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Bismuth(III) salts mediated regioselective ring opening of epoxides: an easy route to halohydrins and β-hydroxy nitrates

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Abstract—The ring opening of various epoxides was achieved under mild conditions using bismuth(III) salts. Halohydrins and β-hydroxy nitrates were efficiently obtained from the corresponding 5α,6α-, 2α,3α-, and 5β,6β-epoxysteroid using $BiCl_3$, $BiBr_3$ or $Bi(NO_3)_3 \cdot 5H_2O$. Considerations about the probable reaction mechanism are provided. 2D homo- and heteronuclear correlation NMR spectroscopic techniques were used to unequivocally demonstrate the *trans*-diaxial nature of the epoxide ring opening.

1. Introduction

Epoxides are versatile synthetic intermediates in organic chemistry. For instance, epoxide ring opening with nucleophilic agents is an easy step for the preparation of several 1,2-disubstituted products,[1] such as vicinal halohydrins and β-hydroxy nitrates.

Chlorohydrins and other halohydrins are an important class of organic compounds and are useful intermediates for the synthesis of a vast range of biologically active natural and synthetic products.[2,3] In biological systems, hypochlorous acid, generated from H_2O_2 and chlorine by myeloperoxidase, is known to form chlorohydrin addition products with unsaturated fatty acids and cholesterol.[4] The formation of cholesterol chlorohydrins has been a subject of intense research[5] and three different chlorohydrin compounds have been identified from the reaction of cholesterol with HOCl.[6] The role of these compounds is not yet fully understood, but in addition to cytotoxicity and a possible action on the physiopathology of atherosclerosis,[5d] they have been proposed as biomarkers of myeloperoxidase-derived HOCl.[7] The vicinal chlorohydrin group has been identified in some steroid natural compounds, such as blattellastanoside B, an aggregation pheromone of German cockroach *Blattella germanica*,[8] marine steroids isolated from coral species[9] and withanolides such as jaborosalactone C and jaborosalactone E isolated from *Jaborosa integrifolia*,[10] and physalolactone,[11a] 4-deoxyphysalolactone[11b] and physalolactone C[11c] from *Physalis peruviana*. 6α-Chloro-5β-hydroxywithaferin A[12] and 6α-chloro-5β-hydroxywithanolide D[13] have also been isolated from *Withania frutescens* and *Withania somnifera*, respectively.

The conventional reagents for the formation of halohydrins from epoxide ring opening reaction are hydrogen halides and hypohalite–water.[14] However, the disadvantages associated with these processes such as intolerance of acid sensitive groups and by-product formation, led to intense research in this field. The use of pyridinium chloride,[15] ammonium halides in the presence of metal salts[16] or $BF_3 \cdot OEt_2$,[17] haloborane compounds,[18] direct halogenation of epoxides[19] and ring opening with halides of a variety of elements[20,21] have been reported for this reaction. Some ionic liquid based systems were also developed for the preparation of halohydrins from epoxides.[22] For steroid substrates, the synthesis of halohydrins from epoxides is mainly performed using hydrogen halides.[23] Alternative methods for this transformation involve the use of phosphine–halogen reagents,[24] palladium–halogen complexes,[25] and Dowex-50/sodium halides as an in situ generator of hydrogen halides.[26]

Organic nitrates have useful applications in organic synthesis[27] including as effective protecting groups for hydroxy groups.[28] The intense research related to nitric oxide (NO) and its biological effects led to the design of new drugs capable to act as NO-donors[29] and to the hybridization of

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NO-donating moieties (e.g., nitrate esters) with well-known drugs, some of them containing the steroid nucleus.[30]

Traditionally, the synthesis of β-hydroxy nitrates has been performed through the reaction of epoxides in concentrated nitric acid[31] and nitration of halohydrins with silver nitrate.[32] Non-attractive features of these methods are the highly acidic conditions used on the first one and the use of an expensive silver salt for the second one. The immobilization of nitrate ions on Amberlite IRA-400 allowed the preparation of β-hydroxy nitrates in a non-catalyzed reaction.[33] Iranpoor et al. used ceric ammonium nitrate (CAN) in stoichiometric amounts to perform the same reaction.[34] CAN,[34] $FeCl_3 \cdot 6H_2O$ supported on SiO_2[16b] and $Ce(OTf)_4$ in micellar media[35] have been used catalytically for the ring opening of several epoxides by the nitrate ion derived from NH_4NO_3, Bu_4NNO_3 or $NaNO_3$. Recently, the use of nitric oxide[36] and zirconyl nitrate[37] emerged as new methods that afford β-hydroxy nitrates. Epoxysteroids were converted into the corresponding β-hydroxy nitrates by treatment with stoichiometric amounts of thallium(III) nitrate,[38] a highly toxic heavy metal derivative. Hanson and co-workers applied CAN to the opening of steroidal epoxides and the corresponding β-hydroxy nitrates were obtained.[39]

The methods previously described for the preparation of halohydrins and β-hydroxy nitrates suffer from one or more disadvantages such as acidity, handling of toxic, sensitive and/or expensive reagents, in situ preparation of the reagents, relative long reaction time, unwanted by-products, and low regioselectivities. Therefore, new methods that use environmental friendly, cheap, and easily available reactants to efficiently perform these reactions would be of considerable interest.

