

THE THYME POLYETHERS

AN APPROACH TO THE SYNTHESIS OF A MOLECULAR KNOTTED RING

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Abstract—Recent progress on a realization of the Möbius strip approach to the synthesis of a molecular trefoil knot is discussed. Specifically, the synthesis and cyclization of a 4-rung ladder-shaped diol-ditosylate composed of crown ether rings fused by the tetrahydroxymethylethylene (THYME) unit are presented. In addition, some novel results in low dimensional topology deriving from consideration of the geometry of the novel molecular graphs defined by the subject compounds are discussed.

Philosophers and scientists have historically delighted in devising explanations of nature based upon geometrically interesting constructions. In chemistry, this pursuit dates back at least to Plato, who developed a theory of the interconversions of matter based upon the Platonic solids.¹ More recently, the pristine Euclidean geometry of the tetrahedron, cube, and pentagonal dodecahedron certainly helped define several very challenging targets for directed total synthesis.²

Topology, that branch of geometry dealing with properties remaining invariant given continuous deformation, has also served to define several interesting targets for total synthesis, including molecular linked rings (catenanes), knots, and Möbius strips. In the context of classical stereochemistry, based upon the Euclidean and topological properties of molecular graphs, such molecules exhibit a unique variety of stereoisomerism. Specifically, *topological stereoisomers* define molecular graphs with identical connectivity but which are topologically distinct.^{3f,g} *Topological stereochemistry* simply deals with the synthesis, characterization, and consideration of the chemically relevant geometry of topological stereoisomers.

Previous efforts in topological stereochemistry have resulted in several syntheses of catenanes,³ progressing from Wasserman's classic statistically random threading approach, affording a linked product in about 1% yield,⁴ through Schill's pioneering directed catenane syntheses,^{3c} and finally to Sauvage and co-worker's beautiful and efficient synthesis of linked rings utilizing Cu(I) as template.⁵ Synthesis of molecular Möbius strips and knots, however, has certainly lagged behind. We have recently developed chemistry affording the first synthesis of a molecular Möbius strip, more correctly termed a *Möbius ladder*, where the edge of the ladder is composed of a polyether chain, and the rungs are C=C bonds.^{3f,g,6} The key functional array in these molecules is the tetrahydroxymethylethylene (THYME) unit, suggesting the general name THYME polyethers to describe the class.

It may be argued that the really classic problem in topological stereochemistry is the synthesis of a molecular knotted ring.^{3,7} To our knowledge, no such molecule has ever been characterized with the important exception of knotted DNAs.^{3g} Our most recent results directed towards the total synthesis of a molecular trefoil knot via the THYME polyether strategy are presented herein.

The Möbius strip approach to synthesis of a trefoil knot

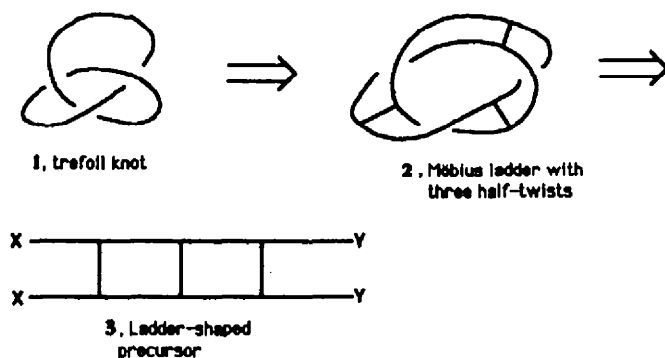
Our general approach to the synthesis of a molecular trefoil knot is based upon the topological properties of twisted bands, and was first suggested in the literature in 1961 by Wasserman, at the time at Bell Laboratories.^{3a,b} This "Möbius strip" approach is outlined in Scheme 1. The target structure **1** results from "cutting in half" a Möbius ladder with three half-twists (**2**).^{3g} The edge of the Möbius ladder defines a unique Möbius strip where the rungs of the ladder are spanning arcs. Breaking the rungs of the ladder is equivalent to cutting the strip "in half" the way one cuts a paper Möbius strip with scissors. For the sake of simplicity a 3-rung Möbius ladder is shown, though a trefoil results from cutting the rungs of any three half-twist Möbius ladder regardless of the number of rungs.

The three half-twist Möbius ladder **2**, in turn, derives from cyclization of the ladder-shaped key intermediate **3**, where the ends of the ladder are functionalized such that they may be joined. Of course, depending upon the details of the actual chemical system employed, several twisted products are possible (the two-braid wreaths), with the desired target **2** being one. The basic concept underlying this strategy for formation of a trefoil knot is that formation of a three half-twist Möbius ladder of type **2** should be more facile than creation of trefoil **1** by direct random knotting in cyclization of a single stranded precursor.

The THYME ladders

Our attempts to realize the synthesis outlined in Scheme 1 utilize as key intermediates the ladder shaped diol-di(*p*-toluenesulfonates) (diol-ditosylates) **4**, composed of crown ether rings fused by the THYME unit (Scheme 2). It was expected that treatment of compounds of type **4** with base under high dilution conditions would afford cyclic wreaths, and that the

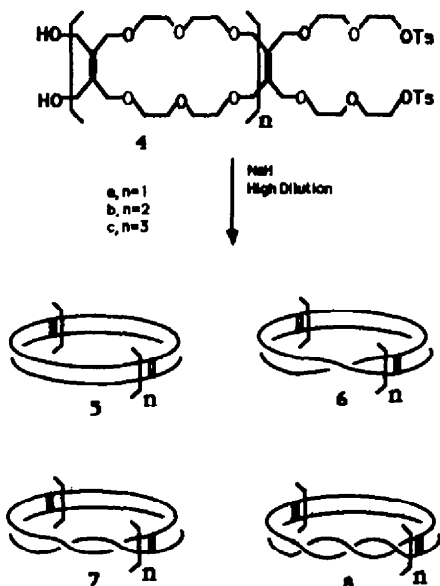
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Scheme 1. A trefoil knot by the Möbius strip approach.

topology of the products (i.e. the number of half-twists in the wreath) would be controlled to some extent by the length of the ladder (the value of n). Examination of CPK molecular models indicated that for the 2-rung diol-ditosylate **4a**, cyclization could give only a single tricyclic product **5a**, since the singly twisted product **6a** appeared highly strained. In addition, upon cyclization of the 3-rung diol-ditosylate **4b**, two products were predicted: the untwisted *prism* **5b**, and the Möbius ladder **6b** with one half-twist. Formation of more highly twisted products in the 3-rung system appeared disfavored sterically.

As reported,⁶ these expectations were indeed borne out. In order to accomplish a synthesis of a trefoil by this strategy, cyclization of a ladder of type **4** must proceed with three half-twists, to give a product of type **2**. Examination of molecular models indicated that the 4-rung diol-ditosylate **4c** might afford four products of cyclization, with zero, one, two, and three half-twists (**5c**, **6c**, **7c** and **8c**, respectively). Of course, the three half-twist isomer **8c** serves as a potentially useful realization of **2**. A description of the synthesis of 4-rung diol-ditosylate **4c** and its cyclization follows.

