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New synthesis of pentacyclic steroids by stereoselective epoxide ring opening

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ABSTRACT

A stereoselective synthesis of pentacyclic steroids has been achieved. Starting from commercially available cholic acid **1**, followed by asymmetric epoxidation and by stereoselective epoxide ring opening, employing nucleophilic species, the corresponding products were afforded in good yields. The compounds were being evaluated for their biological activity.

The classical approach to drug development from a known lead structure remains the systematic variation of substitution pattern and the alteration of stereochemical relationships. The efforts of various groups reported after the discovery of the first progesterone antagonist RU 486 (Mifepristone) can be viewed as a typical example.[1]

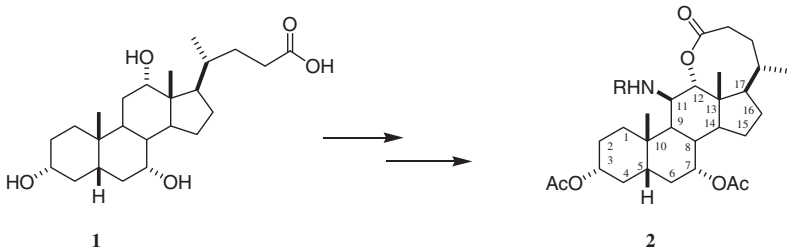
The modifications made in a biologically active compound can result in a very useful homologue eliciting a subtle biological difference from the patent substance. For example, the 11β-methyl homologue of ethinodiol diacetate is 10–25 times more progestational.[2] The direction of the change in the biological activities of a homologue is unpredictable. It could result in a more potent agonist, a more selective agonist or an antagonist.

The C-11 position of the steroid ring has a major effect on biological properties, such as corticoid activities. Recently, it was reported that 11-amino-12-hydroxy/keto steroids are potential inhibitors of HIV-1 protease.[3] Otherwise, there are many examples of pentacyclic steroidal derivatives of pharmacological and biological importance.[4] The incorporation of short carbon bridges spanning characteristic positions of the steroid backbone continues to be a popular stratagem in the search for new, biologically active steroid hormone analogues.

So, it would be interesting to combine both by introducing a new ring and a new function at the C-11 position of the steroidal skeleton, in order to obtain a new class of steroids.

We report herein the stereoselective synthesis of pentacyclic steroids **2** possessing an amino function at C-11, derived from readily available cholic acid **1** (Scheme 1).

The synthesis of aminolactones **2** is described in Scheme 2. Methyl 3,7-diacetoxycholate **3** was prepared according to a known procedure.[5] Treatment of **3** with a slight excess of mesyl chloride in the presence of pyridine gave a quantitative yield of methyl 3,7-diacetyl-12-mesyl cholate **4**. Dehydromesylation of **4** was done applying the conditions described by Chen.[6] Mesylate



1 2

Scheme 1. Aminolactones **2**.

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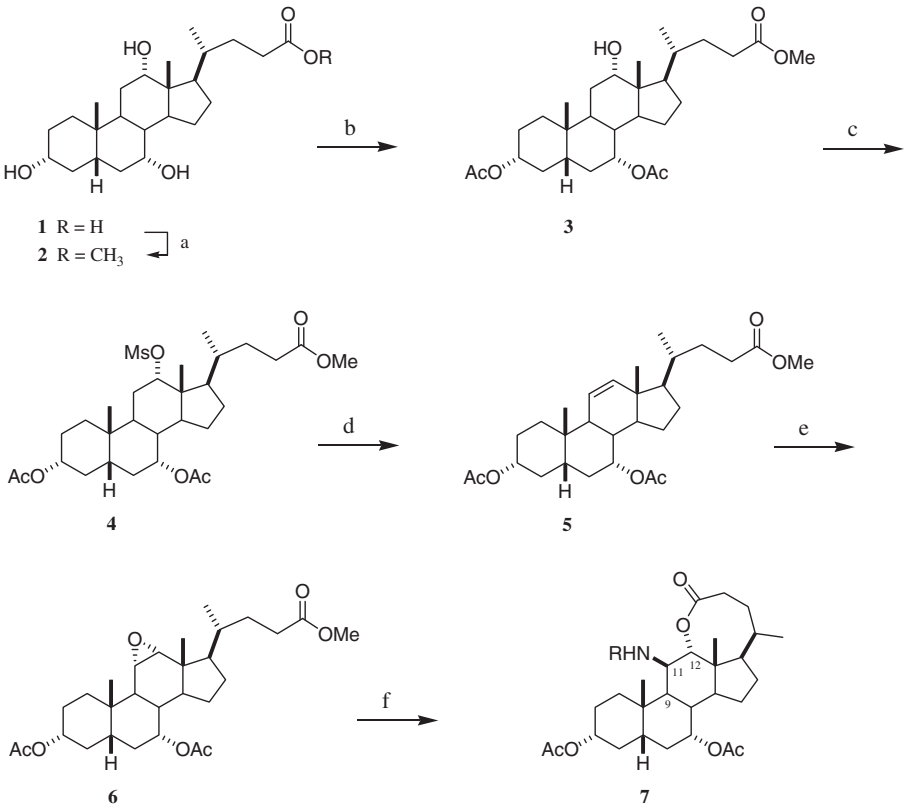


Scheme 2. Stereoselective synthesis of pentacyclic steroids from cholic acid. Reagents and conditions: (a) MeOH, PTSA, Δ; (b) Ac_2O, pyridine, DMAP; (c) MsCl,pyridine, 0 °C to rt, 24 h; (d) AcOK, HMPT, 100 °C, 48 h; (e) *m*-CPBA, CH_2Cl_2, rt, 24 h; (f) RNH_2, EtOH/toluene (1/1), Δ, 24 h.

