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Ring-closing metathesis towards functionalised pentacyclic steroids

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ABSTRACT

A new synthetic pathway towards pentacyclic steroids was described via a ring-closing metathesis reaction as the key step.

Due to their high profile biological activity, the steroids are among the most important secondary metabolites. Pentacyclic steroids constitute an important class of steroids. There are many examples of pentacyclic steroidal derivatives of pharmacological and biological importance.[1] 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. Moreover, pentacyclic steroids obtained by the fusion of a carbocyclic ring such as benzene or cyclohexane or cyclopentane to the steroid nucleus or pentacyclic steroids derived by the fusion of a carbocyclic ring to a heterosteroid skeleton are known to exhibit interesting and diverse biological properties.[2] We note that most of the partial and total syntheses of pentacyclic steroids reported in the literature till now, were concentrated on the synthesis of steroids containing a new ring fused to ring A,[3] ring D[4] or bridging rings A and B.[5]

Olefin metathesis has become one of the most powerful and attractive tools for the formation of carbon–carbon double bonds widely used in organic synthesis. The spectacular improvements in this reaction achieved over the last two decades are well known to most chemists. An increasing number of papers devoted to the applications of olefin metathesis in the synthesis of natural products are observed.[6] Although ring-closing metathesis (RCM) is known to be a powerful tool for the preparation of macrocycles,[7] in the field of steroid chemistry, only few syntheses have been reported based on metathesis reactions.[8] Herein, we report a new and simple preparation of pentacyclic steroids possessing a macrocycle using a ring-closing metathesis reaction as the key step.

Firstly, we turned our attention to the synthesis of steroids containing a new ring bridging rings C and D, and in particular 12,17-annulated steroid pentacycles which were never described till now. The key reactions leading to these new steroids are depicted in Scheme 1. Cholic acid **1**, a commercial bile acid both inexpensive and readily available, was chosen as starting material. First, simple esterification of cholic acid **1** led to methyl cholate, which was methylated with methyl iodide-sodium hydride in THF affording methyl 3α,7α-dimethoxy cholate **3** in a yield of 93%. Next, the C-24 ester function of the lateral chain was reduced in excellent yield with lithium aluminium hydride in diethyl ether to the tetraol diprotected **4**.

In the next step, we had to prepare the key precursor of this synthesis, possessing two terminal alkene functionalities suitable for metathesis. This reaction constitutes a new and very interesting result. Indeed, hydroxyls at different positions on the nucleus have different reactivities towards alkylating agents, generally in the order C-3 > C-7 > C-12.[9] It was not clear that it would be possible to alkylate a hindered hydroxyl group such as the 12α-OH in a molecule with several other functional groups. Indeed, attempts to allylate diol **4** using classical methods [(a) allylbromide, sodium hydride and tetrabutylammonium iodide in THF,[10] (b) allylbromide and silver oxide in DMF,[11] ...] all failed to give the desired product **5**. However, the method of Bundle and co-workers[12] relative to the benzyl protection of hydroxyl functions, employing in our case, *O*-allyl 2,2,2-trichloroacetimidate and trifluoromethanesulphonic acid, was more successful. The conversion was not entirely clean due to the formation of byproducts, but careful optimisation

