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# Metathesis reactions of $\Delta^{22}$-steroids

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ABSTRACT

Metathesis reactions of $\Delta^{22}$-steroids are studied. The cross metathesis reactions of model $\Delta^{22}$-steroids with excess of simple alkenes are sluggish or do not occur at all. In contrast, derivatives of both *trans*- and *cis*-$\Delta^{22}$-cholesterol undergo ring closing metathesis reactions but the former reacts faster. However, the side chain double bond in stigmasterol and ergosterol is too crowded for metathesis reactions promoted by currently available catalysts.

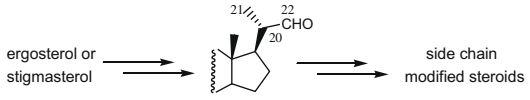


Steroids containing a C22–C23 double bond in the side chain, such as stigmasterol (**1a**) or ergosterol (**1b**), have been frequently used for the synthesis of various medicinally important compounds, for example, vitamin D derivatives hydroxylated on the side chain.[1] The key intermediates in these syntheses are C22-aldehydes that are available by ozonolysis of the C22–C23 double bonds in the protected steroid precursors. Various olefination methods exist to reconstruct the double bond. However, the C22-aldehydes are very sensitive to bases and may epimerize at C20 during the olefination step (Scheme 1).

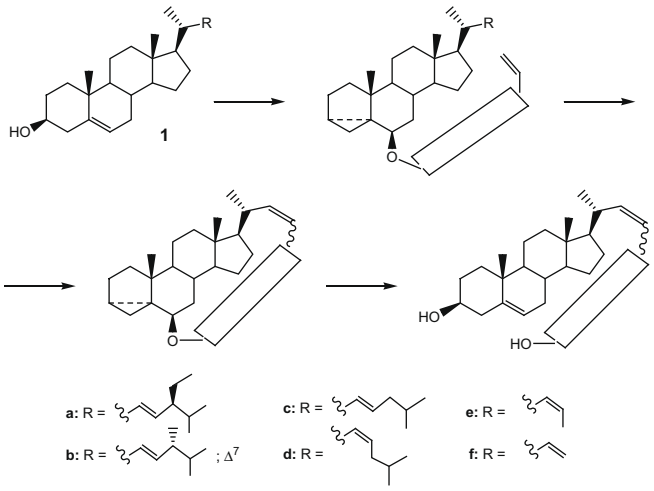
There is no such danger if an olefin metathesis step is applied instead. In addition, a cross metathesis approach might afford the desired products in the most direct way. However, a preliminary study showed that the steroid C22–C23 double bond is poorly accessible to metathesis catalysts. Modern ruthenium and molybdenum carbene complexes are known to promote various challenging metathesis reactions including formation of tetrasubstituted double bonds,[2] but they do not catalyze reactions of stigmasterol or ergosterol. These steroids contain a double bond on the side chain sterically hindered at both allylic positions and do not react even with simple terminal olefins (e.g., ethylene).

We have recently shown[3] that occasionally, metathesis reactions that do not proceed intermolecularly may be carried out successfully via ring closing metathesis (RCM). Therefore a RCM approach to steroids with unsaturated side chains was attempted (Scheme 2). The idea was to transfer an alkylidene group from the remote 6β position.

Thus *i*-steroidal alcohols were obtained and subjected to esterification with different-sized ω-alkenyl monoterephthalates in the presence of DCC/DMAP. The stigmasterol derived esters were subjected to metathesis reactions promoted by various second




**Scheme 1.**




**Scheme 2.**

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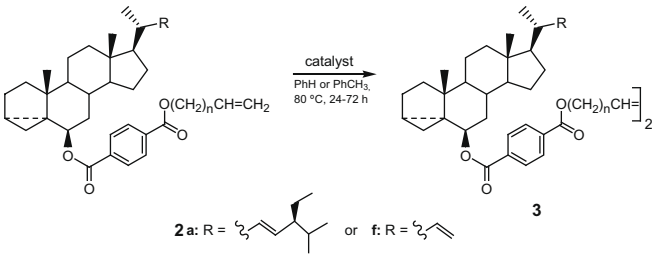
generation catalysts. Unfortunately, the RCM did not occur and the side chain double bond remained intact. Only self-metathesis was observed leading to the corresponding dimers.

