Selective Lithium Ion Binding Involving Inositol-Based Tris(spirotetrahydrofuranyl) Ionophores: Formation of a Rodlike Supramolecular Ionic Polymer from a Homoditopic Dimer

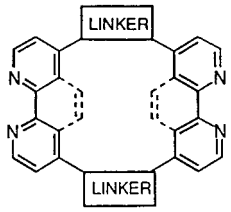
Leo A. Paquette* and Jinsung Tae

Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Received January 10, 2001

Abstract: The stereoselective replacement of all three hydroxyl groups in *myo*-inositol orthoformate by spirotetrahydrofuran rings in that manner which projects the C−O bonds in the molecular interior has been examined. The heterocyclic components were introduced sequentially, a protocol that demonstrated the utility of precomplexation to $LiClO_4$ as a stereocontrol tactic. The capability of **3** to coordinate to alkali metal ions was quantified. The conformationally restricted nature of this ligand conveys high selectivity for binding to lithium ion. Beyond that, the ionophore prefers to form 2:1 complexes with Li^+ and exhibits little tendency for 1:1 stoichiometry. These properties are shared by the "dimer" **36**, in which two building blocks of type **3** have been conjoined by a 1,3-butadiyne tether positioned at the ortho ester terminus. This bifacial ligand reacts with one equivalent of $LiClO_4$ or $LiBF_4$ to form rodlike ionic polymers. Alternative recourse to lithium picrate results in production of the doubly capped homoditopic complex **41**. Various other aspects of the chemistry peculiar to these systems are discussed.

Very recently, attention has been turned to the preparation of macrocyclic systems having at least two exotopic binding sites because of the latent potential of these systems to serve as precursors to new types of metallosupramolecular structures. To the present time, interest has been focused to a large extent on 2,2′-bipyridines[1] and phenanthrolines [2] of the general formula **1** to capitalize on the capability of these ligands to bind to transition metal ions in a well-defined way.[3,4] 4,4′-Dipyridines of type **2** have similarly been utilized as building blocks[5]



1

2

for the construction of rodlike metal-coordinated network polymers.[6]

In connection with our studies of polyspiro(tetrahydrofuranyl) compounds,[7] we have sought to develop synthetic routes to ligands that have their oxygen-centered binding sites covalently anchored to an inositol orthoformate platform. Structure **3**, which represents a prototypical member of this new heterocyclic family, was targeted because of its potential for serving as a very specific ionophore for lithium ion. The need for developing lithium-sensitive electrodes for monitoring Li^+ concentrations in the blood of manic depressive patients being administered large daily doses of lithium carbonate[8] continues to attract strong interest.[9] Beyond that, the utilization of alkali metal ions for the preparation of ionic supramolecules is an attractive goal. In this connection, the anticipated good selectivity of **3** for chelating

(1) (a) Schmittel, M.; Ganz, A. *Synlett* **1997**, 710. (b) Schmittel, M.; Ganz, A. *Chem. Commun.* **1997**, 999.

(2) (a) Kelly, T. R.; Lee, Y.-J.; Mears, R. J. *J. Org. Chem.* **1997**, *62*, 2774. (b) Kaes, C.; Hosseini, M.; Rickard, C. E. F.; Skeleton, B. W.; White, A. H. *Angew Chem., Int. Ed.* **1998**, *37*, 920. (c) Kaes, C.; Hosseini, M. W.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1997**, *38*, 3901. (d) Schmittel, M.; Ammon, H. *Synlett* **1999**, 750.

(3) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995; p 138.

(4) (a) Philip, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154. (b) Conn, M. M. *Chem. Rev.* **1997**, 1647.

(5) (a) Sauvage, J.-P.; Collin, J.-P.; Chambron, J.-C.; Guillerez, S.; Coudret, C.; Balzani, V.; Barrigelletti, F.; De Cola, L.; Flamigni, L. *Chem. Rev.* **1994**, *94*, 993. (b) Abrahams, B. F.; Hardie, M. J.; Hoskins, B. F.; Robson, R.; Sutherland, E. E. *J. Chem. Soc., Chem. Commun.* **1994**, 1049. (c) Whiteford, J. A.; Lu, C. V.; Stang, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 2524. (d) Carlucci, L.; Ciani, G.; Proserpio, D. M. *J. Chem. Soc., Chem. Commun.* **1999**, 449. (e) Champness, N. R.; Khlobystov, A. N.; Majuga, A. G.; Schröder, M.; Zyk, N. V. *Tetrahedron Lett.* **1999**, *40*, 5413.

(6) (a) Yaghi, O. M.; Li, H.; Davis, C.; Richardson, D.; Troy, T. L. *Acc. Chem. Res.* **1998**, *31*, 474. (b) Batten, S. R.; Robson, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1451. (c) Champness, N. R.; Schröder, M. *Curr. Opin. Solid State Mater. Chem.* **1998**, *3*, 419. (d) Blake, A. J.; Champness, N. R.; Li, W.-S.; Withersby, M. A.; Schröder, M. *Coord. Chem. Rev.* **1999**, *183*, 117.

