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Helixanes. The First Primary Helical Molecules: Polyoxapolyspiroalkanones

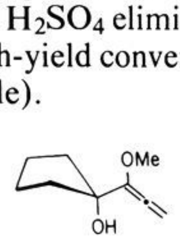
Sir.

The suggestion in the early fifties that the secondary structure of polypeptides has an α-helix conformation[1] led the way for extensive studies of helical topology, especially in biopolymers.[2] In particular the far-reaching double-stranded helical conformation for DNA[3] and the helical nature of many polymers[2,4] highlight the fact that helical molecules have a preeminent place in macromolecular chemistry. Molecules that have helical topology but do not fall into the above classes are helicene,[5] skewed paracyclophane,[6] and helical triphenylmethane systems.[7]

All of the above helical molecules owe their helical topology to their secondary and tertiary structure.[8] To date that is no molecule that is helical because of the primary bonding structure.

Here we report a rational synthesis of the *first primary helical molecules,* based upon the shape (bond angles and bond lengths) of the *tetrahydrofuran ring system.*

The adduct **1** between cyclopentanone (a starting block) and α-lithio-α-methoxyallene, on treatment with potassium *tert*-butoxide (0.2 equiv) in *tert*-butyl alcohol containing 18-crown-6 (0.05 equiv) heated at reflux for 15 h gave **2.**[9] Acid hydrolysis (6 N H_2SO_4) of **2** gave **3.** The choice of conditions for the release of the dihydrofuranone carbonyl group is crucial in this step and in the subsequent hydrolysis procedures of the enol ethers described, since 1 N H_2SO_4 or two-phase systems (oxalic acid–dichloromethane) gave **3** contaminated with decomposition products, whereas increasing the strength of the acid to 6 N H_2SO_4 eliminated degradation and produced only a clean high-yield conversion of **2** into **3** (82% overall yield on a 8.0-g scale).



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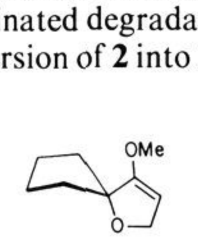

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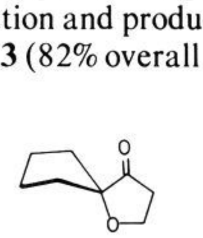
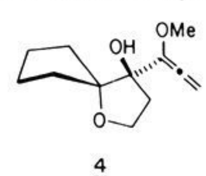


3

Since we started with a carbonyl compound, cyclopentanone, and spiroannulated a dihydrofuranone onto it, and since we have ended up with a new carbonyl compound, namely 1-oxaspiro[4.4]nonan-4-one (**3**), the product in principle is capable of being subjected to another spiroannulation sequence. The carbonyl group of **3** is relatively hindered, but it reacts cleanly with α-lithio-α-methoxyallene to give the adduct **4,** after aqueous ammonium chloride workup, in 95–98% yield.[10] The adduct **4** on treatment with KOBu^t (0.1 equiv)/HOBu^t/18-crown-6 (0.05 equiv) heated at reflux for 15 h gave **5,** which on acid hydrolysis (6 N H_2SO_4) gave **6** (70%).[11]



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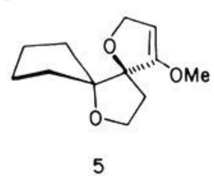

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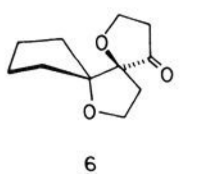
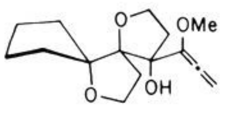


6

At this point we have reached a crucial stage. The first and only stereochemical issue arises. The carbonyl group in **6** has two diastereotopic faces available for the addition of a nucleophilic species. Dreiding models and space-filling models indicate that one face of **6** is severely hindered by the two five-membered rings already present. In particular the cyclopentane ring sits under one face of the carbonyl group in **6.** In the event, **6** adds α-lithio-α-methoxyallene to give a single crystalline adduct **7,** mp 133–137 °C in $\geq$90% yield.[12] Treatment of this adduct with KOBu^t (0.2 equiv)/HOBu^t 18-crown-6 (0.05 equiv) heated at reflux led to **8,** which on acid hydrolysis (6 N H_2SO_4) gave the beautifully crystalline cyclopentyl[3]helixane **9,** mp 88.5–90 °C (67% overall from **7**).



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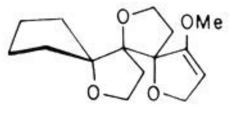

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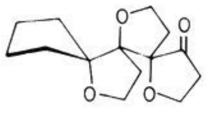
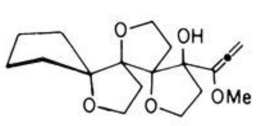


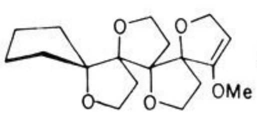
9

We hoped that, as we extended the spiro rings, the allenyl adducts would undergo ring closure under increasingly mild conditions. This optimistic view is based upon the idea that the steric compression of the alkoxide of **10** would favor cyclization since covalent association of a metal counterion (Li or K in the cases described) is sterically hindered, and furthermore **10** may act as its own crown ether ionophore and effectively remove the counterion (Li or K) from covalent association with the alkoxide.

