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Rapid synthesis of macrocycles from diol precursors

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Dedicated to the memory of Magnus John Wingstrand, 1975–2006

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ABSTRACT

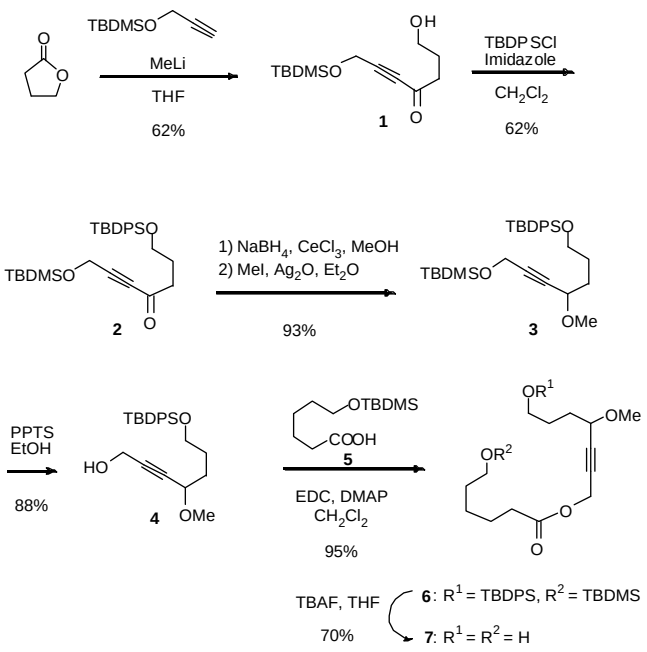
A method for the formation of synthetic macrocycles with different ring sizes from diols is presented. Reacting a simple diol precursor with electrophilic reagents leads to a cyclic carbonate, sulfite, or phosphate in a single step in 25–60% yield. Converting the cyclization precursor to a bis-electrophilic iodide or aldehyde enables preparation of a cyclic sulfide and amine, respectively, the latter using a double-reductive amination to induce ring closure.

In connection with an ongoing program to produce libraries of macrocyclic compounds from simple building blocks, we were interested in the possibility of forming large rings from bifunctional precursors.

An important challenge in forming large ring molecules is the fact that it is often necessary to tailor reaction conditions to individual substrates,[1] which can render the generation of libraries impractical. With this in mind, we decided to investigate the cyclization in one to two synthetic steps with the added potential for diversity in the ring-forming step. Our initial efforts, reported here, have been focused on using a diol and its electrophilic derivatives as cyclization precursors, and reacting them with bifunctional reagents in a single cyclization step.

In order to test different cyclization methods, we synthesized the simple precursor **7** (Scheme 1). Addition of lithium 3-(*tert*-butyldimethylsilyloxy)propynide to γ-butyrolactone followed by TBDPS protection of the resulting alcohol afforded the acetylenic ketone **2**. Reduction of the alkynone[2] followed by neutral methylation[3] gave **3**, which could be selectively monodeprotected by acidic solvolysis. Esterification with the known[4] acid **5** and deprotection with TBAF yielded the desired diol **7**.

Our first macrocyclic target was the carbonate **8** (Scheme 2 and Table 1). Treatment of the precursor **7** with carbonyl diimidazole (entry 1) or phosgene,[5] either as a solution (entry 2) or prepared in situ from triphosgene (entries 3 and 4), all resulted in no or low conversion. Using *p*-nitrophenyl chlorocarbonate (PNPCC) with DMAP as the base led to a 19% yield of **8** by NMR (entry 6), and enabled isolation of the desired product. Optimized conditions called for slow addition of separate solutions of DMAP and the car-



Scheme 1. Synthesis of the cyclization precursor.

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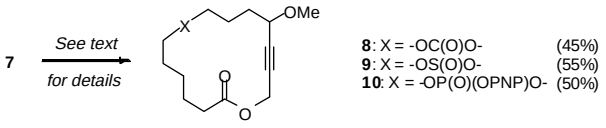


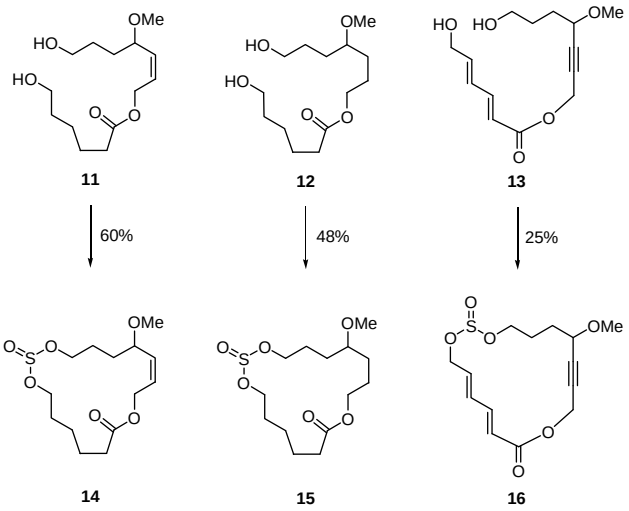
Scheme 2. Formation of macrocycles from diol precursors.

bonate to a methylene chloride solution of the diol over 24 h with a final concentration of 25 mM (entry 7). This protocol gave the desired product in 45% yield. By-products were of an oligomeric nature; we did not isolate any larger cyclic structures in any of the experiments.