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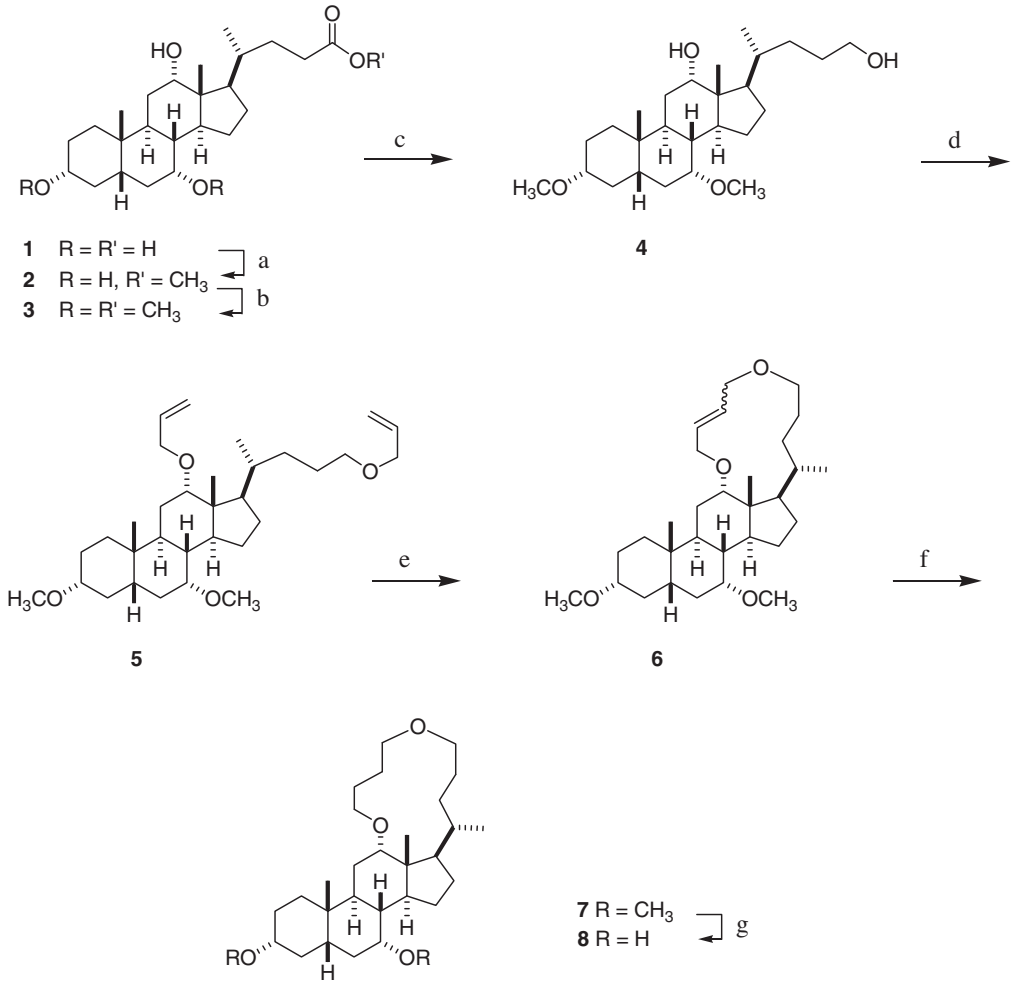


Scheme 1. Synthesis of a steroidal macrocycle **8** from cholic acid through seven steps sequence. Reaction conditions: (a) MeOH, PTSA, Δ, 2 h, 99%; (b) CH_3I, NaH, THF, rt, 12 h, 94%; (c) $LiAlH_4$, Et_2O, 0 °C to rt, 12 h, 96%; (d) *O*-allyl 2,2,2-trichloroacetimidate, CSA cat, CH_2Cl_2, 24 h, 64%; (e) $(PCy_3)_2Cl_2Ru{=}CHPh$ = Grubbs catalyst, first generation, CH_2Cl_2, Δ, 12 h, 36%; (f) H_2/Pd-C/Na_2CO_3, EtOAc, 88%; (g) $ISi(CH_3)_3$, $CHCl_3$, rt, 24 h, 92%.

(10 mol % of CSA instead of CF_3SO_3H) resulted in a procedure giving **5** in a 64% yield. So, we disclosed in this Letter a method to allylate efficiently cholic acid derivatives at the C-12 position.