Treatment of **9** with α-lithio-α-methoxyallene gave **10,** mp 92–99 °C (45%),[13] which cyclized to **11** at *room temperature* (28 °C) when treated with KOBu^t (0.2 equiv)/HOBu^t/18-crown-6 (0.05 equiv) to give cyclopentyl[4]helixane **12,** mp 123–124 °C (67%), after acid (6 N H_2SO_4) hydrolysis. Models (CPK) (see photograph) show that cyclopentyl[4]helixane **12** is a helix-shaped molecule. The oxygen atoms and methylene groups spiral around the central core of the molecule. To establish the structure of **12** unequivocally and confirm speculations concerning stereochemistry, a single-crystal X-ray analysis was conducted. The results are as follows.



10



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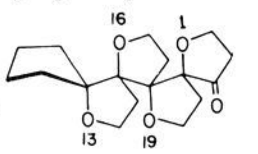

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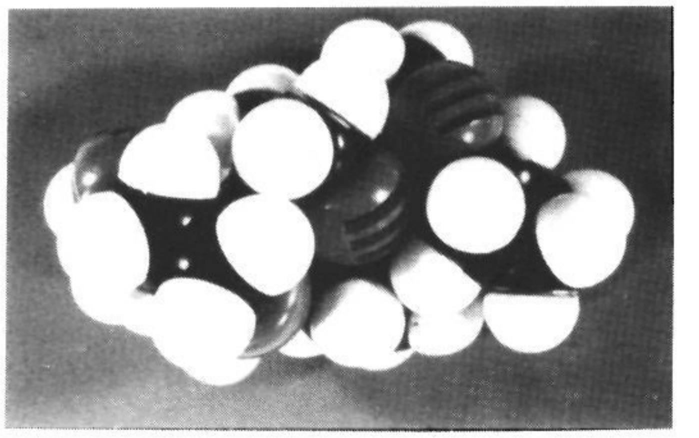

Cyclopentyl[4]helixane crystallized in the triclinic space group $P\bar{1}$ with four molecules per unit cell. Accurate lattice parameters are $a = 13.881$ (4), $b = 8.853$ (2), $c = 13.668$ (3) Å; $\alpha = 104.83$ (2), $\beta = 76.60$ (2), $\gamma = 78.71°$. The structure was solved by direct methods and has currently been refined

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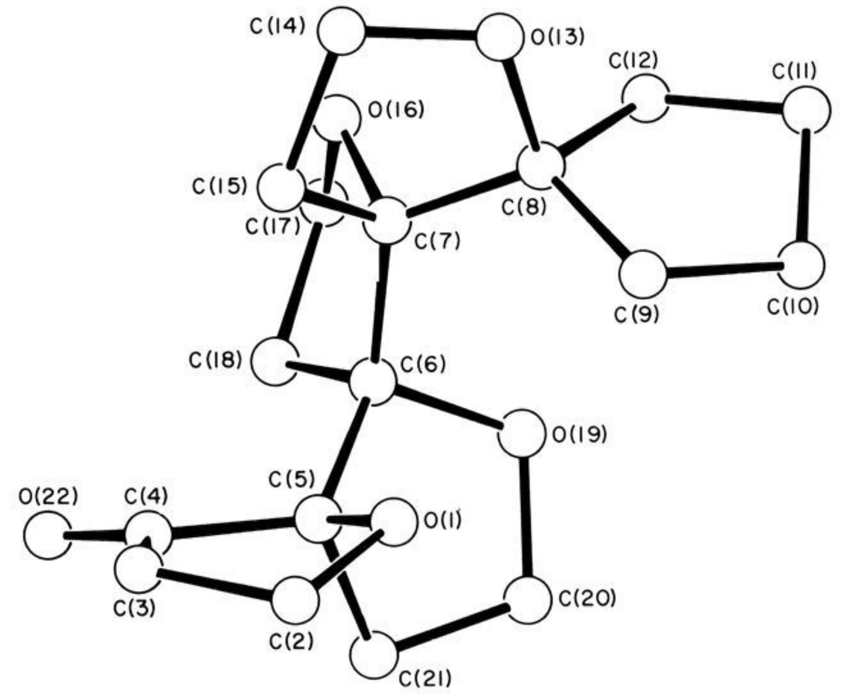
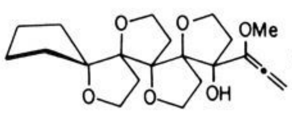


Figure 1.

to $R = 0.08$ for the 3085 diffractometer measured intensities. Both molecules in the asymmetric unit have the same geometry and Figure 1 is a computer-generated drawing of them.

