Pergamon

Tetrahedron Letters, Vol. 35, No. 30, pp. 5509-5512, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01060-9

Sequential Alkoxy Radical Fragmentation-Cyclopropylcarbinyl Rearrangement. Synthesis of Highly Functionalized Eleven-Membered Rings.

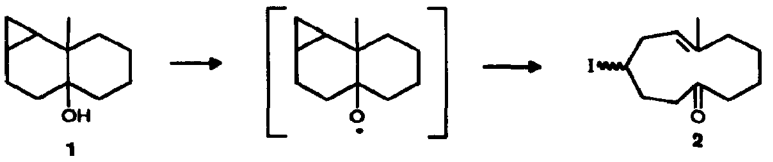
Alicia Boto,[a] Carmen Betancor,[b] Ernesto Suárez*[a]

[a]Instituto de Productos Naturales y Agrobiología del C.S.I.C., Carretera de La Esperanza 2, 38206-La Laguna, Tenerife, Spain. [b]Departamento de Química Orgánica, Universidad de La Laguna, Tenerife, Spain

Abstract: The steroidal 5α-alcohol (3) with (diacetoxyiodo)-benzene and iodine under irradiation with visible light undergoes a tandem alkoxy radical β-fragmentation-cyclopropylcarbinyl rearrangement reaction to give the eleven-membered cyclic ketone (4). Under oxygen pressure peroxidation of the C-radical intermediate takes place to afford the highly functionalized eleven-membered cyclic ketone (6) in moderate yield.

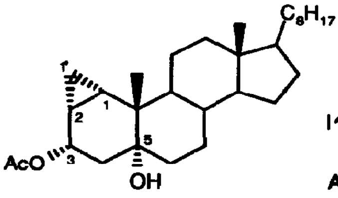
We have recently reported that photolysis of cyclic alcohols with (diacetoxyiodo)benzene (DIB) and iodine generates an alkoxy radical which subsequently undergoes β-fragmentation.[1] The resulting C-radical is able to react with a molecule of oxygen forming a peroxy radical that can eventually add to a suitably positioned C-C[1a] or C-O[1b] double bond.

Continuing with these studies we decided to explore this reaction on 5-hydroxydecalinyl compounds containing a suitably positioned cyclopropane ring (1) (Scheme I). The alkoxy radical formed would undergo a tandem β-fragmentation-cyclopropylcarbinyl rearrangement reaction to afford eleven-membered cyclic ketones (2). The rapidity of the cyclopropane ring opening by an adjacent carbon radical is well known and has been used not only as a probe of reaction mechanisms but also in synthetic organic chemistry.[2]

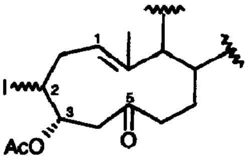


Scheme I

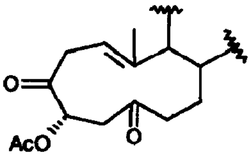
As a model, the steroidal alcohol (3)[3] was prepared and irradiated with two 100 W tungsten-filament lamps, in the presence of DIB and iodine under the conditions summarized in the Table. When the reaction was performed under argon (entry 1) the expected double ring expansion reaction was produced and the iodo-derivative (4)[4] obtained. However, when the reaction was conducted under oxygen pressure (entry 2) diketone (5)[5] was also obtained. When the oxygen pressure was increased (entry 3) a new product (6)[6] was



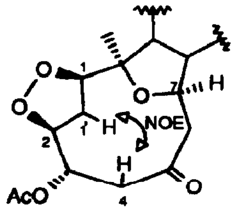
3



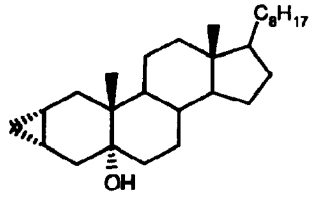
4



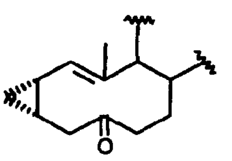
5



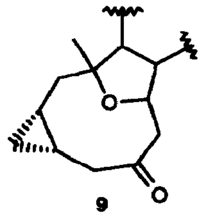
6



7



8



9

formed. The yield of these two oxygenated products (**5**) and (**6**) increased when the initial amount of iodine was reduced from 1.5 eq. to 0.5 eq. (entries 3 and 4). Hence, the peroxidation of the C_2-radical intermediate was favoured with respect to iodination. The structure and stereochemistry of dioxolane (**6**) was determined by extensive studies of ^1H and ^{13}C NMR spectroscopy. COSY, ROESY and NOEDIF experiments were also utilized, the most important feature being the transannular ROESY and NOE effects observed between one of the hydrogens at $C_{1'}$ and a hydrogen at C_4. The observed coupling constants of the low field protons at C_1-C_7 and $C_{1'}$ are in good agreement with those calculated over a minimized structure using the program PCMODEL.[7]

