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Article

A Temperature-Controlled Switch between Fürst–Plattner Rule and Anti-Fürst–Plattner Rule Ring Opening of 2,3-Epoxy-steroids with Various Halide Sources in the Presence of Imidazolium Ionic Liquids

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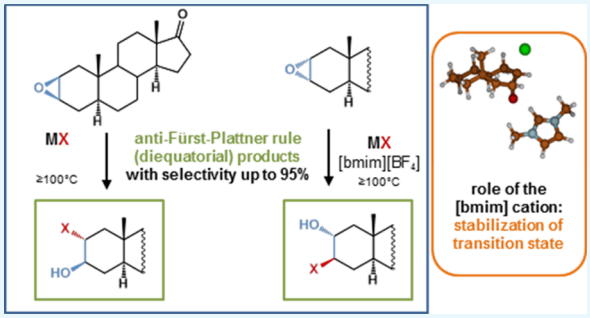
ABSTRACT: The ring opening of 2α,3α- and 2β,3β-epoxy-5α-androstan-17-one with halide reagents ($AlCl_3$, TMSCl, LiCl, and LiBr) was investigated using imidazolium ionic liquids in the dual role of solvent and catalyst. The application of the ionic liquid was shown to result in an increase in the amount of the unusual diequatorial halohydrins especially at temperatures above 100 °C. With a careful choice of reaction conditions, the latter derivatives could be produced with 43−96% selectivity depending on the nature of the halide ion. Moreover, the usual diaxial products could also be isolated in 70−85% yields by a proper change in the reaction conditions. The reusability of the ionic liquid was demonstrated in both types of reactions. The structures of the products were proved unequivocally by nuclear magnetic resonance (NMR) measurements including two-dimensional (2D) techniques as well as high-resolution mass spectrometry (HRMS). Based on quantum chemical calculations, the effect of the ionic liquid could be explained by the stabilization of the transition state leading to the diequatorial product.



INTRODUCTION

The vicinal halohydrin group can be identified in some natural products with steroid skeleton, such as in chlorinated marine sterols yonarasterols G, H, and I[1] and in chloro-pregnanes[2] isolated from the Okinawan soft coral *Clavularia viridis* and the eastern Pacific octocoral *Carijoa multiflora*, respectively (Figure 1). The presence of halogenated steroids could be detected not only in sea organisms but also in higher plants. Some of these natural products were even shown to exert cytostatic activity.[3] Another example of a natural steroidal halohydrin with known biological activity is a chlorinated steroid glucoside with the 5β-stigmastane skeleton, Blattellastanoside B, the aggregation pheromone of the German cockroach.[4]

Several synthetic derivatives with promising therapeutical and pharmacological properties have also been reported. Fluoxymesterone is an anabolic steroid with strong androgenic properties.[5] Androgens substituted with fluorine atoms in the C-16 or C-20 positions[6] are potential receptor-mediated diagnostic imaging agents. Similarly, 16-halo estradiols may serve as estrogen-receptor-based imaging agents for human breast tumors.[7] Some 17-chloro-D-homo-estranes showed antiprogestin activity.[8] 3α-Halo-2β-hydroxy-androstanes were synthesized due to their ability to inhibit dicotyledenous seed germination and hepatic cholesterol synthesis.[9]

The most prevalent method for the synthesis of these compounds involves the ring opening of the corresponding steroidal epoxides. In the first examples, hydrogen halides were used as reagents and this methodology remained the simplest route toward halogenated steroids.[9,10] At the same time, motivated by the necessity to apply less corrosive reagents, researchers are on a continuous quest for other methodologies. Elemental halogen was used as a halide source in the presence of PPh_3[11] or polymeric-supported triphenylphosphine[12] that forms ionic adducts with halogens. Steroidal epoxides were also converted to the corresponding halohydrins with a wide range of metal halides. The addition of a stoichiometric amount of dichlorobis(benzonitrile)palladium(II)[13] to steroidal epoxides led to the formation of the corresponding chlorohydrins after hydrolytic workup. A similar Pd complex, $PdCl_2(CH_3CN)_2$, accelerated the ring opening of 2α,3α-epoxy-5α-cholestane and 2β,3β-epoxy-5α-cholestane using $CuCl_2$ as the reagent.[14] Other metal halides, such as $AlCl_3$[15] or $BiCl_3$,[16] may play the dual role of a Lewis acidic catalyst and the halide source. The silica-supported version of the latter was found to

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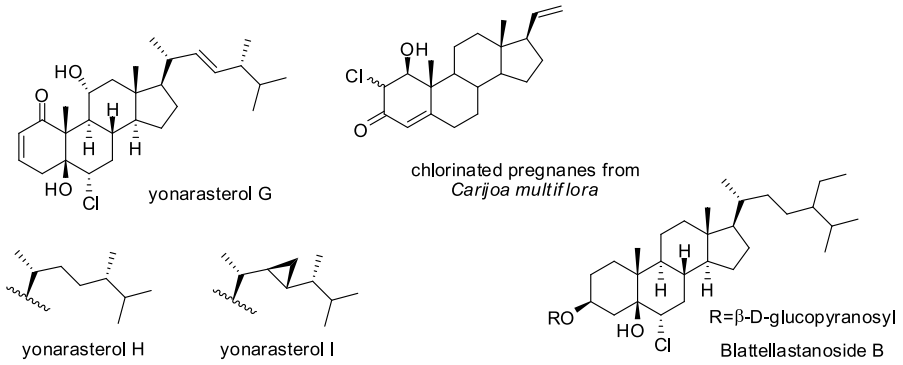

Figure 1. Some steroidal halohydrin natural products.

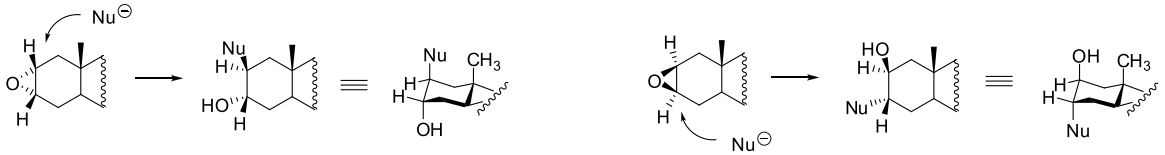

Figure 2. Fürst−Plattner rule ring opening of 2,3-epoxy-steroids.

be even superior in terms of catalytic performance to the Bi-salt used in homogeneous reactions.[17] Other Lewis acids, such as BF_3, may also serve as the catalyst and reagent.[18] Another possibility is the application of chlorotrimethylsilane and flame-dried zinc amalgam that resulted in the formation of the corresponding trimethylsiloxychlorohydrin from 2α,3α-epoxy-5α-cholestane and produced the chlorohydrin on hydrolytic workup.[19] The ring opening of steroidal epoxides almost uniformly follows the Fürst−Plattner rule,[20] leading to the diaxial 2β,3α-substituted products starting from either 2α,3α- or 2β,3β-epoxides (Figure 2). This stereochemical outcome can be explained by a kinetically controlled ring opening that takes place via the more stable chair-like conformation of ring A in the transition state.