Over the last decade the increasing concern about the environment has put focus on bismuth and its compounds,[40] mainly due to their relatively non-toxic character[41] that makes them suitable 'ecofriendly' reagents for a large variety of processes. We have recently reported the use of bismuth(III) salts as efficient catalysts for selective allylic oxidation reactions[42] and for the one-step conversion of epoxides into *vic*-acylamino hydroxy compounds.[43]

In this work we report the use of bismuth(III) salts for the regioselective ring opening of epoxides. These new processes proved to be easy, economical, and efficient for the preparation of halohydrins and β-hydroxy nitrates from epoxides in high yields and under mild conditions.

2. Results and discussion

2.1. $BiCl_3$ and $BiBr_3$ mediated ring opening of epoxides: synthesis of halohydrins

Although in most reactions bismuth(III) compounds act as Lewis acid catalysts, some processes have been reported where they are used in stoichiometric amounts.[40c]

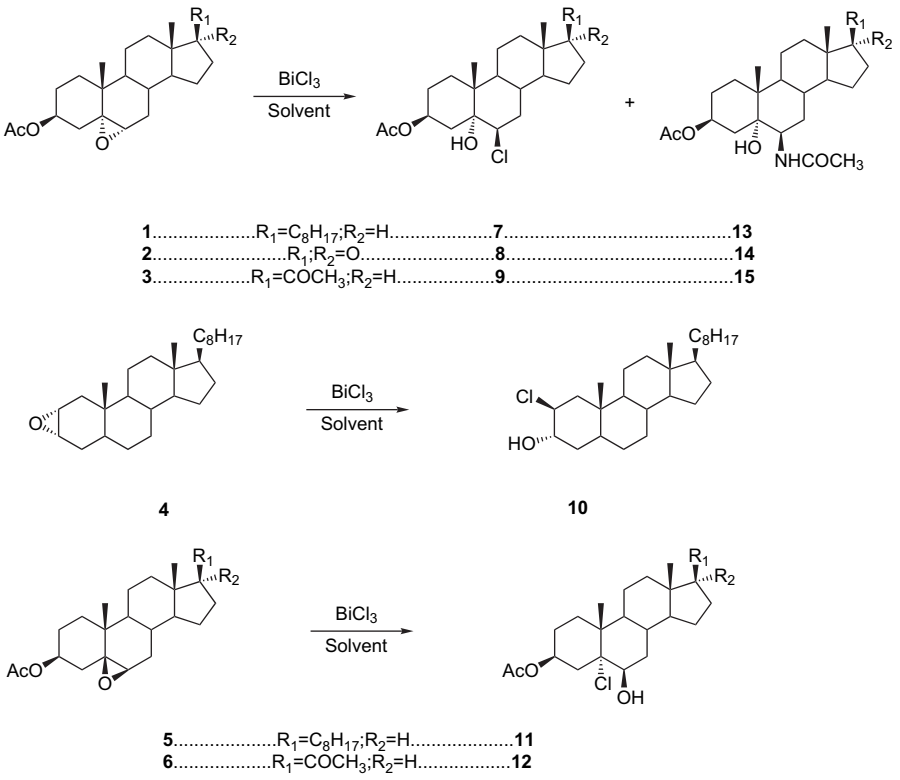
In a previous communication, we reported the synthetic application of bismuth(III) salts in the ring opening of epoxides with nitriles (Ritter reaction).[43] The reaction with 5α,6α-epoxycholestan-3β-yl acetate **1** was performed in acetonitrile under catalytic (10 mol % of $BiBr_3$, 48 h, 93% yield) or stoichiometric conditions (1.5 equiv of $BiBr_3$, 4.5 h, 91% yield) to afford the 6β-acetamido-5α-hydroxy derivative **13**.[43]

When catalytic amounts of $BiCl_3$ (10–20 mol %) were used for the same conversion no significant reaction occurred. However, the use of 1.5 equiv of $BiCl_3$ led to the formation of the 6β-acetamido-5α-hydroxy compound **13** and 6β-chloro-5α-hydroxycholestan-3β-yl acetate **7** (Scheme 1, Table 1, entry 1). McCluskey et al. reported that ring opening of cyclohexene oxide with $BiCl_3$/acetonitrile, in the presence of an amine or H_2O afforded the corresponding *trans*-chlorohydrin.[44] The only by-products identified were the *trans*-diol or β-amino alcohol derivatives in some of the experiments. Under our reaction conditions, where the amine was absent, we verified that there was competition between the Ritter reaction and the formation of a chlorohydrin derivative, a situation not described by those authors. In light of such discrepancy, we decided to study the influence of a base either inorganic (NaN_3) or organic (4-dimethylaminopyridine, DMAP), in the $BiCl_3$ mediated ring opening of epoxysteroids in acetonitrile (Scheme 1, Table 1, entries 2–8). We observed that using 1.5 equiv of NaN_3 (Table 1, entries 2, 7, and 8) or 10–30 mol % of DMAP (Table 1, entries 3–5) the 6β-chloro-5α-hydroxy products were preferentially obtained. On the other hand 50 mol % of DMAP dramatically decreases the reaction rate and only traces of products were observed after 8 h (Table 1, entry 6). These results suggest that the presence of a base stabilizes the reaction medium, making chlorohydrin the *major* reaction product.

