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Synthesis of cholaphanes by ring closing metathesis

Dorota Czajkowska and Jacek W. Morzycki*

Institute of Chemistry, University of Bialystok, al. Pilsudskiego 11/4, 15-443, Poland

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Abstract—The synthesis of cholaphanes by ring closing metathesis (RCM) of 3α,7α,12α,24-tetraol allyl derivatives, obtained from cholic acid, was attempted. The reactions of tetraol 3,24-diallyl ether or 3,24-diacrylate were not satisfactory. However, diallyl derivatives of disteroidal 3,3′- or 24,24′-*ortho*-phthalates reacted smoothly affording cyclic dimers in good yields. In all the reactions studied, the *E* isomers of the macrocycles were obtained in excess.

Dimeric steroids with or without spacer groups can be used as chiral building blocks to construct artificial receptors and can serve as architectural components in molecular recognition chemistry.[1] The most valuable steroid unit used for the synthesis of dimers is cholic acid or its derivatives.[2] There are several structural features which render cholic acid, an inexpensive natural product, an ideal building block for artificial enzymes. One of them is the rigidity of the steroid framework that insures the formation of a cavity. The cis-junction of rings A and B imparts a curvature to the ring system required for the synthesis of the cyclic dimers: cyclocholates or cholaphanes, the latter bearing spacer groups between the two steroid units. A very important feature of cholic acid congeners is that the two faces of the steroid differ significantly in polarity. The more polar α face with hydroxyl groups is able to form hydrogen bonds with a guest molecule, while the β face is entirely hydrophobic. Therefore, various cholaphanes have been used as host molecules in biomimetic chemistry.

Cholaphanes have been synthesized by numerous methods, preferably by macrolactonization[3] or macrolactamization.[4] However, olefin metathesis, to the best of our knowledge, has not yet been applied to the synthesis of cholaphanes. A series of macrocyclic ethers composed of two steroid units was designed. A synthesis of these compounds from tetraol **2**, obtained by the reduction of cholic acid **1**, was attempted via metathesis of its 3,24-diallyl derivative **3** (Scheme 1). However, this reaction proved rather difficult to perform successfully. The starting molecule has two ends of similar reactivity and both head-to-tail and head-to-head connections between the two steroid units are possible. In addition, larger rings consisting of three or more units or a linear polymer may be formed. Another problem, common for all cross metathesis reactions, is the formation of *E* and *Z* isomer mixtures.[5]

In the first experiment, tetraol 3,24-diallyl **3** ether was treated with Grubbs' second generation catalyst, however, no metathesis products were formed. The reason was fast isomerization of the allyl ethers to vinyl ethers under the reaction conditions.[6] Apparently, catalysis of this transformation by the Grubbs II complex is more efficient than promotion of the metathesis reaction. Replacement of the catalyst with the much cheaper first generation Grubbs' complex proved successful.[7] The reaction afforded a homogenous product by TLC; the mass spectrum showed a molecular ion corresponding to the cyclic dimer, but ^{1}H NMR analysis showed that the product was a complex mixture of isomers. In order to reduce the number of isomers, the crude product was hydrogenated and an inseparable mixture of head-to-tail and head-to-head cyclic dimers **A** and **B** was obtained.

The metathesis of tetraol 3,24-diacrylate was also briefly studied. However, the reaction was rather sluggish and also afforded a complex mixture of products.

To avoid the formation of regioisomers, we instead prepared 3,3′-disteroidal *ortho*-phthalate **8**. The tetraol

* Corresponding author. Tel.: +48 85 7457585; fax: +48 85 7457581; e-mail: morzycki@uwb.edu.pl