Besides the reaction routes discussed above for the synthesis of steroidal halohydrins, there is a great plethora of synthetic methodologies to effect the ring opening of simple epoxides with halide reagents.[21] The reactions of alkali halides are catalyzed by acetic acid,[22] solid acids such as Amberlyst 15[23] or silica gel,[24] as well as Lewis acids, e.g., $InCl_3$.[25] Lewis acids also promote ring opening with trimethylsilyl-halides.[26] At the same time, the use of strong Lewis acids often results in a low yield of halohydrins when applied to acid-sensitive substrates. Instead of Lewis acids, ionic liquids (ILs) may also be used to promote epoxide ring opening with lithium halides[27] or chlorotrimethylsilane (TMSCl).[28] Some ILs[29] may serve as reagents themselves in the absence,[11,29a-c] or the presence of another catalyst.[29d]

Imidazolium ionic liquids had been shown to activate epoxides by forming a hydrogen bond between the acidic 2-H of the imidazolium cation with the epoxide oxygen that facilitates C−O bond cleavage without a proton transfer (Figure 3).[30] The existence of the H-bond had been proved by the downfield shift of the C2 proton of the imidazolium ring in the presence of an epoxide.[30]

During our previous studies,[31] ILs were found to be very effective catalysts in the ring opening of steroidal epoxides with amine and thiol reagents. In continuation of this work, we investigated the reaction of epoxysteroids with lithium halides and other halide sources in ILs. We have found that the

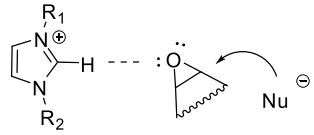

Figure 3. Catalytic effect of imidazolium ILs in ring-opening reactions.

stereoselectivity of the ring-opening reaction of 2,3-epoxides can be influenced effectively by the modification of the reaction conditions and, in some cases, the diequatorial 2α,3β derivatives could be obtained with good to excellent selectivity.

RESULTS

Based on the previous results of ring opening of steroidal epoxides catalyzed by ILs,[31] [bmim][BF_4] ([bmim]: 1-butyl-3-methylimidazolium) was chosen as the reaction medium and catalyst during the synthesis of halohydrins. In contrast to the IL with PF_6^- anion, no decomposition and HF formation had been observed in the case of [bmim][BF_4] under very similar conditions.[32] Accordingly, 2β,3β-epoxy-5α-androstan-17-one (**1**, Figure 4) and its 2α,3α-isomer (**2**) were reacted with

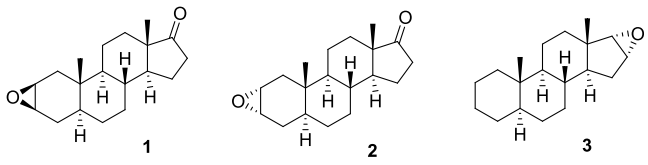

Figure 4. Steroidal substrates used during the ring-opening reactions.

various halide sources under different reaction conditions. As a comparison, a similar reaction of 16α,17α-epoxy-5α-androstane (**3**) was also investigated.

Ring Opening of 2β,3β-Epoxy-5α-androstan-17-one (1). Ring opening of 2β,3β-epoxy-5α-androstan-17-one (**1**) in the presence of $AlCl_3$ (Table 1, entry 1) or TMSCl (entry 4) as the halogen source took place smoothly at room temperature in [bmim][BF_4]. The application of the latter reagent led directly to the chlorohydrin similarly to the reaction of simple

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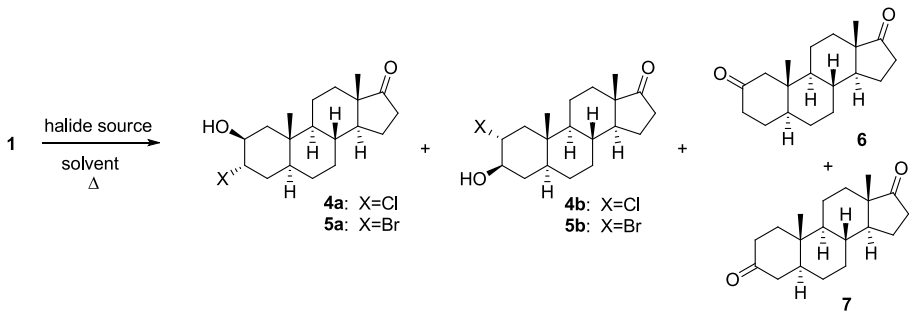
ACS Omega 2021, 6, 26846−26856

Table 1. Ring Opening of 2β,3β-Epoxy-5α-androstan-17-one (1)[a]

							selectivity [%][b]		
entry	halide source	1/halide source ratio	solvent	r. temp. [°C]	r. time [h]	conv. [%][b]	4a or 5a	4b or 5b	6 + 7
1	$AlCl_3$	1/1	[bmim][BF_4]	25	24	100	96	4	
2[c]	$AlCl_3$	1/1	[bmim][BF_4]	25	24	95	95	5	
3[d]	$AlCl_3$	1/1	[bmim][BF_4]	25	24	95	96	4	
4	TMSCl	1/1	[bmim][BF_4]	25	24	98	97	3	
5[c]	TMSCl	1/1	[bmim][BF_4]	25	24	95	96	4	
6[d]	TMSCl	1/1	[bmim][BF_4]	25	24	94	96	4	
7	LiCl	1/10	THF[e]	25	168	100	94	6	
8	LiCl	1/6	[bmim][BF_4]	100	24	100	89	11	
9	LiCl	1/2	[bmim][BF_4]	100	24	100	82	18	
10	LiCl	1/2	[bmim][BF_4]	100	10	100	89	11	
11	LiCl	1/2	[bmim][BF_4]	100	48	100	66	34	
12	LiCl	1/2	[bmim][BF_4]	60	24	100	96	4	
13	LiCl	1/1	[bmim][BF_4]	100	24	82	40	60	
14	LiCl	1/1	[bmim][BF_4]	120	24	100	5	95	
15[c]	LiCl	1/1	[bmim][BF_4]	120	24	100	5	95	
16[d]	LiCl	1/1	[bmim][BF_4]	120	24	100	5	95	
17	LiCl	1/2	[Hmim][BF_4]	100	24	100	83	17	
18	LiCl	1/2	[emim][PF_6]	100	24	45	100		
19	LiBr	1/10	THF[e]	25	168	100	96	4	
20	LiBr	1/1	[bmim][BF_4]	100	24	100	2	64	34
21[c]	LiBr	1/1	[bmim][BF_4]	100	24	100	2	69	39
22[d]	LiBr	1/1	[bmim][BF_4]	100	24	100	1	66	33
23	LiBr	1/1	[bmim][BF_4]	80	24	93	8	92	
24	LiBr	1/1	[bmim][BF_4]	120	24	100	4	46	50
25			[bmim]Br	100	24	100			62 (6) + 38 (7)[f]

[a]Reaction conditions: 0.2 mmol **1** in 600 mg ionic liquid. [b]Determined by ^{1}H NMR. [c]First reuse of the ionic liquid. [d]Second reuse of the ionic liquid. [e]Acetic acid catalyst (0.3 mmol) was added. [f]Ratio of **6** and **7** was determined by GC.

Scheme 1. Ring Opening of 2β,3β-Epoxy-5α-androstan-17-one (1)



epoxides.[28a] No formation of the corresponding TMS ether could be detected probably as a result of a rapid deprotection in the presence of the ionic liquid catalyst[33] and traces of water. The reactions led to the formation of the awaited diaxial 3α-chloro-2β-hydroxy derivative (Scheme 1, **4a**) as the main product with 96 and 97% selectivity, respectively. That means that ring opening occurs by the attack of the halide in position C-3 resulting in a more stable chair-like conformation of ring A in the transition state with a nearly linear disposition of the partial bonds (see also Discussion).

After the extraction of the products by diethyl ether, the IL could be reused by adding fresh reagents (steroidal substrate and halide source) with only a small loss of activity (entries 2, 3 and 5, 6).

Similarly excellent conversion and selectivity (entry 7) could be achieved with LiCl as the halide source in THF using acetic acid as the catalyst with a long reaction time based on the procedure reported by Anderson.[22a] Although no reaction could be observed at room temperature in [bmim][BF_4], complete conversion of the substrate was achieved at 100 °C with a selectivity of 89% toward compound **4a** in the presence of a sixfold excess of the halide reagent (entry 8). Interestingly, a decrease in the excess of LiCl resulted in a somewhat lower diaxial (**4a**)/diequatorial (**4b**) ratio (entry 9). The selectivity could even be reversed, obtaining the 2α-chloro-3β-hydroxy isomer (**4b**) as the main product using an equimolar amount of the halide source (entry 13). Based on these observations, a more detailed investigation of the effects of the reaction conditions was carried out. The selectivity of the reaction was found to depend not only on the LiCl/substrate ratio but also on the reaction time (entries 9−11). A total conversion of the substrate could be achieved already in 10 h at 100 °C (entry 10). A prolonged reaction resulted in some increase in the ratio of the more stable diequatorial product **4b** (entries 9 and 11), which suggests a reversible reaction under the present conditions.