In order to avoid any traces of Ritter reaction products we explored the reactivity of $BiCl_3$ towards the epoxysteroids **1**–**6** in a different solvent, 1,4-dioxane, and the corresponding chlorohydrins **7**–**12** were obtained in high yields (Scheme 1, Table 2). The reaction occurred at room temperature (Table 2, entry 1) but it was faster when performed at 80 °C (Table 2, entry 2). Under similar conditions the 5α,6α-epoxysteroids **2** and **3** and 2α,3α-epoxy-5α-cholestane **4** were efficiently converted to the chlorohydrins **8**, **9**, and **10**, respectively, with yields ranging from 92 to 94% (Table 2, entries 3–5). The *trans*-diaxial ring opening of 5β,6β-epoxysteroids **5** and **6** at room temperature gave the corresponding 5α-chloro-6β-hydroxy products **11** and **12** (Table 2, entries 6 and 8). In the case of substrate **5** the selectivity was lower and the yield after flash column chromatography was 76% (Table 2, entry 6). Increasing the reaction temperature decreased the yield of 5α-chloro-6β-hydroxy derivative **11** (Table 2, entry 7).

Using $BiBr_3$ in 1,4-dioxane, the 6β-bromo-5α-hydroxy product **16** was also prepared from the 5α,6α-epoxysteroid **1** at room temperature in 90% yield (Scheme 2).

To check if the observed reactivity is due to the in situ formation of HCl from $BiCl_3$, we performed the reaction in the presence of 2,6-di-*tert*-butylpyridine, a known proton scavenger, which only binds to protons and is unable to coordinate to metal ions due to the bulky *tert*-butyl groups.[45] Using substrate **1** in the conditions of the general procedure, the 6β-chloro-5α-hydroxy product **7** was isolated in 90%



Scheme 1.

yield after 3.5 h.[46] This result suggests that the ring opening is mediated by the Lewis acidity of bismuth towards the epoxide, alike the Bi–O interaction proposed by Keramane and co-workers for the chlorination of alcohols with $BiCl_3$.[47]

The stereochemistry for compounds **10** and **11** was determined using COSY, HMQC, HMBC and NOESY experiments to unequivocally confirm the *trans*-diaxial ring opening of 2α,3α-epoxysteroid **4** and 5β,6β-epoxysteroid **5**.

For compound **10**, the two protons with high chemical shifts (4.16 and 4.09 ppm) correspond to 2-H and 3-H, respectively. 2-H was distinguished by the coupling with a geminal pair at 1.82 and 1.99 ppm attached to a carbon with a chemical shift of 40.0 ppm, which showed a cross peak with 19-CH_3 (at 1.06 ppm) in the HMBC spectrum, being thus assigned as C-1. On the other hand, the carbon atom (31.0 ppm) that is attached to the geminal pair at 1.36 and 2.02 ppm, giving cross peaks with the proton at 4.09 ppm in the COSY spectrum, showed no coupling to 19-CH_3, so it can be assigned as C-4. Thus, the product is a 2-chloro-3-hydroxy derivative. Strong correlations of 19-CH_3 with 1β-H (1.99 ppm) and 4β-H (2.02 ppm) and a weak interaction with 3-H were detected in the NOESY spectrum, but none with 2-H. These observations are in accordance with a 2β-chloro-3α-hydroxy structure where the A-ring is in a chair conformation and both 2-H and 3-H are in equatorial positions. The steroselectivity for this reaction is consistent with the classical *trans*-diaxial opening of 2α,3α-epoxysteroids.[48]

For compound **11**, the observed multiplicity for the proton at 5.38 ppm (triplet of triplets, J_1=10.9 Hz and J_2=5.5 Hz), attributed to 3-H, was indicative of a *trans*-fused (5α,10β)-steroid structure with the hydrogen in an axial

Table 1. Ring opening of 5α,6α-epoxysteroids with $BiCl_3$ in MeCN[a]

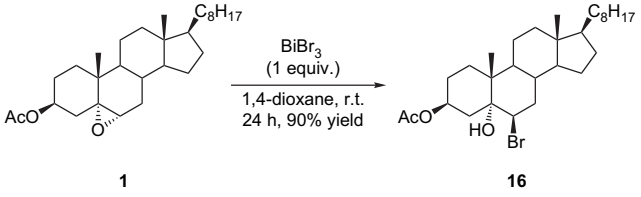
Entry	Substrate (mmol)	Solvent (mL)	$BiCl_3$ (mmol)	Base (mmol)	Time (h)	Product[b]	Yield[c] (%)	Ratio[d]
1	**1**/0.125	MeCN (3)	0.19	—	0.5	**7+13**	94	45:55
2	**1**/0.125	MeCN (3)	0.19	NaN_3 (0.19)	0.5	**7+13**	93	87:13
3	**1**/0.25	MeCN (6)	0.25	DMAP (0.08)	2	**7+13**	91	71:29
4	**1**/0.25	MeCN (6)	0.25	DMAP (0.05)	1	**7+13**	91	63:33
5	**1**/0.25	MeCN (6)	0.25	DMAP (0.03)	0.5	**7+13**	94	63:33
6	**1**/0.25	MeCN (6)	0.25	DMAP (0.13)	8	—[e]	—	—
7	**2**/0.25	MeCN (6)	0.37	NaN_3 (0.37)	0.5	**8+14**	93	83:17
8	**3**/0.25	MeCN (6)	0.37	NaN_3 (0.37)	1	**9+15**	93	87:13

[a] Reactions performed at 80 °C.
[b] Analytical data for the Ritter reaction products **13**–**15** were in accordance with literature.[43]
[c] Yield of the reaction crude based on chlorohydrin.
[d] Calculated by ^{1}H NMR integration of 6α-H in the crude product.
[e] Only traces of products were observed in TLC plate after 8 h.

