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Bismuth(III) Triflate-Catalyzed Direct Conversion of Corticosteroids into Highly Functionalized 17-Ketosteroids by Cleavage of the *C*17-Dihydroxyacetone Side Chain

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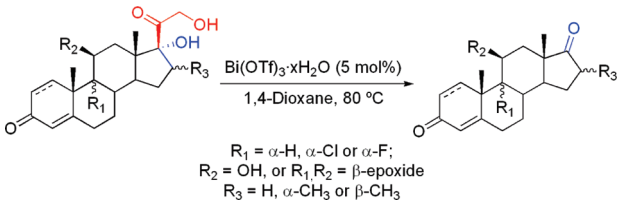
Received September 2, 2009



The use of bismuth(III) triflate as catalyst for the direct conversion of corticosteroids into highly functionalized 17-ketosteroids by cleavage of the *C*17-dihydroxyacetone side chain is reported. This catalytic process is very chemoselective, since functionalities of the starting corticosteroids, such as Δ^4-3-keto, $\Delta^{1,4}$-3-keto, 11β-hydroxyl, and 9β,11β-epoxide, remained intact.

The industrial production of corticosteroids, an important drug class in the treatment of clinical situations ranging from moderate skin rash to severe acute inflammatory disorders,[1] reaches several tones per year.[2] In fact, these compounds are readily available from a number of commercial sources.

The metabolization of corticosteroids to C_{19}-steroids by side-chain cleavage at position C17 is a well-known process that occurs in vivo.[3] Although corticosteroid side chain removal has been shown to occur in adrenal glands, kidney, and by gut microflora, the enzyme responsible for this biotransformation has not been identified yet.[4]

The degradation of the *C*17-dihydroxyacetone moiety of corticosteroids has been performed by several classical oxidative chemical procedures, such as those that use CrO_3, $Pb(OAc)_4$, HIO_4, and $NaBiO_3$.[5] Among these reactants, the best results have been achieved with $NaBiO_3$;[5] however the need of various equivalents of this reactant is not compatible with the actual paradigm of green chemistry[6−10] and green pharmaceutical chemistry.[11]

The use of basic reaction conditions for the cleavage of the *C*17-dihydroxyacetone side chain has been reported by Simons and co-workers.[12] Later, an optimized procedure that uses 5.0 equiv of sodium methoxide in refluxing 1,4-dioxane has been described.[13] More recently, the direct conversion of corticosteroids into 17-ketosteroids by using iodine in the presence of an excess of aqueous ammonia has also been reported.[14]

The lack of selectivity and the moderate reaction yields of some of the classical methods associated with the use of large amounts of oxidative or basic reactants make the classical approaches for the cleavage of the corticosteroid side chain inconvenient at laboratory scale and inadequate for the large-scale synthesis of 17-ketosteroids. In this context, new catalytic processes that use environmentally friendly, cheap, and easily available reactants to perform the one-step conversion of corticosteroids into 17-ketosteroids would be of considerable interest.

Bismuth(III) salts[15−21] have emerged in the past few years as suitable reagents for the development of new chemical processes[22−24] under more "ecofriendly" reaction conditions.

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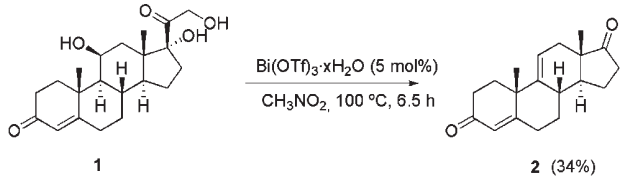
Published on Web 10/02/2009 DOI: 10.1021/jo9018478

Moreover, the application of bismuth(III) salts to the synthesis of compounds of pharmaceutical interest is rapidly increasing.[25−31] As part of our current interest on the development of new bismuth-based processes[32] applied to natural product chemistry,[33−38] we report herein the bismuth(III) triflate-catalyzed direct conversion of corticosteroids into highly functionalized 17-ketosteroids by cleavage of the *C*17-dihydroxiketone side chain.

Quite recently, we reported the use of $Bi(OTf)_3 \cdot xH_2O$ as catalyst in the Wagner−Meerwein rearrangement of terpene derivatives. Under appropriated reaction conditions, a double rearrangement has been observed in lupane compounds, involving contraction of the six-membered ring A, along with expansion of ring E and formation of an additional O-containing ring. The reactivity observed at ring A was triggered by the $Bi(OTf)_3 \cdot xH_2O$-promoted dehydration of the 3β-hydroxyl group.[38] This nonexpected reactivity of $Bi(OTf)_3 \cdot xH_2O$ turned our attention to the study of other chemical transformations involving a possible dehydration of suitable hydroxyl groups. Thus we decided to study the reactivity of bismuth(III) salts toward several corticosteroids, which typically contain the tertiary 17α-hydroxyl group, the 21-hydroxy-20-keto moiety at C17 side chain, and several other chemical functions, including, in most cases, additional hydroxyls at position C11.

