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HYPERVALENT ORGANOIODINE REAGENTS IN THE β-FRAGMENTATION OF UNSATURATED LACTOLS LEADING TO SPIROCOMPOUNDS

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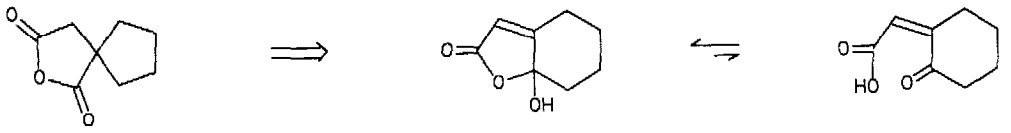
Summary: Treatment of the unsaturated γ-lactol (1) with (diacetoxyiodo)benzene in the presence of iodine leads to β-fragmentation-intramolecular cyclization of the initially formed alkoxy radical to yield spiro[4.4] iodoanhydrides (2) and (3).

The β-fragmentation of alkoxy radicals, generated by reaction of intramolecular hemicetals with (diacetoxyiodo)benzene in the presence of iodine, is a convenient procedure for the synthesis by ring expansion of medium-sized lactones.[1] This reaction has also been accomplished using other oxidation systems, such us mercury (II) oxide[2] and lead tetraacetate.[3] Some synthetic applications of this reaction have been developed.[4]

Attempts to extend this reaction to γ-ketoacids gave anhydrides albeit in low yield.[5] The major compounds obtained were β-iodoketones, formed by oxidative iododecarboxylation of the acids.[6]

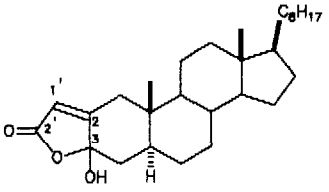
We considered that if we performed the reaction with unsaturated γ-ketoacids, which are mostly equilibrated to the cyclic lactols, we could have a route to spiro[4,4]anhydrides (Scheme 1). This type of spiro[4.4]compounds are present in the structure of important natural products.[7]



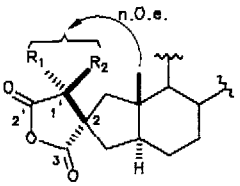
Scheme 1

The reaction has been tested on the steroidal lactol (1), easily obtained by condensation of glyoxylic acid with 5α-cholestan-3-one.[8] To a solution of (1)[9] (1 mmol) in cyclohexane (65 ml) and dichloromethane (20 ml) containing iodine (2 mmol) was added (diacetoxyiodo)benzene (3 mmol) portionwise at a rate of 1 mmol every 60 min at reflux temperature under argon and irradiation with two 100-W tungsten-filament lamps. The reaction mixture was then washed with aqueous dilute sodium thiosulfate and water. Silica gel chromatography[10] of the residue (n-hexane:ethyl acetate 95:5) gave the spiroanhydrides (2)[11] (56%) and (3)[12] (24%).

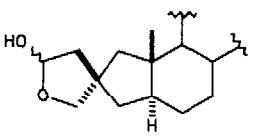
The structures of the isomeric anhydrides were determined on the basis of spectral and chemical evidence. In particular, the IR spectra of both isomers show carbonyl stretches at 1850 and 1780 cm^{-1}, and two carbonyl signals in the ^{13}CNMR spectra (DEPT experiments). Their ^{1}HNMR spectra are very



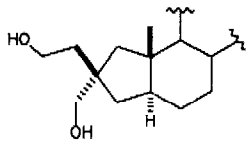
(1)



(2) R_1 = H; R_2 = I
(3) R_1 = I; R_2 = H
(4) R_1 = R_2 = H



(5)



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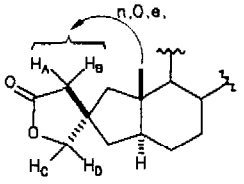
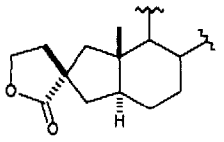


(7)



(8)

similar, the only differences being the chemical shifts of the 1'-H singlet and that of the 10-Me. Their molecular composition is also in agreement with accurate mass spectrometric measurements.