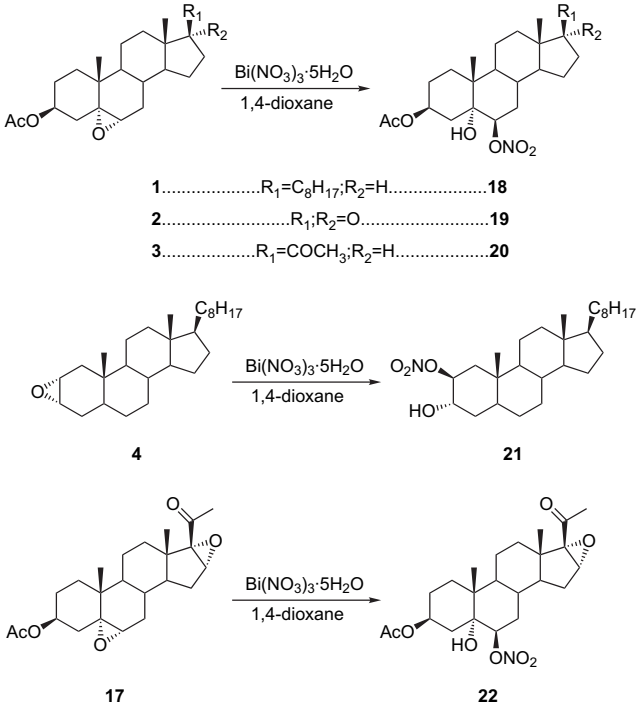
Table 2. $BiCl_3$ mediated ring opening of epoxysteroids: synthesis of chlorohydrins

Entry	Substrate (mmol)	Solvent (mL)	$BiCl_3$ (mmol)	Temp (°C)	Time (h)	Product	Isolated Yield (%)
1	**1**/0.10	1,4-Dioxane (3)	0.10	rt	9	**7**	94
2	**1**/0.10	1,4-Dioxane (3)	0.15	80	1	**7**	94
3	**2**/0.25	1,4-Dioxane (6)	0.37	80	1	**8**	94
4	**3**/0.25	1,4-Dioxane (6)	0.37	80	1.5	**9**	92
5	**4**/0.10	1,4-Dioxane (3)	0.10	rt	4.5	**10**	92
6	**5**/0.50	1,4-Dioxane (15)	0.50	rt	9	**11**	76[a]
7	**5**/0.125	1,4-Dioxane (3)	0.19	80	0.5	**11**	61[a]
8	**6**/0.10	1,4-Dioxane (3)	0.10	rt	19	**12**	89

[a] Purified by flash column chromatography on silica gel (toluene/diethyl ether 7:3).



Scheme 2.



Scheme 3.

α-conformation. The signal at 3.96 ppm was assigned to 6-H and showed in COSY spectrum a correlation with the protons at 1.61 and 2.03 ppm. These protons were correlated with a carbon located at 34.1 ppm, which showed a cross peak with C-6 (75.6 ppm) in HMBC. This experiment provided further information about the carbon nucleus located in the vicinity of C-6. Cross peaks with carbons assigned as C-4 (37.6 ppm), C-5 (83.3 ppm), C-10 (39.7 ppm), C-7 (34.1 ppm), and C-8 (30.4 ppm) were found in HMBC spectrum and were in accordance with the one previously reported for 5α-chloro-3β,6β-dihydroxycholestane.[6] The NOESY experiment did not show any correlations between 6-H and 19-CH_3, which in addition to the nature of the 6-H signal (doublet of doublets, J_1=5.3 Hz and J_2=2.3 Hz), is indicative of equatorial conformation and supports the proposed structure for 5α-chloro-6β-hydroxycholestan-3β-yl acetate **11**.

2.2. $Bi(NO_3)_3\cdot 5H_2O$ mediated ring opening of epoxides: synthesis of β-hydroxy nitrates

The use of bismuth salts for the selective ring opening of epoxides was extended to $Bi(NO_3)_3\cdot 5H_2O$ and under these specific reaction conditions, the β-hydroxy nitrate products **18**–**22** were obtained from epoxysteroids **1**–**4** and **17** in very high yields (Scheme 3, Table 3). The reaction can be performed at room temperature or at 80 °C with 1 equiv per mole of $Bi(NO_3)_3\cdot 5H_2O$ (Table 3, entries 1 and 2), but faster reactions were obtained using 1.5 equiv of $Bi(NO_3)_3\cdot 5H_2O$ at 80 °C (Table 3, entries 3–7).

Interestingly, using acetonitrile as solvent[49] the reaction of 5α,6α-epoxysteroid **1** with $Bi(NO_3)_3\cdot 5H_2O$ gave mainly the Ritter reaction product **13** and only small amounts of 5α-hydroxy-6β-nitrate derivative **18** were observed (Scheme 4, Table 3, entry 8). The addition of 1.5 equiv of NaN_3 to this reaction increased the yield of 5α-hydroxy-6β-nitrate product **18** to 61% (Table 3, entry 9).

It is noteworthy that the ring opening of the 5α,6α;16α,17α-diepoxysteroid **17** with $Bi(NO_3)_3\cdot 5H_2O$ proved to be highly selective for the 5α,6α-epoxide group and a new steroid compound **22** was obtained in 91% yield (Scheme 3, Table 3, entry 7). The 16α,17α-epoxide group remains intact allowing further important funtionalizations. Thus the reaction performed on substrate **17** is chemo-, regio- and stereoselective, which shows the synthetic applicability of the reported process.