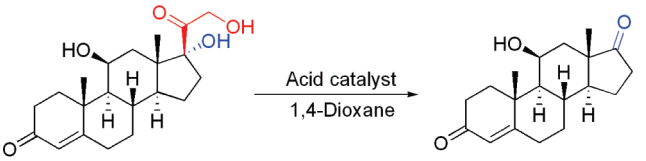
Initially, we performed the reaction of hydrocortisone (cortisol) **1** under the reaction conditions previously established for the double Wagner−Meerwein rearrangement of lupanes (20 mol % of $Bi(OTf)_3 \cdot xH_2O$, at refluxing CH_2Cl_2). Although some reactivity has been detected, low selectivity and substrate conversion were obtained, after 24 h of reaction, as observed by TLC control. Other solvents, temperatures, and catalyst loadings were tested. For instance, when compound **1** was treated with 5 mol % of $Bi(OTf)_3 \cdot xH_2O$, in CH_3NO_2, at 100 °C, full conversion was observed after 6.5 h. Although several products were visible on the TLC plate, the major one was isolated in 34% yield, by flash column chromatography. Analysis of its spectroscopic data indicated that cleavage of the side chain had occurred as well as dehydration of the 11β-hydroxyl group to afford the $\Delta^{4,9(11)}$-3,17-diketosteroid **2**[39] (Scheme 1).

SCHEME 1. $Bi(OTf)_3 \cdot xH_2O$-Catalyzed Synthesis of $\Delta^{4,9(11)}$-3,17-Diketosteroid 2



1 → **2** (34%)

TABLE 1. Catalyst Screening for the C-17 Side-Chain Cleavage of Hydrocortisone 1[a]



1 → **3**

entry	catalyst (mol %)	time (h)	product	Yield (%)[b,c]
1	$Bi(OTf)_3 \cdot xH_2O$ (10)	6.5	**3**	84
2	$Bi(OTf)_3 \cdot xH_2O$ (5)	8	**3**	93 (75)[d]
3	$Bi(OTf)_3 \cdot xH_2O$ (5)[e]	22.5	**3**	71
4	$Bi(OTf)_3 \cdot xH_2O$ (2)	22	**3**	90
5	$BiBr_3$ (10)	24	**1** + **3**	77 (33:67)[f]
6	$BiCl_3$ (10)	24	**1** + **3**	81 (34:66)[f]
7	$La(OTf)_3$ (10)	24	**1** + **3**	86 (57:43)[f]
8	HOTf (15)	7		—[g]

[a]Reaction conditions: 0.5 mmol of **1**; 15 mL of 1,4-dioxane, 80 °C. [b]Yield of the reaction crude after aqueous workup obtained as colorless oil. [c]^{1}H NMR spectrum of the reaction crude showed the selective synthesis of **3**, along with unidentified nonsteroidal side products in variable amounts (δ 3.50−4.10 ppm, several multiplets and 8.04−8.10 ppm, singulet). [d]Isolated yield by flash column chromatography. [e]The reaction was performed at 50 °C. [f]Ratio between **1** and **3**, as determined by integration of their 4-H signals (**1**, δ 5.72, br s; **3**, δ 5.67, br s) in the ^{1}H NMR spectrum of the reaction crude. [g]Full conversion of **1** was observed, but several products were seen on the TLC plate, after 7 h of reaction.

Despite the low yield, this result was quite interesting because catalytic amounts of Bi(III) salt were enough to induce the cleavage of the *C*17-dihydroxyacetone side chain of corticosteroid **1**. The rough reaction conditions were most likely responsible for the loss of the 11β-hydroxyl function.

The use of 1,4-dioxane as solvent, at a lower temperature, significantly improved the selectivity of the reaction. Thus, treatment of **1** with either 10 mol % or 5 mol % of $Bi(OTf)_3 \cdot xH_2O$, in 1,4-dioxane/80 °C, gave the 11β-hydroxy-Δ^4-3,17-diketosteroid **3**,[13] in good yields (Table 1, entries 1 and 2).