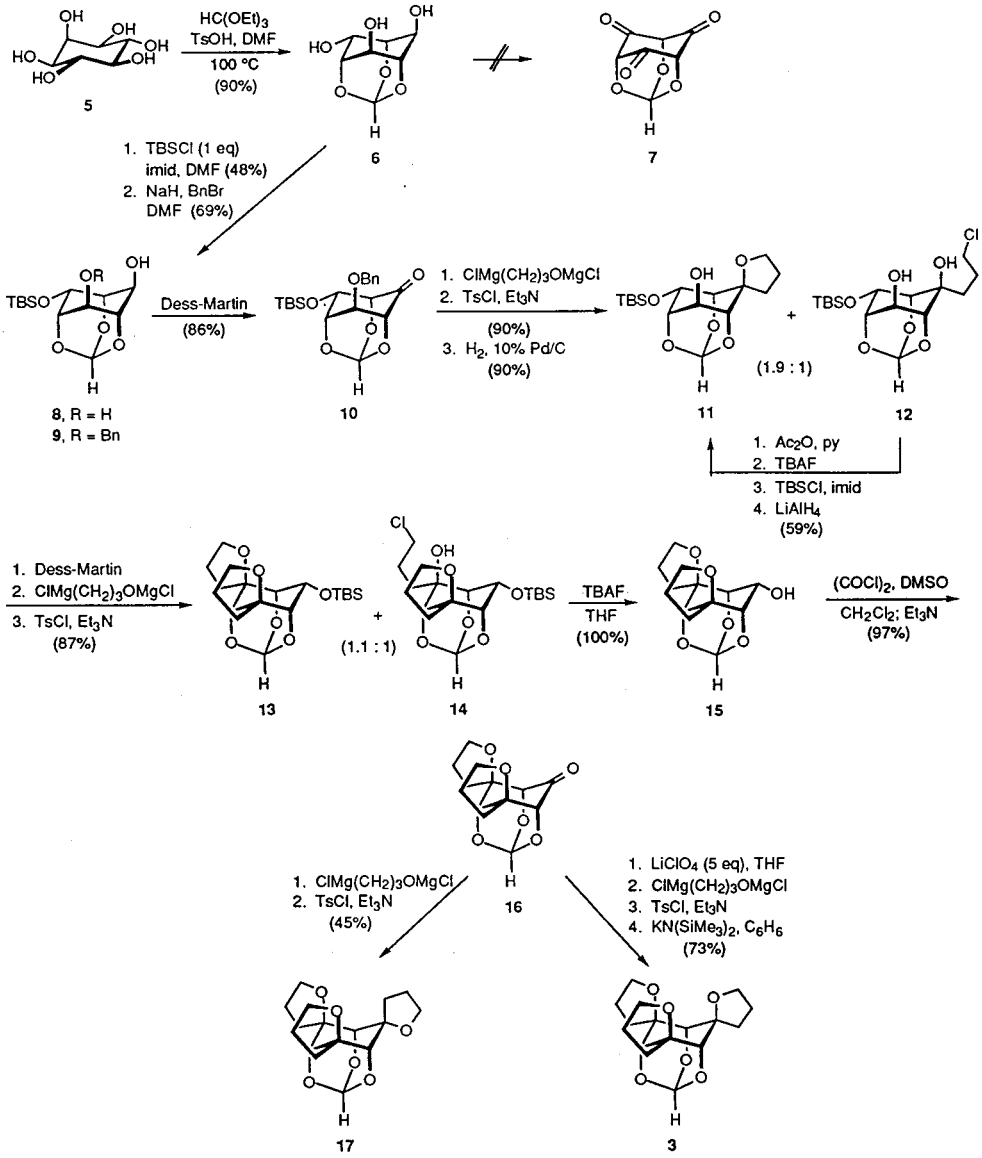
(7) (a) Paquette, L. A.; Branan, B. M.; Stepanian, M. *Tetrahedron Lett.* **1996**, *37*, 1721. (b) Paquette, L. A.; Stepanian, M.; Branan, B. M.; Edmondson, S. D.; Bauer, C. B.; Rogers, R. D. *J. Am. Chem. Soc.* **1996**, *118*, 4504. (c) Paquette, L. A.; Lowinger, T. B.; Bolin, D. G.; Branan, B. M. *J. Org. Chem.* **1996**, *61*, 7486. (d) Paquette, L. A.; Stepanian, M.; Mallavadhani, U. V.; Cutarelli, T. D.; Lowinger, T. B.; Klemeyer, H. J. *J. Org. Chem.* **1996**, *61*, 7492. (e) Stepanian, M.; Trego, W. E.; Bolin, D. G.; Paquette, L. A.; Sareth, S.; Riddell, F. G. *Tetrahedron* **1997**, *53*, 7403. (f) 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. (g) Paquette, L. A.; Tae, J.; Hickey, E.; Rogers, R. D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1409. (h) Paquette, L. A.; Tae, J.; Branan, B. M.; Eisenberg, S. W. E.; Hofferberth, J. E. *Angew. Chem., Int. Ed.* **1999**, *38*, 1412. (i) Paquette, L. A.; Tae, J. *Tetrahedron Lett.* **1999**, *40*, 5971.

(8) Birch, N. J., Ed., *Lithium: Inorganic Pharmacology and Psychiatric Use*; IRL Press: Oxford, 1988.

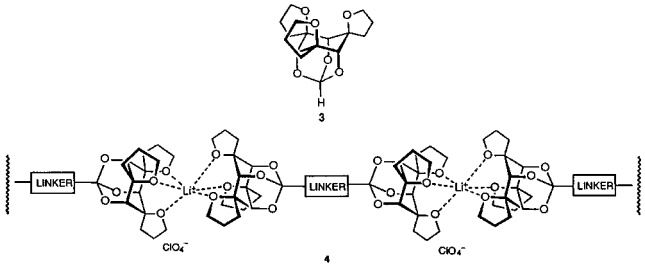
(9) (a) Kimura, K.; Yano, H.; Kitazawa, S.; Shono, T. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1945. (b) Kataky, R.; Nicholson, P. E.; Parker, D. *J. Chem. Soc., Pertin Trans. 2* **1990**, 321. (c) Kataky, R.; Nicholson, P. E.; Parker, D.; Covington, A. K. *Analyst* **1991**, *116*, 135. (d) Suzuki, K.; Yamada, H.; Sato, K.; Watanabe, K.; Hisamoto, H.; Tobe, Y.; Kohiro, K. *Anal. Chem.* **1993**, *65*, 3404. (e) Faulkner, S.; Kataky, R.; Parker, D.; Teasdale, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1761.

10.1021/ja010103x CCC: $20.00
Published on Web 05/03/2001

Scheme 1



Li^+ was believed to offer positive prospects for the generation of the novel homopolymers typified by **4**.



In the present paper, we describe in detail our comprehensive efforts in this area, both preparative and analytical.[10] Particularly noteworthy is the high selectivity with which **3** and a "dimer" thereof bind Li^+ relative to Na^+. This property lends itself very suitably to arrival at **4**. Moreover, this polymerization can be controlled under the proper conditions, thus enabling the isolation of a discrete bifacial complex.

(10) For preliminary reports describing select aspects of this work, consult: (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.

Results and Discussion

Elaboration of the Conformationally Fixed Ionophore 3. In view of the ease with which inexpensive *myo*-inositol (**5**) can be transformed into **6**,[11] we first explored direct conversion of the latter into triketone **7** (Scheme 1). This obvious maneuver would presumably set the stage for three-fold "capping"[12] and very direct conversion to **3**. Unfortunately, however, the close proximity of the hydroxyl substituents in **6** and the aldol nature of partially oxidized intermediates served effectively to render the conversion to **7** inoperative under a wide variety of conditions. Recourse was therefore made to installation of the spirotetrahydrofuran rings in a stepwise manner.

