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Synthesis of a conformationally restricted polyoxygenated crownophane

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Abstract—A new polyoxygenated crownophane has been synthesized from syringaldehyde and diethyleneglycol by means of McMurry pinacol reaction, whereas ring closing metathesis with Grubbs' catalyst failed in producing the macrocyclization to the corresponding stilbenophane. The NMR data of the crownophane show a restricted conformational space accessible to the phenyl rings.

During our research directed at the synthesis and evaluation of new cytotoxic agents based on natural products,[1] we became interested in macrocyclic polymethoxylated bisarylethanes with oligoethyleneglycol linkers between the *para* positions of the aromatic rings. These compounds combine a flexible polyether chain with rigid aromatic systems and belong to the class of compounds known as crownophanes (see Fig. 1). The crownophanes have been extensively studied since they are expected to show specific properties and functions compared to crown ethers, cyclophanes, etc.[2]

We planned our synthesis of the depicted crownophane[3] starting with a double Mitsunobu[4] reaction of syringaldehyde and diethyleneglycol, followed by a Wittig olefination to give the divinyl derivative. We envisaged a ring closing metathesis[5] (RCM) as the key macrocyclization step, previous to a final hydroxylation of the double bond (Scheme 1).

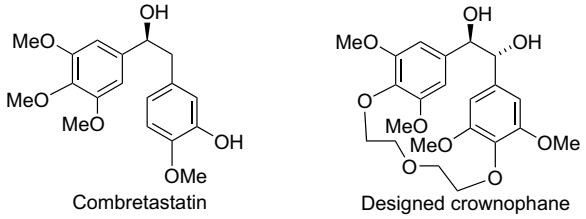

Figure 1. Structures of the natural antimitotic combretastatin and the analogue crownophane.

The synthetic sequence up to the Wittig olefination step works as predicted. However, the key ring closing metathesis failed to produce the expected stilbenophanes under conditions that have been used in related macrocyclizations.[6] We assayed different solvents (chloroform, methanol or benzene) at either room temperature or reflux and we increased the catalyst to substrate mole ratio up to one to one but in no case the cyclized product was detected, even after several months (no dimerization is produced under the high dilution conditions employed). As the activity of Grubb's catalyst [bis(tricyclohexylphosphine) benzylidene ruthenium(IV) chloride] had been checked with model compounds, we conclude that the tension required to approach both ends of the molecule is responsible for this lack of reactivity. Considering that related strategies would encounter the same problem, we decided to explore more expeditious approaches.

Accordingly, we turned to the carbonyl coupling reactions, which would lead to shorter synthetic routes by effecting the key macrocyclization directly from the intermediate dialdehyde of the previous route. We selected the McMurry pinacol[7] reaction which we had initially considered too harsh and less tolerant to functional groups than the RCM. The retrosynthetic sequence is shown in Scheme 2.

Keywords: Crownophane; McMurry; Polymethoxylated; Conformationally restricted.
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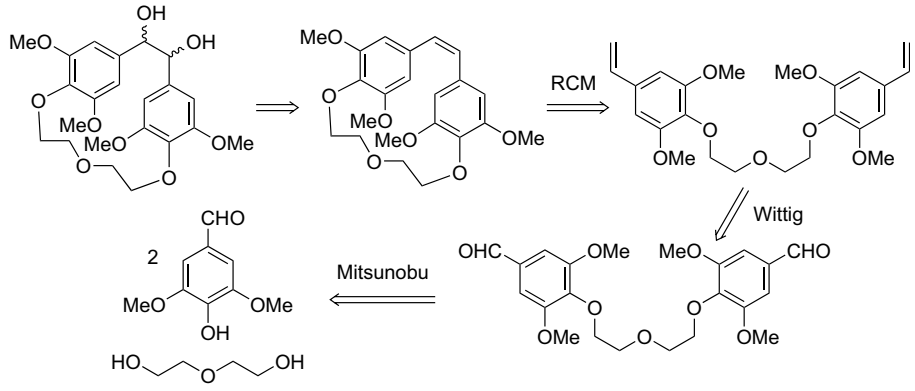
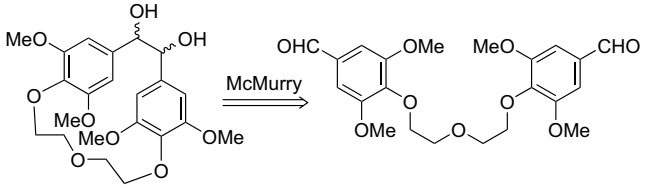


Scheme 1. Retrosynthetic analysis via ring closing metathesis (RCM).