Cyclopentyl[4]helixane **12** was treated with α-lithio-α-methoxyallene to give the adduct **13** (90%),[13] which cyclized to **14** when exposed to KOBu^t (0.1 equiv)/HOBu^t/18-crown-6 (0.05 equiv); acid hydrolysis (6 N H_2SO_4) of **14** gave cyclopentyl[5]helixane **15,** mp 195–197 °C. Again **12** has only one face of the carbonyl group available for nucleophilic addition, and as a result **15** is a single, stereochemically pure compound. It should be noted that **15** has five quaternary carbons adjacent to one another in the carbon backbone, and each quaternary carbon is part of a tertiary ether function.



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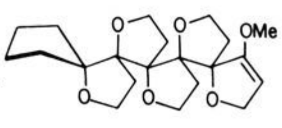

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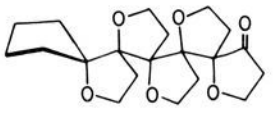
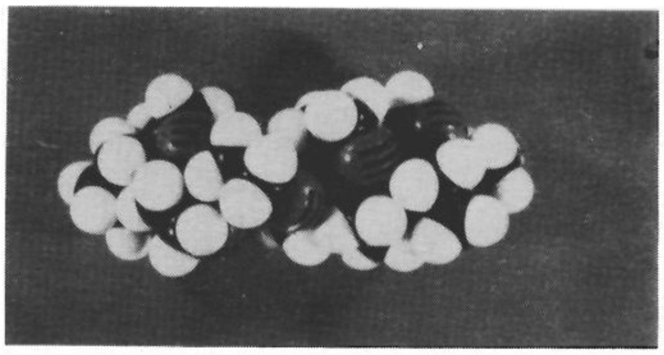
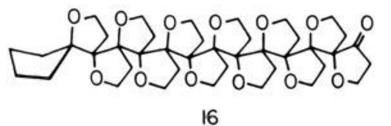


15

One can in principle continue this *reiterative* reaction and make extended verisons of **15** such as the cyclopentyl[12]-helixane **16** (see CPK model photograph) where the helicity is more readily seen. We are pursuing this objective and the more general concept of synthesizing primary helical molecules, along with studies of their physical and chemical properties.





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Acknowledgments. P.M. thanks the National Institutes of Health (GM25231-01) for their support and J. C. thanks NIH-NCI-CA24487 for their support.

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(8) For the reader who is not familiar with the terms primary, secondary, and tertiary structure, they may be briefly described as follows: primary, structural formula (bond lengths and bond angles) of the monomeric unit; secondary, the manner in which the monomeric units are folded to form geometric structures—nonbonded interactions; tertiary, results from small periodic variations in the secondary structure. See ref 2 for a more extensive discussion.

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(10) All yields refer to distilled or recrystallized pure compounds. All new compounds were characterized by IR, NMR, MS, and microanalytical data.

(11) The naming of these compounds is as follows: **6,** 1,11-dioxadispiro-[4.0.4.3]tridecan-4-one; **9,** 1,12,15-trioxatrispiro[4.0.0.4.3.3]heptadecan-4-one; **12,** 1,13,16,19-tetraoxatetraspiro[4.0.0.0.4.3.3.3]heneicosan-4-one; **15,** 1,14,17,20,23-pentaoxapentaspiro[4.0.0.0.0.4.3.3.3.3]-pentacosan-4-one. A more descriptive system of naming is to use the prefix cyclopentyl to indicate the starting carbonyl compound, the suffix helixane to indicate the helical nature of the total molecule, and a number to indicate the number of spiro linkages. Thus **6** becomes cyclopentyl[2]helixane; **9** becomes cyclopentyl[3]helixane; **12** becomes cyclopentyl[4]helixane; **15** becomes cyclopentyl[5]helixane. Sherry Anthony (*Chemical Abstracts*) is thanked for the naming of these compounds.

(12) Formulas from **6** on are drawn without spatial implications.

(13) If the addition of α-lithio-α-methoxyallene is carried out twice, the yield of **10** is increased to 90%. The reported yield of **13** was obtained in this way.

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*Book Reviews**

The Pendulum and the Toxic Cloud. By THOMAS WHITESIDE (New Yorker Magazine). Yale University Press, New Haven, Conn. 1979. 205 pp. $4.95 paper, $15.00 cloth.

The story of tetrachlorodibenzodioxin, the extraordinarily toxic substance produced in the manufacture of the herbicide 2,4,5-trichlorophenoxyacetic acid, which it sometimes contaminates, is the subject of this book. It focusses on the infamous industrial accident at Seveso, Italy, in 1977, but reviews the whole field in perspective. The treatment of the subject is suitable for the informed layman, but documentation is very thorough, and the book can be recommended to the chemist who wishes to become well acquainted with the matter. A five-page index is included.

Modern Cost Engineering: Methods and Data. By Chemical Engineering Magazine staff. McGraw-Hill Book Co., New York. 1979. 579 pp. $35.00.

The contents of this book have been collected from *Chemical Engineering* magazine articles over the past decade. The treatment is of engineering in general, but with emphasis on chemical plants. A large quantity of useful information is presented in text, tables, and

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*Unsigned book reviews are by the Book Review Editor.