Novel mixed-heteroatom macrocycles via templating: a new protocol

Karem J. Sabah a,b,⁎, Rauzah Hashim a

⁎Chemistry Department, Faculty of Science, University of Malaya, Lembah Pantai, 50603 Kuala Lumpur, Malaysia
a Chemistry Department, College of Science, University of Kufa, 54001 Najaf, Iraq

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ABSTRACT
A series of novel thia diaza and triaza crown ether attached galactose- and glucose-based glycolipids is synthesized, applying a new strategy. The key step is the formation of α-chloroacetamido precursors (14 and 21) from selectively protected bis(cyanomethyl)-glycolipids (13 and 19) in two steps. The cyclization reaction furnishes good yields in relatively short times in aqueous ethanol or acetonitrile. To generalize this method, macrocycles 3 and 25 are reported as well. Attempts to use the traditional synthetic approaches for cyclization failed to provide reasonable yields.

Complex carbohydrates are involved in recognition events of many biological processes, mostly by the interaction between the proteins and the carbohydrate moiety of glycoconjugates. Generally the terminal carbohydrate head-group is responsible for the attachment to the protein receptor. Since glycolipids are essential components of cell membranes, several synthetic analogues have been produced in order to understand the self-organizing properties with respect to their structures. Although there are numerous modified carbohydrates with macrocycles, most of these were based on simple glycosides, that is, methyl or phenyl glycosides. These compounds have been suggested to participate in various tasks including molecular recognition, extraction of either metal cations or organic molecules, asymmetric catalysis, and chiral separation. Furthermore, sugar-attached crown ethers with long alkyl chains on the 4,6-hydroxyl groups of the methyl glycoside have been synthesized to study aggregation and molecular recognition features.

We previously reported a novel class of glycosidic alkyl chain glycolipids containing crown ethers and studied their self-assembly in water. These crown ethers attached to the sugar head-group played a crucial role in self-assembly by shifting the assembly of the parent glycolipids from lamellar to more curved structures, that is, hexagonal and cubic phases. Interestingly, among all the liquid crystal phases, the cubic phases appeared most promising as candidates to use in protein crystallization. Indeed, mixed N, O, S donor macrocycles represent an interesting category of compounds. They exhibit high affinities toward soft metal cations, act as chemosensors and as models for the active sites of some enzymes. However, owing to the difficulties in forming the macrocycles on the sugar, the synthesis has so far been limited to oxa-, aza-, diaza-, and thia-crown ethers.

As a part of our ongoing program to develop new protocols to synthesize novel macrocycles and to study their applications, we report here an effective general strategy for preparing mixed-heteroatom macrocycles.

A mixed-heteroatom 15-crown-5 can be synthesized using various techniques. Among these methods, the high dilution approach is commonly used, which is inconvenient due to tedious simultaneous addition of the starting materials to a large quantity of solvent. Another approach reported by Tabushi used slightly more concentrated conditions. This method had disadvantages too, as it required a dry solvent and a long reaction time (7 days). For example, the synthesis of thia diaza-crown 3 under these conditions gave only a 21% yield of the expected product (Scheme 1). Attempts to synthesize macrocycles 6 and 7 from precursor 4 applying high dilution conditions, gave only 14% and 11% yields, respectively (Scheme 2).

Instead, we designed the intermediates 14, 21, and 24 in such a way as to achieve the following advantages: (1) increased reactivity of the precursor, that is, an α-chlorocarbonyl derivative, (2) reduction of the cost of the synthesis (i.e., by omitting dry solvents), (3) increased chance of sodium templating assisted by the oxygen of the carbonyl compound, and (4) a significantly shortened reaction time.