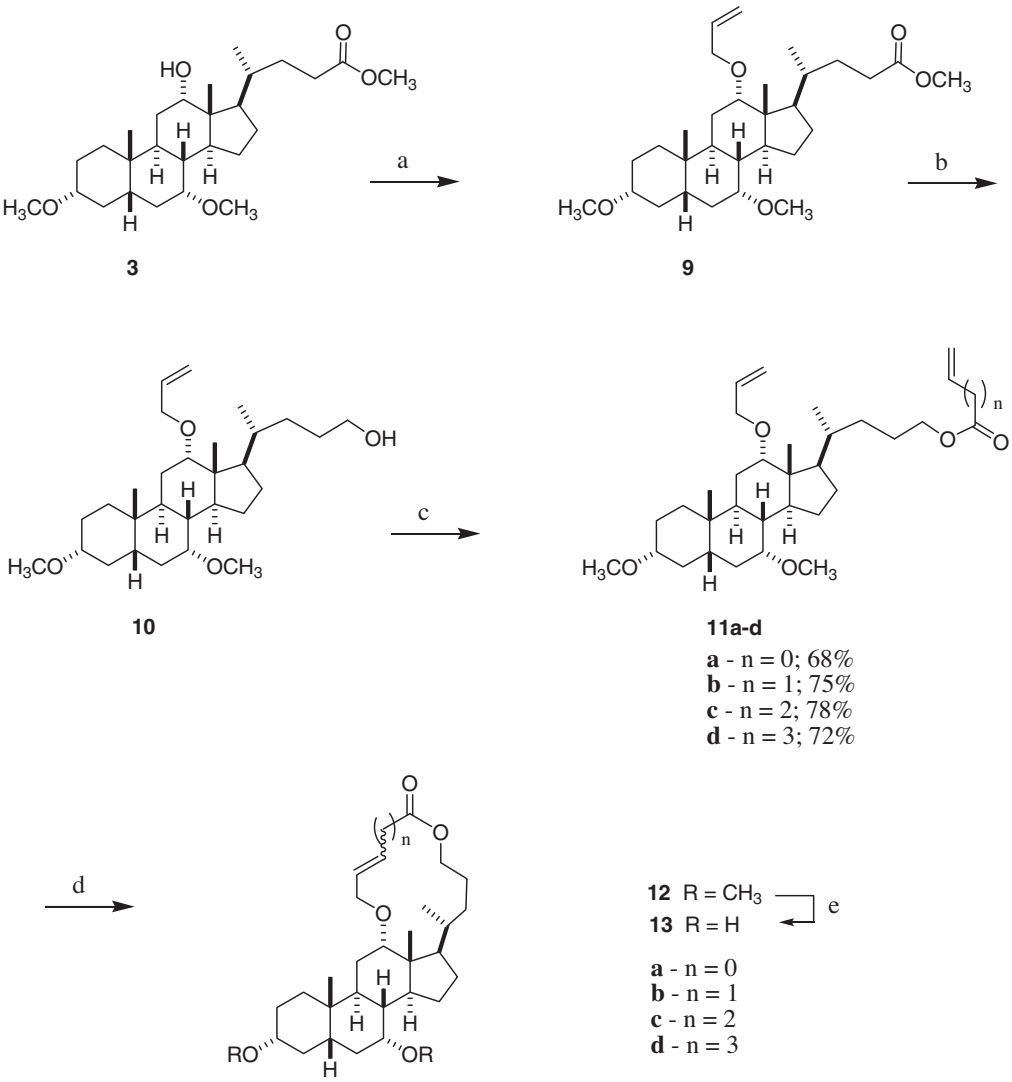
Cyclisation of **5** in the presence of first generation Grubbs catalyst[13] in CH_2Cl_2 led to the pentacyclic steroid **6** possessing a 13-membered macrocycle within 12 h and in a 36% yield (mixture of *E/Z* isomers). The remaining material was mainly the unreacted starting diene **5**. Hydrogenation of the double bond and subsequent cleavage of the protecting groups gave the saturated macrocycle **8**.[14] Despite extensive research on steroids, the synthesis of such a compound has not been described before.

Encouraged by this result and to show that this ring enlargement is generally applicable, different types of olefins were subjected to metathesis reaction (Scheme 2 and Table 1). 3α,7α-Dimethoxy cholate **3** was allylated as described above leading to **9** in 66% yield. The latter was reduced with lithium aluminium hydride in diethyl ether providing the alcohol **10** in good yield. Then, the dienes **11a–d** were prepared in high yields by the reaction of steroid **10** with alkenoic acids in the presence of DCC and DMAP. All esters obtained were found to be stable and were subjected to RCM reactions. According to the literature, synthesis of unsaturated lactones through RCM has been accomplished using either Grubbs, first or second generation, or Hoveyda catalyst.