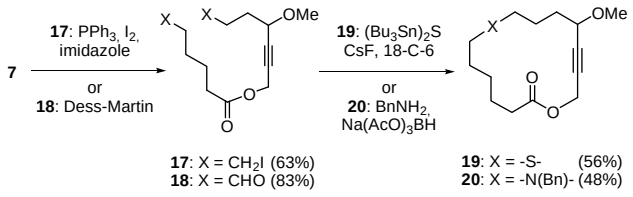
Encouraged by the results of the one-pot approach to the carbonate, we next prepared a cyclic sulfite.[6] Dropwise addition of thionyl chloride to a 10 mM solution of **7**, triethylamine and DMAP in methylene chloride led to the isolation of cyclic sulfite **9** in 55% yield as a 1:1 mixture of inseparable diastereoisomers. Similarly, we were able to prepare the macrocyclic phosphate **10** by reaction with *p*-nitrophenyl phosphorodichloridate ($PNPOPOCl_2$) in 50% yield.

Due to the large influence of the conformations of the precursors on macrocyclizations,[7] it was important to test other substrates under the standard conditions for cyclization. To elucidate whether the approach was general, we studied the formation of cyclic sulfites from other diols (Scheme 3).[8] Gratifyingly, partial (substrate **11**) or full (precursor **12**) reduction of the triple bond did not negatively affect the yield of the cyclization under our standard conditions in a significant manner. On the other hand, combining **4** with a sorbic acid derivative to form precursor **13** did result in a decreased yield for the cyclization—perhaps not surprising, considering that the resulting 17-membered macrocycle **16** contains 5 sp^2 and 2 sp-hybridized carbon atoms. Substrates that cyclize reluctantly under these conditions generally led to oligomers or eventually conversion of the alcohols into chlorides, which was also the case for the reaction of **13**. Overall, we were pleased that identical conditions led to a reasonable isolated yield for all the cyclizations without the need for optimization of the individual reactions.

To investigate the potential of macrocyclizations involving reactions with nucleophiles, we prepared two bis-electrophilic derivatives of **7**, the diiodide **17** and the dialdehyde **18** (Scheme 4). Reaction of **17** with sodium or lithium sulfide in a range of solvents did not afford the desired product. However, using the organic sulfide equivalent bis(tributyltin)sulfide in the presence of CsF and 18-crown-6[9] led to the isolation of the 15-membered



Scheme 3. 17-Membered cyclic sulfites.



Scheme 4. Electrophilic precursors and their reactions with nucleophiles.

cyclic sulfide **19** in 56% yield. To the best of our knowledge, the use of double-reductive amination of dialdehydes with a monoamine to prepare macrocyclic compounds has never been reported.[10] It was therefore with great pleasure we noted that benzylamine reacted with **18** in the presence of sodium triacetoxyborohydride to give the product **20**, proving that cyclization is also feasible when nucleophilic reagents are reacted with bis-electrophiles.

In conclusion, we have demonstrated that a simple diol and its electrophilic derivatives can serve as precursors for cyclic molecules formed in a single step under standard conditions. We believe that this method will help gain easy access to large ring

Table 1
Conditions for the formation of cyclic carbonate **8** from diol **7**

Entry	CDI[a] (equiv)	$COCl_2$ (equiv)	Triphosgene (equiv)	PNPCC[b] (equiv)	Pyridine (equiv)	Et_3N (equiv)	DMAP (equiv)	Concn of **7** (mM)	Yield of **8**[c] (%)
1	1	—	—	—	—	—	0.1	10	No conv.
2[d]	—	1.2	—	—	—	1.4	0.2	10	<5
3[d]	—	—	0.5[e]	—	3	3	0.05	20	<5
4[d]	—	—	0.6[f]	—	5	—	0.05	10	<5
5	—	—	—	1.2	—	—	2.4	25	<10
6	—	—	—	1.35	—	—	2.4	12.5	19
7[g]	—	—	—	1	—	—	1.3	25	45

[a] Carbonyl diimidazole.
[b] *p*-Nitrophenyl chlorocarbonate.
[c] Determined by ^1H NMR of the crude after aqueous work-up.
[d] Reagents added at −78 °C.
[e] 0.05 equiv of LiCl added.
[f] 0.02 equiv of Aliquot 336 added.
[g] Separate CH_2Cl_2 solutions of DMAP and PNPCC added over 24 h.

molecules, and we are currently pursuing libraries of macrocycles based on this strategy.

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Supplementary data

Supplementary data (experimental procedures, characterization data and copies of NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.100.

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