Synthesis and Conformational Properties of Several Maximally Substituted Hexa(spirotetrahydrofuranyl)cyclohexanes. Assessment of the Pronounced Bias of the *All-Trans* D_{3d}-Symmetric Isomer for Total Equatorial Oxygen Occupancy

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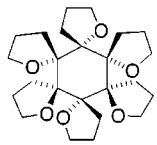
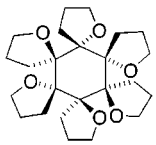
The poly(spirotetrahydrofuranyl)cyclohexanes **1**−**4** were prepared in a series of steps that began with oxidative demercuration of pentaspirocyclic chloromercurials. Once the resulting alcohols were transformed into their ketones, it proved possible to cap this center with the Normant reagent and introduce the final heterocyclic ring. The cyclohexanones and the title compounds showed a strong tendency to project their C−O bonds equatorially to the maximum extent possible. The reluctance of these systems to participate in chair-to-chair conformational equilibration was made apparent during measurements to assess their coordination capability toward alkali metal ions. Although **3** was superior to its isomers, this polyether was overshadowed by **15** to an extent in excess of two powers of 10 in their relative capability to coordinate lithium cations. The synthesis, conformation, and low-level dynamic character of **5** are also detailed. To set the stereochemistry of the sixth spirotetrahydrofuranyl ring properly in this case, it was necessary to implement a novel strategy involving late-stage introduction of the oxygen atom. This protocol required intermediate formation of homoallylic alcohol **39**, the epoxidation of which proceeded principally in the desired direction. X-ray crystallographic analysis of **5** established that the chair conformation which is adopted has all six C−O bonds projected equatorially. The total inability of **5** to bind to Li^+, Na^+, and K^+ denotes the existence of a substantial barrier to ring inversion. DNMR studies undertaken to assess the magnitude of this barrier demonstrated no change in high-field ^1H and ^{13}C line shapes up to 573K in 1,3-([D_3]methoxy)benzene. Consequently, **5** may qualify as the cyclohexane having the highest chair-chair conformational inversion barrier to the present time.

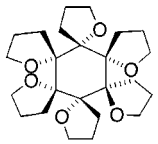
During the past several years, we have been investigating protocols designed to prepare, in a stereocontrolled manner, select isomers of the nine possible hexa(spirotetrahydrofuranyl)cyclohexanes.[1] Motivated by the possible bifacial complexation capability of the **1,3,5**-isomer **5**,[2] we have developed an efficient route to this polyether[3] based on the 2-fold ring expansion of cyclobutanone via oxonium ion-activated pinacol rearrangement.[4] The generality of this strategy has enabled direct access to be gained to four additional members of this subset of sterically crowded heterocycles (viz. **1**−**4**). In this report, full details of the syntheses of these five isomers are given, together with some indication of their conformational properties and effectiveness as ligands for alkali metal ions.



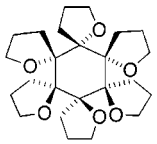
(**1**,**3**; C_s; 16)
1



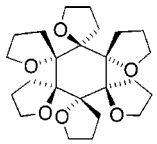
(**1**,**2**,**4**; C_2; 12)
2



(**1**; C_s; 16)
3



(**1**,**2**,**3**; C_{2h}; 12)
4



(**1**,**3**,**5**; D_{3d}; 4)
5

Background

The seminal 1967 paper by Pedersen[5] in which macrocyclic polyethers were shown to be capable of complexing simple metal ions has resulted in the preparation of many thousands of crown ethers.[6] Structural characterization of a large number of these compounds and their complexes by X-ray crystallography has been reported.[7]

(1) Paquette, L. A.; Stepanian, M.; Mallavadhani, U. V.; Cutarelli, T. D.; Lowinger, T. B.; Klemeyer, H. J. *J. Org. Chem.* **1996**, *61*, 7492.

(2) The convention proposed to distinguish these isomers is to specify initially in bold font that numerical designation which delineates the unique locus of the b-oxygen atoms.[1] The last digit defines the number of ^{13}C signals each polyether will exhibit. The symmetry designations are for structures averaged over two chair conformations, equivalent to planar six-membered rings, having flexible spirocyclic appendages. Only the C_2-symmetric **1,2,4**-isomer is chiral.

(3) Paquette, L. A.; Tae, J.; Branan, B. M.; Eisenberg, S. W. E.; Hofferberth, J. E. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1412.

(4) Review: Paquette, L. A. *Recent Res. Devel. in Chemical Sciences* **1997**, 1.

(5) Pedersen, C. *J. Am. Chem. Soc.* **1967**, *89*, 7017.

(6) Gokel, G. *Crown Ethers and Cryptands*, The Royal Society of Chemistry, 1991.

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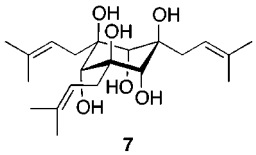
Despite the vigor with which research in this area has been pursued, the issue of possible *bifacial complexation* appears to have been accorded little prior attention. This term is intended to encompass any ligand that finds it possible because of its unique structural features *to bind an ion (either the same or different) on two of its surfaces*.

Where belted ionophores[8] consisting of a central six-membered ring are concerned, six syn-axial heteroatoms are required to achieve suitable binding to a metal ion. Very few molecules having this potential have been made available. The arrangement is not found in sugars, and only *scyllo*-inositol (**6**)[9a,c] has the requisite all-trans arrangement among the many known cyclitols.[10] Like its hexamethyl ether,[11] however, the stable conformation of **6** is the fully eclipsed all-equatorial form shown. On the other hand, muellitol (**7**) has its six hydroxyl groups disposed in *syn*-axial fashion[12] as a consequence of the three added prenyl substituents. This remarkable natural product and its hexahydro derivative enter rapidly into complexation with dipositive cations, and slowly with tripositive cations.[13a] Isomuellitol (**8**), the acid-catalyzed cyclization product of **7**, has afforded no evidence of complexation to Eu^{3+}, likely because of a reversal in conformational bias.[13a]



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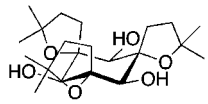
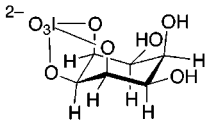


8

On the other hand, Angyal has noted that the periodate ion enters into complexation with three neighboring hydroxyl groups present in an axial−equatorial-axial arrangement, but not with three *syn*-axial hydroxyl groups. Borate ions exhibit the reverse preference.[13b] This crossover is nicely reflected in the conversion of *cis*-inositol (**9**) to the **1,2,3**-periodate (**10**) and the **1,3,5**-borate (**11**), respectively.



