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Lead tetraacetate–iodine oxidation of 23-spirostanols

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Abstract—Reactions of 23*R*- and 23*S*-23-spirostanols in the 25*R* and 25*S* series with lead tetraacetate–iodine were studied. The reactions carried out at low temperature afforded D-*seco*-iododialdehydes and C_{22} lactones, while similar reactions performed in refluxing tetrachloromethane yielded 20-chlorolactones and their 21-acetoxy derivatives irrespective of the hydroxyl group configuration at C-23. The reaction mechanisms are discussed.

The chemistry of spirostanes was intensively studied during the last century.[1] The reason for this study was the search for an efficient route to medicinally important steroids by degradation of plant sapogenins.[2] The recent revival of interest in the chemistry of spirostanes stems from studies on cephalostatins[3] and the natural products isolated from plants used in traditional medicine.[4] Although many spirostane based natural products have been known for several decades, methods for their synthesis are rather limited.

We have recently described the solvolytic reactions of 23-bromospirostanes and 23-spirostanol tosylates.[5] Now, the results of our studies on lead tetraacetate and iodine promoted hypoiodite reactions of 23-spirostanols are reported. The hypoiodite reactions have not been studied yet in the chemistry of spirostanes, except for the Suarez's iodine[III] oxidative spirocyclization.[6] However, the Hofmann–Löffler–Freytag reaction of the 23*R*-23-nitroamine derived from sarsasapogenin led to functionalization of the 27-methyl group.[7]

The starting 23-spirostanols were prepared from the naturally occurring sapogenins: diosgenin and sarsasapogenin. Both compounds have an α-oriented 21-methyl group (20*S*) and an *R* configuration at the spirocarbon atom; they differ in configuration at C-25 (*R* for diosgenin and *S* for sarsasapogenin). The sapogenins were oxidized to the corresponding 23-oxo derivatives by a known method.[8] Lithium aluminum hydride reduction of the 23-ketones afforded the epimeric mixtures of 23-alcohols. Each of the 23-alcohols **1**–**4** (Fig. 1) was separately treated with the oxidizing agent.

The transformations of the 23-oxygen radicals were studied in the hope of achieving an efficient remote intramolecular functionalization of the neighboring methyl groups.[9] The inspection of the Dreiding models and the computer assisted molecular modeling (MM^+)[10] indicated that the oxygen radical generated from the axial 23-hydroxy group (23*R*) may attack the 21-methyl group and, in the case of the sarsasapogenin derivative, also the 27-methyl group. In contrast, the 21- and 27-methyl groups are too far away from the alkoxy radical derived from the equatorial 23*S*-23-spirostanols. In this case, the closest methyl group is 18-CH_3 (Table 1). However, the intramolecular functionalization is also possible at C-20. Abstraction of the 20-methine hydrogen gives the stabilized carbon radical. It must be stressed that the C-20 radical may be formed upon

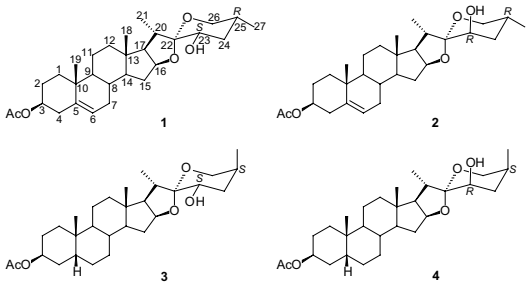

Figure 1. The structures of starting 23-spirostanols.

