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SYNTHESIS OF MEDIUM-SIZED LACTONES: IODOSOBENZENE DIACETATE AN EFFICIENT REAGENT FOR β-FRAGMENTATION OF ALKOXY-RADICALS[1]

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SUMMARY: Photolysis of several steroidal lactols in the presence of iodosobenzene diacetate (IBDA) and iodine leads to alkoxy-radicals, which undergo β-fragmentation to produce medium-sized lactones in good yields.

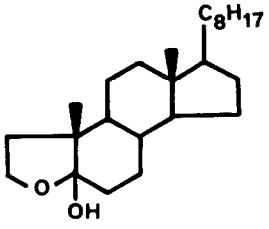
We have recently introduced iodosobenzene diacetate[2](IBDA)-iodine, as a reagent to generate alkoxy[3] and neutral aminyl[4] radicals, which are able intramolecularly to abstract one hydrogen atom to produce cyclic ethers and 1,4-epimino compounds, respectively. We have also used this reagent to decarboxylate carboxylic acids.[5]

The system IBDA-iodine was found to be superior to the heavy metal derivatives customarily used for these reactions, such us lead tetraacetate and mercuric oxide. Continuing our interest in the study of iodine(III) derivatives as mild oxidizing reagents for the generation of alkoxy-radicals, we describe here the reaction of IBDA-iodine with γ- and δ-lactols, by photolysis with two 100-W tungsten-filament lamps. This reaction produces medium-sized lactones in good yields, through ring-expansion.

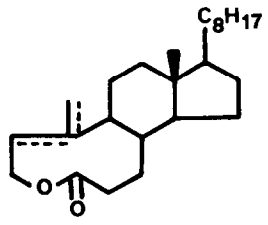
Previously reported syntheses[6] of medium-sized lactones by ring expansion reactions, usually involving more steps and strong oxidation conditions, have moderate yields. As we learned after completion of this work, a synthesis of medium-sized lactones has been achieved by Yamada and Suginome[7], by irradiation with a high-pressure mercury lamp, of the hypoiodites of γ- and δ-lactols in the presence of an excess of mercury (II) oxide and iodine.

We extended our reaction to different types of steroidal lactols. Therefore, ring-expansion of γ-lactol (1)[8] (Scheme 1) (1 mmol) was accomplished by reaction with iodosobenzene diacetate (1.1 mmol) and iodine (1 mmol) in cyclohexane (100 ml) and irradiation, under argon, with visible light from two 100-W tungsten-filament lamps for 1h. at 40°C, yielding (85%) a mixture of the olefinic lactones (2)[9] and (3)[10] in a 1:1 ratio, which was separated by column chromatography with benzene:n-hexane 8:2 as eluant. In the ^{1}HNMR spectrum of (2) broad signals are observed for the protons, at C-2 and at C-19, as a consequence of the slow conformational

Scheme 1

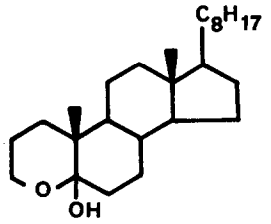


1



2 $\Delta^{10,19}$

3 $\Delta^{1,10}$



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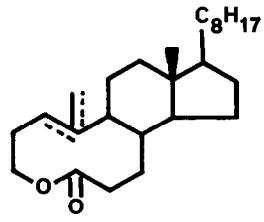
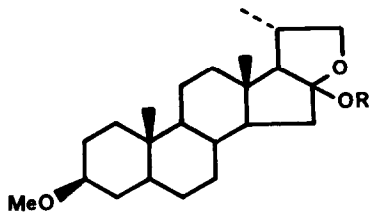


5 $\Delta^{10,19}$

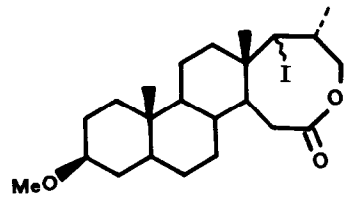
6 $\Delta^{1,10}$ E

7 $\Delta^{1,10}$ Z



8 R = H

9 R = Me



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interconvertion of the nine-membered lactone ring. A similar situation is observed for several carbons in its ^{13}CNMR spectrum. Nevertheless the AMX system formed by the protons at C-1 and C-2 is clearly distinguished in the ^{1}HNMR spectrum of lactone (3).