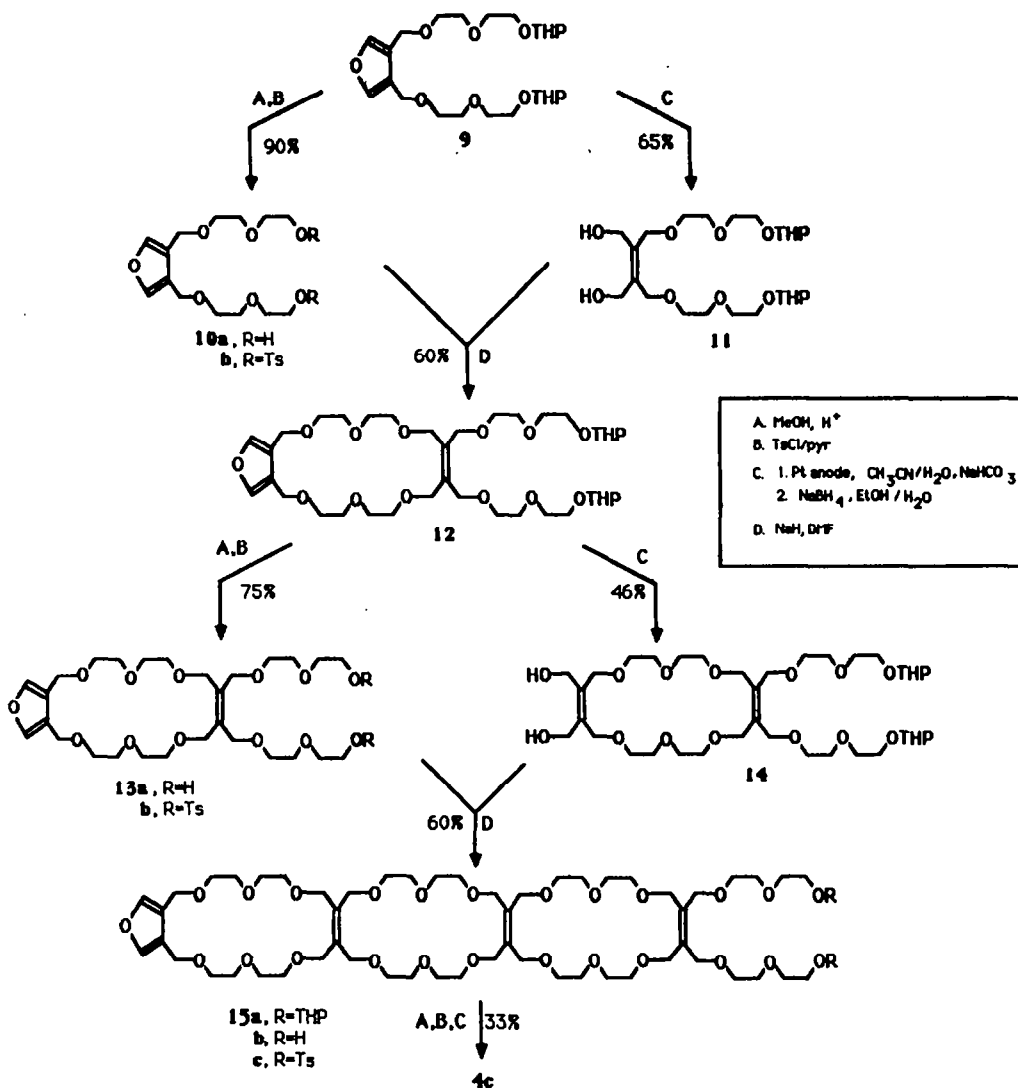


Scheme 2. Cyclization of the THYME diol-ditosylate ladders.

Synthesis of the 4-rung THYME diol-ditosylate **4c**

The synthesis of diol-ditosylate **4c** is shown in Scheme 3. A glance at this scheme readily indicates the highly convergent nature of the approach. The two-arm furan di(tetrahydropyranyl) ether (diTHP ether) **9** serves as starting material for synthesis of all the THYME polyethers.⁶ This material is readily prepared from diethyl 3,4-furandicarboxylate, chloroethoxyethanol, and dihydropyran (all available from Aldrich) in three steps and an overall yield of 88% based on the diethyl 3,4-furandicarboxylate. The rest of the sequence leading to diol-ditosylate **4c** requires iterative application of only four different reaction protocols: (1) methanolysis of the THP groupings of a furan diTHP compound; (2) conversion of the resulting furan-diol to the furan-ditosylate by treatment with *p*-toluenesulfonyl chloride; (3) conversion of a furan ring of either a furan-diTHP or a furan-ditosylate to the THYME diol moiety by application of Magnusson's anodic oxidation procedure,⁸ followed by direct sodium borohydride reduction of the resulting maleic dialdehyde bis-hemiacetal; and (4) intermolecular coupling of a furan-ditosylate with a diol-diTHP in a standard 22-crown-6 forming process. The crucially important point here is that the furan ring serves as a stable precursor for the THYME diol unit, and that the unmasking process occurs under very mild conditions (1° tosylates and THP ethers survive the deprotection in tact).

Several aspects of the sequence shown in Scheme 3 deserve some special comment. Specifically, considerable effort has been expended towards optimization of the all important chemistry by which the THYME diol unit is generated. The process involves two steps, as shown in Scheme 4, though the intermediate bis-hemiacetals **17** are quite labile and are not isolated. Early on an interesting observation concerning the anodic oxidation reaction (**16** \rightarrow **17**) was made. The oxidation reactions are run in a water-jacketed beaker utilizing a simple magnetic stir bar, a cylindrical Pt gauze anode, and a square Pt gauze cathode. The electrodes are first fixed rigidly in the reaction vessel with clamps, the vessel is charged with a solution of furan substrate in acetonitrile, a small volume of saturated aqueous sodium bicarbonate is added, then the reaction is run as described in the experimental section below. Interestingly, the process seems to proceed most efficiently when the saturated aqueous sodium bicarbonate is added to a rapidly



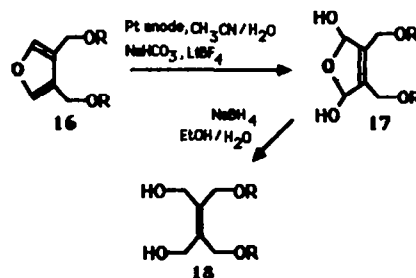
Scheme 3. Synthesis of diol-ditosylate 4c.

stirred solution of the furan in acetonitrile. If the order of addition of these reagents is reversed, the yield of the process becomes erratic.

The key difference seems to involve coating of the electrode surface with an insoluble aqueous bicarbonate slurry when the addition is done in the preferred way, suggesting that perhaps this coating of the working electrode is important in the reaction. In fact, the mechanism of anodic oxidation of furans under the Magnusson conditions is not known. Initially, we had assumed the process involved direct electron transfer from the furan ring to the electrode, resulting in formation of a stabilized radical cation intermediate. Subsequent reaction with water, followed by a second single electron oxidation and addition of water results in formation of the observed product 17.

To gain some insight into the actual processes

occurring in these reactions, oxidation of some furans of type 16 were run under much more carefully controlled conditions in the laboratories of Koval.[†] The electrochemistry of furan diTHP 9 was investigated using cyclic voltammetry at a Pt working electrode in dried acetonitrile (0.1 M LiBF₄). When the



Scheme 4. Generation of the THYME unit.

[†] We wish to give special thanks to Professor Carl Koval, of this department, for his help with the electrochemical studies.

electrode potential was scanned in a positive direction, oxidative decomposition of the solvent occurred at +1.5 V vs SCE. Anodic waves attributable to direct oxidation of the furan ring of **9** were not observed. When saturated aqueous sodium bicarbonate was added to the acetonitrile, the solvent decomposition limit became approximately 0.5 V, but again no direct oxidation of the furan ring was observed.

These results cast considerable doubt on the direct electron transfer hypothesis, and indicate that some other species is actually carrying the oxidation equivalents (holes) from the electrode to the furan substrate. We suggest this is the reason why the bicarbonate slurry coating the anode surface is important to obtain a good yield in the reaction. The relatively good efficiency of the reaction when run on rather large polyether molecules seems to preclude hydroxyl radicals as the hole carriers. While the actual carrier is not known, it is attractive to consider that oxidized bicarbonate (HCO_2^-) may act as the actual selective oxidant in these reactions.

Isolation of the bis-hemiacetals **17** proved problematical, often leading to polymerization. The best yields of THYME diol are obtained when a trace of hydroquinone is added to the crude electrochemical oxidation mixture, followed by filtration, removal of solvent at reduced pressure, then direct reduction of the resulting residue with sodium borohydride. However, some interesting problems with the hydride reduction also deserve comment. Specifically, when the reduction is carried out in ethanol solvent, a bothersome by-product, difficult to separate from the required diol **18**, is produced. This type of by-product has been tentatively identified by $^1\text{H-NMR}$ as over-reduced material, wherein the THYME double bond is saturated.

Attempts to alleviate this problem by running the reduction in the presence of cerium(III) chloride,⁹ or by use of 9-BBN as reducing agent¹⁰ proved ineffective. Over-reduction with sodium borohydride occurs even in the presence of the Ce(III) ion, while the bis-hemiacetal system is relatively inert toward 9-BBN in our hands. The problem is solved, however, by a simple change of solvent. Thus, it was found that reduction of **17** in 50% aqueous ethanol gave THYME diol with none of the saturated by-product detectable by TLC.

Finally, some very interesting differences in the course of similar reactions run on different substrates shown in Scheme 3 were observed. Most importantly, the time required for borohydride reduction of bis-hemiacetals **17** varied dramatically depending upon which actual substrate was involved. For example, reduction of the bis-hemiacetal deriving from two-arm furan-diTHP **9** required 12 h to go to completion, while reduction of the bis-hemiacetal derived from furan-ditosylate **15c** was complete in 45 min under identical conditions of concentration and solvent. If the reduction of **15c** was allowed to proceed for 2 h, the yield of the desired product was dramatically reduced, with formation of an unidentified by-product which still contained two toluenesulfonate moieties by $^1\text{H-NMR}$. In general, the reaction is accelerated by increasing the relative concentration of crown ether rings in the reaction, and it is suggested that a simple activation of the borohydride by the 22-crown-6 moieties (or simply by the polyethyleneglycol chains) is responsible for this behavior.