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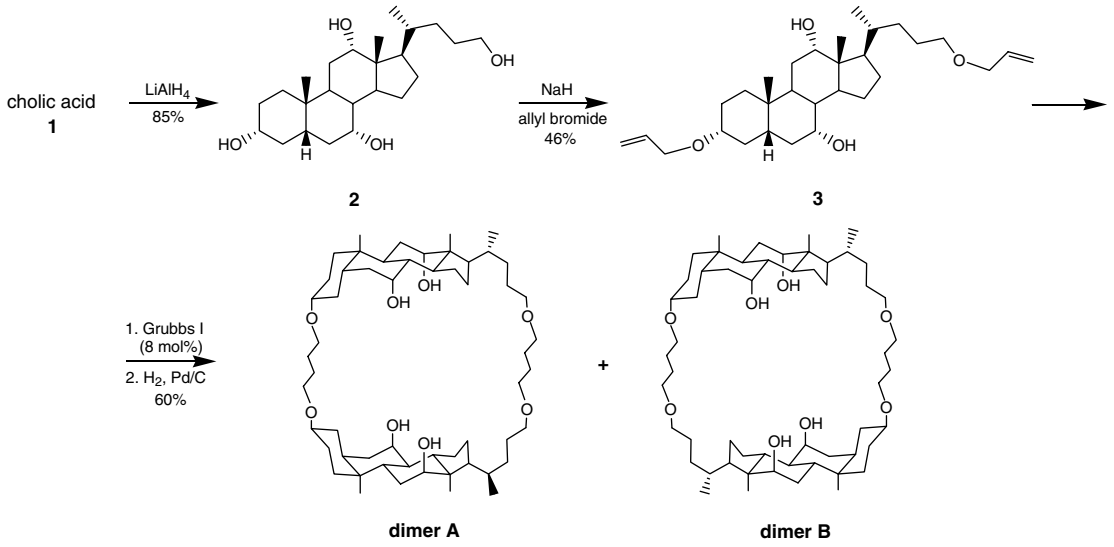
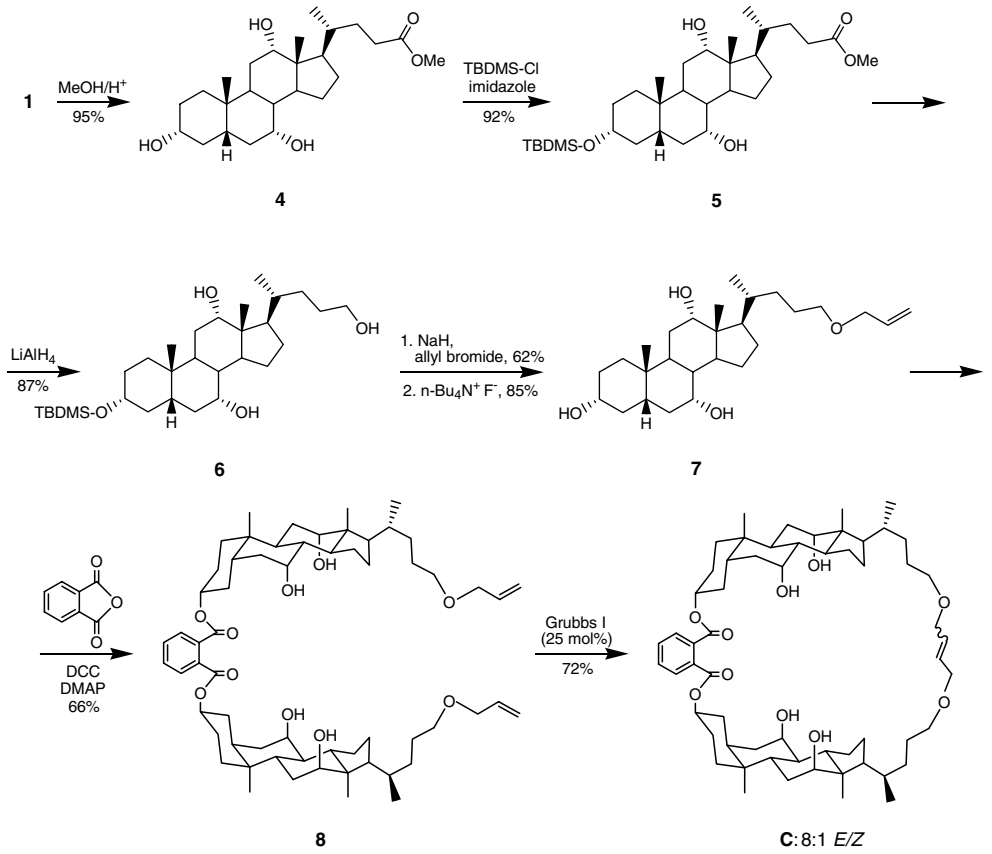


Scheme 1.



Scheme 2.