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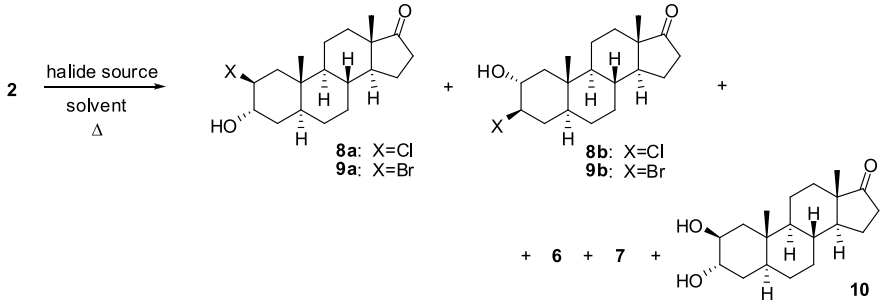
Table 2. Ring Opening of 2α,3α-Epoxy-5α-androstan-17-one (2)[a]

							selectivity [%][b,c]			
entry	halide source	2/halide source ratio	solvent	r. temp. [°C]	r. time [h]	conv. [%][b]	8a or 9a	8b or 9b	6	7
1	$AlCl_3$	1/1	[bmim][BF_4]	25	24	93	95	5		
2[d]	$AlCl_3$	1/1	[bmim][BF_4]	25	24	94	94	6		
3[e]	$AlCl_3$	1/1	[bmim][BF_4]	25	24	94	97	3		
4	$AlCl_3$	2/1	[bmim][BF_4]	100	30	100	76	24		
5	TMSCl	1/1	[bmim][BF_4]	25	24	58	95	5		
6	LiCl	1/6	[bmim][BF_4]	100	30	100	62	38		
7	LiCl	1/2	[bmim][BF_4]	100	30	100	55	45		
8	LiCl	1/2	[bmim][BF_4]	100	10	100	79	21		
9	LiCl	1/1	[bmim][BF_4]	100	30	100	25	75		
10	LiCl	1/1	[bmim][BF_4]	80	30	81	88	12		
11	LiCl	1/1	[bmim][BF_4]	120	30	100	4	96		
12[d]	LiCl	1/1	[bmim][BF_4]	120	30	100	6	94		
13[e]	LiCl	1/1	[bmim][BF_4]	120	30	100	4	96		
14	LiCl	1/10	THF[f]	25	168	59	95	5		
15	LiCl	1/1	dioxane[f]	100	30	75	95	5		
16	LiCl	1/1	[bmim][BF_4][f]	100	30	100	37	63		
17	LiBr	1/1	[bmim][BF_4]	100	30	100[g]			98	2
18	LiBr	1/2	[bmim][BF_4]	100	30	100[g]			91	9
19[d]	LiBr	1/2	[bmim][BF_4]	100	30	100[g]			89	11
20[e]	LiBr	1/2	[bmim][BF_4]	100	30	100[g]			82	18
21	LiBr	1/6	[bmim][BF_4]	100	30	100[g]			76	24
22			[bmim]Br	100	24	100[g]			53	47
23			TBAB	100	24	100[g]			49	51
24	NaI	1/1	[bmim][BF_4]	100	30	82[g]			87	13
25	NaI	1/2	[bmim][BF_4]	100	30	91[g]			76	24
26[d]	NaI	1/2	[bmim][BF_4]	100	30	99[g]			64	36
27[e]	NaI	1/2	[bmim][BF_4]	100	30	100[g]			58	42
28	NaI	1/6	[bmim][BF_4]	100	30	100[g]			17	93
29	$FeBr_3$	1/1	[bmim][BF_4]	100	30	100		43[h]		
30	LiBr	1/10	THF[f]	25	168	95	92	8		

[a]Reaction conditions: 0.2 mmol **2** in 600 mg ionic liquid. [b]Determined by ^{1}H NMR. [c]Ratio of **6** and **7** was determined by GC. [d]First reuse of the ionic liquid. [e]Second reuse of the ionic liquid. [f]Acetic acid catalyst (0.3 mmol) was added. [g]Determined by GC. [h]Other product: 2β,3α-dihydroxy-5α-androstan-17-one (**10**) (57%).

Scheme 2. Ring Opening of 2α,3α-Epoxy-5α-androstan-17-one (2)



Moreover, an increase in the amount of the product **4b** was observed when the ring opening was carried out at higher temperatures (compare entries 9 and 12, or 13 and 14). This isomer could even be obtained with excellent selectivity at 120 °C (entry 14). The recyclability of the IL catalyst/solvent was also proved under the optimized conditions (entries 15 and 16). At a lower temperature, the usual diaxial derivative **4a** could be prepared in good yield (entry 12).

The possibility of the application of other ILs was also investigated. Similar results were obtained in ILs with the [BF_4] anion (compare entries 9 and 17, [Hmim]: 1-methylimidazolium), while [emim][PF_6] ([emim]: 1-ethyl-3-methylimidazolium) showed lower activity but better selectivity toward the diaxial product **4a** (entry 18).

The usual diaxial product (**5a**) was formed with excellent selectivity from epoxide **1** and LiBr in the reaction catalyzed by acetic acid (entry 19).[22a] In accordance with the previous results, the other isomer, *i.e.*, the diequatorial derivative **5b**, could be produced in good yield by the use of the IL [bmim][BF_4] (entries 20−23). At the same time, the formation of two side products, ketones **6** and **7**, was observed probably via HBr elimination from **5a** and **5b**. The latter reaction was especially marked at a higher temperature (entry 24), while no diones (**6**, **7**) could be detected in the reaction

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ACS Omega 2021, 6, 26846−26856

mixture obtained at 80 °C (entry 23). The recyclability of the IL was also proved in three successive runs (entries 20−22). It should be mentioned that the application of an IL with bromide anion ([bmim][Br]) as the reagent and catalyst led to the exclusive formation of diones **6** and **7** (entry 25).

Ring Opening of 2α,3α-Epoxy-5α-androstan-17-one (2). A very similar behavior was observed upon reacting the isomeric 2α,3α-epoxy-5α-androstan-17-one (**2**) with various halide sources under different conditions (Table 2, Scheme 2). The application of $AlCl_3$ (entry 1) or TMSCl reagents (entry 5) resulted in the formation of the diaxial isomer **8a** with excellent selectivity, although the reactivity of the 2α,3α-epoxide (**2**) was a bit lower than that of the 2β,3β-derivative **1**. The recyclability of the IL was proved in the reaction of $AlCl_3$ in three successive runs (entries 1−3). Similarly to the ring opening of steroid **1** with LiCl, an increase in the temperature and the substrate/halide ratio led to an increase in the amount of the diequatorial product **8b** even in the reaction with $AlCl_3$ (entry 4). In the presence of LiCl, the same effect of the changes in the reaction conditions was observed: the use of an equimolar amount of the halide source, a higher reaction temperature, and a longer reaction time led to an increase in the content of the steroid **8b** (entries 6−13). It should be mentioned that a similar change in the conditions of the acetic-acid-catalyzed version of the reaction did not lead to an altered selectivity (entries 14 and 15).

The reaction was repeated under the optimized conditions (entry 11) on a larger scale (2 mmol), and product **8b** could be isolated in 90% yield in the first cycle and in 91% yield when the ionic liquid was recycled.

A 600 mg portion of the IL [bmim][BF_4] applied as the solvent in a reaction of substrate **2** (resulting in total conversion and producing **8b** with 97% selectivity at 120 °C in 30 h) was used to convert substrate **1** into ring opening products. The reaction resulted in the total conversion of epoxide **1** and produced halohydrins **4b**/**4a** with a ratio of 88/12 at 110 °C in 24 h.