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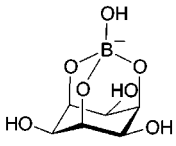
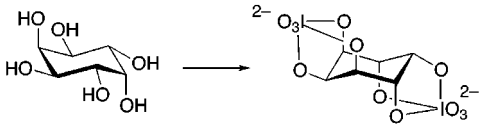


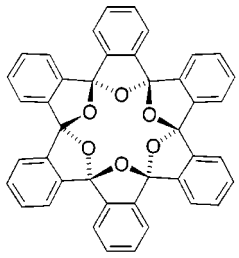
11

These binding preferences are reflected in a particularly informative manner in the behavior of *neo*-inositol (**12**). The stereochemical features of **12** disallow formation of a triaxial borate complex. However, while **12** has no *ax-eq-ax* sequence in its more stable conformation, ring inversion (at an estimated cost of 3.1 kcal/mol[13c]) gives rise to a pair of such sequences, thereby allowing formation of complex **13** with two periodate ions, one on each surface of the cyclohexane core.[9d]



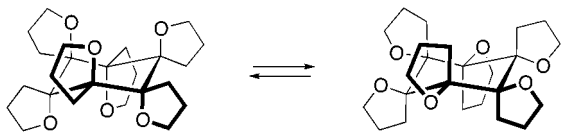
12 **13**

Along different lines, Lee and co-workers developed a relatively short synthetic route to **14**, a spirobicyclic polyketal in which the oxygen centers are conformationally locked in an alternating up−down arrangement.[14] However, ab initio and AMBER force field calculations predict that this starand binds lithium ion not at the center but on the outside of the cavity.[15,16] Thus, although **14** is one of the most preorganized ionophores known, it is conformationally locked, has no single bonds able to rotate, and exhibits no unique properties.[17]



14

From among the several possible isomeric hexa(spirotetrahydro-furanyl)cyclo-hexanes,[18] the all-trans isomer **5** was viewed to be an enticing potential ionophore for several reasons.[3] In particular the **5-ax** conformer is a particularly well disposed receptor for Li^+ on both its upper and lower surfaces. The conformational changes



5-ax **5-eq**

that accompany the coordination of *cis,cis*-1,8,14-trioxatrispiro[4.1.4.1.4.1]octadecane (**15**) to Li^+ and Na^+ constitute appropriate precedent for monofacial complexation.[19] Accordingly, the possibility of gaining access to ladder polymers consisting of alternating ligand and metal ion components was considered to be a realistic

(7) Hilgenfeld, R.; Saenger, W. *Top. Curr. Chem.* **1982**, *101*, 1.

(8) (a) Negri, J. T.; Rogers, R. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 5073. (b) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3947.

(9) (a) Anderson, R. C.; Wallis, E. S. *J. Am. Chem. Soc.* **1948**, *70*, 2931. (b) Kohne, B.; Praefks, K. *Liebigs Ann. Chem.* **1985**, 866. (c) Angyal, S. J.; Hickman, R. J. *Aust. J. Chem.* **1975**, *28*, 1279. (d) Barker, G. R. *J. Chem. Soc.* **1960**, 624.

(10) Hudlicky, T.; Cebulak, M. *Cyclitols and Their Derivatives*; VCH Publishers: New York, 1993.

(11) (a) Anderson, J. E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 441. (b) Anderson, J. E.; Angyal, S. J.; Craig, D. C. *Carbohydr. Res.* **1995**, *272*, 141.

(12) (a) Fazideen, H.; Hegarty, M. P.; Lahey, F. N. *Phytochemistry* **1978**, *17*, 1609. (b) Fazideen, H. *Aust. J. Chem.* **1982**, *35*, 2589.

(13) (a) Angyal, S J.; Greeves, D.; Littlemore, L. *Aust. J. Chem.*. **1985**, *38*, 1561. (b) Angyal, S. J.; Greeves, D.; Pickles, V. A. *Carbohydrate Res.* **1974**, *35*, 165 and references therein. (c) Angyal, S. J.; McHugh, D. J. *Chem. Ind. (London)* **1956**, 1147.

(14) (a) Lee, W. Y.; Park, C. H.; Kim, S. *J. Am. Chem. Soc.* **1993**, *115*, 1184. (b) Lee, W. Y.; Park, C. H. *J. Org. Chem.* **1993**, *58*, 7149.

(15) Cui, C.; Cho, S. J.; Kim, K. S. *J. Phys. Chem. A* **1998**, *112*, 1119.

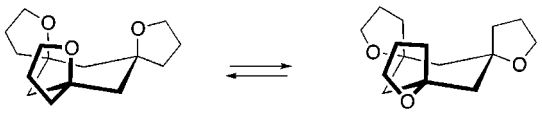
(16) Cho, S. J.; Kollman, P. A. *J. Org. Chem.* **1999**, *64*, 5787.

(17) (a) Cho, S. J.; Hwang, H. S.; Park, J. M.; Oh, K. S.; Kim, K. S. *J. Am. Chem. Soc.* **1996**, *118*, 485. (b) Lee, W. Y.; Park, C. H.; Kim, H.-J. *J. Org. Chem.* **1994**, *59*, 878. (c) Lee, W. Y. *Synlett* **1994**, 765.

(18) Paquette, L. A.; Stepanian, M.; Mallavadhani, U. V.; Cutarelli, T. D.; Lowinger, T. B.; Klemeyer, H. J. *J. Org. Chem.* **1996**, *61*, 7492.

(19) Paquette, L. A.; Tae, J.; Hickey, E. R.; Rogers, R. D. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1409. (b) Paquette, L. A.; Tae, J.; Hickey, E. R.; Trego, W. E.; Rogers, R. D. accompanying paper. (c) For lithium ion complexation to a 2,7,11-trioxatricyclo[8.4.0.0^{3,8}]tetradecane, consult Hoffmann, R.; Münster, I. *Liebigs Ann./Recueil* **1997**, 1143.