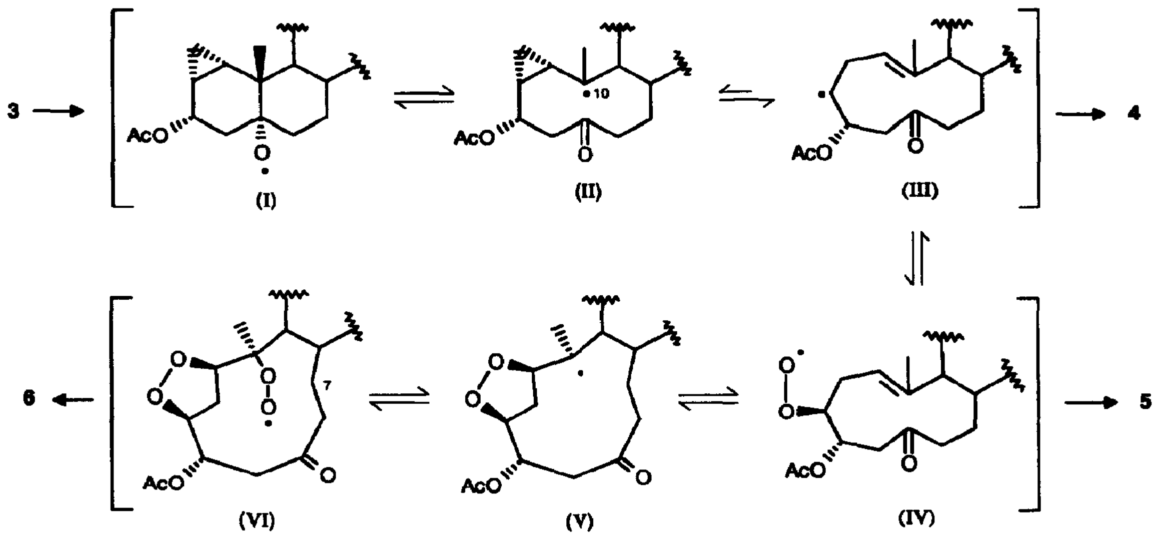
A plausible mechanism for the formation of these products is shown in Scheme II: β-fragmentation of the initial alkoxy radical (I) generates a C-radical at C_{10} (II). This radical induces ring opening of the adjacent cyclopropane unit generating intermediate (III), which may stereoselectively react with iodine to form compound (**4**). A regioselective *endo* cyclopropane ring opening to the secondary radical (III) is exclusively observed.[2] The radical (III) may also be stereoselectively attacked by a molecule of oxygen yielding peroxy radical (IV), which may lead to ketone (**5**) or may add to the C_1-C_{10} double bond creating the dioxolane ring.[8] The new C_{10} radical formed reacts with another molecule of oxygen, generating a second peroxy radical intermediate (VI). The formation of compound (**6**) from peroxy radical (VI) is consistent with a reduction to alkoxy radical and subsequent hydrogen abstraction at C_7, and has been commented previously.[9]

On the other hand, the steroidal model (**7**)[10] was prepared in order to determine whether direct opening of the cyclopropane ring by a peroxy radical eventually formed at C_{10} would take place. As can be seen in the Table, under an inert atmosphere the expected β-fragmentation occurred and compound (**8**)[11] was obtained in good yield (entry 5). Increased oxygen pressure (entries 6-8) led to a new tetrahydrofuran derivative (**9**)[12] formed by peroxidation of the C_{10} radical intermediate.[1b,e,9] However, no products coming from attack of the C_{10} peroxy radical to the cyclopropane ring could be detected.

Table. Fragmentation of alcohols (3) and (7).[a]

Entry	Substrate	Reagents[b] (mmol)	Conditions T (°C)	Conditions P (atm)	Conditions Time (h)	Products (Yield %)
1	3	DIB/I_2 (2.5/1.5)	40	Ar (1)	1.5	4 (50)
2	3	DIB/I_2 (2.5/1.5)	40	O_2 (3)	1	4 (21), 5 (21)
3	3	DIB/I_2 (2.5/1.5)	40	O_2 (5.5)	1	4 (20), 5 (24), 6 (11)
4	3	DIB/I_2 (2.5/0.5)	40	O_2 (5.5)	3	4 (5), 5 (32), 6 (15)
5	7	DIB/I_2 (3.5/2)	40	Ar (1)	1	8 (71)
6	7	DIB/I_2 (2.5/1.5)	40	O_2 (3)	1	8 (21), 9 (30)
7	7	DIB/I_2 (2.5/1.5)	40	O_2 (5)	1.75	8 (18), 9 (39)
8	7	DIB/I_2 (3.5/2)	r t	O_2 (10)	1.3	8 (20), 9 (26)

[a] All reactions were performed in cyclohexane (0.2 mmol in 15 ml) under irradiation with two 100 W tungsten-filament lamps; those under pressure were performed in a borosilicate Griffin-Worden pressure vessel (Kontes K-767100). [b] per mmol of substrate; DIB=(diacetoxyiodo)benzene.