Cyclization of diol-ditosylate **4c**

Cyclization of the 4-rung diol-ditosylate **4c** was accomplished under standard high dilution cyclization conditions (Scheme 2). Thus, addition of a solution of **4c** in very dry dimethylformamide to a stirred slurry of oil-free sodium hydride in dry DMF was accomplished over a period of 15 h utilizing a syringe pump. After an additional 2 h of stirring at room temperature, the solvent was removed utilizing a rotary evaporator fitted with a dry-ice condenser and attached to a vacuum pump. The resulting residue was partitioned between water and dichloromethane, and the crude product was isolated from the organic extract.

In the homologous 3-rung system, alumina and silica gel both served to separate the two products produced in the cyclization very efficiently.^{6b} In the 4-rung system, however, silica gel and alumina both failed to resolve the products. Flash chromatography on silica gel did readily afford a clean mixture of cycles in 65% total yield, which was clearly multicomponent by ^{13}C - and $^1\text{H-NMR}$ of the mixture. Success in resolution of this mixture was finally achieved by reversed phase HPLC. Chromatography of the clean mixture obtained as described above on C18 RP silica gel in fact resolved four products, designated A, B, C, and D in order of elution (A appears first) off the column, though unfortunately compounds A and B were produced in such small amount (< 1% of the mixture combined) that identification of these minor products has proven impossible. The two major products C and D, on the other hand, were readily purified and characterized as described below.

Compound C showed two singlets, in a 1 : 2 ratio, in the 250 MHz $^1\text{H-NMR}$ spectrum, while compound D showed an AB quartet and a singlet in the same ratio. Based upon this evidence alone, it was possible to assign compound C the untwisted prism structure **5c** based upon the following reasoning. In the 3-rung system, **5b** showed an AB pattern for the allylic protons, indicating that the prism cannot "turn inside-out" rapidly on the NMR time scale. We had predicted^{3g} that in the 4-rung system such an "inside-out" conformational deformation would be facile enough to allow permutation of the inside and outside allylic protons on the edge of the prism on the NMR time scale, resulting in isochrony of the signal from these protons in an achiral environment (the protons become enantiotopic in the time average). For any of the twisted isomers **6-8c**, it is not possible for the edge protons to become enantiotopic or homotopic by any conformational change.

The $^1\text{H-NMR}$ spectrum of compound D (an AB pattern for the allylic methylene grouping) is consistent with any of the structures **6-8c**. Based upon arguments presented below, it seems very likely that compound D possesses an odd number of half-twists. We tentatively assign the 4-rung Möbius ladder structure **6c** to compound D, though structures **8c**, or even **7c** cannot be ruled out. Additional characterization of these novel constitutional isomers follows.

That compound C is, in fact, the 4-rung prism **5c** is proven unequivocally by single crystal X-ray analysis, as discussed in more detail below. When a solution of **5c** in deuteriodichloromethane was examined by variable temperature NMR at 250 MHz, splitting of the singlet corresponding to the allylic methylene protons into an AB quartet occurred, with $T_c = 250\text{ K}$, $\Delta\nu = 33.701\text{ Hz}$, and $J_{a,b} = 10.65\text{ Hz}$. These parameters allow an

estimation of the barrier to "inside-out" deformation of the prism of about $12.2 \text{ kcal mol}^{-1}$.

Both the prism **5c** and presumed Möbius ladder **6c** show four peaks in the ^{13}C -NMR spectrum at 62.9 MHz. As discussed in detail in previous reports, this observation is consistent with any of the structures **5**–**8**.^{3a,6a} That compound **D** is not a dimeric structure is strongly indicated by the observation of a strong protonated molecular ion in the FAB mass spectrum. A fascinating result was obtained when **5c** and **6c** were analyzed by gel permeation chromatography. Utilizing a Waters 500 Å ultra styragel column, with dichloroethane as eluting solvent, **5c** showed a longer retention time than the furan-diol precursor **15b**, implying on average that it is a smaller species in solution. This was expected since it was thought that cyclization to the prism should afford a product with reduced radius of gyration relative to the uncyclized precursor. However, when **6c** was subjected to the same analysis, it showed a *reduced* retention time relative to either the prism or furan-diol! When **5c** and **6c** are coinjected, they are resolved almost completely by the 500 Å ultra styragel column ($R_s = 1.08, 2844$ theoretical plates for the prism).

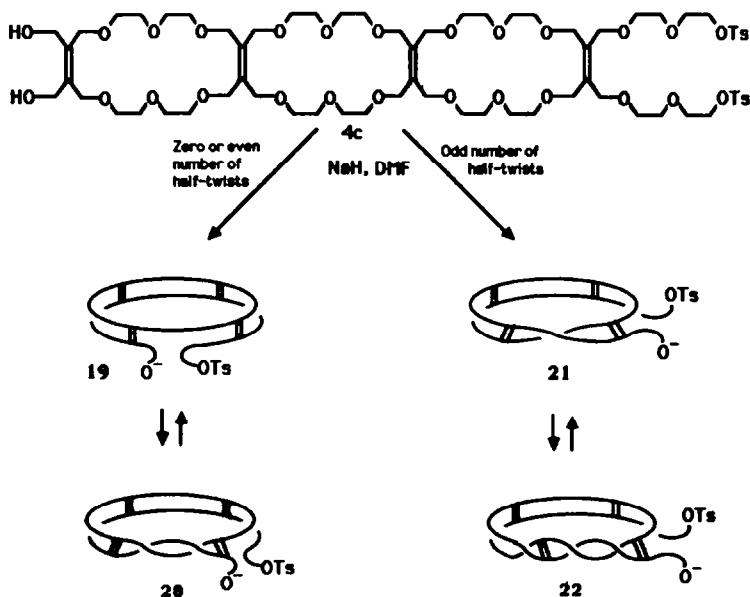
This observation has several interesting implications. First, the twisted product (probably **6c**) is behaving as if it has a larger average size in dichloroethane solvent than the prism **5c**. Thus, the topology of the "double helix" is controlling the conformation of the molecule in a manner vaguely reminiscent of the behavior of circular duplex DNAs.^{3a} Operationally, gel permeation chromatography offers an exceptionally facile method for preparative separation of these isomers, and it is hoped that size exclusion chromatography will also afford a method for separation of larger THYME polyether prisms and Möbius ladders.

While we find the results obtained in the 4-rung system interesting, the disappointing bottom line is that

the target three half-twist Möbius ladder **8c** was probably not formed efficiently enough to allow purification and characterization. Why were only two products produced in significant yield in the 4-rung cyclization reaction shown in Scheme 2? First, consider the possible courses for cyclization of the 4-rung diol-ditosylate **4c**. As shown in Scheme 5, it seems likely that initially **4c** is deprotonated to afford an alkoxide or bis-alkoxide. Initial intramolecular cyclization can then occur in one of two equally likely modes. Cyclization in the "even number of half-twists" mode gives intermediate **19**, which presumably could exist in equilibrium with the two half-twist conformer **20**. Conformer **19** could then cyclize to form the untwisted prism **4c**, while **20** could cyclize to form the chiral prism **7c** with two half-twists. The initial cyclization event in this case involves a 40-membered ring formation.

Alternatively, cyclization of **4c** by an equally likely 41-membered macrocyclization event leads to the "odd number of half-twists" manifold, giving **21** and **22**, again presumably in equilibrium. Thus, it is expected that the products deriving from the "even half-twist" and "odd half-twist" modes should be formed in an equal amount. Since it is unequivocally established that **5c**, deriving from cyclization of conformer **19**, is a major product, we feel that the other major product formed in the reaction must be either **6c** or **8c** deriving from **21** or **22**, respectively. While our examination of CPK models indicate that conformers **20** and **22** do not seem unusually strained, the results of the cyclization seem to indicate that only cyclization via **19** occurs in preference over cyclization of **20**. By analogy, we assign compound **D** structure **6c**, deriving from cyclization of **21**, though this is not proved. Our best guess at present is that conformers **20** and **22** are, in fact, strained relative to their less twisted relatives, or that **19** and **21** are formed initially, and equilibration to **20** and **22** is slow relative to the rate of the second cyclization event.