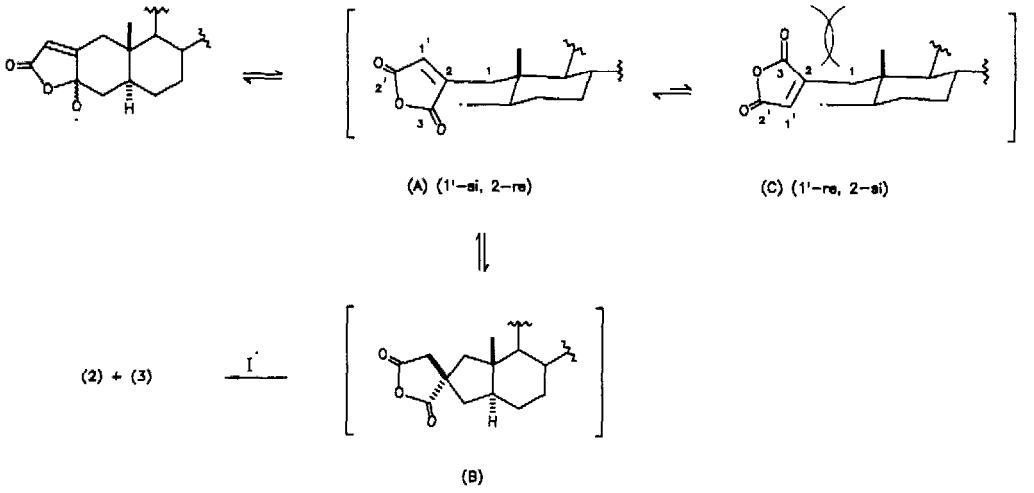
Assignment of S stereochemistry at C-2 was made by difference n.O.e. experiments. Irradiation of the C-10 methyl group results in a clear increase (7%) of the 1'-H proton signal for both isomers. Reduction of either iodo anhydride with n-BuSnH/AIBN in benzene at reflux temperature leading to the same anhydride (**4**)[13] confirms that they are isomers at C-1'. The stereochemistry at C-1' was tentatively assigned using the MM2 molecular mechanics program,[14] the major product corresponding to the isomer of lowest calculated energy.

Reduction of the crude fragmentation reaction with $LiAlH_4$ in THF at room temperature gave compounds (**5**)[15] (35%) and (**6**)[16] (40%). The hemicetal (**5**) can be transformed into the diol (**6**) (100%) by further reduction with $LiAlH_4$.

Oxidation of diol (**6**) with Ag_2CO_3/Celite in benzene yielded a mixture of lactones (**7**)[17] (45%) and (**8**)[18] (51%). Although we tried this reaction with several solvents, no improvement in the chemoselectivity was observed.[19]

Further evidence of the stereochemistry at C-2 was obtained by a difference n.O.e. experiment. Upon irradiation of the methyl group at C-10 an enhancement of the signal of the protons H_A and H_B on C-1' was observed in the ^{1}HNMR spectrum of lactone (**7**) and no effect was detected on H_C and H_D protons.

A plausible mechanism for the fragmentation reaction is shown in Scheme 2. The initially formed alcoxy radical undergoes β-fragmentation to give the C-4 radical (A) which after closure *via* a favoured 5-exo-trig cyclization[20] provides spiroradical (B). Radical (B) is stabilized by trapping an iodo radical in



Scheme 2

an unstereoselective manner to give the mixture of iodoanhydrides (**2**) and (**3**). The intramolecular cyclization step proceeded with complete regio- and stereoselectivity since the addition was realized exclusively on the (1'-si,2-re)-face of the double bond. No product originated by cyclization on the (1'-re,2-si)-face (C) has been isolated, probably because the necessary rotation of the double bond is sterically hindered, nor have products originated by the disfavoured but sometimes observed 6-endo-trig cyclization been detected.[21]

Spiro[4.4]lactones of this type are present in several sesquiterpenes of terrestrial (i.e. bakkenolide A)[7b] or marine origen (i.e. herbadysidolide),[7c] and a β-fragmentation of the appropriate unsaturated γ-lactol could be a good approach to their syntheses.

Further investigations on the scope and mechanism of this reaction as well as the exploration of its synthetic application are underway.