The detrimental effect of the presence of a Brønsted acid to the selectivity toward the 3β-chloro-2α-hydroxy derivative **8b** is shown by the change in the ratio of products when acetic acid was added to the [bmim][BF_4]-catalyzed system (compare entries 16 and 9). The recyclability of the ionic liquid was proved under the optimized conditions to produce steroid **8b** with excellent selectivity (entries 12 and 13).

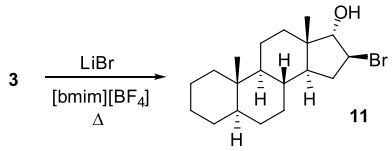
The ring opening products of epoxide **2** obtained from bromide-containing reagents seemed to be more prone to HBr elimination than those of the 2β,3β-epoxide **1**. No bromohydrins were present in the reaction mixtures obtained with LiBr in [bmim][BF_4], or with [bmim]Br or TBAB (tetrabutylammonium bromide) (entries 17−23). The only products were diones **6** and **7** that were formed in different ratios depending on the reaction conditions. The application of an equimolar amount of LiBr led to the almost exclusive formation of dione **6** (entry 17). As the 3-one derivative **7** is the elimination product of the diaxial halohydrin **9a**, while dione **6** can be formed from the diequatorial isomer **9b**, it can be concluded that the formation of dione **6** is the result of an initial diequatorial ring opening followed by HBr elimination. A noticeable and increasing amount of dione **7** was present in reaction mixtures with the rise of the LiBr/steroid ratio (entries 18 and 21). Also, the reuse of the IL of the reaction mixture with an excess of LiBr (entries 18−20) resulted in a similar change. As unreacted LiBr remained in the IL phase after the extraction of the steroid product with diethyl ether, the recycling of the IL and addition of fresh reagents led to an accumulation of the salt. That means that a higher halide ratio again resulted in an increased formation of the diaxial product and, consequently, a higher **7**/**6** ratio. Accordingly, diones **6** and **7** were formed in almost equal amounts when [bmim]Br (entry 22) or TBAB (entry 23) was used as the solvent and catalyst, ensuring a high excess of halide ions in the reaction mixtures. Similar conclusions can be drawn from experiments carried out in the presence of NaI instead of LiBr.

The diequatorial derivative **9b** could be obtained in moderate yield using $FeBr_3$ as the halide source. In this reaction, the main product was 2β,3α-dihydroxy-5α-androstan-17-one (**10**) formed via ring opening with water as the nucleophile. Due to the highly hygroscopic nature of the halide salt, water contamination of the reaction mixture could not be avoided.

It should be mentioned that the usual diaxial product **9a** was produced with excellent selectivity in the usual acid-catalyzed reaction using acetic acid as the catalyst in THF (entry 30).

Ring Opening of 16α,17α-Epoxy-5α-androstane (3). The ionic liquid [bmim][BF_4] was also found to be a recyclable solvent/catalyst in the ring opening of the 16α,17α-epoxide **3** with the LiBr reagent (Scheme 3). Exclusive

Scheme 3. Ring Opening of 16α,17α-Epoxy-5α-androstane (3)



formation of the awaited 16β-bromo-17α-hydroxy-5α-androstane (**11**) and total conversion of the starting material were observed at 100 °C in 24 h with a steroid/reagent ratio of 1/1. The selectivity was identical with that of the reaction of the same substrate with NaN_3 under acid-catalyzed conditions.[34] The ionic liquid was reused twice, resulting in 99% conversion and total selectivity toward product **11** in both cases. It should be mentioned that no Wagner−Meerwein rearrangement products could be detected here. Such rearrangements leading to different derivatives had been reported to take place either in the presence of an acid[35] or even in ionic liquids in the absence of a nucleophilic reagent.[32]

Determination of the Structures of the Products. Although some of the products described above are known compounds (**4a**,[9] **4b**,[36] **5a**,[9] **8a**,[37] **9a**,[37] and **11**[38]), no detailed structural data are reported with the exception of **4b**, for which some ^{1}H NMR signals are available.[36] The diaxial ring opening products of 2,3-epoxides (**4a**, **8a**, and **9a**) and the 16-bromo derivative **11** had been prepared by the reaction of the corresponding epoxides and hydrogen halides, with the exception of the 3α-bromo compound **5a** that had been produced from the 2-ene with *N*-bromosuccinimide and perchloric acid.[9] To the best of our knowledge, the only known diequatorial product is compound **4b**, prepared by the separation of an epimeric mixture obtained by the reduction of the 2α-chloro-3-one.[36]

The structures of the products were proved unequivocally with the help of HRMS and NMR (^{1}H and ^{13}C NMR, NOESY, zTOCSY, 2D gHSQCAD, and 2D gHMBCAD)

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measurements. The molecular masses of the products corresponded well to the assumed structures in all cases. (The methodology used for the allocation of the positions of the X═Cl/Br and OH groups, assignment of signals 2-H and 3-H, and determination of the α/β configuration of these protons is described in detail in the Supporting Information.)

DISCUSSION

Ring opening of 2,3-epoxy steroids usually results in the formation of products with diaxial functional groups at C-2 and C-3 (Figure 2). This can be explained by the fact that, during diaxial ring opening, the transition state adopts a more stable chair-like conformation of ring A with a nearly linear nature of the partial bonds. Moreover, in this transition state, the reagent is in the same plane as the epoxide ring. In contrast, the thermodynamically more stable diequatorial product would be formed via a less stable boat-like transition state.[39] That means that the ring opening reactions of steroidal substrates reported before led to the products via kinetic control. In exceptions to this rule, altered stereoselectivity can be explained by the presence of some polar functional groups close to the epoxide ring. For example, neighboring hydroxyl groups may modify the stereochemical outcome of the reaction due to competition between polar and steric effects that leads to the destabilization of the diaxial transition state.[40] As another example, the formation of a diequatorial chlorohydrin from the 23α,24-epoxy derivative of tigogenin acetate was supposed to be the result of the initial coordination of the reagent $TiCl_4$ to the pyranose oxygen in the epoxy-pyranose moiety followed by an intramolecular transfer of chloride from the titanium atom to C-24.[41]

In the present case, there are no functional groups in the vicinity of the epoxide moiety that could alter the selectivity. The favored formation of diequatorial products at higher temperatures (Table 1, entries 13 and 14 and Table 2, entries 10 and 11) and longer reaction times (Table 1, entries 10 and 11 and Table 2, entries 7 and 8) might be explained by the operation of thermodynamic control in a reversible reaction. It should be emphasized that the halide ion seems to play a crucial role, as ring opening using amines[31a] or thiols[31b] as nucleophiles led to the exclusive formation of the usual diaxial products. Also, the isomerization of primarily formed halohydrins seems to be slow based on the catalytic results (see, e.g., Table 1, entries 9−11).

To clarify the possibility of such an isomerization, the products of the acetic-acid-catalyzed reaction (Table 1, entry 7 or 20) were heated in [bmim][BF_4] under different conditions (Table 3).

At 100 °C, a slow isomerization could be observed only in the presence of halide ions (compare entries 1 and 3). Although a more pronounced conversion of diaxial products to diequatorial derivatives was observed at higher temperatures, the selectivity obtained at 120 °C in the original reaction (Table 1, entry 14) could not be reached. The bromo-derivative **5a** was found to be more prone to isomerization probably due to the better leaving group character of bromide than chloride. As it was also observed in the catalytic experiments, both high temperature and the presence of bromide ions led to an increased amount of dione side products **6** and **7**. The results show that the transformation of the originally formed, less stable diaxial product to the more stable diequatorial derivative cannot be the main cause of the unusual selectivity of the reaction.

Table 3. Isomerization Experiments[a]

	composition of the starting material				composition of the product mixture[b]		
entry	**4a** or **5a**	**4b** or **5b**	reagent	r. temp. [°C]	**4a** or **5a**	**4b** or **5b**	**6** + **7**
1	94 (**4a**)	6 (**4b**)		100	93	7	
2	94 (**4a**)	6 (**4b**)		120	62	38	
3	94 (**4a**)	6 (**4b**)	LiCl	100	86	14	
4	96 (**5a**)	4 (**5b**)		120	8	71	21
5	96 (**5a**)	4 (**5b**)	LiBr	120	5	52	43

[a]Reaction conditions: 0.1 mmol isomeric mixture and 0.1 mmol halide source as indicated in 300 mg of [bmim][BF_4], 20 h. [b]Determined by NMR.