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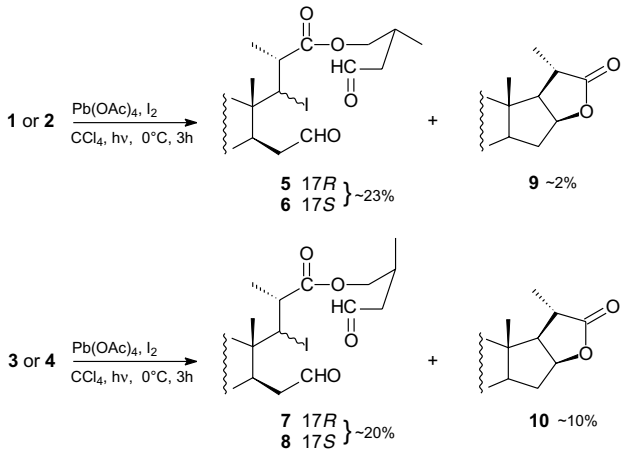
Table 1. The calculated distances from the oxygen atom to the methyl carbons and C-20

Distances compound	O23–C18 (Å)	O23–C21 (Å)	O23–C27 (Å)	O23–C20 (Å)
1	3.61	4.12	4.92	2.99
2	4.84	3.27	4.36	2.90
3	3.62	4.14	4.42	3.00
4	4.77	3.26	3.01	2.87

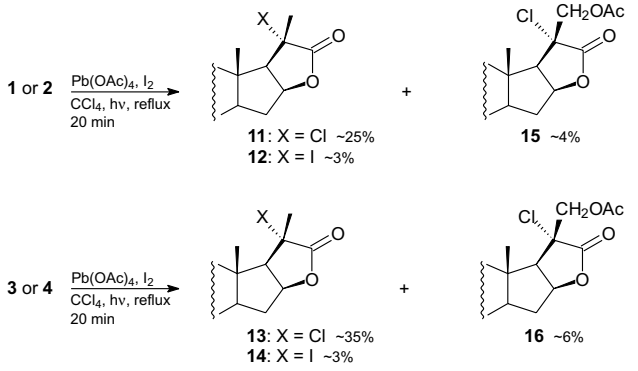
attack of both axial and equatorial oxygen radicals (O23–H20 distances are in the range 2.69–2.76 Å for axial and 2.54–2.56 Å for equatorial oxygen radicals).

The reactions of **1**–**4** with $Pb(OAc)_4$–I_2 were carried out in tetrachloromethane at 0 °C using a 100 W tungsten lamp. The results obtained are shown in Scheme 1. The major products of these reactions were D-*seco*-iododialdehydes **5**–**8**.[11] In addition, the C_{22} lactones **9**–**10** were obtained.[12] More lactone was formed in the 25*S* series. Interestingly, similar products were formed irrespective of the configuration of the 23-hydroxy group. There was an apparent difference between the axial and equatorial alcohols in the reaction rate; the former being faster (especially, the reaction of compound **4**). The D-*seco*-iododialdehydes (formed as mixtures of epimers in a ratio close to 1:1) were separated and fully characterized, but their configuration at C-17 could not be unequivocally established. The analogous reactions of **1**–**4** performed in cyclohexane at 0 °C yielded the same products. Also the iodobenzene diacetate and iodine promoted hypoiodite reactions gave similar results.

In the next series of experiments the reactions with $Pb(OAc)_4$–I_2 were irradiated in CCl_4 with the 100 W tungsten lamp without cooling. The reactions were very fast (20 min) and afforded different products from those obtained at the low temperature. The major products were the 20-chlorolactones **11**[13] or **13** and their 21-acetoxy derivatives **15**[14] or **16**, accompanied by small amount of the 20-iodolactones **12** or **14** (Scheme 2). The same set of products was formed irrespective of the hydroxyl group configuration at C-23. In a separate



Scheme 1. Reactions carried out at 0 °C (in the case of compounds **1** and **3** about 50% of the starting material was recovered under these conditions).



