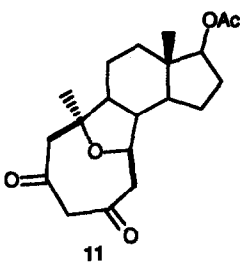

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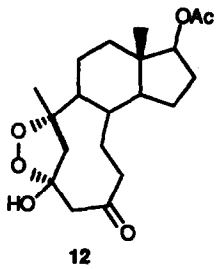

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The structure and stereochemistry at C-10 of (**8**) were determined on the basis of spectral and chemical evidence. Treatment of (**8**) with sodium periodate and ruthenium(IV) oxide[7] gave after methylation with excess of ethereal diazomethane, methyl ester (**9**), identical with a sample prepared previously. The C-10 stereochemistry of this compound was determined by X-ray crystallographic analysis of an appropriate derivative.[8]

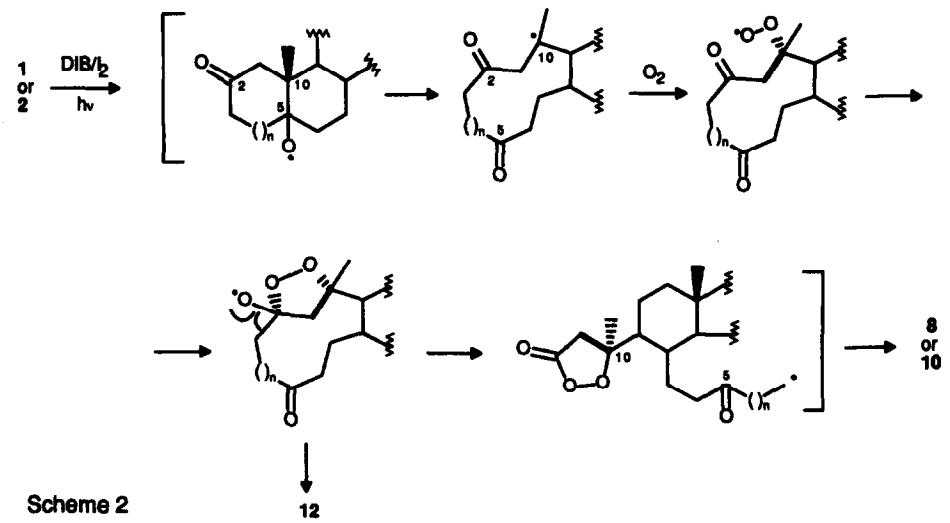
Compound (**2**) was prepared for the purpose of promoting the β-fragmentation; the reaction proceeded as expected to give β-peroxylactone (**10**)[9] (entries 9-13), the best yield being obtained under an atmosphere of air (entry 9). Nevertheless, the reaction was more complex and two new compounds were formed, the tetrahydrofuran derivative (**11**)[10] and in some experiments (entries 11 and 13) the peroxyhemiacetal (**12**).[11] The peroxyhemiacetal (**12**) was transformed by photolysis with DIB/I_2 under argon into the β-peroxylactone (**10**), providing good support for the proposed structure.

The mechanism for the formation of compound (**11**) is consistent with a hydrogen atom abstraction at C-7 from an alkoxy radical at C-10 and has been commented previously.[8] A plausible mechanism for the formation of compounds (**8**), (**10**) and (**12**) is shown in Scheme 2. The alkoxy radical initially formed undergoes β-fragmentation to give the C-10 radical which was stereoselectively attacked by a molecule of oxygen. The peroxyradical obtained was added to the carbonyl group, and the new alkoxy radical formed underwent a second β-fragmentation to give a C-radical at C-3 which was stabilized by losing a hydrogen radical to give (**8**) or trapping an iodine radical from the medium to give (**10**). The isolation of the peroxyhemiacetal intermediate (**12**) and its transformation in the reaction conditions under argon, into the peroxylactone (**10**) is in agreement with the proposed mechanism.

Table. Fragmentation of hydroxy-ketones (1) and (2).[a]

Entry	Substrate	Solvent	Reagent[b] (mmol)	Conditions		Products (yield %)
				P (atm)	Time (h)	
1	1	CCl_4	DIB/I_2 (2/1.3)	Ar (1)	0.3	3 (38), 7 (17), 5 (14)
2	1	CCl_4	HgO/I_2 (5.5/2)	Ar (1)	7	3 (42), 7 (46), 5 (10)
3	1	CCl_4	DIB/I_2 (3/1)	air (1)	2	8 (45), 3 (9), 7 (9)
4	1	CCl_4	DIB/I_2 (2/1)	O_2 (5)	0.5	8 (42)
5	1	CCl_4	DIB/I_2 (1.5/1)	O_2 (10)	0.75	8 (23)
6	1	CCl_4	HgO/I_2 (4/2)	air (1)	2	8 (42)
7	1	CCl_4	HgO/I_2 (2.7/1.5)	O_2 (5)	2	8 (49)
8	2	Cy	DIB/I_2 (1.5/1)	Ar (1)	4.75	4 (48), 6 (17)
9	2	Cy	DIB/I_2 (1.5/1)	air (1)	3.5	10 (43), 4 (9), 11 (12)
10	2	CCl_4	DIB/I_2 (1.5/1)	O_2 (1)	2	10 (16), 4 (8), 11 (16)
11	2	Cy	DIB/I_2 (1.5/1)	O_2 (3)	5.5	10 (17), 11(16), 12 (23)
12	2	Cy	HgO (5/1)	air (1)	9	10 (39), 4 (16), 6 (14), 11 (16)
13	2	Cy	HgO (5/1)	O_2 (1)	9	10 (20), 4 (13), 6 (10), 11 (9), 12 (7)

