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Metathesis reactions of Δ^{22}-steroids

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ABSTRACT

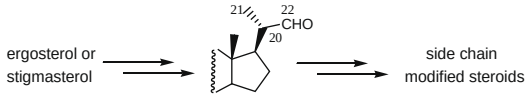
Metathesis reactions of Δ^{22}-steroids are studied. The cross metathesis reactions of model Δ^{22}-steroids with excess of simple alkenes are sluggish or do not occur at all. In contrast, derivatives of both *trans*- and *cis*-Δ^{22}-cholesterol undergo ring closing metathesis reactions but the former 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).

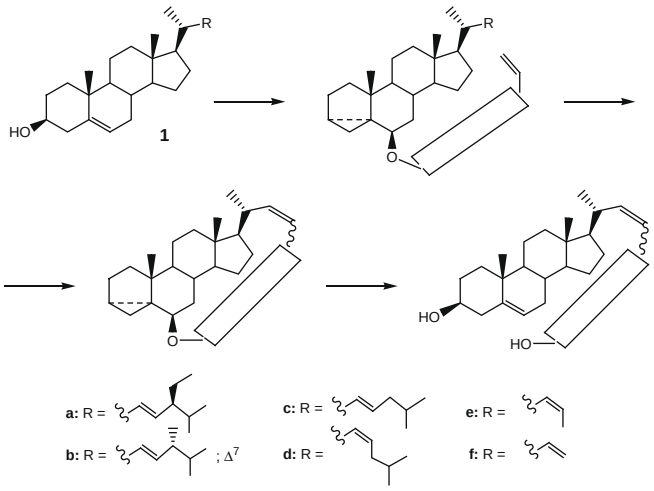
There is no such danger if an olefin metathesis step is applied instead. In addition, a cross metathesis approach might afford the desired products in the most direct way. However, a preliminary study showed that the steroid C22–C23 double bond is poorly accessible to metathesis catalysts. Modern ruthenium 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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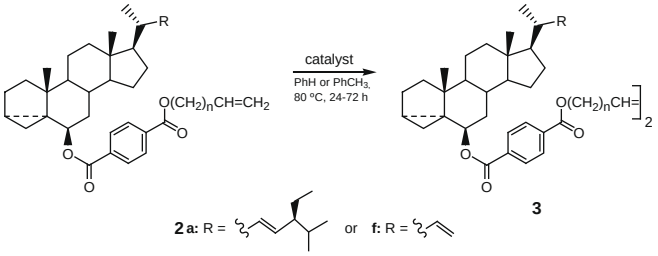
generation catalysts. Unfortunately, the RCM did not occur and the side chain double bond remained intact. Only self-metathesis was observed leading to the corresponding dimers.

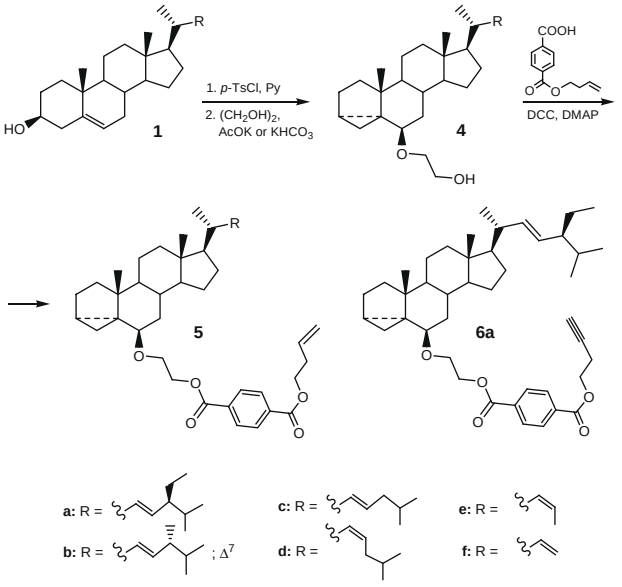
To check if the above approach is conceptually correct the model olefin **2f** lacking steric hindrance in the side chain was prepared from the corresponding aldehyde. However, even in this case, no RCM reaction was observed and only dimeric products were formed (Scheme 3).



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).

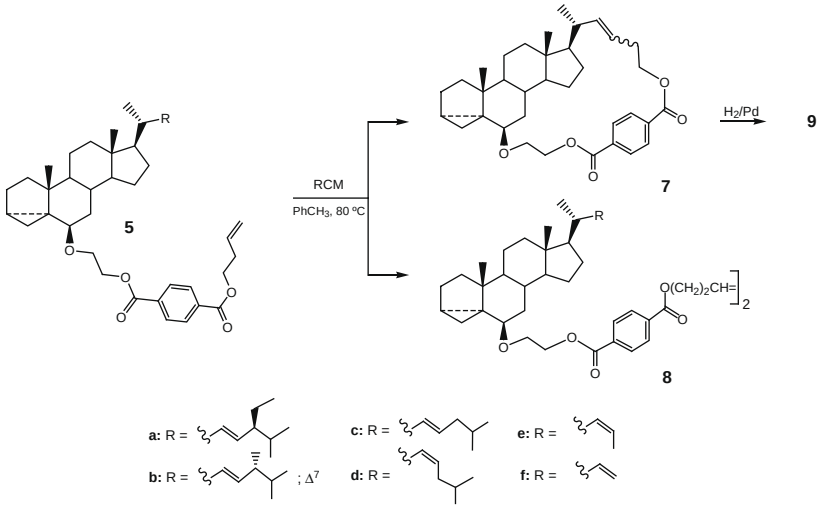


Scheme 4.