It should be emphasized that reaction conditions that were found to increase the ratio of diequatorial product in [bmim][BF_4] (equimolar amount of halide source and higher temperature) did not lead to a change in the selectivity of the acid-catalyzed reaction in ether solvents (Table 2, entries 14 and 15). This implies that the ionic liquid plays a crucial role in the unusual ring-opening reaction.

To clarify the effect of the imidazolium cation, free energy differences of different transition states of ring opening with a chloride ion were calculated by the long-range corrected CAM-B3LYP density functional method using 2,3α-epoxy-10β-methyl-*trans*-decalin instead of the steroidal substrate and a 1,3-dimethylimidazolium cation instead of [bmim]$^+$ to simplify the system. In the absence of the imidazolium ion, the energy difference between the less stable transition state with the boat-like conformation, bearing the oxygen in position 2α (TS1, Figure 5), and the more stable 3α (TS2) derivative in chair conformation is 14.6 kJ/mol in THF. When the epoxide ring is protonated (acid-catalyzed ring opening), this difference decreases to 2.9 kJ/mol. In the presence of the imidazolium ion, the formation of a H-bond between the 2-H of the cation and the oxygen atom on the decalin ring could be detected. Besides, the energy difference between the two transition states bearing the coordinated imidazolium ion and using [bmim][BF_4] as the solvent is reduced to 1.7 kJ/mol (Figure 6). In the latter two cases, the free energy calculations were also evaluated at 100 °C, giving free energy differences of 3.0 and −0.9 kJ/mol in the presence of a proton and the imidazolium cation, respectively. This shows that, in accordance with the experimental results (Table 2, entries 14 and 15), a raise in the temperature does not change the selectivity in the acid-catalyzed reaction. At the same time, by the coordination of the imidazolium cation, the pathway through TS1 becomes even more favorable at higher temperatures, which opens the path for the formation of the diequatorial product.

According to the catalytic experiments, the addition of a Brønsted acid led to a decrease in the ratio of the diequatorial product **8b** even in [bmim][BF_4] (Table 2, entry 16). This can be explained by the competition of the other pathway involving the usual ring opening via the protonation of the epoxide ring.

CONCLUSIONS

Imidazolium ionic liquids were shown to be efficient solvents/catalysts in the ring opening of steroidal epoxides using various halides as reagents. According to the Fürst−Plattner rule, such reactions of cyclic epoxides lead to the formation of diaxial

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ACS Omega 2021, 6, 26846−26856

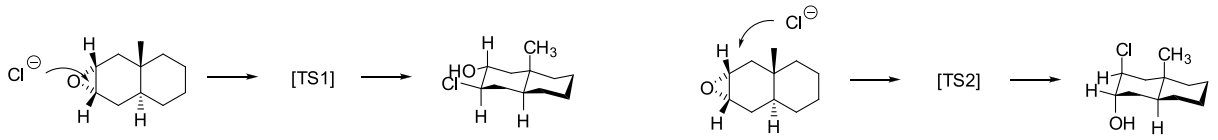

Figure 5. Ring opening of 2,3α-epoxy-10β-methyl-*trans*-decalin with chloride anion leading to diequatorial (left) and diaxial (right) products.

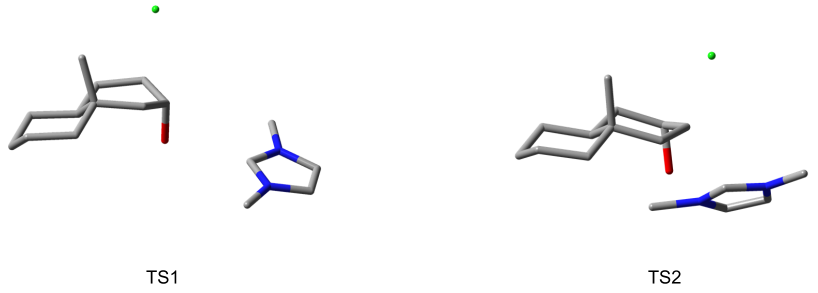

Figure 6. Transition states of the ring-opening reaction of 2,3α-epoxy-10β-methyl-*trans*-decalin with chloride anion in the presence of dimethylimidazolium cation using CAM-B3LYP density functional with the 6-311++G** basis set in the [bmim][BF_4] solvent.

products via kinetic control. In contrast to acid-catalyzed reactions, in the present case, the selectivity could be changed between the awaited diaxial and the unusual diequatorial derivatives with 2,3-epoxides as substrates. The formation of the diequatorial product could be facilitated by the use of a higher temperature, longer reaction time, and lower halide/steroid ratio. The role of the ionic liquid could be explained based on quantum chemical calculations. The imidazolium cation was found to form a hydrogen bond with the O-substituent of the steroid skeleton, thus lowering the energy gap between the transition states leading to the isomers and facilitating the formation of the thermodynamically stable diequatorial derivative. Even a reversed stability order was obtained by calculating the energy differences at 100 °C.

At the same time, by a careful choice of conditions, not only the diequatorial but also the diaxial isomer could be produced with good selectivity in the ionic-liquid-catalyzed reaction. The recyclability of the ionic liquid was also demonstrated.

While smooth ring opening was observed in the presence of chloride ions, the reaction of 2α,3α-epoxy-5α-androstan-17-one (**2**) with bromide and especially iodide salts was more problematic. In these cases, a preferred hydrogen halide elimination led to the formation of a mixture of 2,17- (**6**) and 3,17-diones (**7**). The ratio of the two products could be interpreted via the effect of the ionic liquid described above. It should be mentioned that the exclusive formation of the awaited 16β-bromo-17α-hydroxy-5α-androstane (**11**) was observed in the reaction of 16α,17α-epoxy-5α-androstane (**3**) and LiBr.

EXPERIMENTAL SECTION

NMR spectra were recorded at 800 MHz (^{1}H) and 201 MHz (^{13}C) on a Varian VNMRS 800 MHz instrument (equipped with a ^{1}H{^{13}C,^{15}N} Triple Resonance ^{13}C Enhanced Salt Tolerant Cold Probe), at 500 MHz (^{1}H) and 125.75 MHz (^{13}C) on a Varian VNMRS 500 MHz instrument (equipped with a ^{1}H{^{13}C,^{15}N} 5 mm PFG Triple Resonance ^{13}C Enhanced Cold Probe), or at 400 MHz (^{1}H) and 100.5 MHz (^{13}C) on a Bruker Avance II 400 MHz NMR system in $CDCl_3$ or DMSO-d_6. ^{1}H and ^{13}C NMR spectral assignments were in each case supported by 2D gHSQCAD, gHMBCAD, and/or zTOCSY spectra. For each molecule, the stereochemistry was deduced with the additional aid of NOESY spectra.

The conversion and ratio of products in reaction mixtures obtained with metal chlorides were determined using ^{1}H NMR based on the integral ratio of 2-H (and/or 3-H) signals. Analysis of reaction mixtures obtained with metal bromides was performed by the combination of ^{1}H NMR and GC results. Due to a partial decomposition of bromohydrins to **6** or **7** under GC conditions, only samples lacking the former compounds (according to ^{1}H NMR) were analyzed by GC. The conversion and ratio of ring-opening products and diones (**6** + **7**) were determined by comparing the integral value of the 2-H (and/or 3-H) signals of epoxides and ring opening products and that of the multiplet at 2.34−2.47 ppm (one proton for bromohydrins and two protons for diones **6** and **7**).