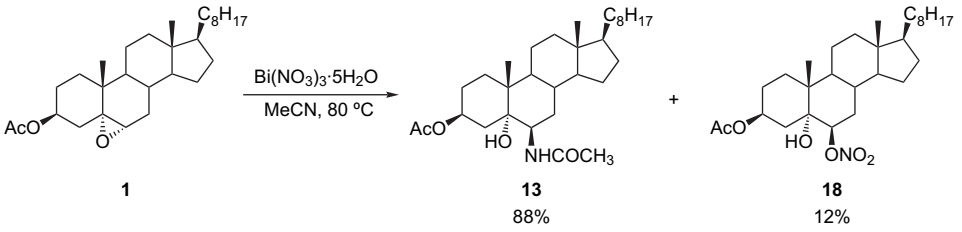
To enlarge the scope of this process, the ring opening of the non-steroidal substrates cyclohexene oxide **23** and styrene oxide **24** was performed with $Bi(NO_3)_3\cdot 5H_2O$ in 1,4-dioxane at room temperature (Scheme 5). For substrate **23**, the corresponding *trans*-β-hydroxy nitrate product **25** was obtained in 83% yield after 1 h of reaction. The expected ring opening at the benzylic position was observed for substrate **24** and thus product **26** was isolated in 90% yield.

The ring opening of 5α,6α-epoxysteroid **1** with $Bi(NO_3)_3\cdot 5H_2O$ in 1,4-dioxane was also investigated in the presence of 2,6-di-*tert*-butylpyridine. After 1.5 h the reaction was complete, which indicates that the nucleophilic attack of the nitrate on the epoxide ring is not due to the in situ formation of HNO_3.[50] This suggests that $Bi(NO_3)_3\cdot 5H_2O$

Table 3. $Bi(NO_3)_3 \cdot 5H_2O$ mediated ring opening of epoxysteroids: synthesis of β-hydroxy nitrates

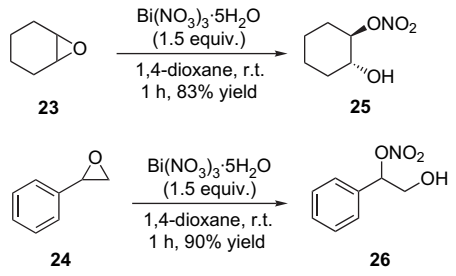
Entry	Substrate (mmol)	Solvent (mL)	$Bi(NO_3)_3 \cdot 5H_2O$ (mmol)	Temp (°C)	Time (h)	Product	Isolated yield (%)
1	**1**/0.10	1,4-Dioxane (3)	0.10	rt	24	**18**	90
2	**1**/0.10	1,4-Dioxane (3)	0.10	80	4	**18**	90
3	**1**/0.10	1,4-Dioxane (3)	0.15	80	2	**18**	93
4	**2**/0.10	1,4-Dioxane (3)	0.15	80	2.5	**19**	93
5	**3**/0.10	1,4-Dioxane (3)	0.15	80	3	**20**	88
6	**4**/0.10	1,4-Dioxane (3)	0.15	80	2.5	**21**	85
7	**17**/0.10	1,4-Dioxane (3)	0.15	80	4.5	**22**	91
8	**1**/0.10	MeCN (3)	0.15	80	0.5	**13+18**	95[a]
9	**1**/0.10	MeCN (3)[b]	0.15	80	1.5	**13+18**	90[c]

[a] Yield of the reaction based on 5α-hydroxy-6β-acetamide derivative **13**; by ^1H NMR integration of 6α-H in the crude product it was found a ratio of 88:12 between the products **13** and **18**.
[b] Reaction performed in the presence of 1.5 equiv of NaN_3.
[c] Yield of the reaction based on 5α-hydroxy-6β-nitrate derivative **18**; by ^1H NMR integration of 6α-H in the crude product it was found a ratio of 39:61 between the products **13** and **18**.



1 **13** 88% **18** 12%

Scheme 4.



23 **25** **24** **26**

Scheme 5.

coordinates with the epoxide, increasing the polarity of the C–O bond and making the adjacent carbons more susceptible to nucleophilic attack.

The *trans*-diaxial nature of 5α,6α-epoxysteroid ring opening with $Bi(NO_3)_3 \cdot 5H_2O$ was determined using 2D NMR techniques to unequivocally attribute the 6β-substitution that results from the nucleophilic attack on C-6 by the β-face of the steroid nucleus. For compound **19**, the protons with chemical shifts at 5.14 and 4.92 ppm were assigned as 3-H and 6-H, respectively. The multiplicity of the 3-H (a triplet of triplets with J_1=11.1 Hz and J_2=5.5 Hz) was indicative of a *trans*-fused (5α,10β)-steroid structure. The coupling pattern observed for 6-H (doublet of doublets, J_1=5.4 Hz and J_2=2.1 Hz) was indicative of equatorial–equatorial and equatorial–axial couplings, consistent with 6β-substitution. The resonance due to 6-H at 4.92 ppm gave strong correlations with a geminal pair at 1.88 ppm and 1.90 ppm in the ^1H–^1H COSY spectrum, which were correlated with a carbon at 29.1 ppm. The HMBC experiment provided useful correlations for 6-H, showing cross peaks with carbon nucleus, which were assigned as C-5 (74.8 ppm), C-10 (38.7 ppm), C-7 (29.1 ppm), and C-9 (30.4 ppm). In the NOESY experiment interactions of 6-H with the geminal pair at C-7 were detected, but none were seen between 6-H and 19-CH_3. These observations allowed us to assign the 5α-hydroxy 6β-nitrate configuration to compound **19**.