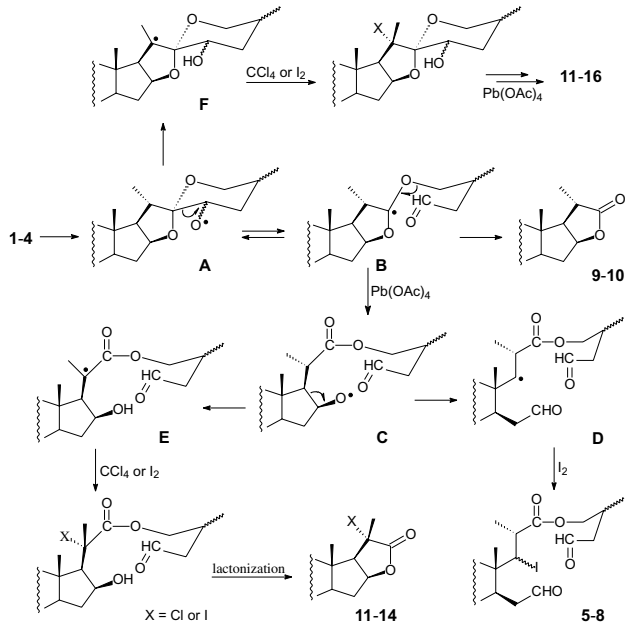
Scheme 2. Reactions carried out in refluxing CCl_4.

experiment it was proved that lactones **9** and **10** were not chlorinated at C-20 under the reaction conditions.

The 20*S* configuration at C-20 in the lactones **11**–**14** was established by selective 1D NOE experiments. Upon irradiation of the 21-methyl protons, an enhancement of the 18-H signals of about 1.0% was observed. The same method was used to demonstrate spatial proximity of the $-CH_2OAc$ group and the 18-methyl group in compounds **15** and **16** (a 2.2% enhancement of one of the two 21-methylene proton signals was found). It is particularly surprising that functionalization of the 21-methyl group took place not only in the case of the axial alcohols **2** and **4**, but also when the alkoxy radical was derived from the equatorial alcohols **1** and **3**.

A tentative mechanism for the $Pb(OAc)_4$–I_2 oxidation of 23-spirostanols is outlined in Scheme 3. The mechanism is radical, without doubt, since there was no reaction in dark. The dominating transformation of the initial alkoxy radical (**A**) is its isomerization to the tertiary carbon radical (**B**) by cleavage of the neighboring carbon–carbon bond. The reaction is reversible allowing for an interconversion between the oxygen radicals. The low energy radicals formed at 0 °C are not very reactive (long reaction) and undergo oxidation with $Pb(OAc)_4$ to the new oxygen radical (**C**). Isomerization of this key intermediate leads to the carbon radical at C-17 (**D**), which affords final products **5**–**8** by reaction with iodine.

At higher temperature the same intermediate (**C**) abstracts the γ hydrogen from C-20 to afford radical (**E**). Intramolecular H-transfers to alkoxy radicals normally favor δ-abstraction (six-membered transition state); that is from C-21 in this case. It is likely that activation of the C-20 hydrogen atom by the carbonyl group accounts for the preference for the γ-abstraction. Once H-transfer is complete, along with halogenation at C-20, the resulting



Scheme 3. A tentative mechanism for the lead tetraacetate–iodine oxidation of 23-spirostanols **1**–**4**.

hydroxy ester probably undergoes spontaneous lactonization to the major products **11**–**14** obtained in refluxing tetrachloromethane (i.e., by transesterification where the 16β-OH group displaces the alkoxy fragment attached to the carbonyl group at C-22). The halogenated lactones may also be formed by a different pathway involving direct hydrogen transfer from C-20 to the initial alkoxy radical (**A**). Halogenation of the resulting tertiary radical (**F**) followed by further oxidation with $Pb(OAc)_4$ would lead to the lactones 11–16. It is likely that both pathways operate. The mechanism of formation of the 20-chlorolactones with an additional acetoxy function at C-21 (compounds **15** and **16**) is less clear. Functionalization of 21-methyl group may occur by intramolecular hydrogen transfer (δ-abstraction) to the alkoxy radicals, for example, **C** or deriving from the axial 23-alcohols.