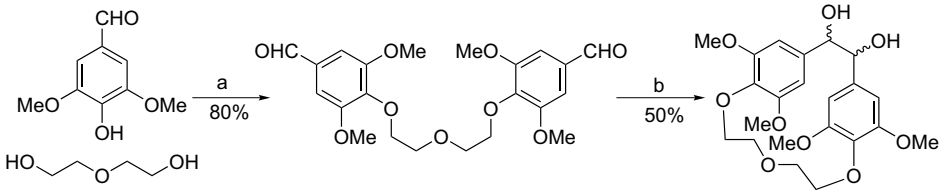
Scheme 2. Retrosynthetic analysis via McMurry pinacol reaction.

Initial attempts of the McMurry reaction were unsuccessful. We attributed the failure to the contamination of the dialdehyde with co-eluting triphenylphosphine oxide from the Mitsunobu reaction. Substitution of the triphenylphosphine by a polymer supported reagent in the Mitsunobu reaction fully avoids this problem and allowed us to isolate a single macrocyclic glycol following the synthetic path depicted in Scheme 3.

The McMurry pinacol reaction is usually not very stereoselective,[8] producing mixtures of diastereomers. However, in this case only one product, other than the starting material, was seen in the reaction crude. Moreover, we did not detect the formation of the olefinic macrocycle under the conditions employed. The relative stereochemistry of the diol was established by means of a combination of spectroscopic and molecular modelling techniques.[9]

The ^{1}H NMR spectra of the isolated crownophane showed two broad singlets corresponding to two aromatic proton pairs ($\delta = 6.55$ and 5.74 ppm) and two pairs of methoxy groups ($\delta = 3.83$ and 3.56 ppm) instead of only one signal for the four aromatic protons or the four methoxy groups, whereas the two hydroxylated methines resonated as a singlet at 4.61 ppm. Such a situation, with two aromatic proton pairs may arise from a conformationally locked *trans* (symmetric) glycol or from a *cis* glycol in fast exchange in the NMR time scale (Fig. 2).

The large chemical shift difference between the two to aromatic proton pairs ($\Delta\delta = 0.81$ ppm) is better accounted for by a ring current effect in the most stable



Scheme 3. Reagents and conditions (1 equiv = 1 mol/mol): (a) diethyleneglycol (0.5 equiv), DBAD (1.5 equiv), PPh_3-polymer bound (1.5 equiv of P atoms) in dry CH_2Cl_2 for 48 h. (b) $TiCl_4{\cdot}Zn$ (5 equiv/10 equiv) in dry THF (20 mL/10 mg of the dialdehyde) for 30 min at 0 °C, then 5 h at rt.

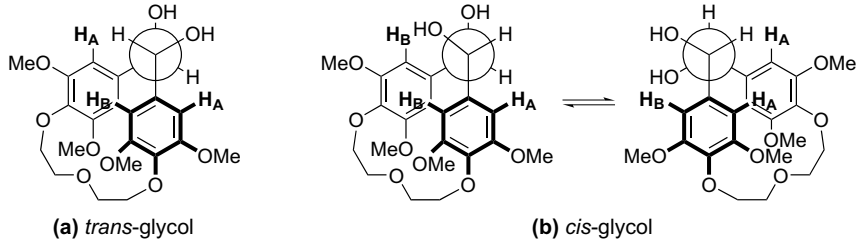


Figure 2. Calculated most stable conformations for either a *trans* (a) or *cis* (b) glycol. For clarity, the protons behind the phenyl ring in bold have been omitted.

conformation of the *trans* glycol (Fig. 2a) than by the different chemical environment of protons H_A and H_B in the conformational equilibrium of the *cis* glycol (Fig. 2b). Also, the roe between the downfield (upfield) aromatic hydrogen and the downfield (upfield) methoxy group indicates that their shifts are caused by a common effect (most likely the ring current effect of the other ring for the upfield ones). Finally, the observed roe between both aromatic protons H_A and H_B and the hydroxylated methines is only compatible with the trans configuration.

In conclusion, the sequence described here provides a new high-yielding stereoselective synthesis of a polymethoxylated crownophane (40% overall yield from syringaldehyde). The *trans* glycol restricts the accessible macrocycle conformations, and the interference of the methoxy substituents with the 3-oxapentamethylene linker hinder phenyl ring rotation and linker motion. Application of the route to related, differently substituted, analogues will be reported in brief.

Acknowledgements

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9. Systematic conformational searches, using Monte Carlo and MM2 and MM3 as molecular force fields, were performed with Macromodel v. 5.1 and clustering of the resulting conformations with XCluster on Silicon Graphics workstations. The most stable conformations for the *cis* and *trans* glycols agree with the schematic drawings depicted in Figure 2.