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Fragmentation of Alkoxy Radicals: Synthesis of Macrolactones by Sequential Ring Expansion Reactions

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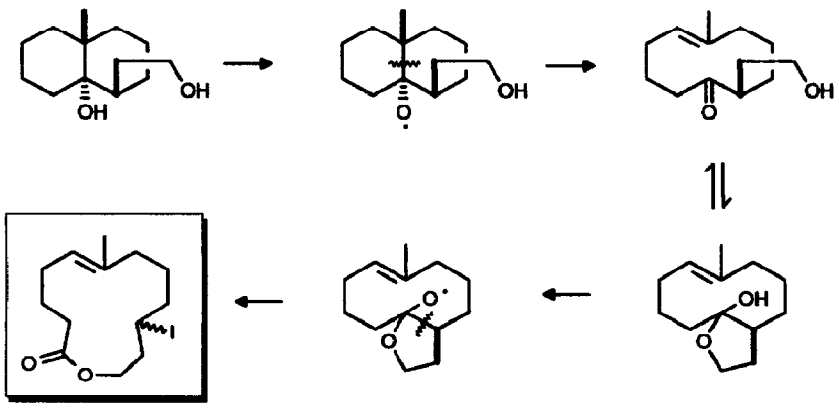
Abstract: The synthesis of thirteen-membered lactones by two sequential ring expansion reactions on a steroidal model (I) is described. These reactions are promoted by β-fragmentation of alkoxy radicals generated from tertiary and hemiacetal alcohols using the (diacetoxyiodo)benzene/I_2 or HgO/I_2 systems.

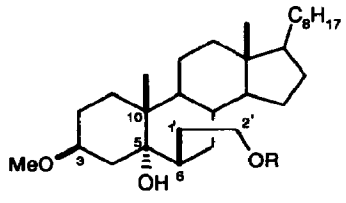
Macrolide compounds can, in general, be synthesized by intramolecular lactonization of open long chain ω-hydroxy acids or by cleavage of internal bonds in polycyclic systems. Although the latter protocol seems to be especially attractive for the introduction of specific substituents into the macrolide ring, it has scarcely been used in organic synthesis.[1]

During the past few years we have examined the β-fragmentation reaction of alkoxy radicals generated by reaction of hemiacetals with hypervalent iodine reagents and iodine.[2] Continuing with these studies we envisioned that macrolactones could be synthesized by a double ring expansion reaction following the methodology shown in Scheme 1.

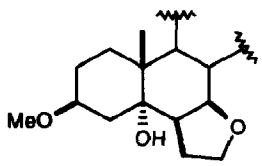


Scheme 1

In principle, the reaction was expected to proceed in a single step. The tertiary alcohol would fragment first and then the intermediate hemiacetal formed would react with an excess of reagent to give a second



1, R = H
3, R = Ac



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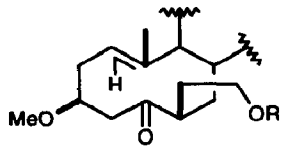
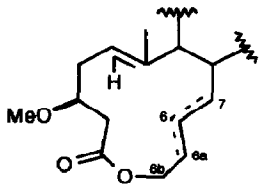
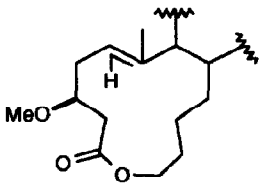


4, R = Ac
5, R = H



6, 6a,6 *EZ*
7, 6*Z*
8, 6*E*



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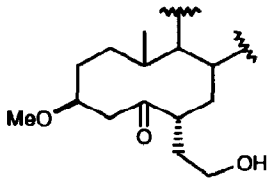

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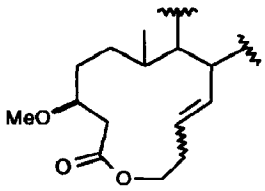

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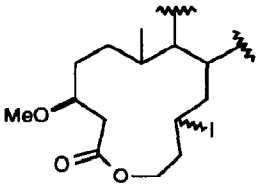
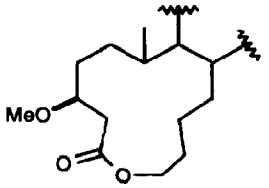


12/13



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ring expansion reaction. Thirteen-membered lactones could be accessible by this methodology, that we expect could be easily extended to other ring systems.