Scheme II

Acknowledgement: This work was supported by the Investigation Programme nº PB90-0083 of the Dirección General de Investigatión Científica y Técnica. A.B. thanks the Ministerio de Educacion y Ciencia, Spain, for a fellowship.

REFERENCES AND NOTES

1. a) Boto, A.; Betancor, C.; Prangé, T.; Suárez, E. *Tetrahedron Lett.* **1992**, *33*, 6687; b) Boto, A.; Betancor, B.; Hernández, R.; Rodríguez, M.S.; Suárez, E. *Tetrahedron Lett*, **1993**, *34*, 4865; c) de Armas, P.; Francisco, C.G.; Suárez, E. *Angew. Chem. Int. Ed. Engl.*, **1992**, *31*, 772; d) de Armas, P.; Francisco, C.G.; Suárez, E. *J. Am. Chem. Soc.* **1993**, *115*, 8865; e) Hernández, R.; Marrero, J.J.; Suárez, E.; Perales, A. *Tetrahedron Lett.*, **1988**, *29*, 5979; f) Hernández, R.; Marrero, J.J.; Melián, D.; Suárez, E. *Tetrahedron Lett.* **1988**, *29*, 6661; g) Freire, R.; Marrero, J.J.; Rodríguez, M.S.; Suárez, E. *Tetrahedron Lett.* **1986**, *27*, 383.
2. For a recent review see: Nonhebel, D.C. *Chem. Soc. Rev.*, **1993**, 347; see also: Harling, J.D.; Motherwell, W.B. *J. Chem. Soc., Chem. Commun.* **1988**, 1380; Batey, R.A.; Grice, P.; Harling, J.D.; Motherwell, W.B.; Rzepa, H.S. *J. Chem. Soc., Chem. Commun.* **1992**, 942.
3. Compound (3): m.p. 129-131 °C (MeOH); $[\alpha]_D$ -41.9° ($CHCl_3$, c, 0.12); IR ($CHCl_3$) ν_{max} 3593, 1727 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.40 (1H, dt, *J* 4.4, 9.3 Hz, 1'-H), 0.68 (3H, s, 13-Me), 0.87 (6H, d, *J* 6.4 Hz, 25-Me_2), 0.91 (3H, d, *J* 6.4 Hz, 20-Me), 1.05 (3H, s, 10-Me), 2.0 (3H, s, MeCO), 5.41 (1H, t, *J* 7.2 Hz, 3-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 170.1 (s, CO), 73.82 (s, 5-C), 69.57 (d, 3-C), 12.11 (d), 7.69 (t); MS *m/z* 458.37370 (M^+, 23%).
4. Compound (4): $[\alpha]_D$ -15.9° ($CHCl_3$, c, 0.13); IR (CCl_4) ν_{max} 1737, 1710, 1456 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.71 (3H, s, 13-Me), 0.87 (6H, d, *J* 6.7 Hz, 25-Me_2), 0.92 (3H, d, *J* 6.4 Hz, 20-Me), 1.65 (3H, t, *J* 1.6 Hz, 10-Me), 2.1 (3H, s, MeCO), 4.5-4.7 (2H, m, 3-H+2-H), 5.1 (1H, m, 1-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 210.03 (s, 5-C), 169.94 (CO), 141.41 (s, 10-C), 123.47 (d, 1-C), 71.33 (d, 3-C); MS *m/z* 584.27272 (M^+, 2%).
5. Compound (5): IR (CCl_4) ν_{max} 1748, 1721 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ_H 0.62 (3H, s, 13-Me), 1.01 (9H, d, *J* 6.5 Hz, 20-Me+25-Me_2), 1.54 (3H, d, *J* 1.3 Hz, 10-Me), 1.85 (3H, s, MeCO), 2.51 (1H, dd, *J* 5.0, 17.0 Hz, 4-H), 2.85 (1H, dd, *J* 17, 5.2 Hz, 1'-H), 3.10 (1H, dd, *J* 17.0, 5.0 Hz, 4-H), 3.43 (1H, dd, *J* 17.2, 11.1 Hz, 1'-H), 5.11 (1H, m, 1-H), 5.42 (1H, t, *J* 5.0 Hz, 3-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 207.90 (2-C or 5-C), 204.29 (2-C or 5-C), 170.04 (CO), 144.45 (1-C), 117.52 (10-C), 73.16 (3-C); MS *m/z* 472.35483 (M^+, 10%).