3. Conclusions

In summary, we developed new processes for the selective *trans*-diaxial ring opening of epoxides using economical, non-toxic, and easily available bismuth salts. These methods allowed the effective synthesis of halohydrins and β-hydroxy nitrates under mild conditions. A remarkable solvent effect in the reactivity of bismuth salts towards epoxysteroids was demonstrated and a probable reaction mechanism was discussed. These procedures were found to be very simple, economic, and ecofriendly leading to high yields and therefore should find a large application in chemical synthesis.

4. Experimental

4.1. General

5α,6α-Epoxysteroids (**1**–**3** and **17**) and 2α,3α-epoxy-5α-cholestane (**4**) were prepared from the corresponding Δ^5-steroids and from 5α-cholest-2-ene, respectively, by epoxidation with *m*-CPBA.[51] 5β,6β-Epoxysteroids (**5** and **6**) were obtained by β-selective epoxidation of Δ^5-steroids using a method developed by our group.[52] The starting materials, bismuth salts and solvents were purchased from Sigma-Aldrich Co. Solvents were distilled before use according to standard procedures. Kieselgel $60HF_{245}$/Kieselgel 60G was used for TLC plates. Melting points were determined on a Buchi Melting point B-540 and are uncorrected. IR spectra were performed in a Jasco FT/IR 420

spectrophotometer. ^{1}H, ^{13}C NMR, 2D homonuclear correlation (COSY), Nuclear Overhauser Enhancement Spectroscopy (NOESY), 2D heteronuclear multiple quantum correlation (HMQC) and 2D heteronuclear multiple bond correlation (HMBC) were recorded in a Bruker AMX 300 MHz and in a Bruker Avance 300 MHz equipped with a BBO-ATMA 5 mm probe. The NMR samples were prepared in $CDCl_3$ solution with Me_4Si as internal standard. Mass spectral analyses were made on a Thermo Quest TSQ 7000; the samples were dissolved in dichloromethane and the spectra were obtained by direct chemical ionization (DCI) using NH_3 as the reactant gas.

4.2. General procedure for BiX_3 mediated ring opening of epoxides

To a solution of 5α,6α-epoxycholestan-3β-yl acetate **1** (44.4 mg, 0.10 mmol) in 1,4-dioxane (3 mL), $BiCl_3$ (31.5 mg, 0.1 mmol) was added. After 9 h under magnetic stirring at room temperature the reaction was complete as verified by TLC control. The reaction mixture was filtered through a Celite pad, the filtrate was concentrated under vacuum and the resulting residue dissolved in ethyl acetate (60 mL). The organic phase was washed with HCl (10% aq), Na_2SO_3 (10% aq), water, dried with anhydrous Na_2SO_4, and evaporated to dryness to give 6β-chloro-5α-hydroxycholestan-3β-yl acetate **7** (45.0 mg, 94% yield). Slow crystallization from ethyl acetate afforded 82% of pure product. Mp 178–181 °C; lit.,[24] 180–182 °C; IR (ATR) 3401, 2933, 1735, 1699, 1364, 1273, 1246, 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.71 (s, 3H, 18-CH_3), 0.87, 0.89 (2d, J=1.3 Hz, each 3H, 26-CH_3 and 27-CH_3), 0.92 (d, J=6.5 Hz, 3H, 21-CH_3), 1.29 (s, 3H, 19-CH_3), 2.05 (s, 3H, CH_3COO), 3.85 (m, 1H, 6α-H), 5.12 (tt, J_1=11.6 Hz and J_2=5.9 Hz, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1 (C-18), 18.2 (C-19), 18.6 (C-21), 21.4 (CH_3COO), 64.0 (C-6), 71.1 (C-3), 76.5 (C-5), 171.0 (CH_3COO); MS [m/z (%)] 516 (1) $[M+N_2H_7]^+$, 499 (100) $[M+NH_4]^+$, 480 (18), 462 (37), 354 (9), 180 (9), 173 (2), 115 (8).

4.2.1. Compound 8. Mp 199–201 °C (MeOH); lit.,[53] 204–205 °C; IR (ATR) 3569, 2947, 1737, 1726, 1372, 1243, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (s, 3H, 18-CH_3), 1.29 (s, 3H, 19-CH_3), 2.05 (s, 3H, CH_3COO), 3.89 (m, 1H, 6α-H), 5.09 (tt, J_1=10.6 Hz and J_2=5.1 Hz, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9 (C-18), 18.2 (C-19), 21.6 (CH_3COO), 63.6 (C-6), 71.1 (C-3), 76.2 (C-5), 171.3 (CH_3COO), 221.3 (C-17); MS [m/z (%)] 417 (2) $[M+NH_4]^+$, 400 (29), 381 (5), 364 (100), 336(4), 304 (6), 234 (6), 216(3), 153 (1).