[a] All reactions were performed at 40-45 °C under irradiation with two 100 W tungsten-filament lamps; those under pressure were made in a borosilicate Griffin-Worden pressure vessel (Kontes K-767100). [b] 0.2 mmol in 15 ml. [c] Reaction made at 19 °C. DIB = (diacetoxyiodo)benzene; Cy = cyclohexane.



Scheme 2

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REFERENCES AND NOTES

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2. Compound (**1**): m.p. 182-184 °C (*n*-hexane-EtOAc); $[\alpha]_D$ +28° ($CHCl_3$, c, 0.46); IR ($CHCl_3$) ν_{max} 3610, 1703 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.64 (3H, s, 13-Me), 0.86 (6H, d, *J* 7.3 Hz, 25-Me_2), 0.90 (3H, d, *J* 6.8 Hz, 20-Me); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 213.13 (2-C), 72.27 (5-C); MS *m/z* 402.34978 (M^+, 38%).
3. Compound (**2**): m.p. 169-171 °C (*n*-hexane-EtOAc); $[\alpha]_D$ -65° (c, 0.372); IR ν_{max} 3604, 1736 cm^{-1}; ^1H NMR δ_H 0.80 (3H, s, 13-Me), 1.09 (3H, s, 10-Me), 2.03 (3H, s, OAc), 2.09, 2.74 (2H, AX, *J* 18.7 Hz, 3-H_2), 2.30, 2.38 (2H, AB, *J* 18.3 Hz, 1-H_2), 4.55 (1H, dd, *J* 7.4, 8.9 Hz, 17-H); ^{13}C NMR δ_C 217.54 (3-C), 171.17 (OCO-CH_3), 82.49 (17-C), 79.50 (5-C); MS *m/z* 334.21487 (M^+, 8%).
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5. Compound (**3**): $[\alpha]_D$ -51° (c, 0.14); IR ν_{max} 1710, 910 cm^{-1}; ^1H NMR δ_H 0.71 (3H, s, 13-Me), 0.87 (6H, d, *J* 6.2 Hz, 25-Me_2), 0.89 (3H, d, *J* 5.8 Hz, 20-Me), 5.04 (2H, br s, 19-H_2); ^{13}C NMR δ_C 211.56 (2-C), 208.53 (5-C); MS *m/z* 400.33256 (M^+, 37%). Compound (**4**): m.p. 126-127.5 °C (*n*-hexane-EtOAc); $[\alpha]_D$ +54° (c, 0.094); IR ν_{max} 1720, 1690 cm^{-1}; ^1H NMR δ_H 0.81 (3H, s, 13-Me), 2.02 (3H, s, OAc), 3.11, 3.20 (2H, AB, *J* 15.2 Hz, 1-H_2), 3.62, 3.73 (2H, AB, *J* 12.7 Hz, 1-H_2), 4.59 (1H, dd, *J* 7.4, 8.9 Hz, 17-H); 5.16 (1H, s, 19-H_a), 5.19 (1H, s, 19-H_b); ^{13}C NMR δ_C 205.24, 201.20, 171.06 (OCO-CH_3), 145.60 (10-C), 118.14 (19-C), 82.28 (17-C); MS *m/z* 332.19769 (M^+, 6%). Compound (**5**): m.p. 106.5-108 °C (*n*-hexane-EtOAc); $[\alpha]_D$ +50° (c, 0.3); IR ν_{max} 1700, 1680, 1620 cm^{-1}; ^1H NMR δ_H 0.69 (3H, s, 13-Me), 0.87 (6H, d, *J* 7.1 Hz, 25-Me_2), 0.91 (3H, d, *J* 6.7 Hz, 20-Me), 1.76 (3H, d, *J* 1 Hz, 10-Me), 5.92 (1H, d, *J* 1 Hz, 1-H); ^{13}C NMR δ_C 213.19 (2-C), 205.52 (5-C), 151.47 (10-C), 128.18 (1-C); MS *m/z* 400.33233 (M^+, 63%). Compound (**6**): m.p. 166-168 °C (*n*-hexane); $[\alpha]_D$ +4° (c, 0.07); IR ν_{max}1720, 1680 cm^{-1}; ^1H NMR δ_H 0.84 (3H, s, 13-Me), 1.76 (3H, d, *J* 1.2 Hz, 10-Me), 2.04 (3H, s, OAc), 3.71, 3.79 (2H, AB, *J* 13.8 Hz, 3-H_2), 4.65 (1H, dd, *J* 7.4, 9.1 Hz, 17-H), 5.91 (1H, d, *J* 1.3 Hz, 1-H); ^{13}C NMR δ_C complex spectrum; MS *m/z* 332.19731 (M^+, 3%). Compound (**7**): $[\alpha]_D$ +33° (c, 0.12); IR ν_{max} 1700, 1690 cm^{-1}; ^1H NMR δ_H 0.73 (3H, s, 13-Me), 0.87 (6H, d, *J* 6.5 Hz, 25-Me_2), 0.90 (3H, d, *J* 5.8 Hz, 20-Me), 1.91 (3H, br s, 10-Me), 5.88 (1H, s, 1-H); ^{13}C NMR δ_C 212.21 (2-C), 203.08 (5-C); MS *m/z* 400.33555 (M^+, 78%).
6. Compound (**8**): $[\alpha]_D$ +4° (c, 0.14); IR ν_{max} 1800, 1715 cm^{-1}; ^1H NMR δ_H 0.69 (3H, s, 13-Me), 0.87 (6H, d, *J* 6.7 Hz, 25-Me_2), 0.90 (3H, d, *J* 7.9 Hz, 20-Me), 1.46 (3H, s, 10-Me), 2.83 (1H, d, *J* 16.6 Hz, 1-H_a), 2.99 (1H, d, *J* 16.6 Hz, 1-H_b), 5.84 (1H, dd, *J* 2.1, 9.5 Hz, 3-H_a), 6.29 (1H, dd, J 17.6, 2.1 Hz, 3-H_b), 6.34 (1H, dd, *J* 17.6, 9.5 Hz, 4-H); ^{13}C NMR δ_C 200.26 (5-C), 175.57 (2-C), 136.31 (4-C), 128.36 (3-C), 91.74 (10-C); MS *m/z* 416 (M^+-O, 3%).
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9. Compound (**10**): IR ν_{max} 1798, 1726 cm^{-1}; ^1H NMR δ_H 0.82 (3H, s, 13-Me), 1.47 (3H, s, 10-Me), 2.04 (3H, s, OAc), 2.87, 3.03 (2H, AB, *J* 16.6 Hz, 1-H_2), 3.80, 3.82 (2H, AB, *J* 9.6 Hz, 3-H_2), 4.60 (1H, dd, *J* 7.4, 8.9 Hz, 17-H); ^{13}C NMR δ_C 202.59 (5-C), 175.27 (2-C), 171.02 (OCO-CH_3), 91.56 (10-C), 82.12 (17-C); MS *m/z* 391.07603 (M^+-$C_4H_5O_3$, 2%).
10. Compound (**11**): IR ν_{max} 1719, 1691 cm^{-1}; ^1H NMR δ_H 0.74 (3H, s, 13-Me), 1.38 (3H, s, 10-Me), 2.05 (3H, s, OAc), 2.36 (1H, ddd, *J* 13.2, 2.8, 0.84 Hz, 6-H_a), 2.55, 2.63 (2H, AB, *J* 12.2 Hz, 1-H_2), 3.21 (1H, dd, *J* 13.3, 4.7 Hz, 6-H_a), 3.21 (1H, dd, *J* 10.4, J_w 1.2 Hz, 3-H_a), 4.09 (1H, ddd, *J* 8.9, 4.8, 2.8 Hz, 7-H), 4.31 (1H, d, *J* 10.4 Hz, 3-H_b), 4.62 (1H, dd, *J* 7.8, 8.9 Hz, 17-H); ^{13}C NMR δ_C 202.62, 201.99, 171.17 (OCO-CH_3), 83.16 (10-C), 81.35 (17-C), 77.13 (7-C); MS *m/z* 348.19456 (M^+, 21%).
11. Compound (**12**): IR ν_{max} 3530, 1720 cm^{-1}; ^1H NMR δ_H 0.81 (3H, s, 13-Me), 1.50 (3H, s, 10-Me), 2.05 (3H, s, OAc), 2.24, 2.91 (2H, AX, *J* 13.6 Hz), 3.07 (2H, s), 4.5 (1H, dd, *J* 7.6, 8.9 Hz, 17-H); ^{13}C NMR δ_C 210.23 (5-C), 171.17 (OCO-CH_3), 106.14 (2-C), 91.10 (10-C), 82.31(17-C); MS *m/z* 366.19337 (M^+-H_2O, 6%).

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