In spite of the fact that tetrahydrofuran or tetrahydropyran derivatives are frequently formed in the lead tetraacetate–iodine promoted hypoiodite reactions,[9] such compounds were not found among the reaction products.

Acknowledgements

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11. Selected spectral data for compounds **7** and **8**: colorless oils; less polar compound: IR ($CHCl_3$, ν, cm^{-1}): 2727, 1724, 1263; δ_H (200 MHz, $CDCl_3$): 9.79 (s, 2H, 2×CHO), 5.09 (m, 1H, 3α-H), 4.89 (d, $J = 2.8$ Hz, 1H, 17-H), 4.08 (dd, $J = 10.9$, 5.0 Hz, 1H, O–CH_2–), 3.93 (dd, $J = 10.9$, 5.9 Hz, 1H, O–CH_2–), 2.05 (s, 3H, AcO), 1.37 (d, $J = 6.6$ Hz, 3H, 21-H), 1.04 (d, $J = 6.5$ Hz, 3H, side chain CH_3), 1.03 (s, 3H, 18-H), 0.93 (s, 3H, 19-H); MS-ESI (in MeOH, m/z): 671 (M+MeOH+Na, 100%), 639 (M+Na, 18%); more polar compound: IR ($CHCl_3$, ν, cm^{-1}): 2726, 1724, 1263; δ_H (200 MHz, $CDCl_3$): 9.89 (s, 1H, CHO), 9.83 (t, $J = 1.4$ Hz, 1H, CHO), 5.07 (m, 1H, 3α-H), 4.22 (d, $J = 2.6$ Hz, 1H, 17-H), 4.01 (dd, $J = 6.5$, 1.7 Hz, 1H, O–CH_2–), 3.98 (dd, $J = 6.5$, 0.8 Hz, 1H, O–CH_2–), 2.05 (s, 3H, AcO), 1.19 (d, $J = 6.7$ Hz, 3H, 21-H), 1.08 (d, $J = 6.5$ Hz, 3H, side chain CH_3), 0.99 (s, 3H, 18-H), 0.93 (s, 3H, 19-H); MS-ESI (in MeOH, m/z): 671 (M+MeOH+Na, 100%), 639 (M+Na, 24%).
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13. Selected spectral data for **11**: mp 223–224 °C; IR ($CHCl_3$, ν, cm^{-1}): 1775, 1726, 1254; δ_H (200 MHz, $CDCl_3$): 5.37 (m,

1H, 6-H), 5.13 (m, 1H, 16α-H), 4.61 (m, 1H, 3α-H), 2.49 (d, $J = 4.1$ Hz, 1H, 17α-H), 2.04 (s, 3H, AcO), 1.90 (s, 3H, 21-H), 1.03 (s, 3H, 19-H), 0.84 (s, 3H, 18-H); MS-EI (m/z): 362 and 360 (M−AcOH, 38% and 100%), 347 (10%), 345 (30%).

14. Selected spectral data for **15**: mp 146–147 °C; IR (CCl_4, v, cm^{-1}): 1792, 1749, 1734, 1260, 1243; δ_H (200 MHz, $CDCl_3$): 5.37 (m, 1H, 6-H), 5.19 (m, 1H, 16α-H), 4.74 (d, $J = 13.0$ Hz, 1H, 21-H), 4.60 (m, 1H, 3α-H), 4.51 (d, $J = 13.0$ Hz, 1H, 21-H), 2.54 (d, $J = 5.8$ Hz, 1H, 17α-H), 2.17 (s, 3H, AcO), 2.04 (s, 3H, AcO), 1.03 (s, 3H, 19-H), 0.88 (s, 3H, 18-H); MS-EI (m/z): 442 (M−HCl, 7%), 420 and 418 (M−AcOH, 26% and 74%), 403 (14%), 324 (78%).