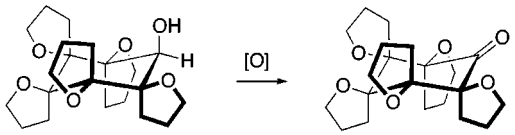
objective. The ready capability with which **15** forms 2:1 complexes to Li^+ and Na^+ is particularly relevant here.[19] Mention should also be made of the likelihood that systems in which the metal stacking would alternate as $Li^+/Na^+/Li^+/Na^+$, etc might be accomplished with equal readiness simply by admixing **5**·Li^+ (if available) with an appropriate sodium salt.[20]



15

Results and Discussion

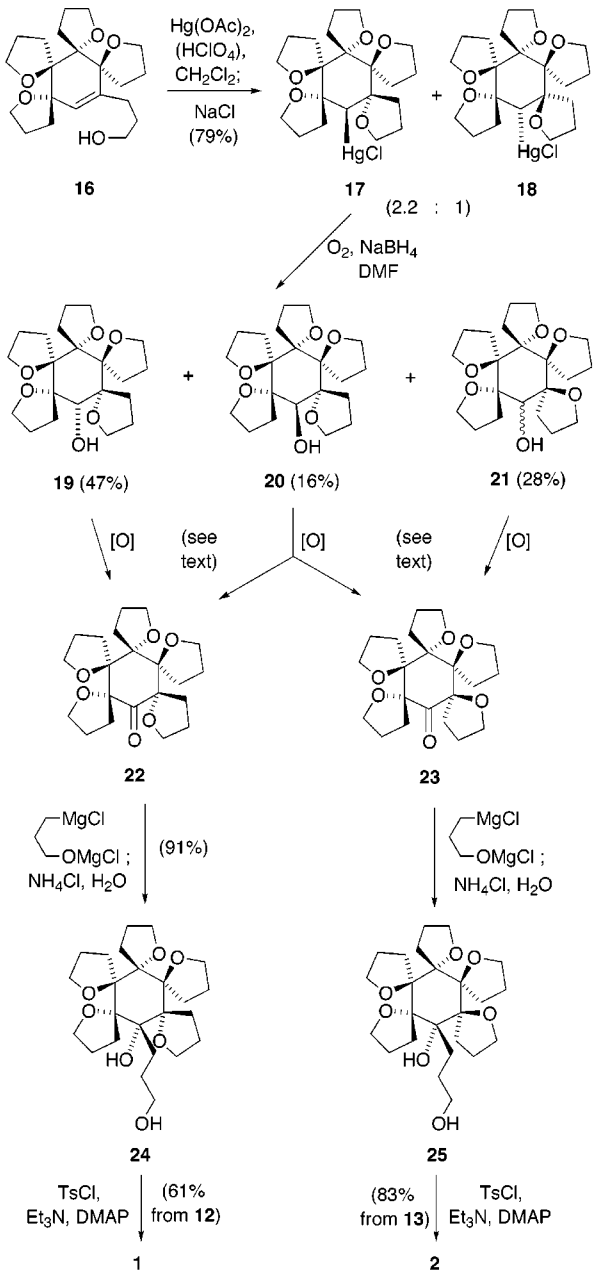
The 1,3- and 1,2,4-Isomers. The mercuric acetate-promoted ring closure of **16** has been reported to give rise to a 2.2:1 mixture of **17** and **18** as a direct consequence of the competitive intervention of two chelated mercurinium ion intermediates (Scheme 1).[21] Without chromatographic separation, this pair of diastereomeric chloromercurials was subjected to oxidative demercuration with sodium borohydride and oxygen in DMF as solvent.[22] This reaction proceeded cleanly to furnish **19** (47%), **20** (16%), and **21** (28%). As a consequence of the strikingly different polarities of these pentaspiro cyclohexanols on silica gel, their purification was readily accomplished. An X-ray crystallographic analysis performed on **19**[23a] indicated the conformation adopted in the solid state to be that shown in **A**. All five of the tetrahydrofuranyl oxygens are seen to be projected equatorially. Submission of **19** to a battery of four oxidative methods (Dess−Martin,[24] Swern,[25] pyridinium dichromate,[26] and tetrapropylammonium perruthenate[27]) resulted in smooth conversion to **22** (77−100%) without any detectable erosion of the extensive stereochemical setting. The low polarity of **22** strongly implicates its adoption of the conformation defined as **B**.



A **B**

Although the conversion of **21** to **23** was equally uneventful, submission of **20** to the identical four oxidants under essentially duplicative conditions furnished both **22** and **23** (Table 1).[23b] The ratio of these ketones varied from 1:1 to 2:1 depending on the reagent. The

Scheme 1



distinction between **22** and **23** is easily made since the C_s symmetry of **22** reduces the number of its ^{13}C signals very significantly. It would appear entirely plausible to formulate **20** as **C**, the oxidation of which requires abstraction of an axial hydrogen atom. As illustrated for the Swern reagent, two competitive options are apparently operative under these circumstances. Pathway *a* is the conventional oxidation option, viz. **C** → **D** → **22**. The second alternative consists of C−H bond cleavage accompanied by *β*-elimination of an oxygen atom as in

(20) For variants on this theme, see: (a) Tae, J.; Rogers, R. D.; Paquette, L. A. *Org. Lett.* **2000**,*2*, 139. (b) Paquette, L. A.; Tae, J.; Gallucci, J. C. *Org. Lett.* **2000**, *2*, 143.

(21) Paquette, L. A.; Bolin, D. G.; Stepanian, M.; Branan, B. M.; Mallavadhani, U. V.; Tae, J.; Eisenberg, S. W. E.; Rogers, R. D. *J. Am. Chem. Soc.* **1998**, *120*, 11603.

(22) Harding, K. E.; Marman, T. H.; Nam, D.-h. *Tetrahedron Lett.* **1988**, *29*, 1627 and relevant references therein.

(23) (a) Paquette, L. A.; Stepanian, M.; Branan, B. M.; Edmondson, S. E.; Bauer, C. B.; Rogers, R. D. *J. Am. Chem. Soc.* **1996**, *118*, 4504. (b) Paquette, L. A.; Branan, B. M.; Stepanian, M. *Tetrahedron Lett.* **1996**, *37*, 1721.

(24) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

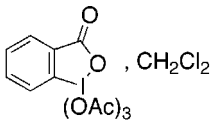
(25) Review: Tidwell, T. T. *Org. React.* **1990**, *39*, 297.

