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Communications

Direct Oxyfunctionalization at Unactivated Sites. Synthesis of 5β-Hydroxysteroids by Perfluorodialkyloxaziridines

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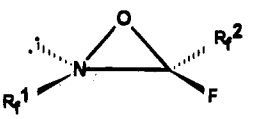
Summary: By treatment with perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine **1a**, 5β-steroids **2a–i** (belonging to different classes, such as androstanes, cholestanes, pregnanes, and cholanic acids) have been hydroxylated in good yields and with complete site selectivity and stereoselectivity to corresponding 5β-hydroxy derivatives **3a–i** independently from the presence of halide, ketone, carboxylic acid, and ester moieties on C-3, C-11, C-12, C-17, C-20, C-21, and C-24.

Perfluoro-*cis*-2,3-dialkiloxaziridines **1a,b** are easily prepared from commercially available perfluorotrialkylamines.[1] They are indefinitely stable at room temperature[2] and have shown to be powerful yet selective oxidizing agents which can work under neutral or acid conditions, in protic or aprotic solvents.[3] In particular, they effect the hydroxylation of unactivated tertiary aliphatic C–H bonds at room temperature and in the condensed phase.[4]

In order to prove the synthetic usefulness and effectiveness of oxaziridines **1** in performing the oxyfunctionalization reaction, we have studied the selective hydroxylation of 5β-steroids **2** with perfluoro-*cis*-2,3-dialkyloxaziridine **1a**. Here we report how the corresponding 5β-hydroxy derivatives **3** are invariably formed in good yields and with complete site selectivity and stereoselectivity (Scheme 1). The 5β-hydrogen is abstracted in preference to the others existing in the substrate (up to 47 in compound **2b**) also when various functional groups are present (up to five in **2i**) just as if the functional group in this reaction is the unactivated 5β-hydrogen.



	R_f^1	R_f^2
1a	*n*-C_4F_9	*n*-C_3F_7
1b	*n*-C_6F_{13}	*n*-C_5F_{11}

All the reactions have been performed by adding to a ca. 1 M solution of the steroid substrate in the solvent an excess of the oxaziridine **1** and stirring the mixture at room temperature. The progress of the reaction has been monitored by TLC, and when a fair conversion was obtained, excess chloroform and perfluorotributylamine were added and the chlorinated phase was separated and evaporated to give a residue which was purified through flash-chromatography. Employing this procedure, we observed the formation of only small amounts of byproducts and we recovered in all cases 10–30% of unreacted substrates **2**. $CFCl_3$ has been the solvent employed for substrates of low polarity (**2a–d,f,g**), with more polar starting materials **2h,i** $CFCl_3/CHCl_3$ or $CFCl_3/CH_2Cl_2$ have been preferred, and the acid **2e** was reacted in 2-methyl-2-propanol/$CHCl_3$. The oxaziridine **1a** has a low solubility in this last mixture, but the hydroxylation process occurs nicely despite the fact that a two-phase system is used. Reaction times ranged from 2 h (**2a, b**) to 60 h (**2i**).

The structures of the title compounds **3a–i** come from mass spectra and ^1H and ^{13}C NMR properties. All these

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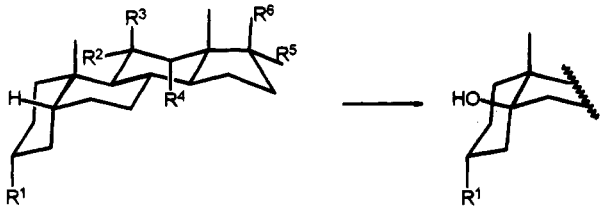
Scheme 1