Clearly, it seemed possible that by varying the



Scheme 5. Cyclization of diol-ditosylate **4c**.

conditions of the cyclization reaction, one could increase the yield of the minor products of the reaction (presumably **7c** and **8c**). If enthalpic problems or slow equilibration between conformers were important, then possibly increasing the temperature of the cyclization reaction could favor more highly twisted products. On the other hand, it seemed possible that conformers **20** and **22** could be disfavored entropically relative to their presumably more flexible counterparts **19** and **21**. If this were true, then possibly lowering the cyclization temperature could favor more twisted products.

In fact, changes in the reaction temperature had no effect on the relative amounts of compounds A–D, as indicated by RP HPLC analysis. Indeed, several completely different cyclization protocols were explored in an effort to increase the amounts of the minor products of the reaction, including CsOH/THF at reflux, and addition of CsCl to the DMF cyclization reaction. Only a lowering of the yield of cycles resulted from any of the alternative reaction protocols explored—no change in the ratio of the products was ever observed.

We feel that the most likely explanation of the results obtained in the 4-rung system is that the twisted products are strained relative to the untwisted prism. This includes the Möbius ladder **6c** with one half-twist. This material is produced, however, since the strain is not introduced until the second cyclization event (**21** → **6c**). Experiments designed to overcome this problem, and to obtain experimental evidence for the proposed twisting strain, are under way.

The crystal structure of the 4-rung prism

X-Ray analysis of the crystalline prism **5c** was accomplished as described in the experimental section

below. Views of the structure of **5c** along three mutually orthogonal axes are shown in Fig. 1. The molecule in the crystal possesses an inversion center, and all four of the THYME double bonds are in similar “anti” conformations. The conformation of the molecule in the crystal does suggest an explanation of the gel permeation results. That is, if the 4-rung prism prefers a conformation in solution similar to that found in the crystalline state, its average size is relatively small. It is not unreasonable to suggest that twisting of the polyether chain could effectively prevent adoption of a “collapsed” conformation such as exhibited by the prism, affording a species with a larger average size in solution.

Several experiments aimed at crystallization of the 4-rung Möbius ladder were also undertaken. As isolated by HPLC, the pure material is an amorphous glass which sometimes appears deceptively crystalline. No crystals, however, have been obtained for this material. Both the prism **5c** and presumed Möbius ladder **6c** complex barium thiocyanate in chloroform, as evidenced by the following observations. When a solution of either host in chloroform-*d* is stirred with solid barium thiocyanate, then the solution is filtered and the filtrate is analyzed by ¹H-NMR, a very complex pattern of signals is observed, suggesting complex formation has effectively frozen out conformations wherein the 16 pairs of allylic protons are no longer homotopic on the NMR time scale. When this solution is extracted with water, and the organic phase is examined by NMR, the spectrum of the free host reappears.

Upon removal of solvent from the barium complex of the Möbius ladder **6c**, a white solid was obtained. Attempts to crystallize this material led to what appeared to be microcrystals. Examination of this solid

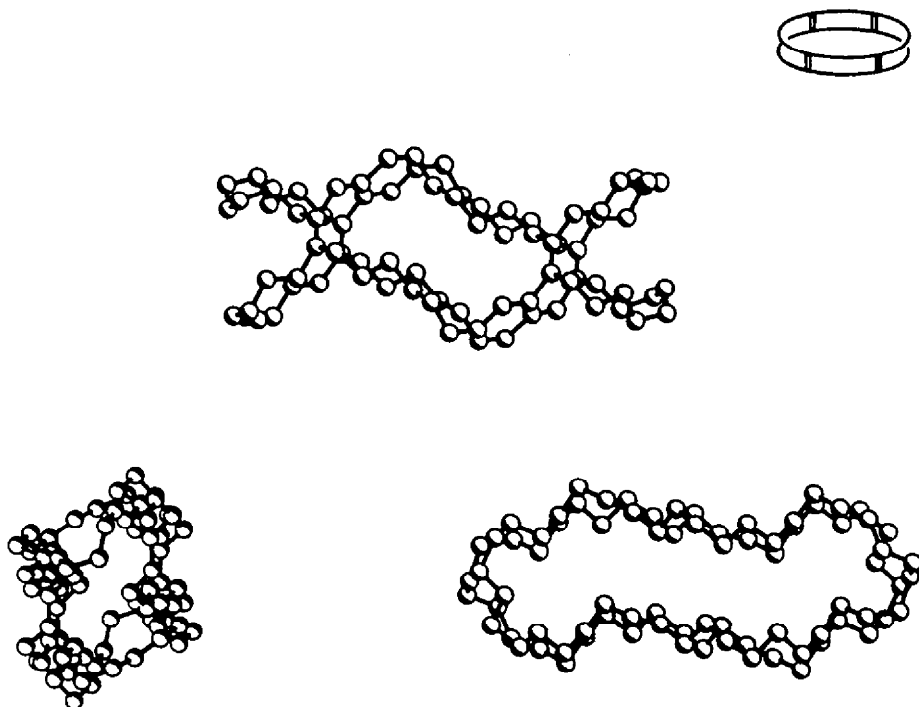


Fig. 1. Crystal structure of 4-rung prism **5c**.

by powder X-ray diffraction, however, showed again that the solid complex is amorphous. Additional experiments directed towards crystallization of this 4-rung Möbius ladder in order to unequivocally prove its structure are in progress.

Breaking the rungs of the THYME prisms and Möbius ladders

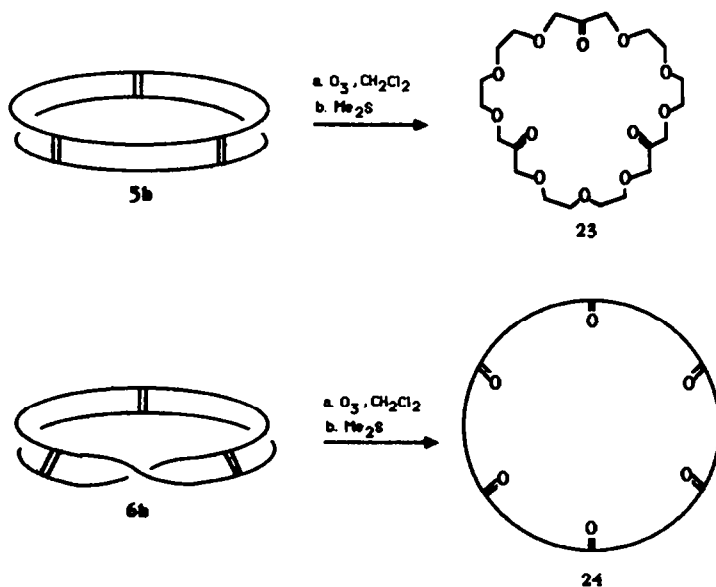
Once a synthesis of a three half-twist Möbius ladder is achieved, the final step in preparation of a trefoil knotted ring must involve cleavage of the C=C bonds. Actually, the cleavage reaction also serves as an important method of structure proof of the twisted ladders, as described below. While our recent efforts have focused on synthesis of the 4-rung ladders, some studies directed towards development of efficient techniques for cleavage of the rungs of the THYME polyethers have been accomplished, and some possible serious pitfalls in the strategy have been uncovered.

Specifically, ozonolysis of the THYME double bonds has been explored as a method for breaking the rungs of the prisms and Möbius ladders. Initial experiments on simple model systems indicated that ozonolysis of THYME tetraethers under carefully controlled conditions affords the expected bis-alkoxyketone in excellent yield. Application of the ozonolysis process to the 3-rung prism and Möbius ladder, however, has proven somewhat problematical. Thus, as shown in Scheme 6, treatment of a dichloromethane solution of 3-rung prism **5b** and the ozonolysis indicator dye Solvent Red 23 (Aldrich) at -70° with ozone until the dye is decolorized,¹¹ then immediate quenching of the reaction by addition of an excess of dimethylsulfide, removal of solvent at reduced pressure, and purification of the product by flash chromatography on silica gel gives the triketone **23**. Similar treatment of the 3-rung Möbius ladder **6b** gives the hexa-ketone **24**. Analysis of these materials by ^{13}C -NMR at 62.9 MHz shows the expected four singlets for

the four unique carbons of each molecule, the ^1H -NMR at 90 MHz showed the expected two singlets in a 1:2 ratio for each product, and the IR spectra are fully consistent with structures **23** and **24**.

Furthermore, analysis of the products by micro styragel gel permeation chromatography shows that the product obtained upon cleavage of the Möbius ladder is larger than the product obtained from the prism. The crucially important mass spectra were finally obtained as follows. When triketone **23** was injected into the source of a chemical ionization mass spectrometer in acetonitrile/water solution (this solvent also acts as the ionizing reagent), the expected protonated molecular ion was observed. Identical analysis of the hexaketone **24**, however, gave *no peaks at all!* This frustrating result is apparently due to the very low volatility of **24**. As expected, both **23** and **24** were good substrates for fast atom bombardment (FAB) mass spectrometry. Utilizing the FAB ion source, a beautiful protonated molecular ion was observed for the hexaketone **24** as well as the triketone **23**.