To construct the macrocyclic backbones 6 and 7 (Scheme 3), we started by synthesizing the glycolipid 11, as the major β-anomer, in three steps starting from galactose. Selective protection of the.
4,6-hydroxyl groups was achieved by benzylidnation to afford 12 as the pure β-anomer in an overall yield of 49% based on galactose 8. Compound 13 was obtained by treatment of 12 with bromoacetone under strongly basic conditions [NaH in DMF or NaOH under phase-transfer catalysis (PTC)]. We found that NaH gave a lower yield compared to PTC. Reduction of the nitrile group was successfully achieved in 86% yield by using LiAlH₄ in THF to furnish the diamine 4. Although the conversion of the amino groups of 4 into chloroacetamides could be carried out with chloroacetyl chloride, the formation of side products made this reaction undesirable. Therefore, chloroacetic anhydride was used instead. The latter process required only extraction with water to obtain 14 in 87% yield and sufficient purity.

The highly reactive intermediate 14 was treated with anhydrous sodium sulfide in absolute ethanol under reflux conditions for 12 h. This gave macrocycle 6 in 50% yield. Increasing the reaction time to 72 h did not improve the yield. On the other hand, absolute ethanol played a poor role in solvation of sodium to template the cyclization. Notably, replacing anhydrous Na₂S with its hydrated analogue in absolute ethanol increased the yield up to 70%. Based on this observation we decided to apply greener conditions by utilizing aqueous ethanol in differing ratios. Interestingly, we found that 10% water content in the ethanol and 1.5 equiv of sodium sulfide gave an excellent yield (85%) of the product. Since no organic side product was observed by TLC, simple extraction was performed to remove other impurities, that is, unreacted sodium sulfide and inorganic salts. Thus, purification by column chromatography could be omitted. After installation of sulfur in the glycolipid–macrocycle, the alternative reaction of intermediate 14 with benzylamine in acetonitrile in the presence of sodium carbonate was performed to furnish the triaza-macrocycle 7 in 58% yield.

The good yields obtained using this approach can be explained in terms of the templating effect. While O-2 of the sugar ring is too far away to interact with sodium, templating was possible by three of the oxygen atoms, O-3 of the sugar ring and the oxygens of the carbonyl groups. On the other hand, the nitrogen and sulfur did not contribute to the templating as they are soft ligands. This assumption was supported by preliminary results of modeling of the transition state upon cyclization, which revealed that the energy of the system dropped from +500 to −4 kJ/mol in the presence of Na⁺ (Fig. 1).

Similarly, macrocycles 22 and 23 were synthesized applying the same strategy (Scheme 4). Benzylidene derivative 18 was prepared from glucose pentaacetate as reported previously.12 Subsequently,
the reaction of 18 with bromoacetonitrile, followed by reduction with LiAlH4 produced the diamine 20 as a white solid in good yield. Conversion of 20 into bis-chloroacetamide 21 using chloroacetic anhydride occurred in 85% yield. Finally, the cyclization of 21 with either Na2S·9H2O, in aqueous ethanol or benzylamine in acetonitrile, produced the macrocycles 22 and 23, respectively.

Another two examples (3 and 25) involved a non-sugar precursor 24 to synthesize the desired macrocycles (Scheme 5). The yields were consistent with the sugar macrocycle analogues.

The formation of the macrocycles could be easily detected by NMR spectroscopy, since the chemical shifts of the CH2Cl group in both the proton and carbon NMR spectra appeared downfield compared to CH2S and CH2NBn.27 For example, the chemical shift of the CH2Cl protons in compound 21 is 4.02 ppm, whereas in the corresponding CH2S protons resonate at 3.20 ppm (Fig. 2). In addition, the 13C NMR spectrum showed that the carbon bearing the chlorine which appeared at 42 ppm was shifted to 37 ppm in the corresponding macrocycle.

In summary, we have demonstrated the successful synthesis of novel mixed-heteroatom macrocycles in high yields. The method applied a new strategy based on nucleophilic substitution of highly reactive species with strong nucleophiles. In addition, applying aqueous solvent assisted the solvation of sodium, and therefore, it could be acting as a template during cyclization of the macrocycles. Furthermore, most of the starting materials used in this approach were extremely reactive, which gave good overall yields and, as a result, reduced the number of column chromatographic purification steps.

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Supplementary data

Supplementary data (experimental procedures and copies of 1H and 13C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.025. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

27. For additional details, see the Supplementary data.