2a-i **3a-i**

Compounds		Isolated yields (%)
2a, 3a	$R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H$	70
2b, 3b	$R^1 = R^2 = R^3 = R^4 = R^5 = H$, $R^6 = CH(CH_3)(CH_2)_2CH(CH_3)_2$,	75
2c, 3c	$R^1 = R^2 = R^3 = R^4 = H$, $R^5 = R^6 = O$	73
2d, 3d	$R^1 = OAc$, $R^2 = R^3 = R^4 = H$, $R^5 = R^6 = O$	68
2e,3e	$R^1 = R^2 = R^3 = R^4 = R^5 = H$, $R^6 = CH(CH_3)(CH_2)_2COOH$	77
2f, 3f	$R^1 = R^2 = R^3 = R^4 = R^5 = H$, $R^6 = CH(CH_3)(CH_2)_2COOCH_3$	79
2g, 3g	$R^1 = OAc$, $R^2 = R^3 = R^4 = R^5 = H$, $R^6 = CH(CH_3)(CH_2)_2COOCH_3$	70
2h, 3h	$R^1 = R^4 = OAc$, $R^2 = R^3 = R^5 = H$, $R^6 = CH(CH_3)(CH_2)_2COOCH_3$	66
2i, 3i	$R^1 = OAc$, $R^2 = R^3 = O$, $R^4 = Br$, $R^5 = H$, $R^6 = COCH_2OAc$	58

products showed molecular peaks 16 mass units higher than corresponding starting materials **2a–i**; in their ^{13}C NMR spectra a methine carbon ($\delta \simeq 43$ ppm) was replaced by a quaternary carbon ($\delta \simeq 74$ ppm), and in their ^1H NMR spectra a broad signal (exchanged with D_2O) appeared at $\delta \simeq 3.1$ ppm (acetone-d_6 solution). The presence of a tertiary OH group is thus unequivocally proven. The localization of the hydroxyl residue in the 5β-position could be easily made for compounds **3d,g,h,i**, which bear a 3α-acethoxy group, by observing that, compared to corresponding starting materials **2**, a downfield shift of ~0.35 ppm has occurred for the H-3β signal, as expected for a 1,3-*cis* diaxial relationship.[5] A strictly similar behavior was revealed in **3a,f** through HETCOR experiments, and the close similarity in the chemical shifts of the carbon atoms near the substitution site in **3a–c,e,f** revealed that the hydroxyl residue was in the 5β-position in all these products[6] too.

It is interesting to observe that several 5β-hydroxy steroids occur in nature.[9] For instance, strophantidin (3β,5,14-trihydroxy-19-oxo-5β,14β-card-20(22)-enolide) is the aglycon of commonly employed cardiotonics isolated from several species of *Strofantus*[10] and periplogenin (3β,5,14-trihydroxy-5β,14β-card-20(22)-enolide) has been isolated[11] from plants of the *Asclepiadaceae* family, and the digitalis-like cardiac activity of these compounds was first reported in 1897.[12] Furthermore, 5β-hydroxy steroids are valuable intermediates in the synthesis of important hormones. For instance, 3α,12α,5β-trihydroxy-5β-cholanic acid **3h** is a useful compound in the synthesis of cortisonic steroids[13] and the 5β-hydroxy lithocolic acid derivative **3g** can be transformed into progestogen hormones,[14] and it can be used as starting materials in the preparation of bufadienolides and cardenolides.[15]

Introduction of 5β-hydroxy function in a steroid moiety with chemical methodologies has been performed through a multistep functionalization starting usually[16] from Δ^4 or Δ^5 substrates.[17] Microbial 5β-hydroxylation of cardioactive steroids[18] and 5β-dihydrotestosterone[19] has also been reported.