4.2.2. Compound 9. Mp 232–234 °C (MeOH); lit.,[53] 237–238 °C; IR (ATR) 3342, 2945, 1731, 1688, 1363, 1248, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.65 (s, 3H, 18-CH_3), 1.28 (s, 3H, 19-CH_3), 2.04 (s, 3H, CH_3COO), 2.13 (s, 3H, 21-CH_3), 3.85 (m, 1H, 6α-H), 5.11 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 63.7 (C-6), 70.9 (C-3), 76.3 (C-5), 171.0 (CH_3COO), 209.6 (C-20); MS [m/z (%)] 445 (2) $[M+N_2H_7]^+$, 428 (72) $[M+NH_4]^+$, 409 (3), 392 (100), 350 (9), 334 (6), 304 (6), 129 (3).

4.2.3. Compound 10. Mp 124–125 °C (MeOH); lit.,[24] 122–124 °C; IR (ATR) 3335, 2931, 1467, 1442, 1376, 1009 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.67 (s, 3H, 18-CH_3), 0.87, 0.89 (2d, J=1.3 Hz, each 3H, 26-CH_3 and 27-CH_3), 0.92 (d, J=6.5 Hz, 21-CH_3), 1.06 (s, 3H, 19-CH_3), 4.09 (m, 1H, 3β-H), 4.16 (m, 1H, 2α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1 (C-18), 14.8 (C-19), 31.0 (C-4), 40.0 (C-1), 59.9 (C-2), 71.2 (C-3); MS [m/z (%)] 440 (3) $[M+NH_4]^+$, 421 (30), 404 (100), 402(14), 318 (3), 304 (8), 117 (3), 100 (7).

4.2.4. Compound 11. Mp 194–196 °C ($CHCl_3$); lit.,[24] 195–197 °C; IR (ATR) 3434, 2936, 1737, 1704, 1379, 1268, 1089, 1034, 891 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.69 (s, 3H, 18-CH_3), 0.87, 0.89 (2d, J=1.3 Hz, each 3H, 26-CH_3 and 27-CH_3), 0.92 (d, J=6.5 Hz, 21-CH_3), 1.30 (s, 3H, 19-CH_3), 2.04 (s, 3H, CH_3COO), 3.96 (dd, J_1=5.3 Hz and J_2=2.3 Hz, 1H, 6α-H), 5.38 (tt, J_1=10.9 Hz and J_2=5.5 Hz, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.2 (C-18), 18.0 (C-19), 21.4 (CH_3COO), 30.4 (C-8), 34.1 (C-7), 37.6 (C-4), 39.7 (C-10), 71.0 (C-3), 75.6 (C-6), 83.3 (C-5), 170.5 (CH_3COO); MS [m/z (%)] 516 (5) $[M+N_2H_7]^+$, 499 (100) $[M+NH_4]^+$, 462 (21), 404 (4), 354 (6), 180 (6), 145 (5), 115 (5).

4.2.5. Compound 12. Mp 203–205 °C (MeOH); lit.,[54] 206–207 °C; IR (ATR) 3402, 2942, 1734, 1700, 1235, 1090, 894 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.65 (s, 3H, 18-H_3), 1.31 (s, 3H, 19-H_3), 2.05 (s, 3H, CH_3COO), 2.13 (s, 3H, 21-CH_3), 3.98 (m, 1H, 6α-H), 5.38 (tt, J_1=11.0 Hz and J_2=5.6 Hz, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.9 (C-3), 75.4 (C-5), 83.2 (C-6), 170.5 (CH_3COO), 209.5 (C-20); MS [m/z (%)] 445 (10) $[M+N_2H_7]^+$, 428 (75) $[M+NH_4]^+$, 392 (100), 378 (9), 351 (18), 334 (20), 332 (15), 304 (10).

4.2.6. Compound 16. Mp 140–142 °C (MeOH); lit.,[24] 140–142 °C; IR (ATR) 3410, 2941, 1734, 1705, 1365, 1246, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73 (s, 3H, 18-CH_3), 0.87, 0.89 (2d, J=1.3 Hz, each 3H, 26-CH_3 and 27-CH_3), 0.93 (d, J=6.4 Hz, 21-CH_3), 1.37 (s, 3H, 19-CH_3), 2.05 (s, 3H, CH_3COO), 3.99 (m, 1H, 6α-H), 5.10 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1 (C-18), 19.1 (C-19), 18.6 (C-21), 21.4 (CH_3COO), 56.2 (C-6), 71.2 (C-3), 76.2 (C-5), 170.9 (CH_3COO); MS [m/z (%)] 542 (100) $[M+NH_4]^+$, 498 (6), 480 (36), 462 (64), 404 (4), 354 (8), 180 (7), 140 (10).

4.3. General procedure for $Bi(NO_3)_3\cdot 5H_2O$ mediated ring opening of epoxides

To a solution of 5α,6α-epoxycholestan-3β-yl acetate **1** (44.4 mg, 0.10 mmol) in 1,4-dioxane (3 mL), $Bi(NO_3)_3\cdot 5H_2O$ (72.7 mg, 0.15 mmol) was added. After 2 h under magnetic stirring at 80 °C the reaction was complete as verified by TLC control. The reaction mixture was filtered through a Celite pad, the filtrate was concentrated under vacuum and the resulting residue dissolved in ethyl acetate (60 mL). The organic phase was washed with HCl (10% aq), Na_2SO_3 (10% aq), water, dried with anhydrous Na_2SO_4, and evaporated to dryness to give 5α-hydroxy-6β-nitratecholestan-3β-yl acetate **18**[38] (46.7 mg, 93% yield). Crystallization from acetone afforded 82% of pure product. Mp 138–139 °C; IR (ATR) 3432, 2940, 1734, 1714, 1632, 1279, 1244, 1032, 849 cm^{-1}; ^{1}H NMR