Both low- and high-resolution MS measurements were performed using EI (electron impact) ionization (70 eV, 220 °C source temperature, Finnigan MAT 95XP) for compounds **4a**,**b**, **5a**,**b**, **8a**, **9b**, and **11**. HRMS of compounds **8b** and **9a** were obtained using a Waters Q-TOF Premier (Waters Corporation, Milford, MA, USA) mass spectrometer in positive electrospray ionization mode. IR (Perkin-Elmer Spectrum 100FT-IR) spectra were recorded in KBr pellets, the resolution was 4 cm^{-1}, and the scanning range was between 4000 and 400 cm^{-1}.

Products **4a**,[9] **4b**,[36] **5a**,[9] **8a**,[37] **9a**,[37] and **11**[38] are known compounds. The NMR spectra of side products **6**,[42] **7**,[43] and **10**[31a] corresponded well to literature data.

Theoretical calculations were performed with the Gaussian 09 software package.[44] Molecular geometries were optimized using the long-range corrected hybrid density functional CAM-B3LYP[45] and the standard 6-311++G** basis set. The optimizations were performed without any symmetry constraint. The initial guess transition state geometries were optimized with Opt = (TS, tight, CalcAll) keywords. The vibrational analysis yielded exactly one imaginary frequency for each transition state structure, verifying that the structure corresponds to a saddle point on the potential energy surface (PES). From the transition state geometries, intrinsic reaction coordinate (IRC) calculations were performed to confirm that the saddle point geometry connects the right minima on the PES. The Gibbs free energies were refined using the CPCM

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solvent model built in the Gaussian 09 suite (with tetrahydrofuran and [bmim][BF_4]). The [bmim][BF_4] solvent was modeled as described by Zhao *et al.*: using the experimentally observed ε = 11.4, solvent radius (4.201 Å), and ρ = 1.192 g cm^{-3}, the other parameters, which were not available for user input, were provided by isoquinoline.[46] For the graphical visualization, the *molden* software[47] and GaussView were used.

General Procedure for the Ionic Liquid Promoted Ring Opening. In a typical procedure, the steroidal epoxide (0.2 mmol), the metal halide (as indicated in the tables), and 600 mg of ionic liquid were placed under argon in a Schlenk tube equipped with a magnetic stirrer and a septum inlet. The reaction mixture was heated at 110 °C in an oil bath for 10−30 h. The mixture was extracted three times with 3 mL of diethyl ether. The combined ethereal extracts were analyzed by TLC and eventually by GC. Before GC measurements, the extracts were allowed to stand overnight to be sure that the GC samples contained no traces of the ionic liquid. After the removal of diethyl ether, the samples were analyzed by ^{1}H NMR. The products were purified by column chromatography (silica gel, ethyl acetate/*n*-hexane = 30/70 (compounds **4a**,**b**, **5a**,**b**, **8a**,**b**, and **9a**,**b**) or ethyl acetate/*n*-hexane = 5/70 (compound **11**)). Melting points were determined after chromatographic separation without recrystallization.

The residual diethyl ether was removed in vacuo from the ionic liquid phase, and the ionic liquid was reused without further purification.

Ring opening of epoxide **2** was carried out on a larger scale: 577 mg (2 mmol) of steroid **2**, 85 mg of LiCl (2 mmol), and 6 g of [bmim][BF_4] were placed in a flask equipped with a gas inlet, a septum inlet, and a balloon. The atmosphere was changed to argon, and the mixture was heated at 100 °C for 30 h. After that, it was extracted with 3 × 20 mL diethyl ether. The solvent was removed in vacuo, and the product was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane = 30/70) to produce 587 mg of **8b** (90%).

*3α-Chloro-2β-hydroxy-5α-androstan-17-one (**4a**).* ^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.19 (d, J = 3.5 Hz, 1H, OH_β-2); 4.17−4.19 (m, 1H, H_β-3); 3.884−3.87 (m, 1H, H_α-2); 2.37 (dd, J = 19.1 Hz, 8.9 Hz, 1H, H_β-16); 2.07 (ddd, J = 14.7 Hz, 12.8 Hz, 3.1 Hz 1H, H_β-4); 1.98 (dt, J = 19.1 Hz, 9.0 Hz, 1H, H_α-16); 1.81−1.85 (m, 1H, H_α-15); 1.75 (dq, J = 12.8 Hz, 3.4 Hz, 1H, H_β-7); 1.64−1.66 (m, 1H, H_β-1); 1.63 (dt, J = 12.4 Hz, 3.4 Hz 1H, H_β-12); 1.59−1.60 (m, 1H, H_α-5); 1.56−1.58 (m, 1H, H_α-11); 1.52 (qd, J = 11.1 Hz, 3.4 Hz, 1H, H_β-8); 1.45 (tt, J = 12.6 Hz, 9.1 Hz, 1H, H_β-15); 1.39 (m, 1H, H_α-4); 1.38 (m, 1H, H_α-1); 1.30 (qd, J = 13.0 Hz, 4.1 Hz, 1H, H_β-6); 1.25 (m, 1H, H_α-14); 1.24 (m, 1H, H_α-6); 1.23 (m, 1H, H_β-11); 1.14 (td, J = 13.1 Hz, 4.0 Hz, 1H, H_α-12); 0.97 (m, 1H, H_α-7); 0.96 (s, 3H, H_3-19); 0.77 (s, 3H, H_3-18); 0.70 (ddd, J = 12.3 Hz, 10.6 Hz, 4.1 Hz 1H, H_α-9).

^{13}C{^{1}H} NMR (125.75 MHz, DMSO-d_6) δ: 219.7 (C-17); 70.0 (C-2); 62.1 (C-3); 54.6 (C-9); 50.5 (C-14); 47.1 (C-13); 39.1 (C-5); 38.1 (C-1); 35.6 (C-10); 35.3 (C-16); 33.9 (C-8) 31.3 (C-12); 31.1 (C-4); 30.4 (C-7); 27.1 (C-6); 21.3 (C-15); 19.7 (C-11); 14.1 (C-19); 13.5 (C-18).

IR (KBr (cm^{-1})): 3455; 3398; 2941; 2841; 1725; 1450; 1373; 1322; 1256; 1117; 1049; 1029; 965; 907; 838; 695.

HRMS (EI): $[M]^+$ m/z 324.1850, calculated value for $C_{19}H_{29}O_2Cl$: 324.1851 (delta: −0.25 ppm).

Isolated yield: 85% (55 mg, obtained with $AlCl_3$), white solid, mp: 197−199 °C.

*2α-Chloro-3β-hydroxy-5α-androstan-17-one (**4b**).* ^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.06 (d, J = 5.4 Hz, 1H, OH_β-3); 3.87 (ddd, J = 12.4 Hz, 9.7 Hz, 4.6 Hz, 1H, H_β-2); 3.33 (m, 1H, H_α-3); 2.37 (dd, J = 19.1 Hz, 8.8 Hz, 1H, H_β-16); 2.10 (dd, J = 12.7 Hz, 4.6 Hz, 1H, H_β-1); 1.99 (dt, J = 19.1 Hz, 9.0 Hz, 1H, H_α-16); 1.83 (m, 1H, H_α-15); 1.72 (dq, J = 13.0 Hz, 3.1 Hz, 1H, H_β-7); 1.63 (dt, J = 12.5 Hz, 3.2 Hz 1H, H_β-12); 1.58 (m, 1H, H_α-4); 1.55 (m, 1H, H_α-11); 1.47 (m, 1H, H_β-8); 1.45 (m, 1H, H_β-15); 1.31 (m, 1H, H_α-6); 1.29 (m, 1H, H_α-1); 1.28 (m, 1H, H_β-4); 1.27 (m, 1H, H_β-11); 1.24 (m, 1H, H_α-5); 1.23 (m, 1H, H_α-14); 1.19 (m, 1H, H_β-6); 1.14 (td, J = 12.7 Hz, 3.9 Hz, 1H, H_α-12); 0.93 (qd, J = 12.4 Hz, 4.1 Hz, 1H, H_α-7); 0.81 (s, 3H, H_3−19); 0.76 (m, 1H, H_α-9); 0.77 (s, 3H, H_3-18).