This reaction takes place similarly with the δ-lactol (4)[11], although a longer time is required (6h.). Thus, lactones (5)[12], (6)[13] and (7)[14] were obtained with an 83% yield in a 1:2:2 ratio, after careful chromatography.

As expected, the slow conformational equilibrium of the ten-membered lactone ring is also observed in the methylene-lactone (5). The Z or E configurations of the Δ^{1-10}olefin in lactones (6) and (7) were determined by ^{13}CNMR spectroscopy[15]. The observed deshielding of the C-19 signal by 5.5 ppm in the ^{13}CNMR spectrum of (7) indicates that the olefin has a Z-configuration.

The γ-lactol (8)[16], that in solution is in equilibrium with the ring-opened form, was

characterized as its methylacetal derivative (9).[17] The photolysis of (8) with IBDA-iodine for 1.5 h. gave the iodo-lactone (10)[18] with 81% yield that exhibits the signals corresponding to the protons at C-15 and C-22 as the AM parts of two AMX systems, and a broad singlet at δ 3.92 assigned to the proton at C-17, geminal to the iodine atom.

These results are consistent with a mechanism of β-fragmentation of alkoxy-radicals as shown in Scheme 2.

Scheme 2

11 R_1 = I(OAc)Ph **13**

12 R_1 = I

The intermediates (11) (R_2=H or Me), produced by equilibrium metathesis of IBDA with the lactol, and the hypoiodite (12) are expected to be the species that by photolysis generate the alkoxy-radicals. The β-fragmentation reaction leads to the carbon-radical (13) that gives rise to the olefins in the case of tertiary radicals (13, R_2=Me) or iodine compounds if it is secondary (13, R_2=H).

It is deduced from the above that the reaction proceeds satisfactorily for those cases where n and m are (2,4), (3,4) and (2,3). The extension of this method to other cyclic systems is in progress.

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8. Compound (1): m.p. 113-5 C (MeOH);$[\alpha]_D$ +63°($CHCl_3$); IR ν_{max} (Cl_4C) 3600 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ inter alia 0.99 (3H, s, 10-Me), 3.88 (2H, m, $W_{1/2}$ 25 Hz, 2-H_2); ^{13}CNMR (50.3 MHz, $CDCl_3$) δ inter alia 105.81 (5-C), 64.08 (2-C); MS m/z 376.3307 (M^+).

9. Compound (2): amorphous; IR ν_{max} ($CHCl_3$) 3060, 1720, 1630, 895 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 4.25 (1H, m, $W_{1/2}$ 25 Hz, 2-H), 4.49 (1H, m, $W_{1/2}$ 30 Hz, 2-H), 4.96 and 4.93 (2H, s, 19-H_2); ^{13}CNMR ($CDCl_3$) complex spectrum; MS m/z 374.3166 (M^+, 15%).

10. Compound (3): amorphous; IR ν_{max} ($CHCl_3$) 1720, 1635 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.66 (3H, s, 10-Me), 4.31 and 4.89 (2H, AMX, 2-H_2), 5.66 (1H, AMX, J_{AM} 6.2, J_{AX} 6.6, J_{MX} 12.8 Hz, 1-H); ^{13}CNMR ($CDCl_3$) δ 179.01 (5-C), 147.14 (10-C), 122.74 (1-C), 62.77 (2-C); MS m/z 374.3213 (M^+, 11%).

11. Compound (4): amorphous; IR ν_{max} ($CHCl_3$) 3580, 1690 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.90 (3H, s, 10-Me), 3.60 (1H, m, $W_{1/2}$ 20 Hz, 3-H), 3.90 (1H, m, $W_{1/2}$ 25 Hz, 3-H); ^{13}CNMR ($CDCl_3$) complex spectrum; MS m/z 390 (M^+, 2%).