The first hints that problems might be encountered with this approach came upon examination of the ^1H -NMR spectra of ketones **23** and **24** at 250 MHz. At the higher field, it became apparent that the ethyleneoxy region of the proton spectrum for the ketones was always integrating high relative to the protons α to the carbonyl (about 2.25:1 for our best samples), well outside of experimental error. In fact, if a sample of the neat triketone **23** is simply stored in an evacuated flask, another spot appears in the TLC of the material, and after several days the triketone is gone, and conversion to the new spot is complete. While this new material has not been identified, the IR, ^{13}C -, and ^1H -NMR spectra are most consistent with the product of an intramolecular aldol condensation. We suggest that the problems encountered in the proton spectra of ketones **23** and **24** are due to formation of small amounts of such intramolecular aldol products formed during purifi-



Scheme 6. Breaking the rungs of a Möbius ladder.

cation of the material. The aldolization of these ketones is probably particularly facile owing to the destabilization of the ketone carbonyl by the two electron-withdrawing alkoxyethyl groupings.

This observation forecasts an interesting problem with synthesis of a trefoil knot by ozonolysis of a three half-twist Möbius ladder. Specifically, in the knotted product it is expected that intramolecular aldol will be especially facile because of the enforced proximity of the ketone moieties. Experiments are now under way to develop a procedure for derivatization of the carbonyl groupings of the cyclic polyketones in order to overcome this problem with unwanted reactivity.

Topology of the Möbius ladders

The chemical aspects of topological stereochemistry as exemplified by synthesis of knots and links has a certain novel character which many chemists find particularly intriguing. It was at first surprising for us to learn that a chemist's way of thinking about this special branch of stereochemistry serves to define novel and challenging problems in mathematical low-dimensional topology also.^{3f} Indeed, we suggest that research in *stereochemical topology* currently under way in the groups of Jonathan Simon of the Mathematics Department at the University of Iowa and Erica Flapan of the Mathematics Department at Rice University, has considerable practical application in chemistry. While this novel interface between topology and chemistry is being vigorously explored, a detailed discussion of results obtained to date is outside the scope of this article. It seems appropriate, however, to include a very short discussion of one particular novel topological result dealing with the following question: What does a twisted THYME polyether of type 6 really have in common with a Möbius strip?

On the topological chirality of the Möbius ladders. As discussed in detail elsewhere,^{3g} topological chirality is quite different from the Euclidean chirality chemists normally deal with. A Euclidean chiral object is not rigidly superimposable on its own mirror image, while a topologically chiral object cannot be deformed into its mirror image by continuous deformation. In this context, continuous deformation includes any bending or stretching as long as no lines are broken or connected, and lines or points are not passed through each other. Under these conditions of infinite flexibility, almost all chemical enantiomers are topologically achiral. For example, the 2-butanol enantiomers require the Euclidean invariance of the tetrahedral angle in order to remain distinct. Topologically, they are interconvertible, and therefore topologically achiral. The trefoil knot, on the other hand, is well known to be topologically chiral. That is, the trefoil is not superimposable on its mirror image, and in addition, cannot be deformed into its mirror image without breaking the line.

It is well known that a Möbius strip is topologically chiral. A Möbius strip, however, is a surface: a two-dimensional object; while the Möbius ladders are one-dimensional objects composed of points and lines (mathematically, any construction composed of points and lines is called a graph—chemical structural formulas are therefore graphs where the points are defined by the nuclei, and the lines (edges) are defined by the bonds). The obvious question: are the Möbius ladders topologically chiral, like a Möbius strip?

Questions such as this one may be answered by the techniques of low-dimensional topology, or more specifically, knot theory. Indeed, as the name suggests, mathematicians have really concentrated on knots and links (various embeddings of circles in three-dimensional space), and have done relatively little work on topological chirality of graphs such as the Möbius ladders. Indeed, the question of the topological chirality of the Möbius ladders remained unanswered until well after the first molecular Möbius ladder had been synthesized. Based partly upon interactions with the author, Professor Simon has recently produced a proof of the topological chirality of the 3- and 4-rung Möbius ladders,¹² and some rather interesting topological results have emerged. Specifically, a 2-rung "Möbius ladder" **6a** is not topologically chiral, and may be deformed into its mirror image by rotation about a double bond. Indeed, the graph defined by structure **6a** is not a Möbius ladder at all, but a tetrahedral graph. While we have not synthesized such a molecule, several compounds with the 2-rung ladder graph have been prepared in other laboratories.^{3g}

Interestingly, the Möbius ladder with 3 rungs (**6b**) is also topologically achiral if all of the edges (lines) in the graph are considered as equivalent! It is a challenging exercise to discover the deformation converting **6b** with nine equivalent edges into its mirror image without breaking any lines. In our molecules, however, the double bonds are certainly different from the polyethyleneoxy chains. Topologically, the graph of the 3-rung Möbius ladder defined by structure **6b** has two differently colored edges: the rungs, and the edges defining the boundary of the Möbius surface. In fact, such a Möbius ladder with three differentiated rungs is now known unequivocally to be topologically chiral based upon Jon Simon's proof. Furthermore, it has been shown that the 4-rung Möbius ladder **6c** is topologically chiral even with all edges identical. Thus, a 2-rung "Möbius ladder" is topologically achiral, a 3-rung Möbius ladder is topologically chiral if it has three differentiated edges (the rungs), and a 4-rung Möbius ladder is unconditionally topologically chiral.

EXPERIMENTAL

All ¹H-NMR spectra were taken at 250 MHz on a Bruker WM-250 instrument unless otherwise indicated. ¹³C-NMR spectra were recorded on the Bruker WM-250 instrument at 62.9 MHz. IR spectra were recorded with a Perkin-Elmer 727B IR spectrometer. Analytical TLC was performed on glass silica gel plates (0.25 mm thick E. Merck silica gel 60-F254), or on alumina plates (alumina 60 F₂₅₄ neutral "Type E", E. Merck). Visualization was achieved with either UV light, vanillin spray reagent, or iodine staining. Chromatographic purifications were performed using flash chromatography on E. Merck 40–63 μm normal phase silica gel, or utilizing a Waters Prep 500A instrument fitted with silica gel cartridges.

THF was purified prior to use by distillation from benzophenone and Na. CH₂Cl₂, acetone and hexanes were fractionally distilled. DMF was purified to "super-dryness" by the method of Burfield and Smithers.¹⁵ Reagent grade MeOH, EtOH, and acetonitrile were used without further purification. Reagent grade pyridine was stored over 3 Å sieves. Dihydropyran (DHP, Aldrich) was distilled from Na under Ar. Diethyl-3,4-furandicarboxylate (Aldrich) was vacuum distilled (b.p. 120.5–122.5/3.0–3.5 mm Hg), 2-(2-chloroethoxy)ethanol (Aldrich), NaBH₄ (Alfa) and LAH (Alfa) were used without further purification. Oil-free NaH was obtained

by washing under Ar a 50% oil dispersion of NaH (Alfa) several times with dry hexanes followed by decantation after each washing. *p*-Toluenesulfonyl chloride (TsCl) was purified according to the procedure of Pelletier.¹⁶

All reactions were stirred magnetically unless otherwise noted. Reactions requiring an inert atmosphere were run under dry Ar. The Ar line was arranged such that reaction vessels could be evacuated and purged with Ar, then kept under a slight positive pressure of Ar using an oil bubbler.

Electrochemical reactions were performed in 50 or 100 ml water cooled beakers with a cylindrical Pt anode (5 × 2.8 cm diam, fine mesh screen) and a square Pt cathode (5 × 3.7 cm, fine mesh screen). An Acopian Series K power supply was used. Ar was bubbled through the mixtures for 10 min prior to and during the period in which current was applied. Supporting electrolyte, LiBF₄ (Alfa), was added to obtain a desired voltage.

Combustion analyses were performed by Galbraith Laboratories, Knoxville, Tennessee, and by Spang micro-analytical laboratories, Ann Arbor, Michigan.