^{13}C{^{1}H} NMR (125.75 MHz, DMSO-d_6) δ: 219.7 (C-17); 74.4 (C-3); 65.2 (C-2); 53.4 (C-9); 50.5 (C-14); 47.6 (C-1); 47.1 (C-13); 43.9 (C-5); 38.0 (C-10); 37.6 (C-4); 35.3 (C-16); 33.9 (C-8); 31.3 (C-12); 30.2 (C-7); 27. (C-6); 21.4 (C-15); 20.2 (C-11); 13.5 (C-18); 12.4 (C-19).

IR (KBr (cm^{-1})): 3486; 2936; 2861; 1734; 1453; 1360; 1233; 1075; 956; 836, 760; 616.

HRMS (EI): $[M]^+$ m/z 324.1850, calculated value for $C_{19}H_{29}O_2Cl$: 324.1851 (delta: −0.10 ppm).

Isolated yield: 57% (37 mg, obtained with 2 eq. LiCl), white solid, mp: 203−205°.

*3α-Bromo-2β-hydroxy-5α-androstan-17-one (**5a**).* ^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.25 (d, J = 3.5 Hz, 0.6 Hz, 1H, OH_β-2); 4.35−4.37 (br s, 1H, H_β-3); 3.96−3.98 (br s, 1H, H_α-2); 2.37 (dd, J = 19.2 Hz, 8.8 Hz, 1H, H_β-16); 2.10 (ddd, J = 15.3 Hz, 12.7 Hz, 3.2 Hz 1H, H_β-4); 1.99 (dt, J = 19.2 Hz, 9.0 Hz, 1H, H_α-16); 1.80−1.85 (m, 1H, H_α-15); 1.75 (dq, J = 12.7 Hz, 3.5 Hz, 1H, H_β-7); 1.67 (m, 1H, H_β-1); 1.64 (m, 1H, H_α-5); 1.63 (m, 1H, H_β-12); 1.58 (m, 1H, H_α-11); 1.53 (m, 1H, H_β-8); 1.49 (m, 1H, H_α-1); 1.47 (m, 1H, H_α-4); 1.45 (m, 1H, H_β-15); 1.31 (qd, J = 13.0 Hz, 3.7 Hz, 1H, H_β-6); 1.27 (m, 1H, H_α-14); 1.25 (m, 1H, H_α-6); 1.23 (m, 1H, H_β-11); 1.15 (td, J = 12.4 Hz, 3.4 Hz, 1H, H_α-12); 0.99 (qd, J = 12.5 Hz, 4.6 Hz 1H, H_α-7); 0.96 (s, 3H, H_3-19); 0.77 (s, 3H, H_3-18); 0.71 (ddd, J = 11.9 Hz, 10.6 Hz, 3.8 Hz, 1H, H_α-9).

^{13}C{^{1}H} NMR (125.75 MHz, DMSO-d_6) δ: 219.7 (C-17); 70.3 (C-2); 57.0 (C-3); 54.6 (C-9); 50.5 (C-14); 47.1 (C-13); 40.2 (C-5); 38.0 (C-1); 35.7 (C-10); 35.3 (C-16); 33.8 (C-8) 31.5 (C-4); 31.3 (C-12); 30.4 (C-7); 27.0 (C-6); 21.3 (C-15); 19.7 (C-11); 14.3 (C-19); 13.5 (C-18).

IR (KBr (cm^{-1})):3506; 3403; 2915; 2840; 1725; 1445; 1400; 1283; 1255; 1027; 904; 654.

HRMS (EI): $[M]^+$ m/z 368.1345, calculated value for $C_{19}H_{29}O_2Br$: 368.1345 (delta: −0.20 ppm).

Isolated yield: 81% (60 mg, obtained with 10 eq. LiBr in THF/AcOH), white solid, mp: 185−187 °C.

*2α-Bromo-3β-hydroxy-5α-androstan-17-one (**5b**) (Determined from a Mixture Containing 18% 5α-Androstan-2,17-dione).* ^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.07 (d, J = 6.1 Hz, 1H, OH_β-3); 4.06 (ddd, J = 12.7 Hz, 9.9 Hz, 4.6 Hz, 1H, H_β-2); 3.43 (tt, J = 10.3, Hz, 5.5 Hz, 1H, H_α-3); 2.38 (dd, J = 19.1 Hz, 8.4 Hz, 1H, H_β-16); 2.23 (dd, J = 12.7 Hz, 4.7 Hz, 1H, H_β-1); 1.99 (dt, J = 18.8 Hz, 8.4 Hz, 1H, H_α-16); 1.83 (m, 1H, H_α-15); 1.72 (dq, J = 12.4 Hz, 2.9 Hz, 1H, H_β-7); 1.63 (m, 1H, H_β-12); 1.60 (m, 1H, H_α-4); 1.54 (m, 1H, H_α-11); 1.50 (m, 1H, H_α-1); 1.46 (m, 2H, H_β-8, H_β-15); 1.33 (m, 1H, H_β-4); 1.30 (m, 1H, H_α-6); 1.26 (m, 1H, H_β-11); 1.25 (m, 1H, H_α-5); 1.23 (m, 1H, H_α-14); 1.20 (m, 1H, H_β-6); 1.14 (td, J = 13.0 Hz, 3.9 Hz, 1H, H_α-12); 0.93 (qd, J = 12.4 Hz, 4.0 Hz 1H, H_α-

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7); 0.81 (s, 3H, H_3-19); 0.77 (s, 3H, H_3-18); 0.76 (m, 1H, H_α-9).

$^{13}C\{^1H\}$ NMR (125.75 MHz, DMSO-d_6) δ: 219.8 (C-17); 74.8 (C-3); 59.9 (C-2); 53.5 (C-9); 50.7 (C-14); 48.9 (C-1); 47.2 (C-13); 44.1 (C-5); 39.0 (C-10); 38.3 (C-4); 35.4 (C-16); 34.1 (C-8); 31.4 (C-12); 30.3 (C-7); 27.4 (C-6); 21.5 (C-15); 20.3 (C-11); 13.6 (C-18); 12.3 (C-19).

HRMS (EI): $[M]^+$ m/z 368.1342, calculated value for $C_{19}H_{29}O_2Br$: 368.1345 (delta: −0.8 ppm).

Isolated yield: 65% (48 mg, obtained with 1 eq. LiBr at 80 °C), white solid.

*2β-Chloro-3α-hydroxy-5α-androstan-17-one (**8a**) (Determined from a Mixture Containing 6% **8b** Isomer).* ^1H NMR (400 MHz, $CDCl_3$) δ: 4.12−4.16 (m, 1H, 3-H); 4.07−4.10 (m, 1H, 2-H) 2.43 (ddd, J = 19.3 Hz, 8.9 Hz, 0.8 Hz, 1H, 16-H_a); 0.71−2.12 (m, 20H, ring protons, 3-OH); 1.07 (s, 3H, 19-H_3); 0.85 (s, 3H, 18-H_3).

$^{13}C\{^1H\}$ NMR (100.5 MHz, $CDCl_3$) δ: 221.3; 71.2; 59.7; 55.6; 51.5; 48.0; 40.5; 38.7; 36.5; 35.9; 34.6; 31.7; 30.9; 30.8; 27.9; 21.9; 20.3; 14.9; 14.04.

IR (KBr (cm^{-1})):3440; 2938; 2859; 1716; 1455; 1420; 1369; 1337; 1254; 1114; 1082; 1054; 1010; 871; 759; 685; 603.

EI-MS (m/z /rel. intensity%): 324 (M^+)/100; 309/16; 306/14; 291/13; 288/14; 280/33; 267/15; 253/20; 215/13; 199/16; 161/10; 147/25; 121/18; 108/48; 105/27; 97/25; 95/20; 93/28; 91/23; 81/25; 79/24; 67/26; 55/19; 41/21.

Isolated yield: 70% (45 mg, obtained with 1 eq. $AlCl_3$), white solid.