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*-Δ^{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.

Table 1
Reactions of compounds **5** in toluene at 80 °C catalyzed by the Hoveyda second generation complex

Side chain structure	Amount of catalyst (mol %)	Reaction time	Recovered **5** (isolated yield, %)	Product **7** (isolated yield, %)	Dimer **8** (isolated yield, %)
c	18	24 h	10	64	10
d	25	48 h	11	19	50
e	20	48 h	18	30	48
f	20	15 min	5	84	0

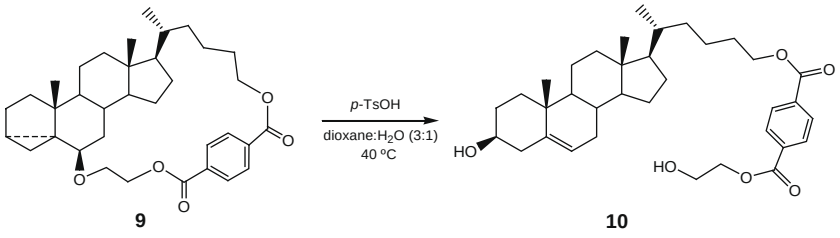
The structure of a macrocyclic compound **7** was proved by characteristic upfield shifts of the 18-methyl group resonances to δ 0.00 and δ 0.17 for the trans and cis isomers, respectively, due to the anisotropic effect of the nearby aromatic ring. A 1.7:1 ratio of isomers was obtained with the trans ($J_{22,23}$ = 15.3 Hz) isomer prevailing over the cis ($J_{22,23}$ = 10.8 Hz) isomer. Hydrogenation of the mixture yielded quantitatively the saturated product **9**, showing the 18-methyl group resonance at δ = −0.10. Finally, cycloreversion of **9** was carried out under routine conditions (*p*-TsOH, dioxane–water 3:1 v/v mixture) to afford compound **10** (Scheme 6).

In general, the RCM reactions of Δ^{22}-steroids proceeded more easily than the analogous cross metatheses (Scheme 7). The reaction of *trans*-Δ^{22}-*i*-cholesteryl methyl ether **11c** with 2 equiv of 3-butenyl stearate, carried out at higher concentration (9–12 mmol/L), yielded only 12% of product **12**, while ring closing metathesis of **5c** gave **7** in 64% yield (Table 2). The much less crowded alkene **11f** afforded a 43% yield of **12** within 48 h. The RCM reaction of analogous alkene **5f** was almost complete in 15 min and afforded **7** in 84% yield. Surprisingly, the RCM approach proved not to be advantageous for cis isomers. The RCM reaction of the *cis* alkene **5e** was not better than the CM reaction of **11e** with the same side chain. The alkenes with stigmasterol (**11a**) or ergosterol (**11b**) side chains did not react at all.

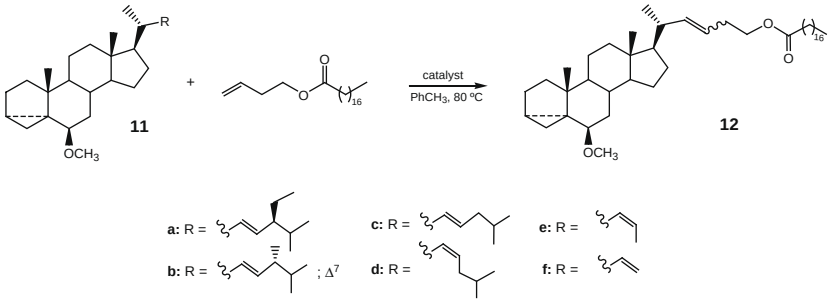
Table 2
Reactions of compounds **11** with 3-butenyl stearate (2 equiv) in toluene at 80 °C, 48 h, Hoveyda second generation catalyst (20 mol %), *c* = 9–12 mmol/L

Side chain structure	Yield (%)
c	12
d	13
e	44
f	43

In conclusion, it should be noted that there is still need for new metathesis catalysts that are less sterically demanding. The cur-



Scheme 6.



Scheme 7.

rently available catalysts are able to react with 1,1-disubstituted olefins yielding tetrasubstituted products.[5] However, 1,1′-disubstituted olefins branched at both allylic positions are still challenging substrates. This study reveals that the RCM approach can be superior to the CM process but only, if the appropriate stereoisomer of the starting olefin is used.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures as well as ^{1}H and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.191.

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