As a model we have prepared the steroidal diol (1)[3] by alkylation of 3β-methoxy-5α,6α-epoxycholestane with allylmagnesium bromide, followed by ozonization and reduction with $LiAlH_4$. Unfortunately, treatment of (1) with (diacetoxyiodo)benzene (DIB) and iodine in the conditions summarized in the Table (entry 1) did not afford any β-fragmentation product, and only a small yield of tetrahydrofuran derivative (2) was obtained instead. Compound (2) was formed by hydrogen abstraction promoted by the primary alkoxy radical. This is not unexpected because hydrogen abstraction, when possible, competes with β-fragmentation.[4]

We therefore decided to perform the fragmentation in two steps protecting the primary alcohol as its acetyl derivative (3). The photolysis of (3) in the presence of HgO/I_2 gave the ten-membered ketone (4)[5] (entry 2) in 85 % yield (97 % based on conversion). The reaction conditions shown in the Table are rather critical, any change of the temperature, reagent stoichiometry or use of other oxidizing agents (e.g. DIB) leading to a substantial loss of yield (compare entries 2-5).[6]

Hydrolysis of acetate (4) with saturated methanolic solution of $NaHCO_3$ at 0 °C gave the alcohol (5) (99 %). Photolysis of alcohol (5) with HgO/I_2 afforded a mixture of macrolactones (6-8)[7] in moderate yield (entry 6) accompanied by a complex mixture of transannular cyclization products from the 5-cyclodecenone system.[8] The mixture of macrolactones was partially resolved by silica gel chromatography into (6) (an irresoluble mixture of 6a,6-*EZ* olefins) and the isomeric 6Z- (7) and 6E- (8) olefins. The structure and

Table. Fragmentation Reactions[a]

Entry	Substrate	Reagents[b] (mmol)	Solvent	Conditions		Products (yield %)
				T (°C)	Time (h)	
1	**1**	DIB/I_2 (1.2/1)	Cy	40	4	**2** (25), **1** (49)
2	**3**	HgO/I_2 (1.5/1.5)	CCl_4	0-5	10	**4** (85), **3** (13)
3	**3**	HgO/I_2 (1.5/1.5)	CCl_4	40	1	**4** (15), **3** (19)
4	**3**	HgO/I_2 (1.8/1.8)	CCl_4	0-5	10	**4** (55), **3** (9)
5	**3**	DIB/I_2 (4/2)	Cy	40	10	complex mixture[c]
6	**5**	HgO/I_2 (1.4/1.4)	CCl_4	0-5	12.5	**6**, **7**, **8** (30)
7	**10**	DIB/I_2 (1.5/1)	Cy	22	5.5	**11** (62), **12**/**13** (17)

[a] All reactions were performed by irradiation with two 100 W tungsten-filament lamps. [b] Per mmol of substrate. [c] The yield of (4) was not determined. DIB = (diacetoxyiodo)benzene; Cy = cyclohexane.

stereochemistry of these macrolactones were determined by ^1H and ^{13}C NMR spectroscopy.

Catalytic hydrogenation of the mixture of macrolactones over PtO_2 gave lactone (**9**) (75 %),[9] in addition to a small amount of an acid obtained from (**6**) by hydrogenolysis of the O-C6b bond.

The moderate yield of the second ring expansion reaction was attributed to the reactivity of the 5-cyclodecenone system to transannular cyclization. In order to avoid this, compound (**10**)[10] was synthesized from (**4**) prior to inversion of configuration at C-6 (2 % KOH/MeOH, reflux, 17 h).

Treatment of (**10**) with DIB/I_2 (entry 7) gave the compounds (**11**-**13**) with a global yield of β-fragmentation of 79 %. Lactone (**11**) is a single compound whose double bond stereochemistry could not be determined by NMR. The iodo derivatives (**12**) and (**13**) could be separated by chromatography but the stereochemistry at C-6 remains undetermined.

Catalytic hydrogenation of (**11**) (PtO_2/EtOH, 60 %) or reduction of the mixture of iodides (**12**) and (**13**) ($^nBu_3SnH$/AIBN, 75 %) led to lactone (**14**).[11]

We believe that this study ilustrates a new method for the synthesis of thirteen-membered macrolides. This method should also find application in the construction of other types of ring systems by prior modification of the starting bicycle or the tether. Further work is under way in order to examine this possibility.