24-monoallyl derivative **7** was obtained as outlined in Scheme 2.

The 1,3-dicyclohexylcarbodiimide (DCC) method was used for regioselective esterification with phthalic anhydride at the 3α-OH. The RCM was promoted by the first generation Grubbs' catalyst and the reaction was very efficient. However, a mixture of geometric isomers (**C**) was obtained with the *E* isomer predominating (*E*:*Z* = 8:1).

This result was rather unexpected since molecular modeling studies showed a slight preference for the *Z* isomer (Table 1). It is also evident from calculations that for the smaller macrocycles (prepared from the nor- or bisnortetraol, vide infra) the difference in the steric energies

Table 1. Calculated steric energies (kcal/mol) of dimers[a]

Macrocycle size	*E*	*Z*	$\Delta G\,(E-Z)$
38-Membered (normal)	115.55	115.10	0.45
36-Membered (nor)	114.79	113.30	1.49
34-Membered (bisnor)	113.80	111.12	2.68
38-Membered (side-chain *ortho*-phthalate)	116.19	117.61	−1.42

[a] HyperChem for Windows, Release 7.5, from Hypercube, Inc.; minimizations employed the MM^{+} force field and the Polak-Ribiere algorithm with RMS gradient 0.001 kcal/Å mol.

between the *E* and *Z* isomers increases. Therefore, the *Z* stereochemistry would be expected for the RCM reactions leading to macrocycles of smaller size.

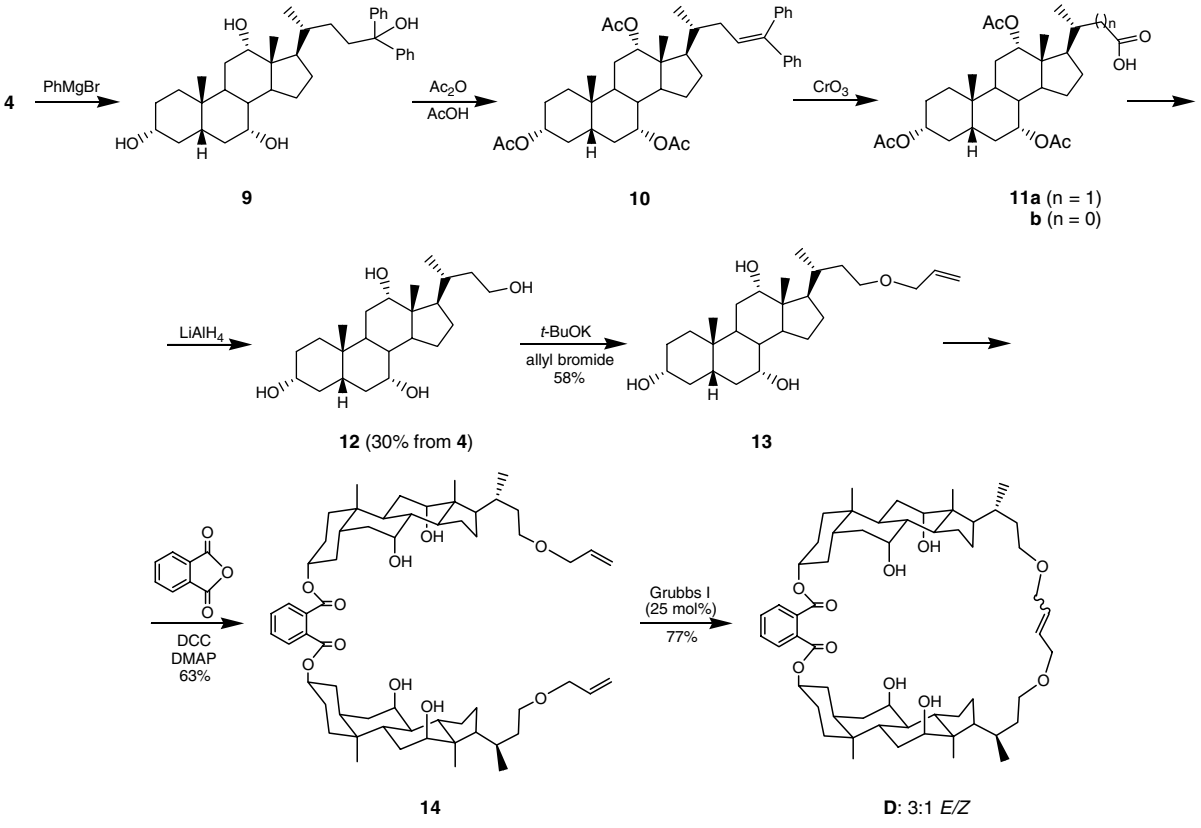
Triacetoxy-24-norcholic acid **11a** was prepared from cholic acid by the known Barbier–Wieland procedure.[8] Its $LiAlH_4$ reduction afforded 24-nortetraol **12**, which was regioselectively allylated at 23-OH. Next, the corresponding 3,3′-disteroidal *ortho*-phthalate **14** was prepared and subjected to RCM with the Grubbs I catalyst (Scheme 3). The reaction proceeded smoothly to afford an *E*,*Z* isomeric mixture of cyclic dimers **D** in the ratio 3:1.

