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The unexpected course of the reaction of steroid sapogenins with diacetoxyiodobenzene and $BF_3{\cdot}Et_2O$ in formic acid

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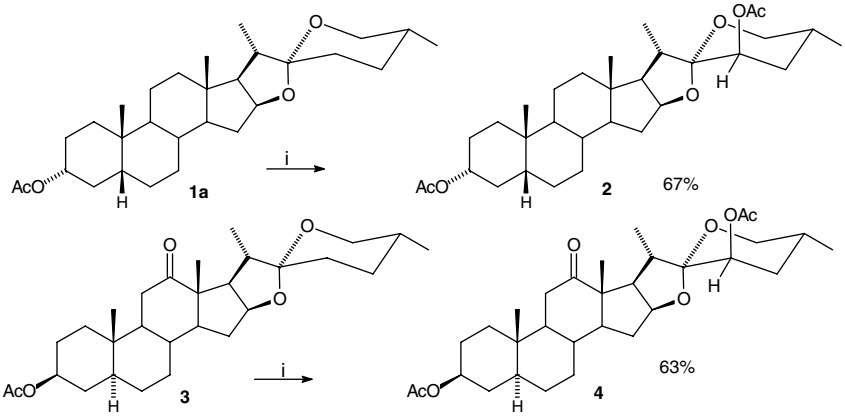
Abstract—The reaction of steroid sapogenins of both the 25*R* and 25*S* series with diacetoxyiodobenzene and $BF_3{\cdot}Et_2O$ in formic acid produced a mixture of an equatorial 23-formyloxysapogenin, a 16β,23:23,26-diepoxy-22-one and a bisnorcholanic lactone. The outcome of this reaction, that drastically differs from the same reaction in acetic acid, opens up new possibilities for the transformation of the side chain of steroid sapogenins.

Hypervalent iodine chemistry has attained a paramount role as a synthetic tool in the past two decades. Diacetoxyiodobenzene (DIB) is known to produce different transformations depending on the functionality present in the substrate and on the reaction conditions.[1,2] In particular, we have recently reported on the introduction of an axial acetoxyl group at position C-23 of the side chain of steroid sapogenins **1a** and **3**, by treatment of such compounds with DIB and $BF_3{\cdot}Et_2O$ in acetic acid, (Scheme 1).[3]



Scheme 1. Reagents and conditions: DIB/$BF_3{\cdot}Et_2O$ in acetic acid, rt 40 min.

In view of the outcome of the above reactions, it seemed logical to us that simply changing the solvent from acetic acid to formic acid would result in the introduction of a formyloxy group at C-23, offering the possibility to differentiate the introduced formylated hydroxyl group from other acetylated hydroxyl groups present in the steroid nucleus.

Unexpectedly, treatment of epismilagenin acetate **(1a)** with DIB and $BF_3{\cdot}Et_2O$ in formic acid at room temperature