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A.; Rodríguez, M. S.; Suárez, E. *J. Chem. Soc. Perkin Trans. 1* **1991**, 3349. de Armas, P.; Francisco, C. G.; Suárez, E. *Angew. Chem. Int. Ed. Eng.* **1992**, *31*, 772. de Armas, P.; Francisco, C. G.; Suárez, E. *J. Am. Chem. Soc.* **1993**, *115*, 8865.

3. Compound (**1**): Prepared from 3β-methoxy-5α,6α-epoxycholestane, reaction with allylmagnesium bromide, ozonolisis and reduction with $LiAlH_4$ (74% overall), m.p. 186.5-187 °C (methanol); $[\alpha]_D$ -23° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 3620, 3435 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.66 (3H, s, 13-Me), 0.86 (6H, d, *J* 6.5 Hz, 25-Me_2), 0.89 (3H, d, *J* 7.2 Hz, 20-Me), 1.00 (3H, s, 10-Me), 3.35 (3H, s, 3-OMe), 3.50 (1H, m, 3-H), 3.60 (2H, m, 2'-H_2); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 55.75 (-OMe), 62.59 (C-2'), 76.68 (C-3), 77.35 (C-5); MS m/z 462.4095 (M^+, 3%).
4. Brun, P.; Waegell, B. In *Reactive Intermediates*; Abramovich, R. A., Ed.; Plenum Press: New York, 1983; Vol. 3, p 392.
5. Compound (**4**): amorphous; IR (CCl_4) ν_{max} 1743, 1699, 1662 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.70 (3H, s, 13-Me), 0.86 (6H, d, *J* 6.5 Hz, 25-Me_2), 0.88 (3H, d, *J* 6.5 Hz, 20-Me), 1.75 (3H, s, 10-Me), 2.06 (3H, s, 2'-OAc), 2.82 (1H, m, 6-H), 2.44 (1H, dd, *J* 9.2, 14.3 Hz, 4-H_a), 2.62 (1H, m, 2-H), 2.63 (1H, dd, *J* 2.9, 14.5 Hz, 4-H_b), 3.43 (3H, s, 3-OMe), 3.79 (1H, m, 3-H), 4.07 (2H, m, 2'-H_2), 5.17 (1H, m, 1-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 56.39 (-OMe), 61.90 (C-2'), 78.51 (C-3), 117.78 (C-1), 145.03 (C-10), 170.69 (-*O*C*O*CH_3), 209.41 (C-5); MS m/z 502.4010 (M^+, 14%).
6. For previous work on alkoxy radical β-fragmentation of 5α-hydroxy-cholestane derivatives see: Mihailovic, M. Lj.; Lorenc, Lj.; Gasic, M.; Rogic, M.; Melera, A.; Stefanovic, M. *Tetrahedron* **1966**, *22*, 2345. Mez, H. -C.; Rist, G.; Ermer, O. Lorenc, Lj.; Kalvoda, J.; Mihailovic, M. Lj. *Helv. Chim. Acta* **1976**, *59*, 1273.
7. Compound (**7**): m.p. 68-70 °C (EtOH), $[\alpha]_D$ +65° ($CHCl_3$); IR (CCl_4) ν_{max} 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.75 (3H, s, 13-Me), 0.86 (6H, d, *J* 6.3 Hz, 25-Me_2), 0.90 (3H, d, *J* 7.4 Hz, 20-Me), 1.66 (3H, s, 10-Me), 3.38 (3H, s, 3-OMe), 3.41 (1H, m, 3-H), 4.25 (2H, m, 6b-H_2), 4.98 (2H, m, 1-H y 7-H), 5.27 (1H, ddd, *J* 3.0, 11.3, 11.3 Hz, 6-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 56.18 (-OMe), 64.34 (C-6b), 78.68 (C-3), 117.64 (C-1), 125.68 (C-6),135.85 (C-7), 141.08 (C-10), 171.50 (C-5); MS m/z 458.3744 (M^+, 10%). Compound (**8**): m.p. 87.5-88.5 °C (MeOH), $[\alpha]_D$ -21.8° ($CHCl_3$). IR (CCl_4) ν_{max} 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.70 (3H, s, 13-Me), 0.86 (6H, d, *J* 6.6 Hz, 25-Me_2), 0.90 (3H, d, *J* 6.4 Hz, 20-Me), 1.57 (3H, s, 10-Me), 3.36 (3H, s, 3-OMe), 3.68 (1H, m, 3-H), 3.89 (1H, m, 6b-H_a), 4.43 (1H, m, 6b-H_b), 4.97 (1H, m, 1-H), 5.03 (1H, dd, *J* 8.8, 15.4 Hz, 7-H), 5.17 (1H, m, 6-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 56.39 (-OMe), 61.76 (C-6b), 77.32 (C-3), 120.21 (C-1), 123.48 (C- 6), 136.04 (C-7), 140.47 (C-10), 170.94 (C-5); MS m/z 458.3767 (M^+, 3%).
8. For radical transannular cyclization of 5-cyclodecenones see: Fan, W.; White, J. B. *Tetrahedron Lett.* **1993**, *34*, 957. Colclough, D.; White, J. B.; Smith, W. B.; Chu, Y. *J. Org. Chem.* **1993**, *58*, 6303.
9. Compound (**9**): amorphous; IR (CCl_4) ν_{max} 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ_H 0.69 (3H, s, 13-Me), 0.87 (6H, d, *J* 6.6 Hz, 25-Me_2), 0.90 (3H, d, *J* 6.6 Hz, 20-Me), 1.55 (3H, s, 10-Me), 3.39 (3H, s, 3-OMe), 3.76 (1H, m, 3-H), 3.90 (1H, m, 6b-H_a), 4.42 (1H, m, 6b-H_b), 5.01 (1H, m, 1-H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ_C *inter alia* 56.39 (-OMe), 62.26 (C-6b), 77.85 (C-3), 120.53 (C-1), 140.87 (C-10), 171.40 (C-5); MS m/z 460.3940 (M^+, 1%).
10. Attempts at catalytic hydrogenation of 6α-(2'-acetoxyethyl)-3β-methoxy-(1E)-5,10-seco-1(10)-cholesten -5-one, obtained from (**4**) by isomerization at C-6 (2% KOH/MeOH, reflux, 17 h, 97%) were unsuccessful. Reduction of the carbonyl group ($LiAlH_4$, 90%), catalytic hydrogenation (PtO_2/AcOH, 78%), selective acetylation of the primary hydroxyl group (Ac_2O/Py, -18 °C, 3d, 70%), and reoxidation (PCC/CH_2Cl_2, 98%) afforded (**10**) as a pure compound whose C-10 stereochemistry could not be determined. Compound (**10**): amorphous; IR (CCl_4) ν_{max} 3640, 3450, 1700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.67 (3H, s, 13-Me), 0.84 (3H, d, *J* 6.2 Hz, 10-Me), 0.85 (6H, d, *J* 7.0 Hz, 25-Me_2), 0.89 (3H, d, *J* 6.4 Hz, 20-Me), 2.66 (1H, dd, *J* 2.9, 16.1 Hz, 4-H_a), 2.78 (1H, m, 6-H), 2.99 (1H, dd, *J* 8.9, 16.1 Hz, 4-H_b), 3.33 (3H, s, 3-OMe), 3.59 (2H, m, 2'-H_2), 3.73 (1H, m, 3-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 56.05 (-OMe), 60.74 (C-2'), 77.89 (C-3), 217.32 (C-5); MS m/z 462.4068 (M^+, 15%).
11. Compound (**14**): amorphous; IR (CCl_4) ν_{max} 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.68 (3H, s, 13-Me), 0.86 (6H, d, *J* 6.7 Hz, 25-Me_2), 0.89 (3H, d, *J* 6.7 Hz, 20-Me), 0.93 (3H, d, *J* 6.1 Hz, 10-Me), 2.50 (1H, dd, *J* 10.5, 13.1 Hz, 4-H_a), 2.76 (1H, dd, *J* 5.3, 13.1 Hz, 4-H_b), 3.34 (3H, s, 3-OMe), 3.80 (2H, m, 6b-H_a, 3-H), 4.45 (1H, m, 6b-H_b); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 56.42 (-OMe), 76.99 (C-3), 171.73 (C-5); MS m/z 462.4045 (M^+, 6%).

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