23,24-Bisnortetraol **18** was obtained by $LiAlH_4$ reduction of triacetoxy-23,24-bisnorcholic acid **11b** prepared by a double Barbier–Wieland approach. Alternately, cholic acid was subjected to a decarboxylation/dehydrogenation procedure leading to 22-olefin **16** (Scheme 4).[9] Ozonolysis of the double bond followed by $LiAlH_4$ reduction afforded 23,24-bisnortetraol **18**. This compound was regioselectively allylated at 22-OH and then treated with 0.5 equiv of phthalic anhydride to give **20**. The RCM of *ortho*-phthalate **20** using Grubbs I catalyst yielded the desired macrocycle. However, even in this case the reaction was not stereoselective. The *E* isomer once again dominated in the mixture of cyclic dimers **E** (*E*:*Z* = 2.8:1).

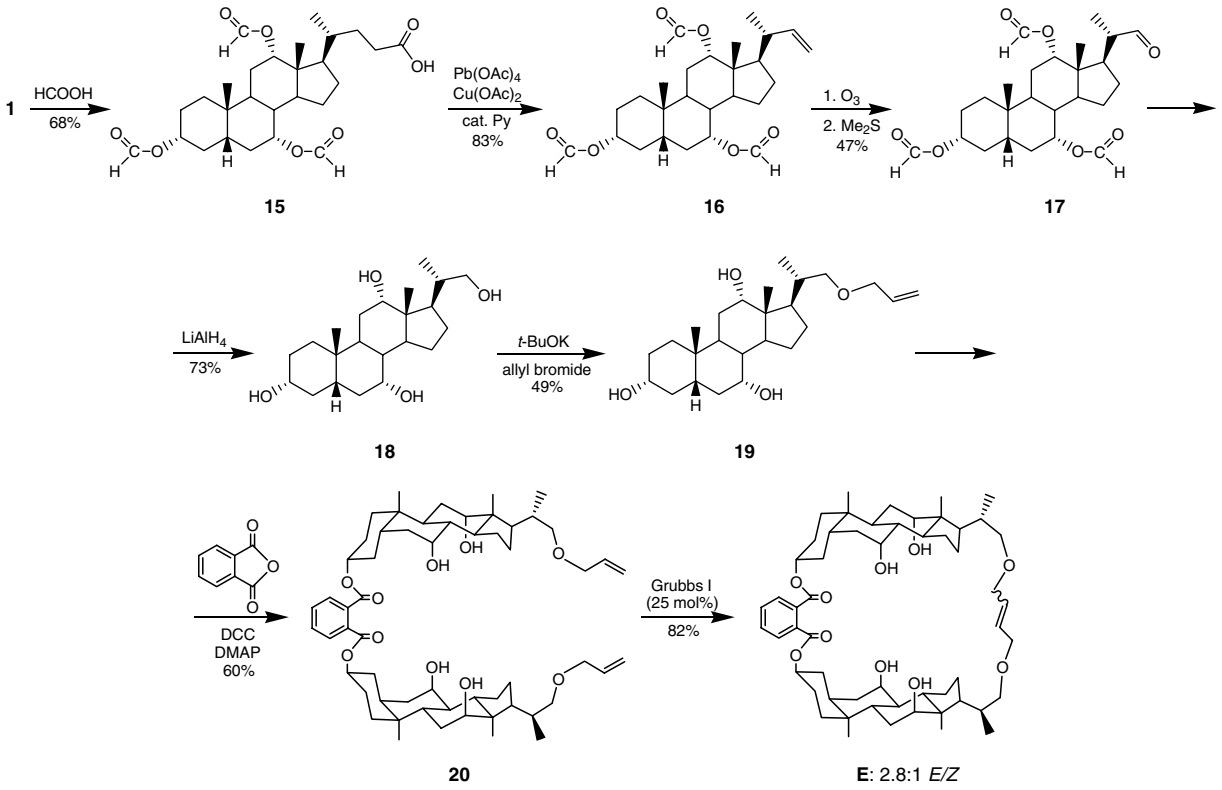
In all the RCM reactions the less thermodynamically stable *E* isomers were formed in excess. It seems that metathetic macrocyclization is not reversible and the reaction is under kinetic control.