We decided to test the catalysts of Grubbs GI and GII (Table 1). In all cases, the Grubbs catalyst of second generation was more efficient than this of first generation. We carried out the first experiments under relatively mild conditions: 20 mol % of catalyst in dry and degassed dichloromethane at room temperature. Using these experimental conditions, fair yields were observed. The yields of the cyclisation products of **11a**, **11b** and **11c** were improved by increasing the temperature (Table 1, entries 3, 6, 9 and 12). The more reactive Grubbs catalyst of the second generation[15] was necessary to obtain the desired product starting with **11d** (Table 1, entries 10 and 11). Thus, cyclisation of **11d** having a 5-pentenester moiety could only be accomplished at reflux temperature in dichloromethane. And its yield was improved with higher temperature (refluxing toluene).

Otherwise, the reaction was not stereoselective. All metathesis products were obtained as mixtures of geometric *E/Z*-isomers with the *E* isomer predominating. The structure of these new pentacyclic steroids **12** was completely characterised by NMR (400 MHz) and mass spectroscopic methods.[16]

Finally, removal of methoxy groups of pentacyclic steroids **12** was carried out with trimethylsilyl iodide[17] to afford the desired compounds **13** in good yields. The problem of formation of isomers can be, of course, overcome by hydrogenation of the newly formed double bond.



Scheme 2. Synthesis of steroidal macrocycles **13** from cholic acid through seven steps sequence. Reaction conditions: (a) *O*-allyl 2,2,2-trichloroacetimidate, CSA cat, CH_2Cl_2, rt, 24 h, 66%; (b) $LiAlH_4$, Et_2O, 0 °C to rt, 12 h, 92%; (c) $CH_2{=}CH(CH_2)_nCOOH$, DCC, DMAP, n = 1, 2, 3 or $CH_2{=}CHCOCl$, NEt_3; (d) catalyst conditions, see Table 1; (e) $ISi(CH_3)_3$, $CHCl_3$, rt, 24 h.

Table 1
Metathesis reactions via Scheme 2

Entry	Olefin	*n*	Cat[a]	Condition	12: Yield (%)
1	**11a**	0	A	DCM, rt, 24 h	26
2	**11a**	0	B	DCM, rt, 24 h	34
3	**11a**	0	B	MePh, Δ, 4 h	48
4	**11b**	1	A	DCM, rt, 24 h	20
5	**11b**	1	B	DCM, rt, 24 h	46
6	**11b**	1	B	MePh, Δ, 4 h	63
7	**11c**	2	A	DCM, rt, 24 h	28
8	**11c**	2	B	DCM, rt, 24 h	32
9	**11c**	2	B	MePh, Δ, 4 h	56
10	**11d**	3	A	DCM, rt, 24 h	—
11	**11d**	3	B	DCM, Δ, 6 h	22
12	**11d**	3	B	MePh, Δ, 4 h	36

[a] A = $RuCl_2(PCy_3)_2{=}CHCHCMe_2$; B = $(IMES)(PCy)_3Cl_2Ru{=}CHPh$; IMES = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene.

In summary, we have presented a novel approach to highly functionalised pentacyclic steroids possessing a macrocycle. Interesting is to note that, in one step, a new ring and a new function were introduced efficiently on the steroidal skeleton. Olefin metathesis seems to be a method of choice for the synthesis of pentacyclic steroids. These molecules can now be exploited for the generation of diverse compound libraries.

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14. *Selected spectral data of* ***8*** *are as follows*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, J = 6.5 Hz, 3H, H-21), 0.89 (s, 3H, H-19), 1.21 (s, 3H, H-18), 2.10 (bs, 1H, OH), 2.98 (m, 1H, H-12), 3.14 (m, 1H, H-3), 3.21 (m, 1H, H-7), 3.52 (m, 6H, CH_2–O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 18.9, 19.8, 24.8, 25.1, 25.9, 26.3, 26.5, 27.6, 28.3, 29.4, 30.9, 32.3, 34.6, 35.4, 36.8, 39.5, 42.6, 43.2, 44.3, 46.3, 46.6, 68.3, 70.6, 70.9, 76.2, 76.5, 82.1. HRMS (EI): m/z: calcd for $C_{28}H_{28}O_4$: 448.3553, [M^+]; found: 448.3559.
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