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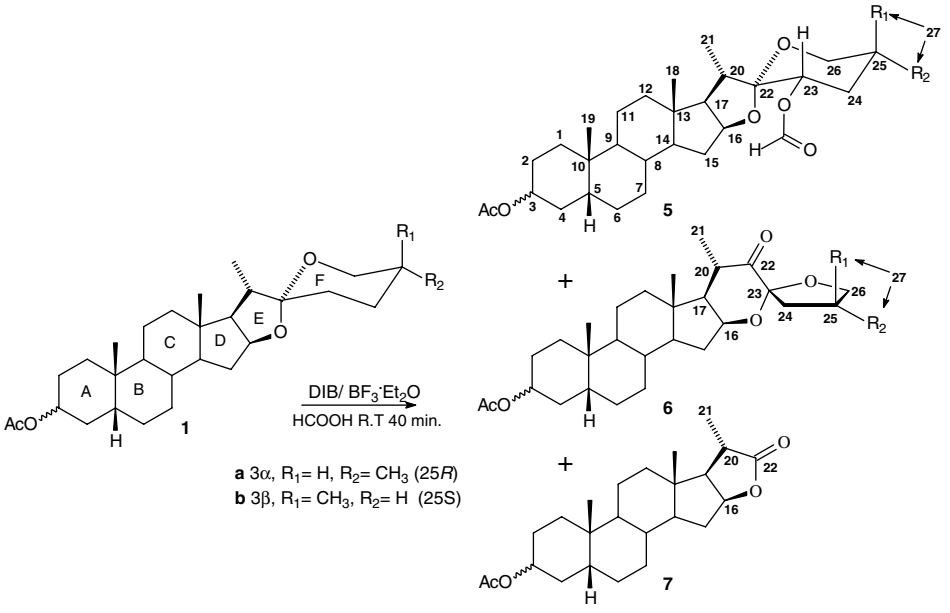
produced the total conversion of the starting material into a mixture of 23-equatorial formyloxy compound **5a**, 16β,23:23,26-diepoxy-22-one **6a** and bisnorcholanic lactone **7a**. The same procedure, when applied to sarsasapogenin acetate **(1b)**, afforded **5b**, **6b**, and **7b**, (Scheme 2).

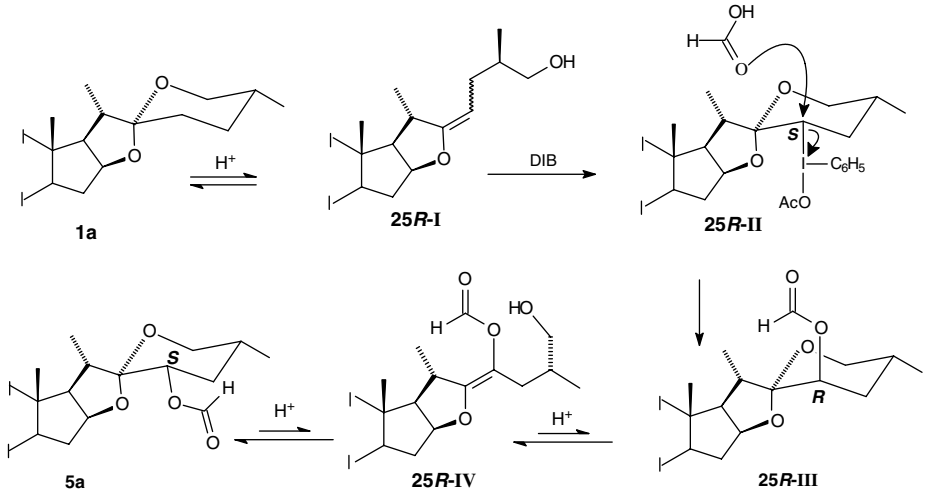
^{1}H and ^{13}C NMR spectra of the obtained products are in good agreement with the previously reported data.[4–7] The equatorial orientation of the formyloxy group introduced at C-23 can be easily corroborated by observation of the coupling pattern of H-23 (11.32, 4.38 Hz for **5a** and 12.11, 5.00 Hz for **5b**), which indicates $axial_{H\text{-}23}$–$equatorial_{H\text{-}24}$ and $axial_{H\text{-}23}$–$axial_{H\text{-}24}$ couplings.

The introduction of the formyloxy group at C-23 should follow a pathway similar to that previously postulated for the introduction of an acetoxyl group at C-23.[3] Epimerization to **5a** may be explained in terms of the enolization of **25*R*-III** to **25*R*-IV**, which on F-ring closure leads to **5a**. The fact that no product was isolated with the formyloxy group in the axial orientation suggests a fast epimerization and is consistent with the expected relative thermodynamic stabilities of **25*R*-III** and **5a**, which should favor the equatorially oriented substituent in which the steric effects are minimized. A similar pathway explains the occurrence of **5b** (Scheme 3).

