Tetrahedron Letters 51 (2010) 93–95

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of heterosteroids. First synthesis of oxa steroid from cholic acid

Malika Ibrahim-Ouali [a,*], Nicaise Botsi-Nkomendi [a], Luc Rocheblave [b]

[a] Institut des Sciences Moléculaires de Marseille, UMR 6263 CNRS and Université d'Aix Marseille III, Faculté des Sciences et Techniques de Saint Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France
[b] Université de Lyon, Université Lyon 1, ISPB-Faculté de Pharmacie, INSERM U863, IFR 62, F-69373 Lyon Cedex 08, France

ARTICLE INFO

Article history:
Received 11 June 2009
Revised 15 October 2009
Accepted 19 October 2009
Available online 10 November 2009

Keywords:
Cholic acid
Oxa steroid
Baeyer–Villiger oxidation
Microwave
Photolysis

ABSTRACT

We wish to report here a new and efficient partial synthesis of 3-oxa-5β-steroid, the first oxa steroid synthesized from cholic acid.

Interest in steroid chemistry arises from significant rating that these compounds have been accorded in medicine. Commercial research on steroid is focused on finding more potent, long acting synthetic drug analogs, possessing essential pharmacological properties.

The use of steroidal hormones, such as corticoids, progesterones, and various anabolic (muscle building) agents, is well known in modern clinical therapy. However, the beneficial properties of these drugs are often, if not usually, accompanied by unwanted side effects.[1] In 1956, the introduction of the 19-norsteroid Nilevar, which is a 2-oxa steroid, proved that the separation of activities is indeed possible.[2] This drug had the desired anabolic property with greatly reduced androgenic side effects when compared to testosterone or its 17α-methyl analog. With the Nilevar success as a background and with the emphasis on the separation of activities rather than on greater potency, several groups began to study the effect of inserting heteroatoms into the steroidal ring.

Ring expansion or the replacement of one or more carbon atoms of the sterane skeleton by a heteroatom affects the chemical properties of the steroid and thus may play a critical role in changing biological activities and in the building of new active pharmaceuticals.

Wolff and Zanati have reported that some A-ring heteroandrostanes have androgenic activity similar to that of testosterone.[3] There has, however, been no report so far on the synthesis of oxa steroids from cholic acid. Surprisingly and to the best of our knowledge, no synthesis of heterosteroid structures from cholic acid has been described in the literature. One reason of that is probably the presence of three hydroxyl groups in the 3α, 7α, and 12α positions in the molecule.

Cholic acid is a relatively inexpensive bile acid, interesting for the preparation of significant quantities of a multistep synthetic product. Cholic acid was chosen as the starting material in the synthesis of 3-oxa steroids.

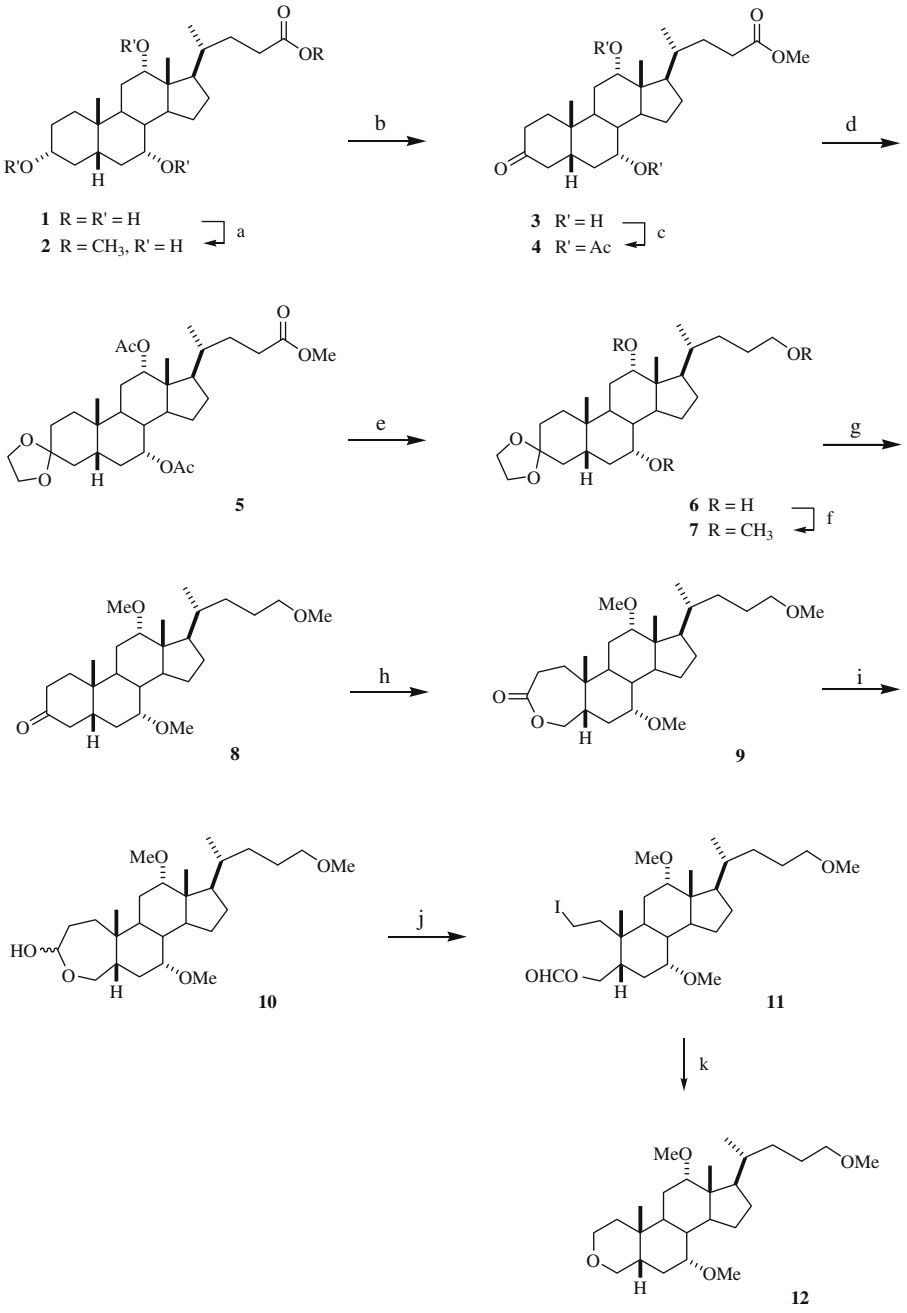
The key reactions leading to this new heterosteroid are depicted in Scheme 1. Our strategy involves the use of a Baeyer–Villiger oxidation of a steroidal ketone to introduce a heteroatom in the A-ring, which was developed by Suginome et al.[4]