The salient feature of the addition of the Normant reagent[13] to **10** is the expectation that the new C−C bond will be formed from the equatorial direction. This trajectory guarantees that the developing tetrahydrofuran ring will be constituted of an axial C−O bond, provided that the initially formed diol is cyclized under basic conditions by way of the primary mono-

(11) Lee, H. W.; Kishi, Y. *J. Org. Chem.* **1985**, *50*, 4402.

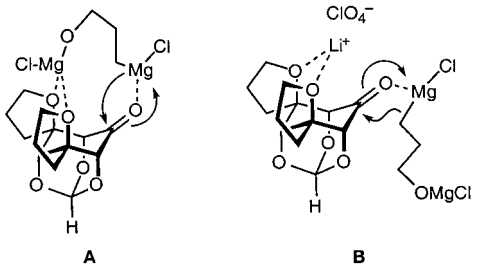
(12) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3947.

(13) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, 3013.

tosylate. Following controlled reaction of the Normant adduct with tosyl chloride and triethylamine, however, two products were seen by ^{1}H NMR to have been formed in a 1.9:1 ratio. Because this pair of products proved to be difficultly separable, the mixture was subjected to hydrogenolysis in advance of chromatography. The conclusion that **11** and **12** were *not* diastereomers was confirmed by a simple four-step chemical interconversion that did not perturb the stereogenic centers (see Scheme 1). Five additional pieces of evidence confirmed that **12** was the alkyl chloride. The white powdery solid **12** exhibited the very same melting point as **11**, in line with anticipated thermal extrusion of hydrogen chloride. The HRMS (EI) spectra of the two compounds exhibited identical fragmentation patterns, a likely consequence of the conversion of **12** to **11** under the conditions of the measurements. The FAB MS of **12** and its combustion analysis were distinctive for $C_{19}H_{33}ClO_6Si$. Last, select key ^{1}H and ^{13}C NMR resonances, for example, δ 3.59 for $-CH_2Cl$ and 44.9 for $-CH_2Cl$ in $CDCl_3$ solution, conform to anticipated chemical shifts. The existence of **12** and related chlorides (see below) reflects the feasibility of tosylate displacement by chloride ion during the functionalization process. This phenomenon has been observed previously.[14]

The ketone obtained following oxidation of **11** with the Dess−Martin periodinane[15] was capped in the predescribed manner. The virtually exclusive operation of exo attack was readily discerned by the C_s-symmetric nature of **13**. The simplified nature of its ^{13}C NMR spectrum was particularly telling. As seen earlier, the generation of **13** was accompanied by formation of the chloride **14** in near-equivalent proportions. The general features of the ^{1}H and ^{13}C NMR spectra of **14** are reconcilable with the absence of any element of symmetry. Treatment of either **13** or **14** with tetra-*n*-butylammonium fluoride in THF delivered carbinol **15**.

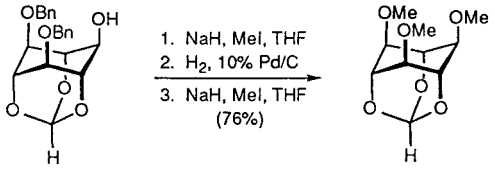
We next addressed the introduction of the third and final tetrahydrofuran subunit. Under entirely comparable Normant conditions, **16** was unexpectedly converted into **17** as the major product.[7i] The source of this remarkable reversal in the stereoselectivity of the 1,2-carbonyl addition was considered to be the coordinated complex **A**, the intervention of which would be followed by nucleophilic attack from the axial surface. To reverse this untoward course of events, a complementary experiment was performed in which 5 equiv of $LiClO_4$ was first added to **16** in the hope that ligation to Li^+ as in **B** would now relegate attack of the nucleophilic reagent entirely to the equatorial π-surface. This ploy proved quite successful in that only **3** was now formed in good yield. The two trispiro products are readily distinguished on the basis of the enhanced (C_{3v}) symmetry of the intended target **3**.



A B

For comparison purposes, the trimethoxy analogue **19** was also synthesized (Scheme 2). This goal was easily reached by sequential *O*-methylation of the known alcohol **18**,[11] 2-fold debenzylation, and repetition of the first step. An X-ray crystallographic analysis of **19**[16] revealed the distances between the methoxyl oxygens to be 2.9606, 2.8852, and 2.9096 Å. Although **3** crystallized well, complications were encountered in gaining access to a comparable solid-state analysis in this instance. Subsequently, however, the derivative **35** was found to lend itself to structural corroboration as discussed below.

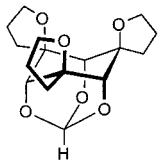
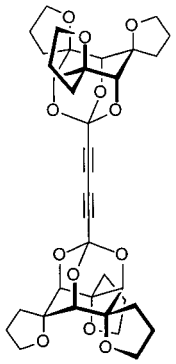
Scheme 2



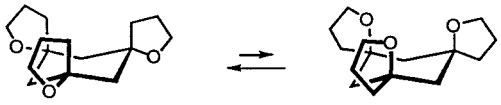
18 19

Table 1. Association Constants (K_a) Determined by Picrate Extraction into Chloroform at 20 °C

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

	Li^+	Na^+	K^+
 **3**	1.1×10^7 $K_a(Li^+)/K_a(Na^+) = 440$	2.5×10^4	5.1×10^3
 **36**	1.1×10^7 $K_a(Li^+)/K_a(Na^+) = 262$	4.2×10^4	1.9×10^3

The Ligating Properties of 3. The association constants K_a for the complexation of **3** to lithium-, sodium-, and potassium picrate were determined by extraction from water into chloroform.[17] At this point, comparison with **20** is warranted.[7g,h] Although this trispiro system adopts the all-equatorial conformation in the ground state, the all-axial arrangement is readily populated and is therefore available for coordination to alkali metal ions without difficulty. As seen in Table 1, the ability of **3** and **20** to bind Li^+ is closely comparable. However, the enhanced geometric constraints imposed on **3** manifest themselves when the larger Na^+ is involved. The fact that **3** cannot accommodate the sodium ion as intimately increases the $K_a(Li^+)/K_a(Na^+)$ selectivity ratio from 32, the value exhibited by **20**, to the significantly elevated value of 440. This heightened level of discrimination on the part of **3** for binding lithium is required of useful sensing ionophores.