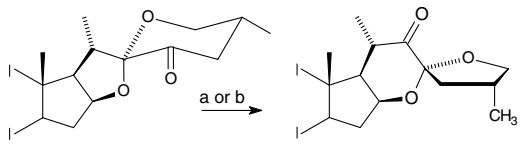
Rearrangement of 23-oxosapogenins to 16β,23:23,26-diepoxy-22-ones by treatment with $TiCl_4$ in CH_2Cl_2 was first described by Suárez.[5] A similar rearrangement, but with lower yield, was observed by Morzycki when 23-oxosapogenins were treated with $BF_3{\cdot}Et_2O$ in THF,[6] (Scheme 4).



Scheme 2.



Scheme 3.



Scheme 4. Reagents: (a) $TiCl_4$ in CH_2Cl_2; (b) $BF_3{\cdot}Et_2O$ in THF.

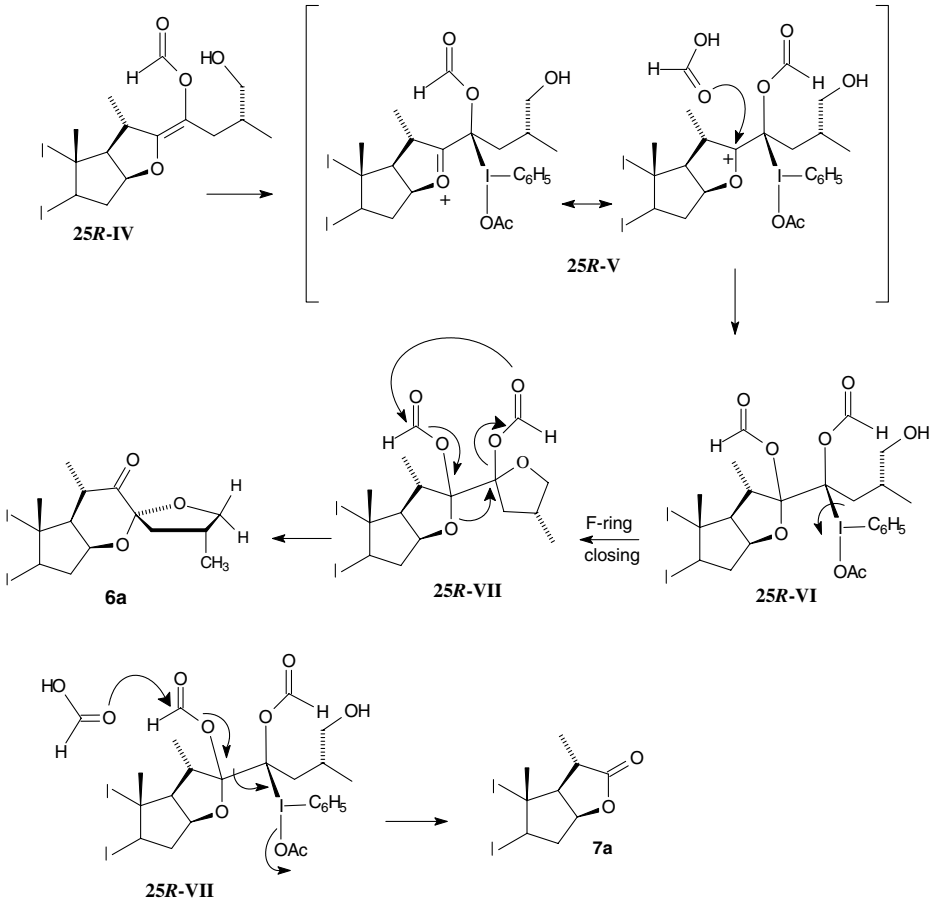
Since the presence of a carbonyl group at C-23 is mandatory in such a rearrangement, an attempt to rationalize the occurrence of **6a** and **6b** must involve the overoxidation of the 23-formyloxy sapogenin.