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9. Compound (**1**): m.p. 164-167 °C (ethyl acetate); $[\alpha]_D$ -94° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 3560, 3500-3100, 1750, 1650 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 0.66 (3H, s, 13-Me), 0.70 (3H, s, 10-Me), 0.86 (6H, d, J 6.4 Hz, 25-Me_2), 0.91 (3H, d, J 6.5 Hz, 20-Me), 2.13, 2.67 (2H, AB, J 12.9 Hz, 2-H_2), 5.71 (1H, d, J 1.8 Hz, 1'-H); ^{13}CNMR (50.3 MHz, $CDCl_3$) δ *inter alia* 105.09 (3-C), 115.54 (1'-C), 169.33 (2-C), 171.67 (2'-C); MS m/z 442.3448 (M^+, 17%), 424.3304 (M^+-H_2O, 100%).
10. Chromatotron chromatography (Harrison Research). The circular plate (Silica gel 60 PF_{254}) was deactivated by standing face down over a water-bath (60 °C) for six hours, and then 24 hours at room temperature before use. If a newly activated plate was used complete decomposition of the anhydrides was observed. Deactivated TLC plates prepared by the dipping technique were used to follow the chromatography.
11. Compound (**2**): m.p. 145-150 °C (n-pentane); $[\alpha]_D$ -56° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 1850, 1780 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 0.66 (3H, s, 13-Me), 0.78 (3H, s, 10-Me), 0.86 (6H, d, J 6.4 Hz, 25-Me_2), 0.89 (3H, d, J 6 Hz, 20-Me), 4.79 (1H, s, 1'-H); ^{13}CNMR (50.3 MHz, $CDCl_3$) δ *inter alia* 168.83, 175.33; MS m/z 568.2381 (M^+, 16%), 287.1654 (100%).
12. Compound (**3**): m.p. 138-140 °C (n-pentane); $[\alpha]_D$ +68° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 1850, 1780 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 0.67 (3H, s, 13-Me), 0.81 (3H, s, 10-Me), 0.86 (6H, d, J 6.2 Hz, 25-Me_2), 0.91 (3H, d, J 6.4 Hz, 20-Me), 4.75 (1H, s, 1'- H); ^{13}CNMR (50.3 MHz, $CDCl_3$) δ *inter alia* 168.98, 174.78; MS m/z 568.2436 (M^+, 21%), 287.1654 (100%).
13. Compound (**4**): m.p. 170 °C (decomp.)(acetone); $[\alpha]_D$ +17° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 1855, 1785 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$ δ 0.67 (3H, s, 13-Me), 0.79 (3H, s, 10-Me), 0.87 (6H, d, J 7.0 Hz, 25-Me_2), 0.91 (3H, d, J 7.0 Hz, 20-Me), 3.08, 2.92 (2H, AB, J 18.8 Hz, 1'-H_2); ^{13}CNMR (50.3 MHz, $CDCl_3$) δ 169.91, 178.99; MS m/z 442.3455 (M^+, 56%), 287.1625 (100%).
14. MM2 calculations were carried out using Molecular Modeling PCMODEL (Serena Software). A difference of 1.6 Kcal/mol was observed between C- 1' epimers.
15. Compound (**5**): hemiacetal mixture; IR ($CHCl_3$) ν_{max} 3590, 3500-3200 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 0.65 (3H, s, 13-Me), 0.77, 0.78 (3H, s,s, 10-Me), 0.86 (6H, d, J 6,7 Hz, 25-Me_2), 0.89 (3H, d, J 7.5 Hz, 20-Me), 2.56 (1H, dd, J 13.6, 4.1 Hz, 1'-H), 3.54 and 3.88, 3.59 and 3.76 (2H, AB, J 7.9 Hz, 3-H_2), 5.53 (1H, m, 2'-H); MS m/z 430.3818 (M^+, 79%), 415.3573 (100%).
16. Compound (**6**): m.p. 150-152 °C (CH_2Cl_2); $[\alpha]_D$ +24° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 3500-3200 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 0.64 (3H, s, 13-Me), 0.77 (3H, s, 10- Me), 0.86 (6H, d, J 6.8 Hz, 25-Me_2), 0.89 (3H, d, J 7.3 Hz, 20-Me), 3.37 (2H, s, 3-H_2), 3.73 (2H, t, J 7.3 Hz, 20-Me); MS m/z 432.3994 (M^+, 4%), 384.3761 (100%).
17. Compound (**7**): m.p. 183-185 °C (acetone); $[\alpha]_D$ +48° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 1770 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 0.66 (3H, s, 13-Me), 0.77 (3H, s, 10-Me), 0.86 (6H, d, J 6.4 Hz, 25-Me_2), 0.90 (3H, d, J 7.0 Hz, 20-Me), 2.46, 2.59 (2H, AB, J 17.0 Hz, 1'-H_2), 3.99, 4.08 (2H, AB, J 8.5 Hz, 3-H_2); ^{13}CNMR (50.3 MHz, $CDCl_3$) δ 80.94 (3-C), 177.41 (2'-C); MS m/z 428.3636 (M^+, 24%), 273.1881 (100%).
18. Compound (**8**): m.p. 178-180 °C (acetone); $[\alpha]_D$ +20° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 1755 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 0.66 (3H, s, 13-Me), 0.80 (3H, s, 10-Me), 0.86 (6H, d, 6.8 Hz, 25-Me_2), 0.90 (3H, d, J 7.5 Hz, 20-Me), 2.22, 2.30, and 4.22 (4H, ABX_2, J_{AB} 12.2, J_{AX} = J_{BX} 6.7 Hz, 1'-H_2 and 2'-H_2); ^{13}CNMR (20.1 MHz, $CDCl_3$) δ 65.50 (2'-C), 183.96 (3-C); MS m/z 428.3651 (M^+, 33%), 273.1848 (100%).
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