20eq 20ax

(14) For example: Reveli, G. A.; Gros, E. G. *Synth. Commun.* **1993**, *23*, 1111.

(15) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

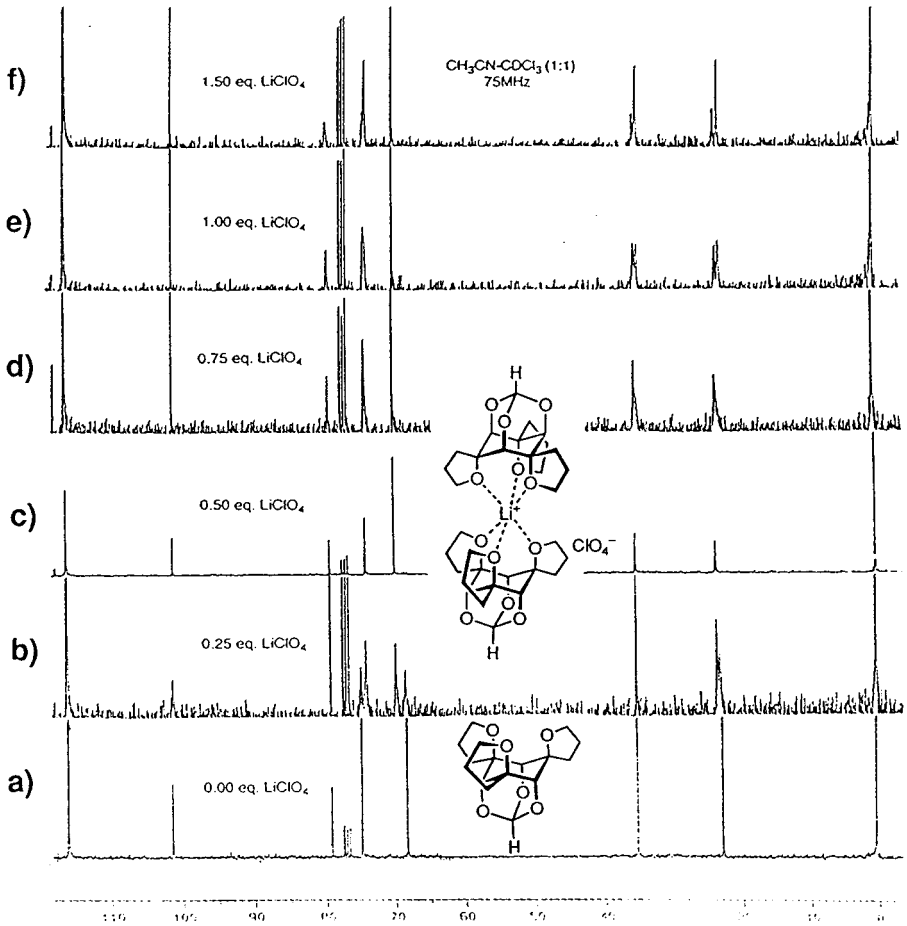
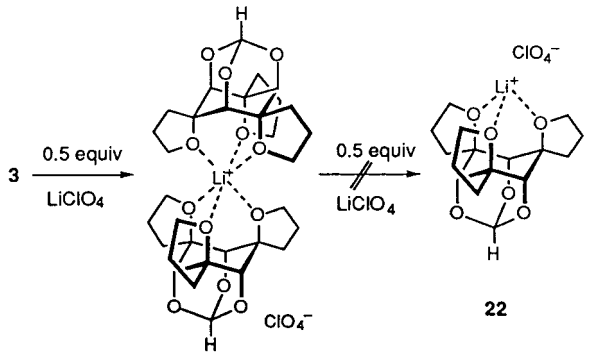


Figure 1. ^{13}C NMR spectra (75 MHz) recorded during the titration of **3** with $LiClO_4$ in 1:1 $CH_3CN/CDCl_3$. Equivalents of added salt: (a) 0.00; (b) 0.25; (c) 0.50; (d) 0.75; (e) 1.00; (f) 1.50.

The contrasting behavior of **19**, which shows no ability to extract any of the picrate salts, establishes that this arrangement of three *syn*-methoxy groups is not conducive to binding. The progression from an acyclic to a cyclic ether, for example, diethyl ether to tetrahydrofuran, has long been recognized to enhance intrinsic basicity and foster improved hydrogen-bonding capability.[18] The steric origins of these phenomena are believed to contribute in important ways here. A further consideration is the need on the part of all three ligating oxygens to orient one of their nonbonded electron pairs toward the central core as binding is initiated. Molecular models indicate that the associated rotational process is more easily accomplished when tetrahydrofuran moieties are involved.

Titration experiments involving the conformationally restricted host **3** were conducted in 1:1 $CH_3CN/CDCl_3$ and monitored by ^{13}C NMR. As seen in Figure 1, **3** is smoothly transformed into the 2:1 sandwich complex **21** upon addition of 0.5 equiv of $LiClO_4$. This response is essentially identical to that exhibited by **20**. The striking difference between these related ionophores manifests itself as additional lithium salt is introduced. Whereas **20** is transformed rapidly into a 1:1 complex when a total of 1.0 equiv is present, **3** does not undergo this chemical change to generate **22**. Figure 1 reveals that only slight line broadening and minor chemical shift changes materialize.



This somewhat more restricted complexation stoichiometry was construed to be ideal for the planned polymerization studies, since molecules of type **4** owe their existence precisely to this mode of binding. When the solution used for the NMR studies in Figure 1 was concentrated, triturated with CH_2Cl_2, and freed of the excess $LiClO_4$ prior to dilution with hexane, crystals of **21** suitable for crystallographic analysis were obtained. The six oxygens around the lithium atom are seen to adopt a nicely staggered arrangement. The melting point of **21** (>254 °C) is reasonably elevated.

Titration of **3** with $NaClO_4$ in an entirely comparable manner does not alter the ^{13}C NMR spectrum of the ionophore. Another glimpse of the ion-selective binding properties of **3** was gained in this way.