6. Compound (6): $[\alpha]_D$ -43° ($CHCl_3$, c, 0.084); IR (CCl_4) ν_{max} 1745, 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.72 (3H, s, 13-Me), 0.87 (6H, d, *J* 6.2 Hz, 25-Me_2), 0.92 (3H, d, *J* 6.4 Hz, 20-Me), 1.26 (3H, s, 10-Me), 2.04 (3H, s, MeCO), 2.20 (1H, d, *J* 11.9 Hz, 6-H), 2.39 (1H, dd, *J* 3.3, 16 Hz, 4-H), 2.61 (1H, ddd, *J* 8.6, 8.9, 15 Hz, 1'-H), 2.95 (1H, ddd, *J* 5.8, 8.8, 15 Hz, 1'-H), 3.02 (1H, dd, *J* 6.9, 11.8 Hz, 6-H), 3.86 (1H, dd, *J* 7.6, 8.8 Hz, 7-H), 3.87 (1H, dd, *J* 16, 11.5 Hz, 4-H), 4.05 (1H, dd, *J* 8.8, 5.8 Hz, 1-H), 4.44 (1H, dt, *J* 3.3, 8.8 Hz, 2-H), 5.67 (1H, dt, *J* 11.5, 3.3 Hz, 3-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 204.75 (5-C), 169.39 (CO), 83.94 (1-C or 2-C), 82.98 (10-C), 80.13 (1-C or 2-C), 79.05 (7-C), 71.18 (3-C); MS *m/z* 504.34606 (M^+, 1.2%).
7. PCMODEL (Serena Software, Box 3076, Bloomington, IN 47402-3076).
8. Feldman, K.S.; Berven, H.M.; Weinreb, P.H.; *J. Am. Chem. Soc.* **1993**, *115*, 11364; Feldman, K.S.; Simpson, R.E.; Parvez, M. *J. Am. Chem. Soc.* **1986**, *108*, 1328; Feldman, K.S.; Simpson, R.E. *J. Am. Chem. Soc.* **1989**, *111*, 4878.
9. Freire, R.; Hernández, R.; Rodríguez, M.S.; Suárez, E. *Tetrahedron Lett.* **1987**, *28*, 981; Hernández, R.; Marrero, J.J.; Suárez, E. *J. Chem. Soc., Chem. Commun.* **1990**, 524; Boto, A.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **1994**, *35*, 2597.
10. Compound (7): m.p. 99-101 °C (MeOH); $[\alpha]_D$ +11.6° ($CHCl_3$, c, 0.21); IR ($CHCl_3$) ν_{max} 3590 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.51 (2H, m, 1'-H_2), 0.64 (3H, s, 13-Me), 0.86 (6H, d, *J* 7 Hz, 25-Me_2), 0.89 (3H, d, *J* 7 Hz, 20-Me); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 73.61 (5-C), 12.22 (1'-C), 8.47 (2-C or 3-C), 7.35 (2-C or 3-C); MS *m/z* 400.3711 (M^+, 4%).
11. Compound (8): m.p. 122.5-124.5 °C (AcOEt-MeOH); $[\alpha]_D$ -28.3° ($CHCl_3$, c, 0.3); IR ($CHCl_3$) ν_{max} 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.36 (1H, m, 1'-H), 0.69 (3H, s, 13-Me), 0.86 (6H, d, *J* 6.7 Hz, 25-Me_2), 0.90 (3H, d, *J* 8.0 Hz, 20-Me), 1.54 (3H, s, 10-Me), 4.92 (1H, d, *J* 6.6 Hz, 1-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 214.31 (5-C), 142.45 (10-C), 126.90 (1-C), 14.90 (2-C or 3-C), 14.38 (1'- C), 13.26 (2-C or 3-C); MS *m/z* 398.3577 (M^+, 14%).
12. Compound (9): $[\alpha]_D$ +2° ($CHCl_3$, c, 0.14); IR ($CHCl_3$) ν_{max} 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H -0.13 (1H, m, 1'-H), 0.62 (3H, s, 13-Me), 0.88 (6H, d, *J* 6.6 Hz, 25-Me_2), 0.94 (3H, d, *J* 6.4 Hz, 20-Me), 1.27 (3H, s, 10-Me), 2.86 (1H, t, *J* 11 Hz, 4-H), 3.05 (1H, dd, *J* 4.3, 13.8 Hz, 6-H), 3.82 (1H, m, 7-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 213.63 (5-C), 83.62 (10-C), 78.71 (7-C), 17.10 (2-C or 3-C), 14.63 (2-C or 3-C), 13.60 (1'-C); MS *m/z* 414.3505 (M^+, 27%).

(*Received in UK* 28 *March* 1994; *revised* 31 *May* 1994; *accepted* 3 *June* 1994)