(26) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(27) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.

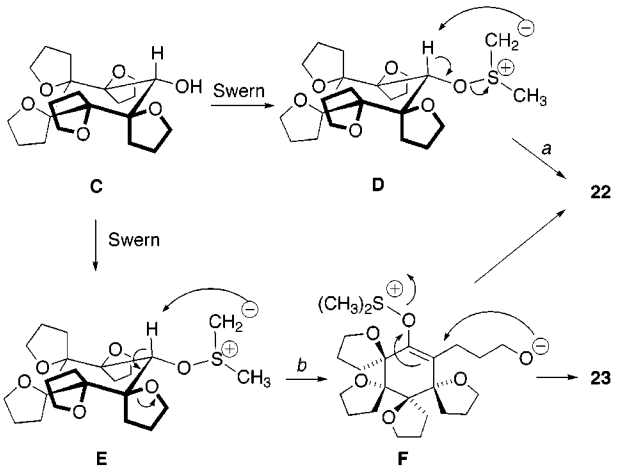
(28) A referee has objected to our mechanistic proposal because of the disfavored involvement of a five-membered transition state structure with syn elimination of an alkoxide. Instead, a pathway advancing via C−C bond cleavage to form an acyclic aldehyde-oxocarbonium ion was suggested. Reclosure on either face of the carbonium ion would lead to epimerization *prior to* removal of the hydrogen to form the carbonyl. We have earlier given consideration to this possibility and searched diligently for stereochemical equilibration of the alcohol as reaction proceeded. This phenomenon was never observed, leading us to conclude that rearrangement is more intimately linked to the oxidation step.

Table 1. Oxidative Results for 20

oxidant	Product distribution, %[a] 22	23
	50	50
DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2	44	44
PDC, 3 Å MS, CH_2Cl_2	52	26
TPAP, 4 Å MS, CH_2Cl_2–CH_3CN (1:1)	61	30

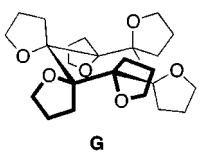
[a] The percentages given are based on isolated yields of the ketones.

E. Once **F** has been formed, ring closure to both **22** and **23** becomes possible, although the intervention of **F** is not necessary to rationalize the formation of structurally unrearranged ketone.[28]



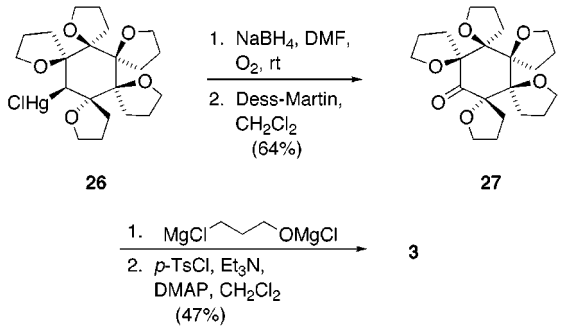
Admixture of **22** with the Normant reagent[29] was met with efficient 1,2-addition and formation of diol **24**. The relative stereochemistry of the newly generated stereogenic center was defined only following tosyl chloride-promoted cyclization of the sixth spirotetrahydrofuran ring. The polyether so obtained exhibited 16 carbon signals and must therefore be the C_s-symmetric **1,3**-isomer **1**. Thus, conformer **B** is experiencing nucleophilic attack uniquely from the equatorial direction. Axial approach would have delivered the **1,3,5**-isomer, which would display only four ^{13}C resonances.[3]

As with the **22** → **1** conversion, it proved operationally simpler to proceed from **23** to **2** without isolation of the intermediate diol. The conformation of **2**, defined by X-ray crystallographic methods,[23] is such that four of its C−O bonds are projected equatorially as in **G**.



G

Scheme 2



The 1-Isomer. A convenient preparation of **26** has been previously reported.[21] The C−Hg bond in this intermediate is again very amenable to oxidative cleavage under radical conditions (Scheme 2). The diastereomeric mixture of alcohols so formed was oxidized efficiently to **27** without evidence of stereochemical isomerization. Spectroscopic examination of this cyclohexanone revealed it to be conformationally mobile as evidenced by broadened ^1H and ^{13}C NMR spectra at room temperature.

The "capping" of **27** proceeded effectively following sequential deployment of the Normant reagent and *p*-toluenesulfonyl chloride in triethylamine. The resulting polyether also exhibited broadened ^1H and ^{13}C NMR spectra under ordinary conditions. The structure of this product was determined to be **3** on the basis of the sixteen unique carbon signals recorded at 303 K. Should 1,2-addition have materialized from the β-surface, the **1,2**-isomer would have resulted. Its symmetry characteristics would be reflected in a 12-line ^{13}C NMR spectrum.

Like its ketone precursor, **3** exhibits conformational mobility at room temperature. Repeated attempts to recrystallize this compound gave only an amorphous white solid, thus precluding crystallography-based definition of its solid-state conformation. It will be recognized that **1**−**5** belong to the family of polysubstituted cyclohexanes, the conformational dynamics of which are known to be dominated by strong, nonbonded steric interactions. Although compounds such as **28**−**30** adopt a ground-state chair conformation,[30] closely related congeners such as **31** and **32** exist in a pure twist boat geometry,[31] and **33** actually prefers a chair-to-twistboat equilibrium.[32] MM3 calculations originally suggested that an increase in the size of the external rings could well be met by an increased stabilization of the chair form.[33] However, these conclusions appear no longer to be valid,