12. Compound (5): amorphous; IR ν_{max} ($CHCl_3$) 3060, 1712, 1630, 885 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.91 (3H, s, 10-Me), 3.86 (1H, m, $W_{1/2}$ 25 Hz, 3-H), 4.62 (1H, m, $W_{1/2}$ 30 Hz, 3-H), 4.83 and 4.74 (2H, s, 19-H_2); ^{13}CNMR ($CDCl_3$) complex spectrum; MS m/z 388 (M^+, 24%).

13. Compound (6): amorphous; IR ν_{max} ($CHCl_3$) 1718 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.62 (3H, s, 10-Me), 4.00 (1H, m, $W_{1/2}$ 20 Hz, 3-H), 4.90 (1H, m, $W_{1/2}$ 30 Hz, 3-H), 5.05 (1H, m, $W_{1/2}$ 20 Hz, 1-H); ^{13}CNMR ($CDCl_3$) δ 176.61 (5-C), 143.13 (10-C), 123.92 (1-C), 65.17 (3-C), 13.14 (19-C); MS m/z 388 (M^+, 18%).

14. Compound (7): amorphous; IR ν_{max} ($CHCl_3$) 1715 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.67 (3H, s, 10-Me), 2.57 (1H, m, $W_{1/2}$ 25 Hz, 2-H), 3.63 (1H, m, $W_{1/2}$ 30 Hz, 3-H), 4.60 (1H, m, $W_{1/2}$ 20 Hz, 3-H), 5.19 (1H, m, $W_{1/2}$ 20 Hz, 1-H); ^{13}CNMR ($CDCl_3$) δ 175.06 (5-C), 143.09 (10-C), 120.46 (1-C), 61.97 (3-C), 18.70 (19-C); MS m/z 388 (M^+, 13%).

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16. Compound (8): m.p. 131-3°C (acetone); $[\alpha]_D$ -52° ($CHCl_3$); IR ν_{max} 3565, 1720 cm^{-1}; ^{1}HNMR ($CDCl_3$) and ^{13}CNMR ($CDCl_3$) complex spectra, mixture of opened and closed forms; MS m/z 362 (M^+, 3%).

17. Compound (9): m.p. 154-6°C (MeOH);$[\alpha]_D$ -46°($CHCl_3$); IR ν_{max} ($CHCl_3$) 1090 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.72 (3H, s, 10-Me), 0.76 (3H, s, 13-Me), 1.00 (3H, d, J 6.8 Hz, 20-Me), 3.1 (1H, m, $W_{1/2}$ 20 Hz, 3-H), 3.16 (3H, s, 3-O-Me), 3.30 (3H, s, 16-O-Me), 3.45 and 4.11 (2H, AMX, J_{AM}= J_{AX}= J_{MX} 8.3 Hz, 22-H_2); ^{13}CNMR ($CDCl_3$) δ 119.94 (16-C), 79.94 (3-C), 77.74 (22-C), 55.66 (3-O-Me), 49.35 (16-O-Me); MS m/z 376 (M^+, 17%).

18. Compound (10): m.p. 180-2°C (pentane-EtOAc);$[\alpha]_D$ -55°($CHCl_3$); IR ν_{max} 1730 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.66 (3H, s, 13-Me), 0.86 (3H, d, J 6.6 Hz, 20-Me), 1.00 (3H, s, 10-Me), 2.06 and 2.84 (2H, AMX, J_{AM} 14.0, J_{MX} 5.9, J_{AX} 6.6 Hz, 15-H_2), 3.0 (1H, m, $W_{1/2}$ 21 Hz, 3-H), 3.22 (3H, s, 3-O-Me), 3.83 and 4.07 (2H, AMX, J_{AM} 12.1, J_{MX} 0, J_{AX} 3.8 Hz, 22-H_2), 3.92 (1H, s, 17-H); ^{13}CNMR ($CDCl_3$) δ 176.27 (16-C), 79.77 (3-C), 71.40 (22-C), 55.66 (3-O-Me); MS m/z 488.1725 (M^+, 1%), 361.2607 (M^+-I, 15%).

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