Enolization to **25*R*-IV** followed by electrophilic addition of DIB leads to oxonium **25*R*-V**, which may react with formic acid to produce **25*R*-VI**. Displacement of the hypervalent iodine moiety as a result of F-ring closure leads to **25*R*-VII**, which on 1,2 migration of O-16 to C-23 and rearrangement of the formyloxy moieties attached to C-22 and C-23 affords 16β,23:23,26-diepoxy-22-one **6a**. A pathway in which the formyloxy moiety attached to C-22 reacts with formic acid to produce the cleavage of the C22-C-23 bond may explain the occurrence of lactone **7a**, (Scheme 5). A similar mechanism accounts for the formation of **6b** and **7b.**

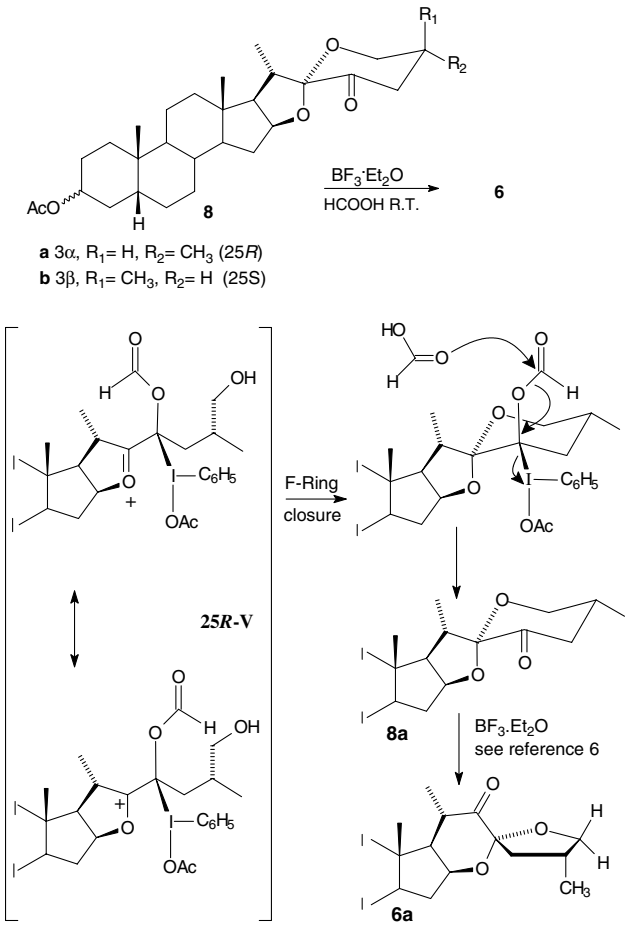
Control experiments carried out under the same reaction conditions but without the addition of DIB showed that treatment of 23-oxosapogenins **8a** and **8b** with $BF_3{\cdot}Et_2O$ in formic acid leads to a mixture of the starting material and the corresponding rearranged product **6a** or **6b,** (Scheme 6) and suggests a pathway from the 23-formyloxysapogenin to the corresponding 23-oxosapogenin that finally undergoes isomerization to afford the observed 16β,23:23,26-diepoxy-22-one following a mechanism similar to that suggested by Morzycki for the $BF_3{\cdot}Et_2O$-catalyzed isomerization of 23-oxosapogenins.[6]

We were pleased to find that addition of an increased amount of $BF_3{\cdot}Et_2O$ and the extension of the isomerization reaction up to 4.5 h produced an increase in the yield of the rearranged products.

In summary, we have found that the reaction of steroid sapogenins with $BF_3{\cdot}Et_2O$/DIB in formic acid affords a mixture of an equatorial 23-formyloxysapogenin, a 16β,23:23,26-diepoxy-22-one and a bisnorcholanic lactone. The outcome of this reaction, that differs from our previously reported results of the same procedure using acetic acid as solvent, opens up new possibilities for the transformation of the steroidal sapogenin side chain. In addition we have found that treatment of 23-oxosapogenins with $BF_3{\cdot}Et_2O$ in formic acid represents a convenient alternative for the isomerization of 23-oxosapogenins to 16β,23:23,26-diepoxy-22-ones.