Synthesis of key intermediate 9

2,2' - (3,4 - Furan-2,5-diylbis(methyleneoxyethyleneoxy))bis - (tetrahydro - 2H - pyran) (9). A soln of 3,4-bis(hydroxymethyl)furan¹⁷ (7.65 g, 59.7 mmol) in 30 ml of DMF was added dropwise over a period of 20 min to a stirred, Ar protected suspension of oil-free NaH (14.5 g, 604 mmol) in 150 ml of DMF. After 2.5 h, a soln of 2 - (2 - (2 - chloroethoxy)ethoxy) - tetrahydro - 2H - pyran¹⁸ (75.3 g, 361 mmol) in 50 ml of DMF was added dropwise over a period of 1 h. The resulting mixture was stirred for 48 h and quenched by addition of 1.1 ml (59.7 mmol) of water. Solvent was removed by evaporation under reduced pressure followed by drying *in vacuo* (12 h). The muddy-brown residue was digested with CH₂Cl₂ (300 ml), filtered through Celite and the solvent removed under reduced pressure. The crude product was purified by chromatography on silica gel to yield after drying *in vacuo* (12 h) 24.95 g (88%) of furan di-THP ether 9 as a clear, colorless oil: ¹H-NMR (CDCl₃) δ 1.30–2.03 (m, 6H), 3.35–4.07 (m, 10H), 4.48 (s, 2H), 4.63 (br t, 1H), 7.45 (s, 1H); ¹³C-NMR (CDCl₃) δ 19.51, 25.53, 30.63, 62.13, 63.68, 66.69, 69.41, 70.67, 98.92, 121.83, 141.63; IR (neat) 3000–2800, 1189–1060 cm⁻¹. (Found: C, 61.41; H, 8.69. Calc for C₂₄H₄₀O₉: C, 61.00; H, 8.53; O, 30.47%.)

Deprotection of di-THP ethers (step A of Scheme 3)

2,2' - (3,4 - Furan-2,5-diylbis(methyleneoxyethyleneoxy)) - diethanol (10a). A suspension of Dowex-50W-x12 ion exchange resin (8.5 g) in a soln of 9 (14.1 g, 29.8 mmol) in 300 ml of MeOH and 300 ml of CH₂Cl₂ was allowed to reflux while stirring under Ar for 24 h. The cooled mixture was filtered and the solvent removed under reduced pressure affording 8.98 g (99%) of crude product. Purification by chromatography on silica gel yielded 8.01 g (88%) of 10a as a colorless oil: ¹H-NMR (CDCl₃) δ 3.28 (br s, 1H, —OH), 3.50–3.83 (m, 8H), 4.50 (s, 2H), 7.43 (s, 1H); ¹³C-NMR (CDCl₃) δ 61.69, 63.58, 69.26, 70.52, 72.71, 121.78, 141.82; IR (neat) 3400 (br s), 3000–2750 (s), 1200–1000 (s) cm⁻¹.

Furan-diols 13a and 15b were prepared in a similar manner. Physical constants for these compounds follow.

2 - 2' - ((6,7,9,10,12,15,17,18,20,21 - Decahydro - 4H,23H - furo(3,4 - i)(1,4,7,12,15,18)hexaoxacyclodocosin - 13,14 - diyl)bis(methyleneoxyethyleneoxy))diethanol (13a). ¹H-NMR (CDCl₃) δ 3.05 (br, 1H, —OH), 3.47–3.87 (m, 16H), 4.20 (s, 2H), 4.23 (s, 2H), 4.50 (s, 2H), 7.43 (s, 2H); IR (neat) 3440 (br s), 1660 (w), 1200–1060 (s) cm⁻¹. (Found: C, 56.11; H, 8.40. Calc for C₂₈H₄₈O₁₃: C, 56.74; H, 8.16; O, 35.09%.)

2,2' - ((6,7,9,10,13,15,16,18,19,22,24,25,27,28,30,33,35,36,38,39,42,44,45,47,48,51,53,54,56,57 - Tricontahydro - 4H,12H,21H,41H,50H,59H - furo(3',4' : 20,21)(1,4,7,12,15,18) - hexaoxacyclodocosino(9,10 - i)(1,4,7,12,15,18)hexaoxacyclodocosino(9,10 - i)(1,4,7,12,15,18)hexaoxacyclodocosin - 31,32 - diyl)bis(methyleneoxyethyleneoxy))diethanol (15b). White amorphous solid; ¹H-NMR (CDCl₃)

δ 3.47–3.78 (m, 33H), 4.08–4.30 (s, 12H), 4.49 (s, 2H), 7.37 (s, 1H); ¹³C-NMR (CDCl₃) 61.83, 63.70, 68.02, 69.60, 69.65, 70.71, 70.83, 70.96, 72.63, 122.28, 136.92, 136.95, 141.54. (Found: C, 57.41; H, 8.43. Calc for C₅₆H₉₆O₂₅: C, 57.52; H, 8.28%.)

Tosylation of furan-diols (step B of Scheme 3)

2,2' - (3,4 - Furan-2,5-diylbis(methyleneoxyethyleneoxy)) - diethanol di - *p* - toluenesulfonate (10). A soln of 10a (8.01 g, 26.3 mmol) in 60 ml of pyridine was cooled while stirring under Ar until frozen. Upon thawing, 20.1 g (105 mmol) of TsCl was added and stirring continued until dissolution was complete. The resulting soln was stoppered tightly and placed in the cold (0°) for 24 h. Pyridine was removed by evaporation under reduced pressure followed by partitioning of the crude product between 200 ml of CH₂Cl₂ and 100 ml of 10% HCl aq. The aqueous layer was extracted with two 200 ml portions of CH₂Cl₂, and the combined organic extracts were dried (K₂CO₃/Na₂SO₄) and evaporated under reduced pressure. Chromatography of the residue on silica gel gave 12.86 g (80%) of 10b as a light yellow viscous oil: ¹H-NMR (CDCl₃) δ 2.42 (s, 3H), 3.47–3.75 (m, 6H), 4.00–4.20 (t, 2H), 4.40 (s, 2H), 7.2–7.43 (s and d, 3H), 7.70–7.93 (d, 2H); IR (neat) 3050 (w), 3000–2800 (s), 1595 (s), 1060–1160 (s).

Furan-ditosylates 13b and 15c were prepared in a similar manner. Physical constants for these compounds follow.

2 - 2' - ((6,7,9,10,12,15,17,18,20,21 - Decahydro - 4H,23H - furo(3,4 - i)(1,4,7,12,15,18)hexaoxacyclodocosin - 13,14 - diyl)bis(methyleneoxyethyleneoxy))diethanol di - *p* - toluenesulfonate (13b). ¹H-NMR (CDCl₃) δ 2.45 (s, 3H), 4.50 (s, 2H), 7.33–7.58 (m, 3H), 7.83–8.00 (m, 2H); ¹³C-NMR (CDCl₃) δ 21.40, 63.39, 67.51, 68.39, 69.36, 70.48, 122.17, 127.70, 129.79, 132.85, 136.58, 141.29, 144.69; IR (neat) 3000–2800 (s), 1600 (m), 1170–1080 (s) cm⁻¹; mass spectrum (VG 70-70 E + FAB, wet glycerol matrix) *m/z* 918 (M + 18). (Found: C, 55.74; H, 6.93; O, 29.57. Calc for C₄₂H₆₀O₁₇S₂: C, 55.99; H, 6.71; O, 30.19; S, 7.12%.)

2,2' - ((6,7,9,10,13,15,16,18,19,22,24,25,27,28,30,33,35,36,38,39,42,44,45,47,48,51,53,54,56,57 - Tricontahydro - 4H,12H,21H,41H,50H,59H - furo(3',4' : 20,21)(1,4,7,12,15,18) - hexaoxacyclodocosino(9,10 - i)(1,4,7,12,15,18)hexaoxacyclodocosino(9,10 - i)(1,4,7,12,15,18)hexaoxacyclodocosin - 31,32 - diyl)bis(methyleneoxyethyleneoxy))diethanol di - *p* - toluenesulfonate (15c). White amorphous solid; ¹H-NMR (CDCl₃) δ 2.43 (s, 3H), 3.44–3.70 (m, 30H), 4.00–4.26 (m, 14H), 4.43 (s, 2H), 7.29–7.43 (m, 3H), 7.72–7.86 (m, 2H); ¹³C-NMR (CDCl₃) δ 43.38, 63.78, 67.98, 68.13, 68.83, 69.21, 69.69, 69.73, 69.76, 70.89, 70.91, 71.01, 122.39, 127.99, 129.83, 136.87, 136.98, 141.57.