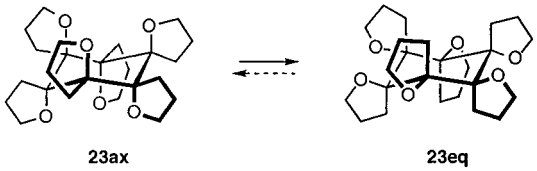
Synthesis of a Bifacial Ligand. The synthesis of structurally intricate ionophores having the capacity to engage in bifacial

(16) This analysis was performed by Prof. Robin Rogers of the University of Alabama.

(17) Cram, D. J.; Lein, G. M. *J. Am. Chem. Soc.* **1985**, *107*, 3657

(18) For a compilation of relevant references, consult: Paquette, L. A.; Tae, J.; Hickey, E. R.; Trego, W. E.; Rogers, R. D. *J. Org. Chem.* **2000**, *65*, 9160.

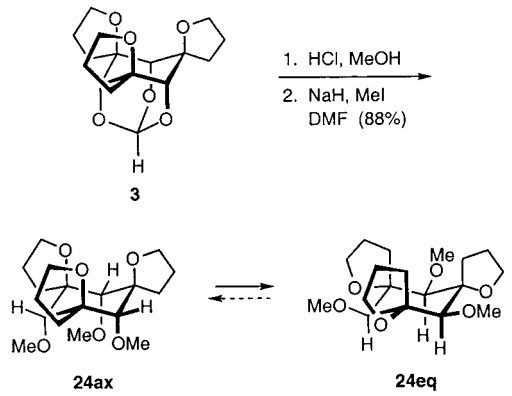
complexation has received little attention.[19] The hexaspirocyclohexane **23** is unable to serve in this capacity as a direct consequence of its inability to exist in the all-axial conformer.[7h]



23ax **23eq**

The same powerful electrostatic effects operate in **24**. This substrate, which has been produced by the acid hydrolysis and *O*-methylation of **3** and therefore originates as the all-axial conformer (Scheme 3), rapidly undergoes essentially irreversible

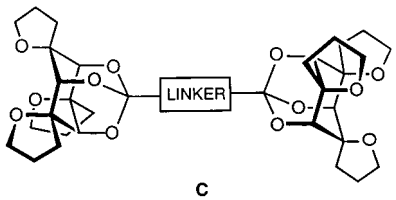
Scheme 3



3 **24ax** **24eq**

chair-to-chair interconversion to the nonpolar, highly crystalline all-equatorial counterpart. Like all-trans hexamethoxycyclohexane,[20] **24ax** exhibits no binding capability to metal ions.

This being the case, there seemed to be an opportunity to produce structurally unique homoditopic ligands by linking two molecules of **3** via the methine carbon of its ortho ester subunit as in **C**. In principle, this synthetic transformation might be most conveniently met by implementation of a dimerization reaction. One such possibility is the Glaser coupling reaction,[21] wherein diacetylenes are produced by the oxidative coupling of terminal alkynes. Accordingly, the route originally developed to access **3** was modified to accommodate a higher level of substitution (Scheme 4).[10b]



C

Since the *p*-methoxyphenyl (PMP) group held the promise of being sufficiently robust to be carried through the synthesis, the decision was made to begin with the ortho ester **25**. The particular choice of **25** was in keeping with its anticipated ready

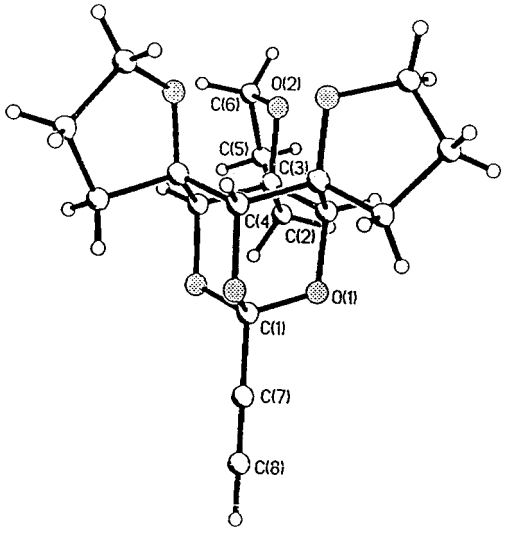


Figure 2. ORTEP diagram of **35**.

availability[22] from the known (*p*-methoxy)phenoxyacetonitrile.[23] In a crucial first step, heating **25** with *myo*-inositol (**5**) in DMF under acid catalysis for 24 h succeeded in delivering **26** in 95% yield at the 57% conversion level. As in the parent series, triol **26** was amenable to chemoselective silylation of its equatorial hydroxyl and mono-*O*-benzylation of the symmetric resulting 1,3-diol. This pair of steps allowed for exploration of the possibility for oxidation to ketone **29** and "capping" of its carbonyl group to generate the monospirotetrahydrofuran **30**. As observed earlier, the chloro diol **31** was formed alongside **30** from which it proved chromatographically separable. The spectral features that distinguish **30** from **31** were recognized to be distinctive and diagnostic. As part of a mini-program of yield enhancement, **31** was transformed into **30** in 67% overall yield via a sequence of four rapidly executed steps.

The route continued uneventfully through installation of the second (as in **32**) and third heterocyclic rings (see **33**). Of course, proper attention was paid to complexation of the dispiro ketone intermediate with $LiClO_4$ to guarantee proper stereoselection in the final addition of the Normant reagent. With this necessary step in place, the yield for the conversion of **32** to **33** was 78% overall.

Deprotection of the PMP group with ceric ammonium nitrate in aqueous acetonitrile proceeded to completion within 10 min at 0 °C. With alcohol **34** in hand, the time had arrived to screen the feasibility of its oxidation to the aldehyde. The use of the Dess−Martin periodinane or tetra-*n*-propylammonium perruthenate proved not to be utilitarian. We soon realized that the highly polar nature of **34** and the aldehyde precluded the use of oxidants that require significant purification during the ensuing workup. In the final analysis, Swern oxidation worked best, although the level of efficiency was only modest. The attendant consequences on homologation of the aldehyde to **35** proved not to be damaging. Direct reaction with dimethyl 1-diazo-2-oxopropylphosphonate[24] and K_2CO_3 in methanol resulted in relatively rapid conversion to the terminal alkyne. A notable property of this substance is its limited solubility in CH_2Cl_2, which permitted the acquisition of crystals well-suited to X-ray crystallograpic analysis (Figure 2). The O(2)- - -O(2) distance in **35** is 2.831 Å.