So, the synthesis started from commercially cholic acid **1**. Simple esterification of **1** led to methyl cholate **2**.[5] Then, the equatorial 3α-OH group in methyl cholate **2** was selectively oxidized with silver carbonate––Celite (Ag_2CO_3/Celite).[6] We suggest in this Letter a novel green synthetic method to oxidize selectively **2** faster and without solvent. Microwave (MW)[7] irradiation of **2** with silver carbonate on Celite furnished monoketone **3** very quickly, in a few minutes, and the yield observed (90%) was the same as under conventional conditions.[6] Then, the resulting ketone **3** was diacetylated, leading to **4**.[8] Indeed, direct ketalization of **3** was also tried but we always observed the formation of by-products corresponding to dehydrated products.

Now, the introduction of a ketal group as 'masked' ketone resulted in increased yields of the expected product **5**, which was obtained in 89% yield. The diacetylated ketal **5** was smoothly reduced with $LiAlH_4$ affording triol **6** in very high yield. Methylation[9] of triol **6** with methyl iodide–sodium hydride in THF afforded 7α,12α,24-trimethoxy ketal **7** in a yield of over 95%. Cleavage[10] of the ketal group of **7** afforded the expected ketone **8** in excellent yield.

* Corresponding author. Tel.: + 33 0491288416; fax: +33 0491288234.
E-mail address: malika.ibrahim@univ-cezanne.fr (M. Ibrahim-Ouali).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.10.141



Scheme 1. Synthesis of 3-oxa-5β-steroid from cholic acid through 11 steps sequence. Reagents and conditions: (a) MeOH, APTS, Δ, 99%; (b) Ag_2CO_3/Celite, MW, 3 min, 90%; (c) Ac_2O, pyridine, DMAP, 87%; (d) $(CH_2OH)_2$, APTS, C_6H_6, 89%; (e) $LiAlH_4$, Et_2O, rt, 95%; (f) CH_3I, NaH, THF, rt, 100%; (g) HCl, acetone, 97%; (h) *m*-CPBA, APTS, CH_2Cl_2, 75%; (i) DIBAL, CH_2Cl_2, 75%; (j) HgO–I_2, pyridine, C_6H_6, *hν*, 90%; (k) MeLi, THF, −78 °C, 76%.