(29) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, 3013.
(30) (a) Wehle, D.; Scheuermann, H.-J.; Fitjer, L. *Chem. Ber.* **1986**, *119*, 3127. (b) Fitjer, L.; Giersig, M.; Wehle, D.; Dittmer, M.; Koltermann, G.-W.; Schormann, N.; Egert, E. *Tetrahedron* **1988**, *44*, 393. (c) Fitjer, L.; Justus, K.; Puder, P.; Dittmer, M.; Hassler, C.; Noltemeyer, M. *Angew. Chem. Int. Ed.* **1991**, *30*, 436.
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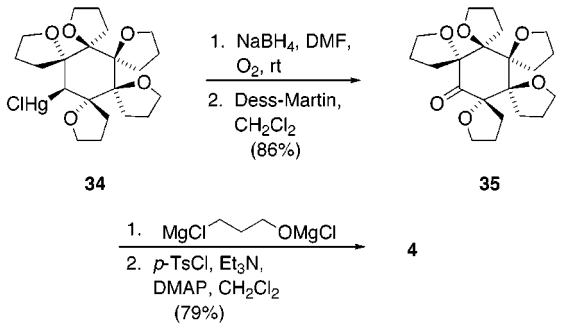
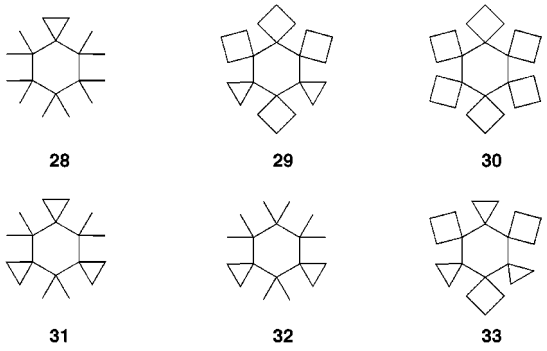
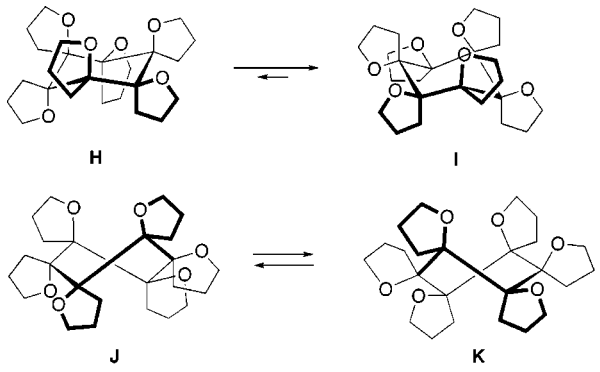
Scheme 3



the reverse actually being more likely.[34]



Although **2**,[23] **4** (see below), and **5**[3] have been shown to populate a chair conformation in the solid state and to maintain these features in solution, these polyspirotetrahydrofurans find it necessary to orient as few as 0, 1, or 2 C−O bonds axially. We have previously documented the considerable preference of cyclohexanes heavily substituted in this manner for equatorial C−O occupancy.[23] As a consequence, it can be concluded that the chair conformation **H** for **3** should be significantly destabilized relative to **I**. The imbalance anticipated for the **H** ⇄ **I** equilibrium is in fact sufficiently high that it constitutes an unlikely pathway for the observed dynamic conformational properties. Such considerations allow for the possibility that **3** is dynamic as a consequence of the facile interconversion between the twist-boat conformers **J** and **K**.



The 1,2,3-Isomer. The available chloromercurial **34**[21] was converted to **35** in the manner described earlier (Scheme 3). The 13-line ^{13}C NMR spectrum of this ketone established the existence of a plane of symmetry. Consequently, the Dess−Martin periodinane-induced oxidation necessarily proceeded without any detectable erosion of stereochemical integrity. The high crystallinity of **35**

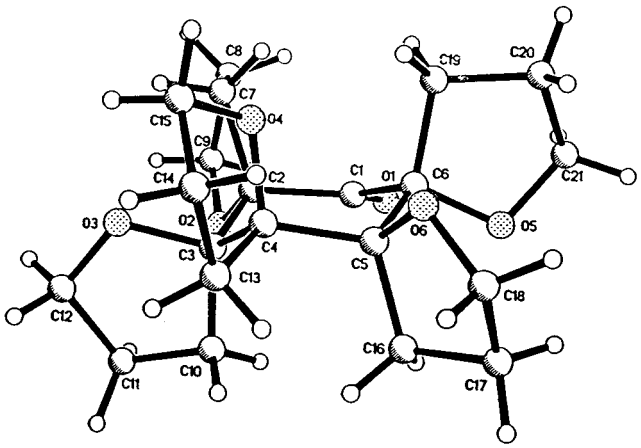


Figure 1. Perspective plot of **35** as determined by X-ray crystallography.

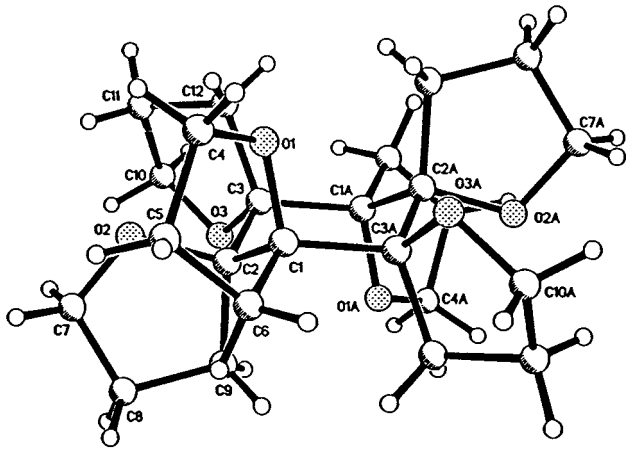
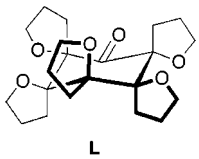


Figure 2. Perspective plot of **4** as determined by X-ray crystallography.

permitted definition of its conformation as in **L** by means of X-ray crystallography (Figure 1). In addition to providing structural confirmation, these data clearly reveal the preference for equatorial status on the part of the C−O bonds.