(19) For background information, see: (a) Paquette, L. A.; Tae, J.; Branan, B. M.; Bolin, D. G.; Eisenberg, S. W. E. *J. Org. Chem.* **2000**, *65*, 9172. (b) Rablen, P. R.; Paquette, L. A.; Borden, W. T. *J. Org. Chem.* **2000**, *65*, 9180.

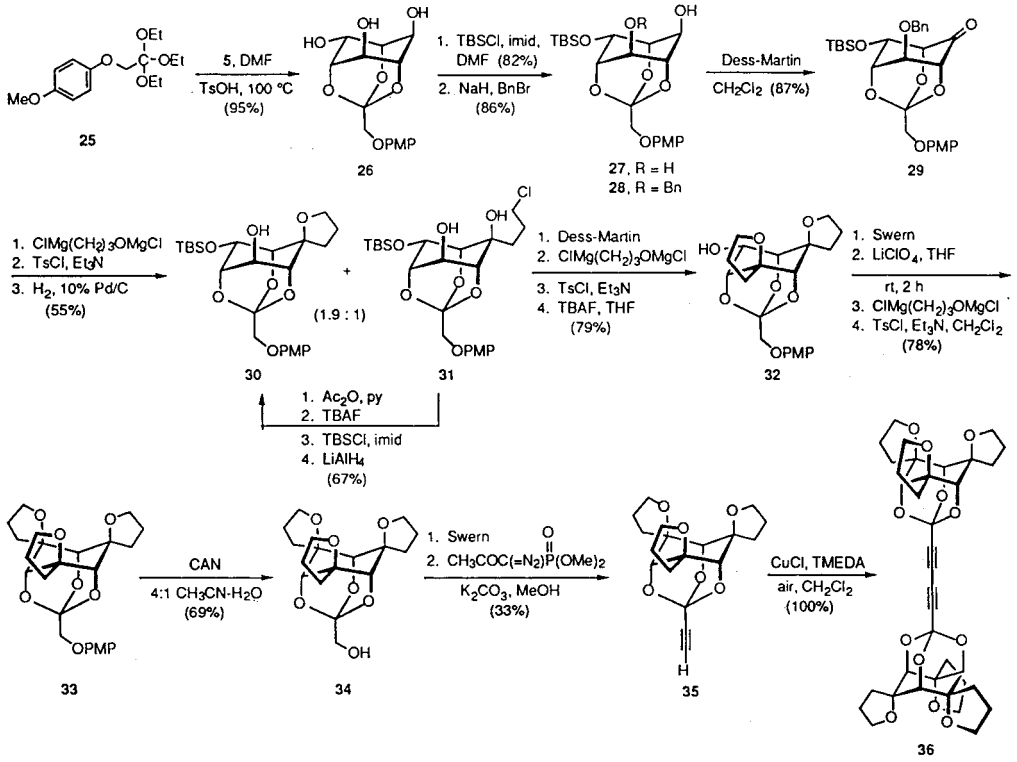
(20) (a) Anderson, J. E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 441. (b) Anderson, J. E.; Angyal, S. T.; Graig, D. C. *Carbohydr. Res.* **1995**, *272*, 141.

(21) (a) Glaser, C. *Ber.* **1869**, *2*, 422. (b) Glaser, C. *Ann.* **1870**, *154*, 159.

(22) Voss, G.; Gerlach, H. *Helv. Chim. Acta* **1983,** *66*, 2294.

(23) (a) Johnson, R. E.; Baizman, E. R.; Becker, C.; Bohnet, E. A.; Bell, R. H.; Birsner, N. C.; Busacca, C. A.; Carabateas, P. M.; Chadwick, C. C. *J. Med. Chem.* **1993**, *36*, 3361. (b) Ferrand, G.; Dumas, H.; Decerprit, J. *Eur. J. Med. Chem.* **1992**, *27*, 309.

Scheme 4

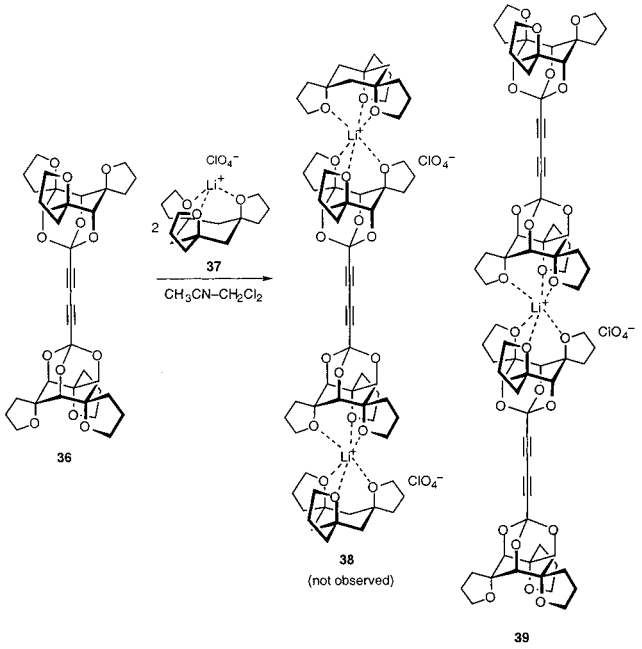


Remarkably, submission of **35** to modified Glaser conditions,[25] consisting of the use of CuCl in TMEDA under an atmosphere of dry air, resulted in quantitative formation of dimer **36**. This product is a highly polar substance that does not melt below 280 °C and is freely soluble in CH_2Cl_2. Slow evaporation of such solutions results in the formation of colorless feather-shaped crystals that turn cloudy on drying.

The Complexation of 36 with Lithium Ions. The association constants for the binding of Li^+-, Na^+-, and K^+ picrate to **36** (Table 1) expectedly reveal that the dimeric compound closely parallels monomer **3** in its strong preference for coordinating to the lithium ion.