Analysis of the ^{1}H NMR spectrum of the crude product showed that unidentified nonsteroidal side products were formed along with **3**. Their presence probably arises from the acid-catalyzed polymerization of the α-hydroxy ketone moiety derived from the cleavage of the corticosteroid side chain. Thus, purification by flash chromatography was needed to obtain pure 11β-hydroxy-Δ^4-3,17-diketosteroid **3** (Table 1, entry 2).

The conversion of hydrocortisone **1** with 5 mol % of $Bi(OTf)_3 \cdot xH_2O$, in 1,4-dioxane, at 50 °C, afforded the 17-ketosteroid **3**, in 71% yield, after 22.5 h (Table 1, entry 3). A similar reaction time was observed when the reaction was carried out in the presence of only 2 mol % of $Bi(OTf)_3 \cdot xH_2O$, at 80 °C (Table 1, entry 4). The use of bismuth(III)

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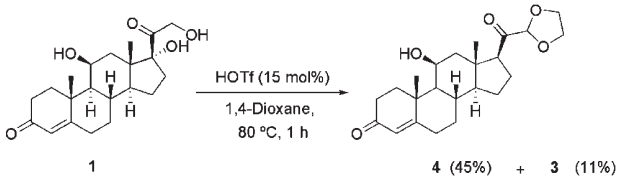
SCHEME 2. HOTf-Catalyzed Reaction of Hydrocortisone 1 in 1,4-Dioxane/80 °C



halides have also been tested (Table 1, entries 5 and 6); however, the reaction of **1** was not complete after 24 h of reaction. The use of $La(OTf)_3$ as a Lewis acid[40] and HOTf as a Brønsted acid was also evaluated (Table 1, entries 7 and 8). After 24 h, the reaction of **1** with 10 mol % of $La(OTf)_3$ afforded only partial conversion of the starting corticosteroid **1** to the 17-ketosteroid **3** (Table 1, entry 7), whereas in the presence of 15 mol % of HOTf, a complex mixture of several products was obtained, after 7 h (Table 1, entry 8).

When the reaction of **1** with 15 mol % of HOTf was stopped after 1 h, the 11β-hydroxy-17-ketosteroid **3** was isolated in 11% yield, along with 21-(1,3-dioxalan-2-yl)-11β-hydroxypregn-4-ene-3,20-dione **4**, in 45% yield, as the major reaction product (Scheme 2). The formation of product **4** may be explained by the acid-catalyzed reaction of the α-hydroxy ketone derived from the cleavage of the side chain of one molecule with the primary alcohol group of substrate **1**, involving dehydration of the 17α-hydroxyl. The 11β-hydroxy-Δ^4-3,17-diketosteroid **3** was also obtained as by-product, showing that the degradation reaction may occur unselectively under Brønsted acid catalysis.

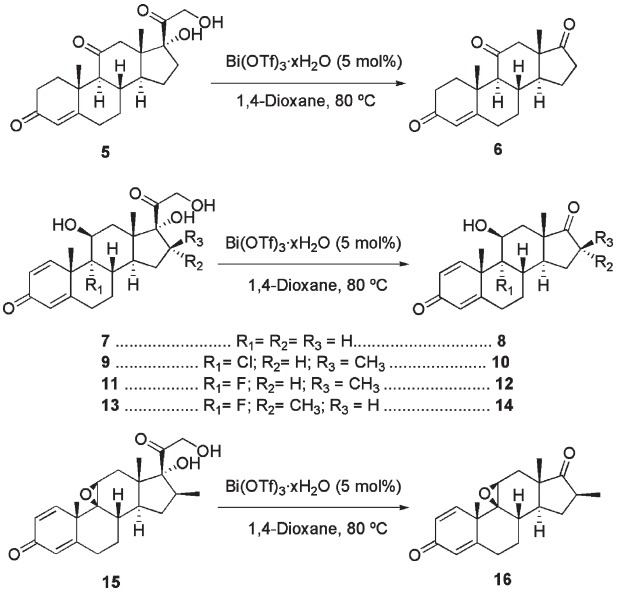
Bearing in mind our recent reports on the participation of an in situ formed Brønsted acid species from $Bi(OTf)_3 \cdot xH_2O$, in the reaction mechanism of Wagner−Meerwein-type rearrangements,[37,38] we carried out the $Bi(OTf)_3 \cdot xH_2O$-catalyzed reaction of hydrocortisone **1** in the presence of 2,6-di-*tert*-butylpyridine (DTBP), a known proton scavenger.[38] Interestingly, full substrate conversion was observed after 20 h of reaction [0.5 mmol of **1**, 5 mol % of $Bi(OTf)_3 \cdot xH_2O$, and 15 mol % of DTBP, in 1,4-dioxane, at 80 °C, 81% isolated yield].