Employed substrates **2** belong to different classes of steroids (androstanes, cholestanes, pregnanes, and cholanic acids) but they invariably undergo oxidation at C-5. While the observed complete selectivity for the attack of **1a** to a tertiary C–H bond of substrates **2**, with respect to secondary or primary C–H bonds, could be easily foretold from previous experiments,[4] the preferential oxidation at C–5, compared to the other steroidal tertiary carbon atoms (C-8, C-9, C-14, C-17, C-20, and C-25) deserves some discussion. Probably, the observed site-selectivity is strictly related to the *cis* junction of the A/B rings of steroids **2**, but further studies are required before the relative relevance of steric and electronic effects can be assessed. A more rapid reaction of alicyclic hydrocarbons carrying equatorial tertiary C–H bonds with respect to isomers having axial C–H bonds has already been observed for oxaziridines **1**. A similar trend has also been reported for some peracids,[20] dimethyldiox-

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(6) Moreover, **3a**, **f** showed, as expected (ref 5), an upfield shift of 0.15 and 0.17 ppm for H-3α, an upfield shift of 0.28 and 0.27 ppm for H-1α, and a downfield shift of 0.55 and 0.47 ppm for H-1β. Additional evidence in favor of the structure of **3b** comes from the fact that its ^{13}C NMR spectrum differs from that of the corresponding 5α-epimer (ref 7). Finally, it must be noted that, in contrast from what was previously reported (ref 8), the ^{13}C chemical shift of C-19 methyl is not fully diagnostic of the configuration at C-5 of 5-hydroxysteroids. For instance, in 5α-cholestan-5-ol the C-19 methyl resonates at 16.1 ppm (ref 7, moving ~3.9 ppm downfield with respect to the corresponding signal in 5α-cholestane due to the γ-trans effect) and is thus quite near to the same methyl in 5β-cholestanol **3b** (17.10 ppm). An unequivocal assignment of configuration through ^{13}C NMR comes from C-9 which, for instance, resonates at 43.20 in **3b** (moving 2.64 ppm downfield from the corresponding signal in **2b** due to the γ-*trans* effect) and at 46.20 in the 5α-epimer (ref 7, 8.70 ppm upfield shift with respect to the signal in the corresponding non hydroxylated 5α-precursor due to the γ-gauche effect).

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irane,[21] and methyl(trifluoromethyl)dioxirane.[22] This may account for the preferential oxidation at C-5 with respect to C-8, C-9, C-14, and partly C-17, but the reasons for the selectivity toward C-20 and mainly[14] C-25 still have to be clarified.

Halide, ketone, carboxylic acid, and ester moieties can be present on different sites of the steroid framework (C-3, C-11, C-12, C-17, C-20, C-21, and C-24) without the course of the reaction being changed. The unique observed effect is an increase of reaction times when the functional group is near the reactive site (e.g., 2, 2, and 20 h for **2a**, **2c**, and **2d**, respectively). This is an argument for the electrophilic character of the reagent **1a**. Heteroatom substituents are, in fact, known to lower the electron density of neighboring C—H bonds,[23] and their presence prevents[24] or diverts[8] the oxidation process.

In general, oxidative properties[3,4] of oxaziridines **1** recall those of dioxiranes[21,22,25] which have been successfully employed, among others, in the oxyfuntionalization of various steroids.[24,26] However, low site-selectivity[8] or double oxyfuntionalization[14] have been observed in some cases when these reagents have been employed on 5β-steroids having structures identical or similar to those reported here.

Nature performs effectively the direct monooxygenation of unactivated C—H bonds on complex and polyfunctional steroids employing enzymatic systems, e.g., cytochrome P-450.[27] In contrast, the realization of the same transformation, while a useful goal, is for a chemist a formidable challenge. Besides dioxiranes, only[28] the use of manganese(III) porphyrins tethered to the steroid[29] and the dehalogenation of steroidal α-bromo ketones[30] allowed preparative yields to be obtained. Oxaziridine **1a** has shown to be an interesting alternative to these systems. Its easy preparation and its indefinite storage stability along with the fact that employed reaction conditions are neutral and the workup is particularly simple represent useful characteristics of this reagent.

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Supplementary Material Available: Detailed experimental procedures for oxyfunctionalization reactions, structure assignment, and identification (^1H, ^{13}C NMR) (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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