Given the previously acknowledged capability of **20** to enter readily into formation of a 2:1 complex with Li^+, and in light of the modestly stronger binding ability of **20** ($K_a(Li^+) = 7.9 \times 10^7$) relative to **3** ($K_a(Li^+) = 1.1 \times 10^7$) toward this guest ion, we envisioned the possibility that admixing of 2 equiv of **37** with **36** might well eventuate in the formation of the bifacial complex **38** (Scheme 5). When this experiment was conducted in a 1:1 $CH_3CN-CH_2Cl_2$ solvent system in which both reactants were soluble, the immediate precipitation of a white powdery solid was observed. Although this substance proved minimally soluble in the most common solvents (CH_3CN, CH_2Cl_2, CH_3OH, H_2O), it did dissolve in DMF and DMSO. Decantation of the reaction solvent and concentration returned half of the original amount of **37**. No free **20** was detected in any of the isolates.

Scheme 5



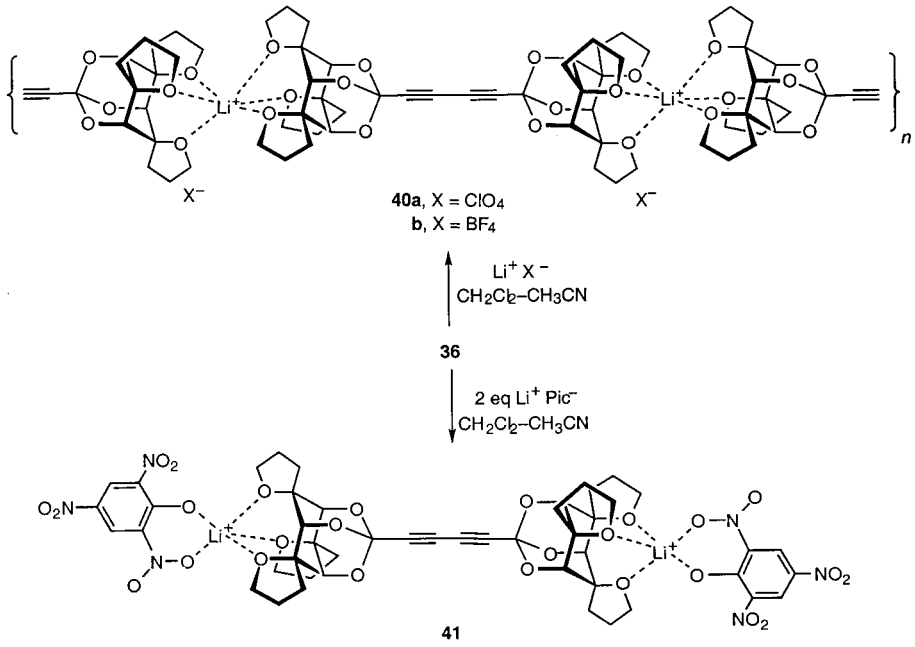
The solid was characterized by electrospray ionization mass spectrometry.[26] The major peaks recorded from dilute CH_3CN solutions of the material were found at $m/z = 674.0$ (100% intensity, **36**·Li^+), 925.9 (20%, **36**·Li^+·**37**), and 1339.8 (5%, **36**·Li^+·**36**). Although the targeted bifacially capped **38** was not observed, the 2:1 sandwich complex **39** was found as the highest molecular ion peak. When an analogous reaction was carried out in 1:1 DMSO−CH_2Cl_2, a clear solution was formed. However, only **37** was recovered following further processing.

(24) (a) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837. (c) Delpech, B.; Lett, R. *Tetrahedron Lett.* **1989**, *30*, 1521. (d) Parry, R. J.; Muscate, A.; Askonas, L. J. *Biochemistry* **1991**, *30*, 9988. (e) Hauske, J. R.; Dorff, P.; Julin, S.; Martinelli, G.; Bussolari, J. *Tetrahedron Lett.* **1992**, *33*, 3715. (f) Nerenbrg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621.

(25) (a) Hamilton, D. G.; Prodi, L.; Feeder, N.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1057. (b) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320.

(26) Schalley, C. A.; Castellano, R. K.; Brody, M. S.; Rudkevich, D. M.; Siuzdak, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 4568 and references therein.

Scheme 6



Quite evidently, the proper complexation equilibria are not established in the presence of DMSO.

Treatment of **36** in $CH_3CN-CH_2Cl_2$ with 1 equiv of lithium perchlorate resulted in the rapid precipitation of a white solid that was insoluble in the most polar solvents including DMF. Alternate use of lithium tetrafluoroborate delivered in quantitative yield a white powder that does not melt up to 280 °C but is soluble in DMF and in DMSO. The material is not crystalline, and its ^{1}H NMR spectrum in DMSO-d_6 is broad. Electrospray mass spectral analysis of these samples in the positive ion mode gave spectra consisting of broad humps of low intensity over the *m*/*z* 2000−6000 range. The lack of resolution of individual peaks indicates that the substances are polymers such as **40** of much higher mass. Consequently, oligomeric rodlike networks of type **4** with spacers constructed of 1,3-butadiyne segments can be readily produced (Scheme 6).[27]

The polymerization process that leads to **40** could be harnessed by making recourse instead to an internally chelated lithium salt such as lithium picrate. Such co-reactants can effectively deliver Li^+ ions to the binding sites of **36** without disruption of the preexisting coordination. A direct consequence of this property is the efficient formation of the bifacially capped complex **41**. Admixture of a solution of **36** in CH_2Cl_2 with 2 equiv of Li^+Pic^- dissolved in CH_3CN resulted in the deposition of yellow crystals well-suited to X-ray crystallographic analysis. These crystals were fragile and turned cloudy as they dried in the air due to loss of solvent of crystallization.

(27) A reviewer has questioned why comparison of the formation of **40** with the reactivity of diacetylenes toward heat and light[28] was not made. While the prior work in the latter field is elegant and defining, the chemistry comprises reactions at the sp-hybridized carbon atoms. The generation of **40** involves instead the coordination of Li^+ to a bifacial ligand along a chain in repetitive fashion. The acetylenic centers play no direct part in this process and serve only to anchor the ligands together. This is not diacetylene polymerization.