Scheme 5.



Scheme 6.

Additional experiments to explore the influence of different carboxylic acids and other solvents in the above-described reactions and to optimize yields are under way.

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Supplementary data

Supplementary data (full experimental details) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.071.

References and notes

1. For reviews see: (a) Prakash, O.; Shing, P. S. *Aldrichim. Acta* **1994**, *27*, 15–23; (b) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179–1255; (c) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893–2903; Selected references: (d) Concepcion, J. I.; Francisco, C. G.; Freire, R.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1986**, *51*, 402–404; (e) Francisco, C. G.; Freire, R.; Rodriguez, M. S.; Suárez, E. *Tetrahedron Lett.* **1995**, *36*, 2141–2144; (f) Francisco, C. G.; Gonzalez, C. C.; Suárez, E. *Tetrahedron Lett.* **1997**, *38*, 4141–4144; (g) Boto, A.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **1999**, *40*, 5945–5948; (h) Lee, S.; Fuchs, P. L. *Org. Lett.* **2002**, *4*, 317–318; (i) Boto, A.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **2002**, *43*, 1821–1824; (j) Iglesias-Arteaga, M. A.; Avila-Ortiz, C. G.; Juaristi, E. *Tetrahedron Lett.* **2002**, *43*, 5297–5300; (k) Iglesias-Arteaga, M. A.; Castellanos, E.; Juaristi, E. *Tetrahedron:Asymmetry* **2003**, *14*, 577–580; (l) Díaz-Sanchez, B. R.; Iglesias-Arteaga, M. A.; Melgar-Fernández, R.; Juaristi, E. *J. Org. Chem.* **2007**, *72*, 4822–4885.
2. For reactions of DIB with enols see: (a) Moriarty, R. M.; John, L. S.; Du, P. C. *J. Chem. Soc., Chem. Commun.* **1981**, 641–642; (b) Turuta, A. M.; Kamernitzky, A. V.; Fadeeva, T. M.; Zhulin, A. V. *Synthesis* **1985**, 1129–1131; Daum, S. J. *Tetrahedron Lett.* **1984**, *25*, 4725–4728; (c) Moriarty, R. M.; Prakash, I. *Tetrahedron Lett.* **1984**, *25*, 5867–5870; Iglesias-Arteaga, M. A.; Velázquez-Huerta, G. A. *Tetrahedron Lett.* **2005**, *46*, 6897–6899.
3. Iglesias-Arteaga, M. A.; Arcos-Ramos, R. O. *Tetrahedron Lett.* **2006**, *47*, 8029–8031.
4. Iglesias-Arteaga, M. A.; Velázquez-Huerta, G. A.; Méndez-Stivalet, J. M.; Galano, A.; Alvarez-Idaboy, J. R. *Arkivoc* **2005**, *VI*, 109–126.
5. Hernández, R.; Marrero-Tellado, J. J.; Prout, K.; Suárez, E. *J. Chem. Soc., Chem. Commun.* **1992**, 275–277.
6. Cyranski, M. K.; Frelek, J.; Jastrzebska, I.; Morzycki, J. W. *Steroids* **2004**, *69*, 395–400.
7. (a) Agrawal, P. K.; Jain, D. C.; Gupta, R. K.; Thakur, R. S. *Phytochemistry* **1985**, *24*, 2479–2496; (b) Iglesias-Arteaga, M. A.; Pérez Gil, R.; Pérez Martínez, C. S.; Coll Manchado, F. *J. Chem. Res. (S)* **1999**, 48–49; (c) Viñas-Bravo, O.; Hernández-Linares, G.; Mata-Esma, M. Y.; Martínez-Pascual, R.; Montiel-Smith, S.; Meza-Reyes, S.; Bernes, S.; Sandoval-Ramírez, J.; Iglesias-Arteaga, M. A. *Arkivoc* **2003**, *XI*, 163–171.