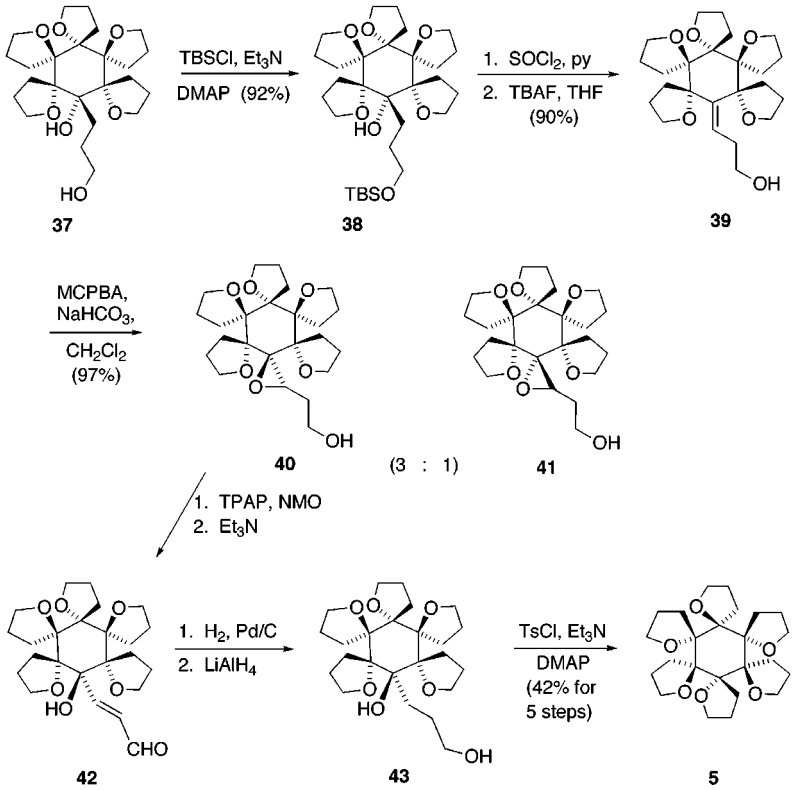
Ketone **35** was capped under the standard conditions. In this case, the single product formed was **4**, as expected from our previous findings. The α- and α′-oxygen atoms in **L** both reside equatorially as in **B**. This scenario may exert a directing effect that delivers the Normant reagent from the same direction. The subsequent ring closure resulted in the placement of two sets of three consecutive oxygen centers on both surfaces of the inner cyclohexane ring. The crystallographically determined conformation of **4** is depicted in Figure 2.



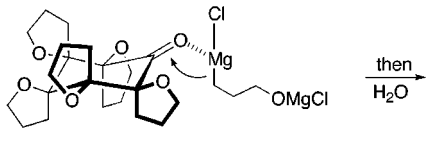
L

The 1,3,5-Isomer. The requisite transformation of **36**[28] into **5** requires that a suitable organometallic reagent attack the ketone carbonyl from that direction syn to the α- and α′-oxygen atoms. However, all attempts to effect the nucleophilic addition of Grignard and organolithium reagents to **36** in this stereochemical sense proceeded

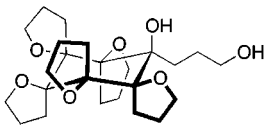
Scheme 4



unilaterally by way of the opposite π-facial selectivity. This high level of discrimination can be understood if **36** resides in that conformation having all five C−O bonds projected equatorially, such that 1,2-addition is relegated entirely to the equatorial direction for obvious steric reasons.



36



37

Since the **36** → **37** conversion culminates in the installation of three contiguous syn oxygen centers, our attention was diverted to alternate protocols that would serve to elaborate the carbon−carbon bond first. The strategy that ultimately emerged as successful is based on the recognition that inversion of the tertiary carbinol site in **37** was uniquely necessary. This key transform was implemented following regioselective *O*-silylation to generate **38** (Scheme 4). This functional group arrangement makes possible dehydration in the exocyclic direction with thionyl chloride in pyridine. Subsequent unmasking of the hydroxyl group to give **39** was followed by epoxidation with MCPBA under buffered conditions. In line with the recognized predilection of this peracid for axial attack on methylenecyclohexanes,[35] **39** was transformed into a 3:1 mixture of **40** and **41**. The desired major isomer **40**, which proved to be readily separable via flash chromatography, was oxidized to the aldehyde level with Ley's perruthenate reagent.[27] The salient feature of this step is that β-elimination with cleavage of the oxirane ring can be easily accomplished without purification.

With arrival at **42**, it proved entirely feasible to achieve sequential reduction of the double bond and carboxaldehyde functionality by means of hydrogenation and exposure to lithium aluminum hydride. Ultimately, monotosylation of **43** produced the target molecule **5**. This hexaspiro ether proved to be a high-melting (mp 249−251 °C dec), colorless crystalline solid of strikingly low polarity. The substance is freely soluble in hexane and dichloromethane, but poorly soluble in acetonitrile and methanol. Its D_{3d} symmetry was clearly evident in its greatly simplified ^{1}H NMR spectrum and four-line ^{13}C NMR spectrum. X-ray crystallographic analysis confirmed that the six oxygen atoms are projected equatorially (Figure 3). This preference on the part of polyoxygenated C−O bonds for equatorial occupancy was not unexpected, having been encountered previously in **36** and numerous other penta- and hexa(spirotetrahydrofuranyl)cyclohexane systems.[23] To our amazement, **5** exhibited no capacity for conformational ring inversion and negligible binding capability to alkali metal ions in the usual picrate extraction experiments. Chelation to $LiBF_4$ and $LiClO_4$ in $CH_3CN-C_6H_6$ (1:1) materialized neither at 20 °C nor at the reflux temperature. The response to $NaBF_4$ was marginal. More forcing conditions

(35) Rablen, P. R.; Paquette, L. A.; Borden, W. T. *J. Org. Chem.* **2000**, *65*, 9180.

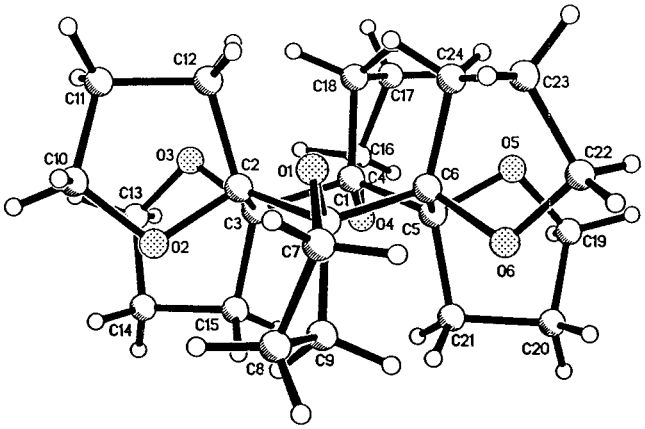
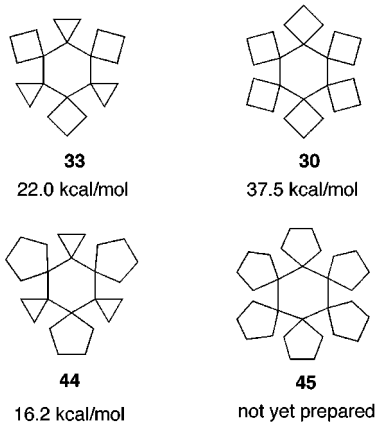


Figure 3. Perspective plot of **5** as determined by X-ray crystallography.