Anodic oxidation—borohydride reduction sequence (step C of Scheme 3)

2,3 - Bis((2 - (2 - ((tetrahydro - 2H - pyran - 2 - yl) - oxy)ethoxy)ethoxy)methyl) - 2 - butene - 1,4 - diol (11). To a 100 ml electrochemical vessel (water-jacketed beaker) fitted with a Pt anode and cathode and a magnetic stir bar, was added furan di-THP ether 9 (5.0 g, 10.6 mmol), and 90 ml of acetonitrile. To the resulting rapidly stirred soln was slowly added 7 ml of sat NaHCO₃ aq. The power supply was turned on and enough LiBF₄ was added (approximately 100 mg) to adjust the voltage to 7 V at 500 mA. Current was passed through the rapidly stirred mixture until no more starting material could be detected by TLC (2 h 21 min or 13.3 min mmol⁻¹ of furan starting material). A trace of hydroquinone was added to suppress polymerization and the mixture was allowed to stir for another 10 min. Filtration through Celite and evaporation of solvent under reduced pressure afforded the crude bis-hemiacetal. To the crude product was added 50 ml of EtOH-H₂O (50:50) and 1.22 g (32.3 mmol) of NaBH₄. The reaction was allowed to stir with cooling (ice-water bath) for 1 h. The bath was removed, and stirring was continued for an additional 11 h. The crude 11 was isolated by evaporation of the EtOH under reduced pressure, addition of 20 ml of water to the resulting aqueous mixture, then extraction of the soln with

CH_2Cl_2 . The organic extract was dried ($\text{K}_2\text{CO}_3/\text{Na}_2\text{SO}_4$), filtered through Celite, stripped of solvent, and the resulting crude product was purified by silica gel chromatography to afford 3.4 g (65%) of **11** as a colorless oil: $^1\text{H-NMR}$ (CDCl_3) δ 1.33–2.00 (m, 6H), 3.33–4.08 (m, 11H), 4.23 (s, 2H), 4.30 (d, 2H, $J = 6$ Hz), 4.63 (t, 1H, $J = 2.5$ Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 19.56, 25.48, 30.58, 60.82, 62.32, 66.69, 69.21, 70.62, 99.11, 138.33; IR (neat) 3600–3200 (s), 1650 (w), 1075–1200 cm^{-1} .

Diol-diTHP ether **14** and **4c** were prepared similarly except for the time required for the borohydride reduction. Physical constants for these compounds, and specific differences in the reaction procedure for their preparation follow.

20.21 - Bis(2 - (2 - ((tetrahydro - 2H - pyran - 2 - yloxy)ethoxy)ethoxy)methyl) - 1,4,7,12,15,18 - hexaoxacyclodocosa - 9,20 - diene - 9,10 - dimethanol 14. The borohydride reduction of the bis-hemiacetal derived from anodic oxidation of **12** was allowed to proceed for 10 min with ice bath cooling, then for 2 h at room temp. Workup and purification by silica gel chromatography then afforded a 46% yield of **14** as a clear colorless oil: $^1\text{H-NMR}$ (CDCl_3) δ 1.33–1.86 (m, 6H), 3.33–3.90 (m, 19H), 3.95–4.30 (m, 8H), 4.52 (br t, 1H, $J = 3$ Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 19.39, 25.36, 30.51, 60.83, 62.07, 66.60, 67.78, 69.19, 69.54, 70.45, 70.52, 70.84, 70.87, 98.87, 136.73, 137.82; IR (neat) 3600–3200, 1650(w), 975–1200 cm^{-1} ; mass spectrum (VG 70-70 E, + FAB, wet glycerol matrix), m/z 798 (M + 18).

3,4,6,7,9,12,14,15,17,18,21,23,24,26,27,30,32,33,35,36,38,41,43,44,46,47,50,52,53,55,56,58 - Dotriacontahydro - 39,40 - bis(2 - (2 - hydroxyethoxy)ethoxy)methyl) - 1H, 20H, 29H, 49H - bis(1,4,7,12,15,18)hexaoxacyclodocosa(9,10 - i:9',10' - t)[1,4,7,12,15,18]hexaoxacyclodocosa - 10,1 - dimethanol - 39,40 - di - p - toluenesulfonate 4c. The borohydride reduction of the bis-hemiacetal derived from anodic oxidation of **15c** was allowed to proceed for 10 min with ice bath cooling, then for 0.5 h at room temp. Workup and purification by silica gel chromatography then afforded a 48% yield of **4c** as a white amorphous solid: $^1\text{H-NMR}$ (CDCl_3) δ 2.45 (s, 3H), 3.05 (br s, 1H, —OH), 3.44–3.81 (m, 32H), 4.03–4.39 (m, 16H), 7.26–7.43 (m, 3H), 7.75–7.88 (m, 2H); $^{13}\text{C-NMR}$ (CDCl_3) δ 21.57, 61.21, 67.86, 67.96, 68.00, 68.10, 68.19, 68.74, 69.22, 69.58, 70.81, 70.92, 127.97, 129.93, 136.84, 136.97, 138.04; mass spectrum (VG 70-70 E, + FAB, wet glycerol matrix), m/z 1514 (M + 18); (MS 50 + FAB, thiodiglycerol matrix), m/z 1519 (M + Na⁺).

22-Crown-6 forming reactions (step D of Scheme 3)

6,7,9,10,12,15,17,18,20,21 - Decahydro - 13,14 - bis(2 - (2 - ((tetrahydro - 2H - pyran - 2 - yloxy)ethoxy)methyl) - 4H,23H - furo(3,4 - i)[1,4,7,12,15,18]hexaoxacyclodocosa 12. To a suspension of oil-free NaH (4.8 g, 209 mmol) in a 213-neck flask fitted with a mechanical stirrer, was added 550 ml of DMF. A soln of **11** (4.9 g, 9.9 mmol) in 200 ml of DMF was added in one portion. After stirring in the dark for 2 h, a soln of **10** (6.2 g, 10.1 mmol) in 250 ml of DMF was added in one portion. The reaction was allowed to proceed at room temp in the dark for 6 h, after which time it was quenched by cooling (ice-water bath) followed by dropwise addition of 100 ml of 50% aq THF. The resulting soln was stirred briefly with 50 g of silica gel and filtered through Celite. Solvent was removed by evaporation under reduced pressure (vacuum pump) and the resulting residue was dried *in vacuo* for 8 h. The crude mixture was digested with CH_2Cl_2 , filtered through Celite to remove sodium tosylate, and stripped of solvent under reduced pressure. The crude product was purified by silica gel chromatography, affording 4.6 g (61%) of **12** as a light yellow viscous oil: $^1\text{H-NMR}$ (CDCl_3) δ 1.33–1.97 (m, 6H), 3.33–4.03 (m, 18H), 4.17 (s, 2H), 4.33 (s, 2H), 4.50 (s, 2H), 4.63 (br t, 1H), 7.44 (s, 1H); IR (neat) 3000–2750(s), 1700–1600(w), 1200–1060 (s) cm^{-1} . (Found: C, 60.11; H, 8.62. Calc for $\text{C}_{38}\text{H}_{64}\text{O}_{15}$: C, 59.98; H, 8.48; O, 31.54%.)

Coupling of **13a** and **14** was accomplished in a similar manner. Physical properties of the product **15a** follow.

6,7,9,10,13,15,16,18,19,22,24,25,27,28,30,33,36,38,39,42,44,45,47,48,51,53,54,56,57 - Triacontahydro - 31,32 - bis(2 - (2 - ((tetrahydro - 2H - pyran - 2 - yloxy)ethoxy)ethoxy)methyl) - 4H,

12H, 21H, 41H, 50H, 59H - furo(3',4':20,21)(1,4,7,12,15,18) - hexaoxacyclodocosa(9,10 - i)(1,4,7,12,15,18)hexaoxa - cyclodocosa(9,10 - t)[1,4,7,12,15,18]hexaoxacyclodocosa 15a. White amorphous solid; $^1\text{H-NMR}$ (CDCl_3) δ 1.33–1.86 (m, 6H), 3.33–4.00 (m, 34H), 4.15–4.38 (s, 12H), 4.55 (s, 2H), 4.63 (br t, 1H, $J = 3$ Hz), 7.46 (s, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 19.46, 25.44, 30.59, 62.14, 63.63, 66.67, 67.80, 67.87, 67.91, 69.15, 69.58, 69.62, 70.53, 70.60, 70.78, 70.89, 98.94, 122.19, 136.82, 136.90, 141.48; mass spectrum (VG 70-70 E, + FAB, wet glycerol matrix), m/z 1354 (M + 18).