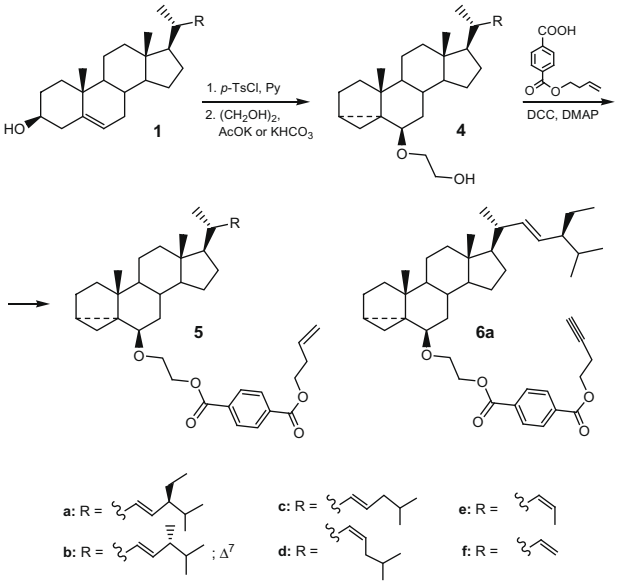
To check if the above approach is conceptually correct the model olefin **2f** lacking steric hindrance in the side chain was prepared from the corresponding aldehyde. However, even in this case, no RCM reaction was observed and only dimeric products were formed (Scheme 3).




**Scheme 3.**

Inspection of the Dreiding models and molecular modeling using the MM+ force-field (HyperChem from HyperCube) suggested that introduction of a short spacer between the oxygen atom at C6 and the ester group would diminish the steric energy of the desired macrocycle. Therefore, a series of *i*-steroidal derivatives were prepared by solvolysis of sterol *p*-tosylates with ethylene glycol (instead of hydrolysis) under buffered conditions (Scheme 4).

The *i*-steroidal hydroxyethyl ethers thus obtained were esterified with 3-butenyl monoterephthalate using the DCC/DMAP method. Thorough computer-assisted analysis showed that a four atom alkene is the most suitable for RCM reactions and therefore 3-butenyl esters were used in further studies (Scheme 5).

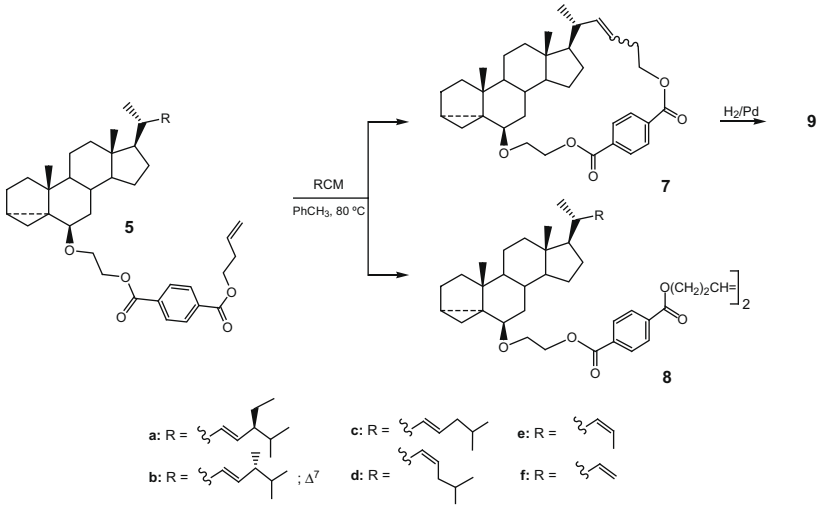



**Scheme 4.**

Unfortunately, stigmasterol and ergosterol derivatives (**5a** and **5b**) did not afford the RCM products. Various first and second generation metathesis catalysts were tested but only products of self-metathesis (dimers) were formed accompanied by trace amounts of isomerization products. In the case of reactions with the Schrock molybdenum catalyst, the starting sterols were recovered. Cycloreversion was due to the slightly acidic character of the Schrock complex or products of its decomposition. Reactions of 4-methylpent-3-enyl esters (instead of 3-butenyl) also proved unsuccessful. Since the RCM reactions of **5a** did not work, the intramolecular enyne reaction was attempted.[4] The analogous 3-butynyl ester **6a** was prepared and subjected to metathesis with the second generation Grubbs' catalyst but the reaction also failed to afford the desired macrocyclic product.

On the other hand, the less hindered esters **5c–f** yielded the same RCM product **7** as an inseparable mixture of cis and trans isomers in addition to the corresponding dimers (in the case of ester **5f**, compound **7** was the only product). The recovered starting ester was usually contaminated by small amounts (less than 5%) of its isomers.

The RCM reaction of the model compound **5f** promoted by the second generation Hoveyda catalyst in toluene at 80 °C proceeded smoothly and was almost complete within 15 minutes (Table 1). Also *trans*-$\Delta^{22}$-cholesterol derivative **5c** yielded the desired macrocyclic product **7** but the reaction required a much longer time (24 h). The cis isomer **5d** appeared to be significantly less reactive—after 48 h only 19% of **7** was isolated in addition to 50% of dimer **8d**. Surprisingly, a similar result was obtained for the cis-configured model compound **5e**.




**Scheme 5.**