4 was heated in hexamethylphosphoric triamide (HMPT) with an excess of potassium acetate at about 100 °C for two days. The desired methyl 3,7-diacetylchol-11-enate **5** was isolated in good yield (80%).

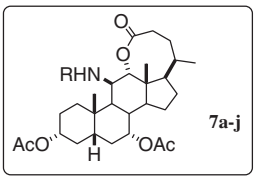
Next, an asymmetric epoxidation in the steroidal double bond (C_{11}=C_{12}) was performed to introduce the desired epoxide functional group in the steroidal nucleus, using *m*-CPBA as the oxidant agent.[7] Epoxidation of **5** with *m*-CPBA in CH_2Cl_2 resulted in the formation of the 11α,12α-epoxide **6** in excellent yield. The epoxide ring was formed with high selectivity in the least hindered face of steroid.[8] The α configuration of the 11,12-epoxide was assigned due to the presence of the C-18 angular methyl group which blocks the β-face of the C ring when the Δ^{11} double bond of **5** was epoxidized. The observed ^{1}H NMR spectrum showed characteristic doublets (J = 4 Hz) for the CH-11 and CH-12 protons at δ_H 2.98 ppm and 3.16 ppm, respectively.

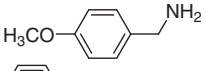
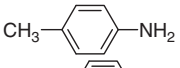
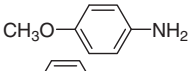
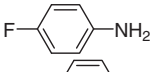
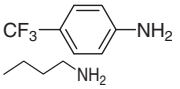
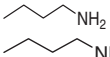
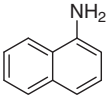
In the last step, we proceeded to a selective epoxide ring opening with nucleophilic amines. Interestingly, we observed two reactions during this step: a stereoselective epoxide ring opening and an intramolecular lactonization. Thus, the 11α,12α-epoxide **6** was treated with different nucleophilic amines in EtOH/toluene (1/1) at reflux during 24 h, affording steroidal lactones **7**. The assignment of structures **7** was supported by the NMR spectra which showed a disappearance of the characteristic singlet (of the lateral chain) at δ_H 3.6 ppm (s, C-23-OMe) and the coupling constant between 11-H and 9-H is 3.9 Hz, which shows the 11-H should be in α position. Furthermore, the positions of the angular methyl groups at δ_H ~0.76 ppm (s, C-13-Me) and δ_H ~ 0.98 ppm (s, C-10-Me) are consistent with a 11-amino-12-oxa structure.

The yields of the corresponding lactones **7** are depicted in Table 1.

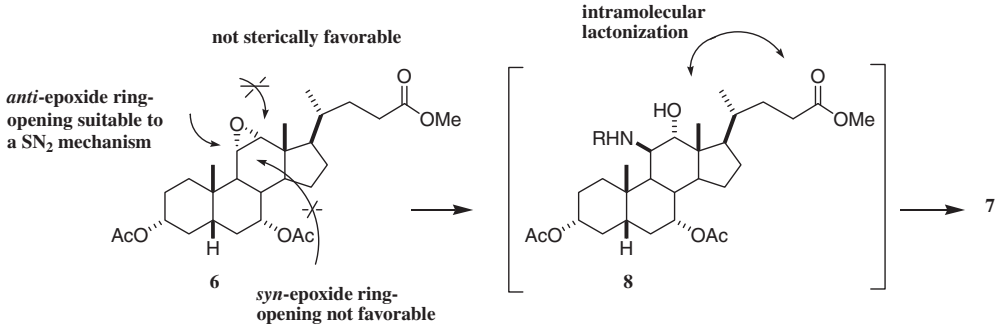
The stereo- and regioselectivity in the epoxide **6** ring opening can be rationalized as shown in Scheme 3.

Table 1
Pentacyclic steroids **7a–j**



Entry	Amines RNH_2	Yield* of 7
1		**7a**: 81%
2		**7b**: 65%
3		**7c**: 88%
4		**7d**: 67%
5		**7e**: 64%
6		**7f**: 83%
7		**7g**: 72%
8		**7h**: 70%
9		**7i**: 75%
10		**7j**: 66%

* Yields are given for isolated products.



Scheme 3. Proposed mechanism of epoxide ring opening.

The nucleophilic attack in the epoxide ring opening would be made exclusively on the least sterically hindered carbon of the epoxide (C_{11}) due to the SN_2 mechanism employed in this methodology. In stereochemical terms, the classical and much stabilized *anti* approximation of nucleophiles species with the α-epoxide produces the respective *trans*-hydroxy amines **8**, which are not isolated (Scheme 3).

By analysing Table 1, it is possible to verify that the epoxide ring opening is not sensitive to electronic effects of the aromatic moiety in the amines. For instance, for compound **7d** (Table 1, entry 4), made from a nucleophile with an activating R group, the yield was 67%, while compound **7g** (Table 1, entry 7), made with a deactivating R group on the ring, had a *quasi* similar yield of 70%. The reaction is also not sensitive to steric effects. Introducing a bulky group as a naphthyl group at C-11 position is possible as shown by the entry 10 (Table 1) which gave product **7j**.

In summary, we describe a new class of pentacyclic steroids[9] from cholic acid, by a stereoselective intramolecular epoxide-opening lactonization as the key step. It is also noteworthy to mention that this synthesis is short, versatile, and moreover interesting moieties can be introduced at the C-11 position of the steroidal skeleton, which is a key position from a biological point of view.[10] An application of this strategy to introduce a sulphur moiety at the same position is in due course.

Acknowledgements

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