We also attempted the RCM of 24,24′-disteroidal *ortho*-phthalate **23** with allyl groups attached to the ring A oxygen atoms. The synthesis of **23** (Scheme 5) consisted of selective protection of the side chain hydroxyl group followed by allylation at the 3α position. The protecting group was removed and 24,24′-disteroidal *ortho*-phthalate **23** was prepared using the same method as described above. The RCM reaction proceeded smoothly leading to *E* and *Z* cyclic dimers **F** in the ratio 5:3. Molecular modeling studies also showed preference for the *E* isomer in this case. The difference in steric energies amounted to 1.4 kcal/mol.

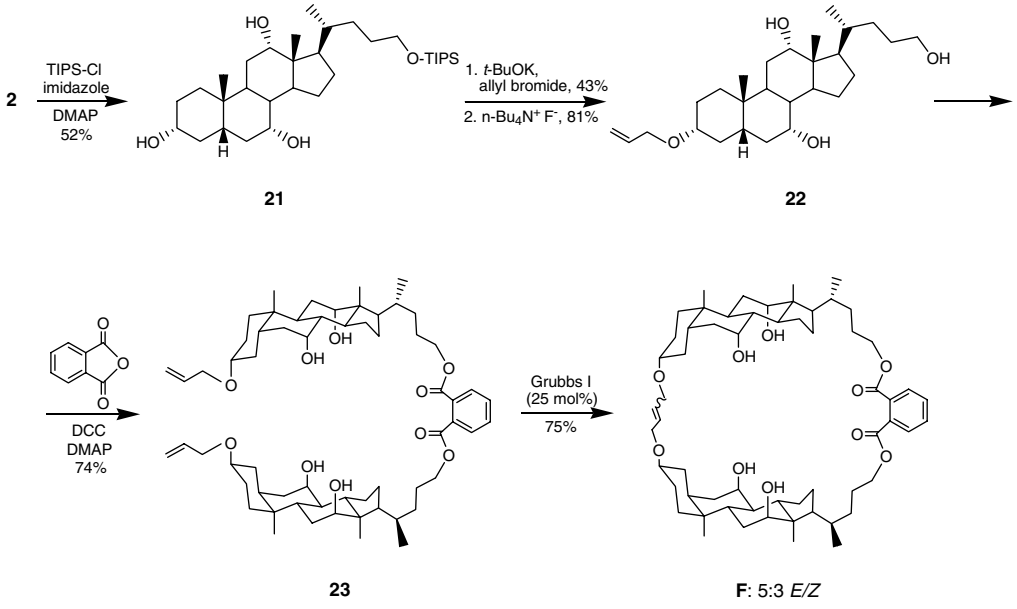
The constrained disteroidal *ortho*-phthalate systems readily undergo RCM promoted by the Grubbs' first generation catalyst. The 34–38 membered cyclic dimers



Scheme 3.



Scheme 4.



Scheme 5.

were obtained in good yields. It is likely that hydrogen bonds between the hydroxyl groups of the two steroid units of the *ortho*-phthalates allow them to attain the suitable conformation for cyclization. However, a serious drawback of the method is the formation of *E* and *Z* isomeric mixtures. In all the cases studied the *E* isomers predominated as in the cross metathesis reactions. The problem of formation of isomers can be, of course, overcome by hydrogenation of the newly formed double bond.

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