($LiBF_4$ in 1:1 benzene-acetonitrile at 175 °C) were also to no avail.

As a consequence of the above, DNMR studies were undertaken in an effort to determine the magnitude of the barrier separating **5-eq** from **5-ax**. Particularly striking were the observations that the ^1H (500 MHz) and ^{13}C NMR spectra (125 MHz) of **5** recorded for solutions in 1,3-([D_3]methoxy)benzene were superimposable over the temperature range of 294K to 573K. Direct measurement of the magnitude of $\Delta H^{\ddagger}$ was thereby precluded. Two limiting scenarios could be responsible for this behavior. The difference in the enthalpies of formation of **5-ax** and **5-eq** could possibly be sufficiently great (in favor of **5-eq**) to render an inversion undetectable because the less stable **5-ax** is insufficiently populated to exert detectable alterations in the recorded spectra. Alternatively, there may be little overall conformational mobility. Recent developments suggest the latter conclusion may be the more accurate. Comparison of the barriers to chair-to-chair interconversion for **33** and **30**[30−34] reveals a major increase (>15 kcal/mol) resulting from enlargement of three rings to the cyclobutane level. A still larger increment should become apparent when proceeding from **44** to the unknown parent [6.5]rotane (**45**). MM3 calculations on **30**, **45**, and [6.6]rotane clearly point in this direction.[34]

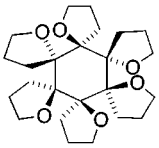
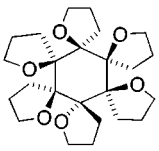
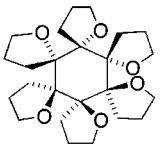
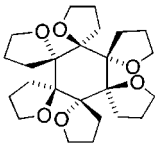
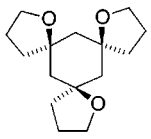


A detailed assessment of the nondynamic nature of **5** is reported in a companion paper.[35]

Complexation Studies. The binding properties of **1**, **3**, and **4** toward lithium, sodium, and potassium ions are compiled in Table 2. The coordinating capacity of **3** is seen to be the best of this triad, and superior to that of the **1,3,5**-isomer (**5**) as well. The improved chelating capability of **3**, most especially for the lithium cation, can be attributed to its conformational "looseness". Its highly dynamic properties place this polyether in a position to be capable of bringing a subset of its oxygen atoms into a geometry appropriate for binding, particularly if twist-boat conformations **J** and **K** are readily populated as has been suggested. The relevant K_a (Li^+) value for **3** is two powers of 10 below that determined for **15**, whose array of heteroatoms are notably well-disposed for this alkali metal ion. The ability of all stereoisomers to extract Na^+ with similar association constants holds interest. It is entirely possible, for example, that **3** finds it possible to complex alkali metal cations in a manner similar to **13**.

Table 2. Association Constants (K_a) Determined by Picrate Extraction into $CHCl_3$ at 20 °C

$[M^+]_{aq} + [Pic^-]_{aq} + [host]_{org} \overset{K_a}{\rightleftharpoons} [M^+\ Pic^-\ host]_{org}$

compd		Li^+	Na^+	K^+
15-crown-5		1.0×10^5 0.94×10^5	4.1×10^6 6.3×10^6	0.77×10^6 [a] 1.1×10^6
 **1**	[1,3]	9.8×10^3	2.6×10^4	1.8×10^4
 **3**	[1]	3.2×10^5	4.5×10^4	1.1×10^5
 **4**	[1,2,3]	8.0×10^3	3.2×10^4	2.5×10^4
 **5**	[1,3,5]	no extraction	1.3×10^4	no extraction
 **15**		7.9×10^7	2.5×10^6	3.3×10^4

Experimental Section

Oxidation of the Mercuri Chlorides 17 and 18. Oxygen was bubbled through a solution of sodium borohydride (124 mg, 3.3 mmol) in dry DMF (10 mL) for 10 min, at which point a suspension of a 2.2:1 mixture of **17** and **18**[21] (392 mg, 0.65 mmol) in dry DMF (10 mL) was introduced dropwise with

continuing oxygenation during 5 min. Upon completion of the addition, the oxygen flow was maintained for 10 min. The reaction mixture was filtered through a cotton plug to remove insolubles and the solvent was removed by evaporative distillation in a Kugelrohr apparatus (70 °C, 0.5 Torr). The residue was triturated with CH_2Cl_2 and the combined extracts were concentrated to leave a residue, chromatography of which on silica gel (elution with 15% ethyl acetate in hexanes containing 1% triethylamine) provided in order of elution 68 mg (28%) of **21**, 40 mg (16%) of **20**, and 117 mg (47%) of **19**.

For **19**: colorless crystals; mp 214−217 °C (from CH_2Cl_2); IR ($CHCl_3$, cm^{-1}) 3700−3540; ^1H NMR (300 MHz, C_6D_6) δ 3.79−3.42 (m, 11 H), 2.73−2.71 (m, 2 H), 2.65−2.51 (m, 2 H), 2.51−2.35 (m, 2 H), 2.30−2.26 (m, 2 H), 2.16−1.75 (series of m, 7 H), 1.73−1.56 (m, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 91.9, 91.6, 91.5, 90.5, 88.9, 78.7, 68.3, 68.2, 68.0, 67.9, 67.5, 33.1, 31.1, 30.8, 30.7, 29.2, 29.0, 28.9, 28.8, 27.5, 26.3; MS *m/z* (M^+) calcd 380.2199, obsd 380.2204.

Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48. Found: C, 66.10; H, 8.43.

This compound was subjected to X-ray crystallographic analysis.[7]

For **20**: white solid; mp 208−210 °C; IR ($CHCl_3$, cm^{-1}) 3800−3500; ^1H NMR (300 MHz, C_6D_6) δ 4.00−3.90 (m, 2 H), 3.78−3.49 (m, 8 H), 3.15 (m, 1 H), 2.72−2.45 (m, 5 H), 2.15−1.54 (series of m, 14 H), 1.25 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 93.3, 92.2, 92.0, 91.6, 89.7, 76.6, 70.7, 69.2, 68.3, 67.8, 67.6, 31.7, 31.5, 30.6, 29.4, 29.2, 29.1, 28.3, 26.8, 26.6 (1 C missing); MS *m/z* (M^+) calcd 380.2199, obsd 380.2203.