($CDCl_3$, 300 MHz) δ 0.69 (s, 3H, 18-CH_3), 0.87, 0.89 (2d, J=1.3 Hz, each 3H, 26-CH_3 and 27-CH_3), 0.92 (d, J=6.5 Hz, 21-CH_3), 1.14 (s, 3H, 19-CH_3), 2.05 (s, 3H, CH_3COO), 4.88 (m, 1H, 6α-H), 5.14 (tt, J_1=10.9 Hz and J_2=5.3 Hz, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1 (C-18), 16.0 (C-19), 18.8 (C-21), 21.4 (CH_3COO), 70.3 (C-3), 75.0 (C-5), 85.4 (C-6), 171.0 (CH_3COO); MS [m/z (%)] 542 (6) $[M+N_2H_7]^+$, 525 (100) $[M+NH_4]^+$, 480 (9), 478 (17), 462 (22), 418 (3), 408 (2), 354 (2).

4.3.1. Compound 19. Mp 187–188 °C (MeOH); lit.,[39] 189–191 °C; IR (ATR) 3559, 2943, 1735, 1727, 1633, 1613, 1284, 1242. 1031, 864 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (s, 3H, 18-CH_3), 1.16 (s, 3H, 19-CH_3), 2.04 (s, 3H, CH_3COO), 4.92 (dd, J_1=5.4 Hz and J_2=2.1 Hz, 1H, 6α-H), 5.14 (tt, J_1=11.1 Hz and J_2=5.5 Hz, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9 (C-18), 16.0 (C-19), 21.4 (CH_3COO), 29.1 (C-7), 30.4 (C-9), 38.7 (C-10), 70.2 (C-3), 74.8 (C-5), 85.0 (C-6), 171.1 (CH_3COO), 220.5 (C-17); MS [m/z (%)] 444 (7) $[M+N_2H_7]^+$, 427 (62) $[M+NH_4]^+$, 380 (83), 364 (100), 320 (22), 304 (39), 242 (13), 180 (18).

4.3.2. Compound 20. Mp 197–198 °C (MeOH); lit.,[55] 194–196 °C; IR (ATR) 3326, 2949, 1729, 1686, 1635, 1281, 1245, 846 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.64 (s, 3H, 18-CH_3), 1.14 (s, 3H, 19-CH_3), 2.05 (s, 3H, CH_3COO), 2.13 (s, 3H, 21-CH_3), 4.88 (m, 1H, 6α-H), 5.14 (tt, J_1=11.1 Hz and J_2=5.6 Hz, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.2 (C-3), 74.9 (C-5), 85.1 (C-6), 171.0 (CH_3COO), 209.4 (C-20); MS [m/z (%)] 472 (7) $[M+N_2H_7]^+$, 455 (100) $[M+NH_4]^+$, 424 (20), 408 (61), 392 (72), 348 (14), 180 (26), 163 (17).

4.3.3. Compound 21. Mp 88–91 °C (MeOH); lit.,[56] 90–91 °C; IR (ATR) 3382, 2929, 1632, 1467, 1279, 1019, 865 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.66 (s, 3H, 18-CH_3), 0.87, 0.89 (2d, J=1.3 Hz, each 3H, 26-CH_3 and 27-CH_3); 0.91 (d, J=6.5 Hz, 21-CH_3), 0.91 (s, 3H, 19-CH_3), 4.02 (m, 1H, 3β-H), 5.01 (m, 1H, 2α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 66.1 (C-3); 82.0 (C-2); MS [m/z (%)] 467 (9) $[M+NH_4]^+$, 423 (9), 420 (100), 404(71), 402 (12), 390 (2), 354(1), 153 (1).

4.3.4. Compound 22. Mp 182–183 °C (MeOH); IR (ATR) 3435, 2937, 2854, 1733, 1683, 1626, 1280, 1244, 853 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 3H, 18-CH_3), 1.13 (s, 3H, 19-CH_3), 2.03 (s, 6H, CH_3COO and 21-CH_3), 3.69 (br s, 1H, 16β-H), 4.86 (m, 1H, 6α-H), 5.11 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 60.3 (C-16); 70.2 (C-3); 70.7 (C-17); 74.8 (C-5); 85.1 (C-6); 171.0 (CH_3COO); 204.8 (C-20); MS [m/z (%)] 486 (2) $[M+N_2H_7]^+$, 469 (100) $[M+NH_4]^+$, 424 (51), 422 (42), 406 (88), 362 (4), 147 (6), 123 (4); Anal. Calc. for $C_{23}H_{33}NO_8$: C, 61.18; H, 7.37; N, 3.10. Found: C, 61.32; H, 7.57; N, 3.07.

4.3.5. Compound 25. Colorless oil;[36b] IR (ATR) 3377, 2944, 2867, 1627, 1454, 1277, 1076, 995, 873 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 3.66 (m, 1H, 2-H), 4.80 (m, 1H, 1-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.5 (C-2), 87.1 (C-1).

4.3.6. Compound 26. Yellowish oil;[37] IR (ATR) 3367, 3066, 3036, 2933, 1633, 1455, 1276, 858, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.78, 3.90 (2 m, 2H, 1-H_2), 5.86 (m, 1H, 2-H), 7.25–7.40 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 67.3 (C-1), 85.5 (C-2).

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