Therefore, although Brønsted acid catalysis was observed, this set of results seems to show that the $Bi(OTf)_3 \cdot xH_2O$-catalyzed cleavage of the *C*17-dihydroxyacetone side chain of corticosteroids is mediated by Lewis acid catalysis. In the absence of proton scavenger, Brønsted acid-assisted Lewis acid catalysis[41] is observed, as suggested by the higher reaction rate.

After these studies that allowed us to gain more insight on the conversion of hydrocortisone **1** into the highly functionalized 11β-hydroxy-Δ^4-3,17-diketosteroid **3**, other corticosteroids were efficiently transformed into the corresponding 17-ketosteroids with use of this process (Table 2).

The reaction of cortisone **5** under the optimized conditions gave the corresponding 17-ketosteroid **6**,[13] in 85% yield (Table 2, entry 1). When 3-keto-$\Delta^{1,4}$-corticosteroids were used as substrates, similar results were obtained. Thus, prednisolone **7** afforded the 11β-hydroxy-$\Delta^{1,4}$-3,17-diketosteroid **8**,[12]

TABLE 2. $Bi(OTf)_3 \cdot xH_2O$-Catalyzed Cleavage of the *C*17-Dihydroxyacetone Side Chain of Corticosteroids[a]



entry	substrate	time (h)	product	yield (%)[b]
1	**5**	5	**6**	85
2	**7**	14	**8**	78
3	**9**	5	**10**	84
4	**11**	5.5	**12**	68
5	**13**	5	**14**	74
6	**15**	1.5	**16**	45

[a]Reaction conditions: 0.5 mmol of substrate; 5 mol % of $Bi(OTf)_3 \cdot xH_2O$, 15 mL of 1,4-dioxane, 80 °C. [b]Isolated yield by flash column chromatography.

in 78% yield, after 14 h of reaction with $Bi(OTf)_3 \cdot xH_2O$/1,4-dioxane (Table 2, entry 2).

When beclomethasone **9** was used as substrate, the corresponding 9α-chloro-11β-hydroxy-16β-methyl-$\Delta^{1,4}$-3,17-diketosteroid **10**, a new steroid compound, was obtained in 84% yield (Table 2, entry 3). Both the epimeric 9α-fluoro-11β-hydroxy-16β-methyl-$\Delta^{1,4}$-3,17-diketosteroid **12**[42] and 9α-fluoro-11β-hydroxy-16α-methyl-$\Delta^{1,4}$-3,17-diketo derivative **14**[43] were efficiently prepared from betamethasone **11** and dexamethasone **13**, respectively, in 68% and 74% yield, under similar reaction conditions (Table 2, entries 4 and 5).

The reaction of the 9β,11β-epoxy-16β-methyl derivative **15**, an intermediate in the synthesis of betamethasone,[44] with 5 mol % of $Bi(OTf)_3 \cdot xH_2O$, in 1,4-dioxane, at 80 °C, afforded the 9β,11β-epoxy-16β-methyl-$\Delta^{1,4}$-3,17-diketosteroid **16**,[42] in 45% yield (Table 2, entry 6). The lower isolated yield of **16** may be explained in light of our recent findings related to the reactivity of bismuth(III) salts toward epoxysteroids.[34−37] Compound **16** has already been synthesized by starting from the corresponding 11β-hydroxy-16β-methylcorticosteroid, in five synthetic steps.[42] Advantageously, our approach gave directly in one step the useful 9β,11β-epoxy-16β-methyl-$\Delta^{1,4}$-3,17-diketosteroid **16** from

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the relatively easily available 9β,11β-epoxy-16β-methyl derivative **15**.[44] The molecular structure of compound **16** was confirmed by single crystal X-ray analysis. The corresponding ORTEP diagram is depicted in the Supporting Information (Figure A7) and some features of its structure are briefly discussed.