Cyclization of diol-ditosylate 4c

3,4,6,7,9,12,14,15,17,18,21,23,24,26,27,30,32,33,35,36,38,41,43,44,46,47,50,52,53,55,56,58 - Dotriacontahydro - 10,40:11,39 - bis(methanoxyethanoxyethanoxy)methano - 1H, 20H, 29H, 49H - bis[1,4,7,12,15,18]hexaoxacyclodocosa(9,10 - i:9',10' - t)[1,4,7,12,15,18]hexaoxacyclodocosa, 4 - rung Möbius ladder 6c. (Interestingly, *Chemical Abstracts* has no accepted nomenclature for differentiating the single half-twist Möbius ladder **6c** from the three half-twist isomer.) To a 50 ml 2-neck flask charged with a suspension of oil-free NaH (15 mg, 0.63 mmol) in 11.3 ml of DMF was added a soln of **4c** (32 mg, 0.0214 mmol) in 5 ml of DMF via syringe pump. The addition was accomplished over 15 h while the soln was stirred in the dark. The mixture was allowed to stir for an additional 2 h, then was quenched by cooling with an ice-water bath followed by dropwise addition of 1 ml of water. After removal of solvent by rotary evaporation (vacuum pump), the crude product was partitioned between water and CH_2Cl_2 , and the aqueous phase extracted with several additional portions of CH_2Cl_2 . The combined organic extracts were dried, stripped of solvent, and the resulting crude product was partially purified by chromatography on silica gel. This procedure afforded 33 mg (55%) of a clean mixture of polyether cyclized product as a white solid. Further purification of the mixture utilizing HPLC (3/4 RP C18 column, 35% water-MeOH eluent) showed four products, designated A, B, C, and D in order of elution off the column (A elutes first). Components A and B were present in very small amounts (<1% of the mixture), and could not be obtained in pure enough form to allow characterization. Components C and D were isolated in approximately equal amounts, though no actual isolated yields for a given run were obtained, recoveries off the RP columns were quite good. Compounds C and D were assigned structures **5c** and **6c**, respectively, and showed the following physical properties.

Compound **5c**: colorless crystalline solid, m.p. 170–171° (*in vacuo*); $^1\text{H-NMR}$ (CDCl_3) δ 3.61 (s, 2H), 4.21 (s, 1H); $^{13}\text{C-NMR}$ (CDCl_3) δ 68.00, 69.88, 71.00, 136.82; mass spectrum (VG 70-70 E + FAB, glycerol matrix), m/z 1154 (M + H⁺); retention time on Waters 500 Å ultra stylagel = 8.30 min at a flow rate of 0.5 ml min^{-1} of dichloroethane. A variable temp $^1\text{H-NMR}$ study of this material was performed on the Bruker WM 250 instrument, utilizing CD_2Cl_2 as solvent. At 213 K the singlet at 4.21 split into a clean AB pattern, with resonances at 1046.7, 1036.1, 1011.4, and 1000.7 Hz (the singlet at 3.61 also split into a complex multiplet). From these data, a J_{AB} = 10.65 Hz and ν = 33.70 Hz were estimated. Upon warming the sample, coalescence of the AB quartet occurred at 250 K, allowing estimation of the free energy of activation for the process interconverting H_a and H_b as 12.2 kcal mol^{-1} . (Found: C, 58.38; H, 8.26. Calc for $\text{C}_{36}\text{H}_{96}\text{O}_{24}$: C, 58.32; H, 8.39%.)

Compound **6c**: colorless oil or amorphous glass: $^1\text{H-NMR}$ (CDCl_3) δ 3.59 (s, 2H), 4.21 (AB quartet, 1H, $J = 11.7$ Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 68.25, 69.73, 71.06, 137.04; mass spectrum (VG 70-70 E + FAB, glycerol matrix), m/z 1154 (M + H⁺). Measurement of the exact mass of this protonated molecular ion relative to bradykinin was accomplished by the procedure

of Clay and Murphy.²³ A mass of 1153.6998 was observed (calc 1153.6398). At this resolution (± 60 mmass units) many molecular formulas are still possible. Exact mass measurements on FAB ions at this mass are not routine. Work on improving the resolution of this measurement is in progress. Several attempts at combustion analysis of this material failed to produce acceptable values. Retention time on Waters 500 Å ultra styragel = 7.65 min at flow rate of 0.5 ml min⁻¹ of dichloroethane. The resolution factor for compounds 5c and 6c when coinjected on the ultra styragel column was $R_s = 1.08$.

Crystal structure determination for the 4-rung prism 5c

Compound 5c was recrystallized from CH₂Cl₂-MeOH. A crystal of dimensions 0.5 × 0.24 × 0.12 mm was selected and mounted on a fiber. Unit cell dimensions were determined on a Nicolet P1 autodiffractometer using graphite monochromatized CuK_α radiation ($\lambda = 1.5418$ Å) and were refined by least-squares fit to 40 high angle reflections ($2\theta > 80.0^\circ$). The compound crystallizes with a triclinic lattice in space group P1¹⁹ with cell dimensions of $a = 9.5603(15)$ Å, $b = 18.586(3)$ Å, $c = 8.5900(11)$ Å, $\alpha = 97.615(11)^\circ$, $\beta = 102.586(12)^\circ$, $\gamma = 84.862(12)^\circ$, $\text{vol} = 1473.6(4)$ Å³, $\rho(\text{calc}) = 1.30$ g ml⁻¹, $z = 1$, $P(000) = 624$, $\mu(\text{CuK}\alpha) = 8.02$ cm⁻¹. In all 6436 reflections were measured using $\theta - 2\theta$ scans to $2\theta(\text{max}) = 100^\circ$ † for values of $\pm h$, $\pm k$, $\pm l$. These were averaged to 3048 unique reflections of which 2307 were observed ($F_o > 6.0\sigma(F_o)$). The data were corrected for Lorentz and polarization factors but not for adsorption.

The structure was solved after some difficulty using a combination of *ab initio* direct methods²⁰ and DIRDIF²¹ and refined using full-matrix least-squares techniques.‡ The scattering curves used were those for neutral atoms.²² At convergence, with all non-H atoms treated anisotropically and with H atoms included in the calculated positions riding on the carbon to which they were attached, the final residuals were $R = 0.08$ and $wR = 0.14$. All of the higher peaks in the final difference map (maximum = $0.4 \text{ e } \text{Å}^{-3}$) are near existing atoms, suggesting some disorder in the rings. As expected, refinement of the model in the acentric space group resulted in no significant changes in the results.

Ozonolysis of the 3-rung prism and Möbius ladder

30-Crown-9 triketone 23. To a 25 ml 3-neck flask fitted with a thermometer and gas inlet tube was added a soln of 35 mg (0.04 mmol) of the 3-rung prism 5b and 0.40 ml of a 0.01% (w/v) soln of solvent red 23 indicator dye (Aldrich).¹² The vessel was cooled with a dry ice-isopropanol bath, and O₃ ebullition was commenced (a Welsback ozonator model T-408 was used to generate the O₃). When the dye decolorized (approximately 30 s), 3 ml of Me₂S was added to the mixture to quench the oxidation. The resulting soln was allowed to warm to room temp overnight, then solvent was stripped and the crude product dried *in vacuo*. Chromatography of the crude product on silica gel gave 25 mg (64%) of 23 as a colorless oil: 90 MHz ¹H-NMR (FX 90 Q instrument) (CDCl₃) δ 3.65 (s, 2.2H, ethyleneoxy Hs), 4.35 (s, 1.0H, Hs alpha to carbonyl); ¹³C-NMR (acetone-d₆) δ 71.48, 71.76, 75.52, 187.04; IR (CHCl₃) 2900 (s, br), 1725 cm⁻¹; mass spectrum (VG 70-70 E + FAB, glycerol matrix), m/z 481 (M + H⁺).

Application of a similar procedure to the 3-rung Möbius ladder 6b gave 24 as a colorless oil: ¹H-NMR (CDCl₃) δ 3.67 (s, 2.6H, ethyleneoxy Hs plus aldol impurity), 4.28 (s, 1.0H, Hs alpha to carbonyl); ¹³C-NMR (acetone-d₆) δ 71.36, 71.76, 75.44, 209.74; ¹³C-NMR (CDCl₃) δ 70.83, 71.30, 75.15, 191.41;

† Additional data was collected at higher 2θ but it was not used because of the low fraction of observed data.

‡ The quantity minimized in the least squares procedure is

$$\sum \{ \omega (|F_o| - |F_c|)^2 \}$$

$$R_1 = \sum \{ |F_o| - |F_c| \} / \sum |F_o|$$

$$R_2 = \sum \{ \omega (|F_o| - |F_c|)^2 \} / \sum |F_o|^2$$

IR (CHCl₃) 2900 (s, br), 1722 cm⁻¹; mass spectrum (VG 70-70 E + FAB, glycerol matrix), m/z 961 (M + H⁺).

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