*3β-Chloro-2α-hydroxy-5α-androstan-17-one (**8b**).* ^1H NMR (400 MHz, $CDCl_3$) δ: 3.69−3.77 (m, 2H, H_β-2, H_α-3); 2.44 (s, 1H, OH); 2.43 (dd, J = 19.3 Hz, 9.0 Hz, 1.2 Hz, 1H, H_β-16); 2.12 (dd, J = 12.7 Hz, 4.2 Hz, 1H, H_β-1); 2.06 (dt, J = 19.3 Hz, 9.1 Hz, 1H, H_α-16); 1.87−1.96 (m, 2H, H_α-15, H_α-4); 1.72−1.85 (m, 3H, H_β-7, H_β-12, H_β-4); 1.64−1.71 (m, 1H, H_α-11); 1.46−1.59 (m, 2H, H_β-8, H_β-15); 1.40−1.45 (m, 1H, H_α-6); 1.20−1.36 (m, 5H, H_β-11, H_α-14, H_β-6, H_α-12, H_α-5), 0.92−1.08 (m, 2H, H_α-1, H_α-7); 0.90 (s, 3H, H_3−19); 0.86 (s, 3H, H_3−18); 0.79 (ddd, J = 12.1 Hz, 10.6 Hz, 4.1 Hz, 1H, H_α-9).

$^{13}C\{^1H\}$ NMR (100.5 MHz, $CDCl_3$) δ: 221.0 (C-17); 72.8 (C-2); 67.6 (C-3); 54.4 (C-9); 51.4 (C-14); 47.9 (C-13); 46.6 (C-5); 45.5 (C-1); 37.9 (C-4); 37.5 (C-10); 35.9 (C-16); 34.5 (C-8); 31.6 (C-12); 30.7 (C-7); 27.5 (C-6); 21.9 (C-15); 20.7 (C-11); 14.0 (C-18); 13.6 (C-19).

IR (KBr (cm^{-1})): 3478; 2918; 2854; 1737; 1711; 1452; 1370; 1257; 1199; 1097; 1049; 1011; 929; 834; 747.

HRMS (ESI): $[M + H]^+$ m/z 325.1943, calculated value for $C_{19}H_{30}O_2Cl$: 325.1934 (delta: 2.8 ppm).

Isolated yield: 88% (57 mg, obtained with 1 eq. LiCl), white solid, mp: 168−171 °C.

*2β-Bromo-3α-hydroxy-5α-androstan-17-one (**9a**) (Determined from a Mixture Containing 6% **9b** Isomer).* ^1H NMR (400 MHz, $CDCl_3$) δ: 4.26−4.30 (m, 1H, 3-H); 4.20−4.24 (m, 1H, 2-H) 2.43 (ddd, J = 19.2 Hz, 8.8 Hz, 0.9 Hz, 1H, 16-H_a); 0.70−2.13 (m, 20H, ring protons, 3-OH); 1.11 (s, 3H, 19-H_3); 0.86 (s, 3H, 18-H_3).

$^{13}C\{^1H\}$ NMR (100.5 MHz, $CDCl_3$) δ: 221.3; 71.5; 55.8; 52.0; 51.5; 48.0; 41.0; 38.6; 36.9; 35.9; 34.5; 31.7; 31.1; 30.8; 27.8; 21.9; 20.3; 15.1; 14.0.

IR (KBr (cm^{-1})): 3458; 2937; 2850; 1720; 1451; 1255; 1210; 1188; 1054; 1027; 1008; 862; 660; 632.

HRMS (ESI): $[M + H]^+$ m/z 369.1419, calculated value for $C_{19}H_{30}O_2Br$: 369.1429 (delta: −2.7 ppm).

Isolated yield: 76% (56 mg, obtained with LiBr in THF), white solid.

*3β-Bromo-2α-hydroxy-5α-androstan-17-one (**9b**).* ^1H NMR (800 MHz, $CDCl_3$) δ: 3.90 (ddd, J = 12.2 Hz, 10.0 Hz, 5.2 Hz, 1H, H_β-2); 3.83 (ddd, J = 11.1, Hz, 10.0 Hz, 5.2 Hz, 1H, H_α-3); 2.44 (dd, J = 19.3 Hz, 8.9 Hz, 1.2 Hz, 1H, H_β-16); 2.15 (dd, J = 12.8 Hz, 4.8 Hz, 1H, H_β-1); 2.07 (dt, J = 19.3 Hz, 9.1 Hz, 1H, H_α-16); 2.01 (ddd, J = 13.4 Hz, 5.2 Hz, 3.1 Hz, 1H, H_α-4);1.91−1.94 (m, 2H, H_β-4, H_α-15); 1.79−1.82 (m, 2H, H_β-7, H_β-12); 1.65−1.68 (m, 1H, H_α-11); 1.52−1.54 (m, 1H, H_β-8); 1.48−1.51 (m, 1H, H_β-15); 1.41−1.44 (m, 1H, H_α-6); 1.32−1.34 (m, 2H, H_β-11); 1.23−1.30 (m, 5H, H_α-5, H_β-6, H_α-12, H_α-14, OH), 1.02−1.05 (m, 1H, H_α-1); 0.96−1.00 (m, 1H, H_α-7); 0.90 (s, 3H, H_3−19); 0.86 (s, 3H, H_3−18); 0.79 (ddd, J = 12.5 Hz, 10.6 Hz, 4.0 Hz, 1H, H_α-9) (determined from a mixture containing 6% **9a** isomer).

$^{13}C\{^1H\}$ NMR (100.5 MHz, $CDCl_3$) δ: 222.0 (C-17); 72.8 (C-2); 61.6 (C-3); 54.4 (C-9); 51.3 (C-14); 47.9 (C-5); 47.7 (C-13); 46.0 (C-1); 39.0 (C-4); 37.5 (C-10); 35.9 (C-16); 34.4 (C-8); 31.6 (C-12); 30.7 (C-7); 27.4 (C-6); 21.9 (C-15); 20.6 (C-11); 13.9 (C-18); 13.6 (C-19).

IR (KBr (cm^{-1})): 3473, 3384, 2919, 2852, 1737, 1709, 1453, 1370, 1259, 1182, 1091, 1048, 1011, 929, 831, 804, 703.

HRMS (EI): $[M]^+$ m/z 368.1345, calculated value for $C_{19}H_{29}O_2Br$: 368.1345 (delta: −0.25 ppm).

Isolated yield: 26% (19 mg, obtained with $FeBr_3$), white solid, mp: 181−183 °C.

*16β-Bromo-17α-hydroxy-5α-androstane (**11**).* ^1H NMR (400 MHz, $CDCl_3$) δ: 4.02 (d, J = 0.8 Hz, 1H, H-17); 3.93 (td, J = 7.9 Hz, 0.8 Hz, 1H, H-16); 2.44 (ddd, J = 14.2 Hz, 8.3 Hz, 6.0 Hz, 1H, H_a-15); 0.65−1.72 (m, 22H, ring protons, OH); 0.97 (s, 3H, H_3-18); 0.79 (s, 3H, H_3-19).

$^{13}C\{^1H\}$ NMR (100.5 MHz, $CDCl_3$) δ: 88.5; 54.4; 53.3; 50.4; 47.0; 45.3; 38.8; 38.7; 36.5; 35.4; 32.5; 31.9; 29.1; 29.0; 26.9; 22.3; 19.9; 18.4; 12.4.

IR (KBr (cm^{-1})): 3419; 2920; 2853; 1454; 1443; 1580; 1288; 1249; 1040; 780; 742.

HRMS (EI): $[M]^+$ m/z 354.1561, calculated value for $C_{19}H_{31}OBr$: 354.1553 (delta: 2.30 ppm).

Isolated yield: 90% (64 mg, obtained with LiBr), white solid, mp: 118−120 °C.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c02470.

FAIR data are available as Supporting Information for Publication and include NMR data and the primary NMR FID files for compounds **4a,b**, **5a,b**, **8a,b**, **9a,b**, and **11**; determination of the structures of the products; and computational details (PDF).

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Notes

The authors declare no competing financial interest.

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