All these obtained 17-keto derivatives are very expensive steroid compounds, specially those bearing the 3-keto-$\Delta^{1,4}$-moiety. Therefore, our new catalytic process stands as an attractive method to obtain highly functionalized 17-ketosteroids directly from corticosteroids bearing a diversity of chemical functionalities. In fact, C_{19}-steroids bearing an oxygen function at C11 are synthetically and biologically[45,46] important molecules. For instance, 11β-hydroxyandrostanes have been efficiently converted into $\Delta^{9(11)}$-3,17-diketosteroids,[39,47] which can then be readily transformed into estrone derivatives by aromatization of ring A.[48] The 17-ketosteroids prepared herein are also suitable intermediates for the synthesis of 17-substituted steroids, by simple modification of the C17-carbonyl group.[49]

In conclusion, we have developed a highly practical protocol for the conversion of corticosteroids into highly functionalized 17-ketosteroids, by cleavage of the *C*17-dihydroxyacetone side chain using the "ecofriendly" bismuth(III) triflate as catalyst. Due to the commercial availability of corticosteroids, this process is an easy route to *C*17-ketosteroids bearing a variety of chemical functions in rings A, B, C, and D. The 17-ketosteroids prepared herein are interesting molecules from the pharmaceutical point of view and are currently under biological evaluation.

Experimental Section

General Procedure for the Cleavage of the *C*17-Dihydroxyacetone Side Chain of Corticosteroids. To a solution of hydrocortisone **1** (181.2 mg, 0.50 mmol) in 1,4-dioxane (15 mL) was added $Bi(OTf)_3 \cdot xH_2O$ (18.2 mg, 0.025 mmol). The color of the reaction mixture gradually turned pale yellow. After 8 h, under magnetic stirring, at 80 °C, full conversion of the starting compound was observed, as verified by TLC control. The solvent was removed under reduced pressure and the resulting mixture was purified by flash column chromatography [toluene/ethyl acetate 2:1 (v/v)] to afford 11β-hydroxyandrost-4-ene-3,17-dione **3**, as a white solid (113.4 mg, 75% yield). Mp (acetone/*n*-hexane) 185−188 °C (lit.[13] mp 188−190 °C); TLC [CH_2Cl_2/MeOH 9:1 (v/v)] R_f 0.67; IR 3473, 2927, 1736, 1663, 1617, 1450, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) see Table A1 in the SI; ^{13}C NMR ($CDCl_3$, 100 MHz) see Table A1 in the SI; EI-MS *m*/*z* (%) 302 (100) M^+, 266 (20), 248 (9), 226 (11), 189 (27), 163 (50), 145 (13), 91 (23).

9α-Chloro-11β-hydroxy-16β-methylandrosta-1,4-diene-3,17-dione, 10. Under the reaction conditions mentioned above, compound **10** was obtained in 84% yield after purification by flash column chromatography [toluene/ethyl acetate 3:1 (v/v)]. Mp (acetone/*n*-hexane):208−212 °C; TLC [CH_2Cl_2/MeOH 9:1 (v/v)] R_f 0.73; IR 3425, 2934, 1731, 1660, 1614, 1448, 884 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) see Table A2 in the SI; ^{13}C NMR ($CDCl_3$, 100 MHz) see Table A2 in the SI; EI-MS *m*/*z* (%) 348 (75) M^+, 331 (17), 311 (49), 293 (46), 193 (17), 89 (100), 75 (40), 73 (31). Anal. Calcd for $C_{20}H_{25}ClO_3$: C, 68.86; H, 7.22. Found: C, 69.01; H, 7.20.

9α-Fluoro-11β-hydroxy-16α-methylandrosta-1,4-diene-3,17-dione, 14. Under the reaction conditions mentioned above, compound **14** was obtained in 74% yield after purification by flash column chromatography [toluene/ethyl acetate 3:1 (v/v)]. Mp (acetone/*n*-hexane) 241−243 °C (lit.[43] mp 245−249 °C); TLC [CH_2Cl_2/MeOH 9:1 (v/v)] R_f 0.68; IR 3450, 2935, 1734, 1663, 1619, 1452, 889 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) see Table A2 in the SI; ^{13}C NMR ($CDCl_3$, 100 MHz) see Table A2 in the SI; EI-MS *m*/*z* (%) 332 (100) M^+, 311 (22), 293 (14), 265 (13), 208 (8), 186 (9), 89 (52), 75 (33).

Acknowledgment. R.M.A.P. thanks Fundação para a Ciência e Tecnologia for a grant (SFRH/BD/18013/2004). J.A.R.S. thanks Universidade de Coimbra for financial support. The authors are grateful to Hovione FarmaCiencia SA, Portugal, for kindly supplying some of the corticosteroids used in this study.

Supporting Information Available: The experimental procedures of compounds prepared herein as well as some considerations about their structural elucidation, including spectral data the ^1H NMR spectra of all compounds obtained herein, the ^{13}C NMR spectra of compounds **4** and **10**, and the CIF file of compound **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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