The Baeyer–Villiger[11] oxidation of ketone **8** with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane for 12 h proceeded regioselectively and gave 4-oxa-A-homo-5β-cholestan-3-one **9** as a single product in a 75% yield, while no isomeric lactone was formed. Obtention of this lactone constitutes a new and very interesting result.[12] Indeed, application of this reaction using the experimental conditions described by Suginome and coll.[4] led to lactone **9** in a very fair yield of 10%, and 52% of the starting material was left. Several attempts were done with MCPBA or potassium persulfate or hydrogen peroxide in glacial acetic acid-concentrated sulfuric acid (3:0.5 in volume) for 10 days at room temperature, which gave very fair yields, as for Suginome and coll., on pregnane series. So, we have optimized this reaction by adding a stoichiometric amount of *p*-toluenesulfonic acid in dichloromethane.[13]

The reduction of lactone **9** with DIBAL in toluene at −78 °C for 2 h readily gave a lactol **10** in a 75% yield. The lactol **10** was converted into the corresponding hypoiodite with a mercury (II) oxide–iodine reagent in benzene, after which the solution was subjected in situ to the photolysis previously reported by Suginome and coll.,[4] to give a iodo formate **11** in an 90% yield. The addition of a small amount of pyridine in this photolysis was found to be essential.

The cyclization of formate **11** to a 3-oxa-5β-steroid **12**[14] was obtained in a 76% yield by treatment of **11** with methyllithium in THF.

In conclusion,[15] the first synthesis of an 3-oxa-5β-steroid was achieved by us via 11 steps from cholic acid, using the Baeyer–Villiger oxidation of a ketone as the intermediate. Thus, considering the optimal procedures reported herein, the overall yield of **12**

from cholic acid may be calculated to be 25%. The biological activity of this oxa steroid is currently being investigated and will be reported in due course.

Acknowledgments

This work has been financially supported by the CNRS, INSERM, and *the Ministère de l'Enseignement Supèrieur et de la Recherche*.

References and notes

1. (a) Frank, E.; Schneider, G.; Messinger, J.; Thole, H.; Wolfling, J. *Synlett* **2005**, 2814; (b) Guzzi, U.; Marnini, G. *Gazz. Chim.* **1977**, *107*, 75; (c) Schneider, G.; Vincze, I.; Hackler, L.; Dombi, G. *Synthesis* **1983**, 665.
2. Pappo, R. *Intra-Sci. Chem. Rep.* **1969**, *3*, 105.
3. (a) Wolff, M. E.; Zanati, G. *J. Med. Chem.* **1970**, *13*, 629; (b) Wolff, M. E.; Zanati, G. J. *Experientia* **1970**, *26*, 1115; (c) Zanati, G.; Wolff, M. E. *J. Med. Chem.* **1971**, *14*, 958.
4. (a) Suginome, H.; Yamada, S.; Wang, J. B. *J. Org. Chem.* **1990**, *55*, 2170; (b) Suginome, H.; Wang, J. B.; Yamada, S. *Chem. Lett.* **1987**, 783.
5. Fieser, T. L.; Rajagopalan, S. *J. Am. Chem. Soc.* **1950**, *72*, 5530.
6. Tserng, K. Y. *J. Lipid Res.* **1978**, *19*, 501.
7. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
8. Bonar-Law, R. P.; Davis, A. P. *Tetrahedron* **1993**, *49*, 9829.
9. The methoxy group was chosen as protective group of the three hydroxyl groups of compound **6** because chemically stable under the Suginome conditions of photolysis.
10. Shu, Y.; Jones, S. R.; Kinney, W. A.; Selinsky, B. S. *Steroids* **2002**, *67*, 291.
11. Ahmad, N. S.; Moinuddin, G.; Khan, I. A. *J. Org. Chem.* **1978**, *43*, 163.
12. To our knowledge, no successful formation of lactones from cholic acid has been previously reported and this seems to be the first example.
13. The typical procedure of Baeyer–Villiger oxidation is as follows: a solution of **8** (0.26 g, 0.6 mmol) in 20 mL of dichloromethane with MCPBA (12 mg) and *p*-toluenesulfonic acid (87 mg) was stirred under argon at room temperature for 12 h. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH; 95:5) to afford lactone **9** (0.4 g, 75%).
14. Selected spectral data of compound **12** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (s, 3H, H-18), 0.99 (d, J = 6.4 Hz, 3H, H-21), 1.02 (*s*, 3H, H-19), 2.84 (m, 2H, H-7 and H-12), 3.20 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 3.45–3.65 (m, 6H, H-2, H-4 and H-24); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8 (q, C-18), 18.9 (q, C-21), 22.6 (q, C-19), 26.5, 27.6, 28.3, 29.4, 30.9, 32.2, 34.6 (7t, CH_2), 35.4, 36.8, 39.5, 42.6, 43.2, 44.3 (6d, CH), 46.0, 46.6 (2s, C-6 and C-13), 56.0, 57.3, 58.7 (q, OCH_3), 68.3, 73.6, 74.9 (3t, OCH_2), 76.7, 82.1 (2d, OCH). HRMS (EI): m/z: calcd for $C_{26}H_{46}O_4$: 422.3396, [M^+]; found: 422.3400.
15. The intermediates compounds **6**–**11** in the synthesis of **12** are all new products, their structures were confirmed by spectroscopic methods and will be reported in due course.