For **21**: white crystals; mp 142−145 °C; IR ($CHCl_3$, cm^{-1}) 3600−3450; ^1H NMR (300 MHz, C_6D_6) δ 3.92 (dd, J = 14.9, 7.6 Hz, 1 H), 3.76−3.61 (m, 6 H), 3.60−3.52 (m, 1 H), 3.51−3.33 (m, 2 H), 3.25 (s, 1 H), 3.20−3.11 (m, 1 H), 2.97 (s, 1 H), 2.79−2.24 (m, 8 H), 2.07−1.87 (m, 5 H), 1.86−1.76 (m, 1 H), 1.75−1.47 (m, 5 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 93.2, 91.5, 91.2, 89.5, 88.7, 78.5, 69.6, 68.3, 67.7, 67.4, 67.3, 31.8, 31.3, 31.2, 30.8, 30.7, 29.3, 29.2, 28.8, 27.8, 25.7; MS *m/z* (M^+) calcd 380.2199, obsd 380.2206.

Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48. Found: C, 66.39; H, 8.50.

(5α,6α,11α,16*β*,21α,26*β*)-1,7,12,17,22,27-Hexaoxahexaspiro[4.0.4.0.4.0.4.0.4.0.4.0]triacontane (1). A solution of **22** (35.5 mg, 0.094 mmol) in dry THF (3 mL) was cooled to −78 °C and treated with the Normant reagent (0.31 mL of 0.365 M in THF, 0.11 mmol). The cooling bath was removed and the reaction mixture was heated to reflux. Over a 10-min period, two additional 0.3 mL portions were added at this temperature prior to cooling, dilution with saturated NH_4Cl solution, and extraction with CH_2Cl_2. The combined organic layers were dried and concentrated to furnish the diol which was taken up in CH_2Cl_2 (3 mL) and treated with triethylamine (0.05 mL, 0.38 mmol), *p*-toluenesulfonyl chloride (27.5 mg, 0.14 mmol), and DMAP (5 mg). After 4 h at 25 °C, the customary workup was applied and the product was purified by chromatography on silica gel (elution with 20% ethyl acetate and 1% triethylamine in hexanes). There was obtained 24 mg (61%) of **1** as a white solid: mp 219 °C dec; IR ($CHCl_3$, cm^{-1}) 1060; ^1H NMR (300 MHz, C_6D_6) δ 4.27−4.02 (m, 2 H), 3.73−3.65 (m, 2 H), 3.63−3.48 (m, 8 H), 3.21−3.12 (m, 2 H), 2.84−2.75 (m, 2 H), 2.54 (t, J = 7.0 Hz, 2 H), 2.48−2.40 (m, 2 H), 2.14−2.00 (m, 2 H), 1.97−1.81 (m, 6 H), 1.79−1.66 (m, 2 H), 1.64−1.52 (m, 4 H), 1.48−1.39 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 94.30, 94.26, 93.0, 92.2, 70.3, 68.0, 67.8, 67.4, 32.3, 31.1, 31.0, 30.1, 29.6, 29.4, 28.7, 26.8; MS *m/z* (M^+) calcd 420.2512, obsd 420.2504.

Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63. Found: C, 68.81; H, 8.71.

(3α,6*β*,11α,16*β*,21α,26*β*)-1,7,12,17,22,27-Hexaoxahexaspiro[4.0.4.0.4.0.4.0.4.0.4.0]triacontane (5). A solution of **40** (185 mg, 0.42 mmol) in 5 mL of 9:1 CH_2Cl_2−CH_3CN was treated with tetrapropylammonium perruthenate (20 mg, 0.057 mmol) and *N*-methylmorpholine *N*-oxide (150 mg, 1.28 mmol), stirred at 20 °C for 1 h, concentrated, and subjected to flash chromatography (silica gel, elution with 20−50% ethyl acetate in hexanes containing 10% methanol). This product was directly treated with triethylamine (1.00 mL, 7.17 mmol) in CH_2Cl_2 (3 mL) for 30 min, concentrated in vacuo, and taken up in ethanol (10 mL). After the addition of 10% palladium on carbon (100 mg), the mixture was hydrogenated under 1 atm of H_2 for 2h, filtered through Celite,® and evaporated. The resulting oil was dissolved in THF (5 mL), stirred with lithium aluminum hydride (67 mg, 1.8 mmol) for 3 h, and quenched with 3 N NaOH solution. The solids were removed by filtration and rinsed thoroughly with CH_2Cl_2. The filtrate was concentrated and the residue was taken up in CH_2Cl_2 (10 mL) and treated in turn with triethylamine (0.40 mL, 2.9 mmol), *p*-toluenesulfonyl chloride (279 mg, 1.42 mmol), and 4-(dimethylamino)pyridine (20 mg). This mixture was stirred for 10 h at room temperature and 13 h at reflux, cooled, concentrated, and chromatographed on silica gel (elution with 2% ethyl acetate in hexanes) to give **5** (74 mg, 42% over five steps) as a white crystalline solid: mp 249−251 °C (from 5% CH_2Cl_2 in hexanes); IR (film, cm^{-1}) 1454, 1265, 1062, 1017; ^1H NMR (300 MHz, C_6D_6) δ 3.58 (t, J = 6.7 Hz, 1 H), 2.49 (t, J = 7.2 Hz, 12 H), 1.88 (d, J = 6.9 Hz, 12 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 92.5, 67.7, 30.4, 29.4; MS *m/z* (M^+) calcd 420.2512, obsd 420.2485.

Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63. Found: C, 68.33; H, 8.60.

This compound was subjected to X-ray crystallographic analysis (Figure 3).

Acknowledgment. This work was supported by the Paquette Research Fund and the National Science Foundation. The authors thank Prof. Robin Rogers (University of Alabama) for the X-ray crystallographic analyses, Dr. Charles Cottrell for the DNMR measurements, and Dr. Kurt Loening for assistance with nomenclature.

Supporting Information Available: Experimental procedures and spectroscopic data for all compounds not described in the printed format, along with X-ray structure reports for **4**, **5**, and **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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