(28) (a) Wenz, G.; Wegner, G. *Makromol. Chem., Rapid Commun.* **1982**, *3*, 231. (b) Lieser, G.; Wegner, G.; Mueller, W.; Enkelmann, V. *Makromol. Chem., Rapid Commun.* **1980**, *1*, 621. (c) Schermann, W.; Wegner, G.; Williams, J. O.; Thomas, J. M. *J. Polym. Sci., Polym. Phys. Ed.* **1975**, *13*, 753. (d) Wegner, G. *Makromol. Chem.* **1971**, *145*, 85. (e) Haedicke, E.; Mez, E. C.; Krauch, C. H.; Wegner, G.; Kaiser, J. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 266b. (f) Wegner, G. *J. Polym. Sci., Part B: Polym. Phys.* **1971**, *9*, 133.

Overview. The conformationally fixed trispiro ether **3** derived from *myo*-inositol has proven to be a lithium ion-selective host molecule. Its $K_a(Li^+)/K_a(Na^+)$ selectivity ratio of 440 constitutes a greater than 10-fold improvement relative to the more flexible **20**, and qualifies it as a neutral, liphophilic, Li^+-sensing ionophore with potential application in ion-selective electrodes having clinical utility. NMR titration experiments have demonstrated that this host molecule prefers to form a 2:1 sandwich complex with Li^+ rather than enter into 1:1 coordination.

In a companion study, a synthesis of a highly preorganized bifacial ionophore was successfully completed. The binding properties of **36** are comparable to those of **3**. Self-assembly of **36** with $LiBF_4$ and $LiClO_4$ gave rise to supramolecular structures that take advantage of the 2:1 coordination preference to deliver alkali metal complexes that are presumably rodlike in nature.

As discussed earlier, one of the goals of our program is to achieve enhanced capacity for the determination of Li^+ activities in biological systems. To this end, we hope to report on the preparation of congeners of **3** and **36**, and to detail their binding characteristics soon.

Experimental Section

General. THF and ether were distilled from sodium benzophenone ketyl under nitrogen just prior to use. For CH_2Cl_2 and benzene, the drying agent was calcium hydride. All reactions were performed under a N_2 atmosphere. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} aluminum-backed plates. All chromatographic purifications were performed on E. Merck silica gel 60 (230−400 mesh) using the indicated solvent systems. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker instruments at 300 and 75 MHz, respectively, except where noted. Elemental analyses were performed at Atlantic Microlab, Inc., Norcross, Georgia. The organic extracts were dried over anhydrous $MgSO_4$. The high-resolution mass spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center.

(1α,5α,6*β*,7α,8*β*,9α)-8-(Benzyloxy)-9-(*tert*-butyldimethylsiloxy)-2,4,10-trioxaadamantan-6-ol (9). To sodium hydride (80%, 1.19 g, 39.6 mmol) in DMF (20 mL) was added the diol **8**[11] (12.4 g, 40.9 mmol) dissolved in DMF (10 mL) followed by benzyl bromide (4.28 mL, 36.0 mmol) at 0 °C. After 30 min, the mixture was warmed to room temperature, stirred for an additional 2 h, quenched with saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3 × 50 mL). The combined

organic layers were dried and concentrated to leave a residue that was purified by chromatography on silica gel (elution with 10−25% ethyl acetate in hexanes) to afford 11.1 g (69%) of **9** as a colorless liquid, along with the dibenzyl ether (3.40 g) and starting material (2.96 g); IR (film, cm^{-1}) 3502, 1472, 1398, 1259, 1166; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.25 (m, 5 H), 5.47 (s, 1 H), 4.66 (s, 2 H), 4.48−4.35 (m, 2 H), 4.30−4.20 (m, 2 H), 4.15−4.10 (m, 2 H), 3.62 (d, J = 10.0 Hz, 1 H), 0.95 (s, 9 H), 0.15 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 128.8, 128.7, 128.0, 102.5, 74.9, 73.1, 72.5, 68.3, 67.5, 60.9, 25.9, 18.3, −4.6, −4.7; HRMS m/z (M^+ − *t*-Bu) calcd 337.1107, obsd 337.1103.

Anal. Calcd for $C_{20}H_{30}O_6Si$: C, 60.89; H, 7.15. Found: C, 61.07; H, 7.57.

(1α,5α,7α,8*β*,9α)-8-(Benzyloxy)-9-(*tert*-butyldimethylsiloxy)-2,4,-10-trioxaadamantan-6-one (10). To a cooled (0 °C) CH_2Cl_2 solution (150 mL) of **9** (6.68 g, 16.9 mmol) was added the Dess−Martin periodinane reagent (10.8 g, 25.4 mmol). After 15 h at room temperature, the stirred reaction mixture was filtered through a short silica gel plug and concentrated. The residue was purified by chromatography on silica gel (elution with 25% ethyl acetate in hexanes) to afford 5.70 g (86%) of **10** as a white solid, mp 62−64 °C (from 5% CH_2Cl_2 in hexanes); IR (film, cm^{-1}) 1733, 1472, 1362, 1254, 1164; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.25 (m, 5 H), 5.64 (s, 1 H), 4.65 (d, J = 11.9 Hz, 1 H), 4.51 (d, J = 11.9 Hz, 1 H), 4.45−4.00 (series of m, 5 H), 0.94 (s, 9 H), 0.14 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 136.5, 128.7, 128.4, 127.8, 102.9, 82.0, 76.7, 72.8, 71.8, 70.8, 66.0, 25.7, 18.2, −4.7, −4.8; HRMS m/z (M^+ − *t*-Bu) calcd 335.0951, obsd 335.0958.

(1′α,5′α,6′*β*,7′α,8′*β*,9′α)-9′-(*tert*-Butyldimethylsiloxy)dihydrospiro-[furan-2(3*H*),6′-[2,4,10]trioxaadamantan]-8′-ol (11). To a cooled (0 °C) solution of **10** (2.36 g, 6.01 mmol) in THF (50 mL) was added 0.26 N Normant reagent[13] (35 mL, 9.02 mmol). The reaction mixture was warmed to room temperature for 2 h, quenched with saturated NH_4Cl solution, and filtered. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (elution with 25% ethyl acetate in hexanes) to afford the diol as a colorless liquid.

This diol was dissolved in CH_2Cl_2 (20 mL), treated with *p*-toluenesulfonyl chloride (2.29 g, 12.0 mmol), triethylamine (3.35 mL, 24.1 mmol) and DMAP (50 mg), stirred at room temperature for 15 h, and refluxed for 3 d. The reaction mixture was washed with water, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 10−25% ethyl acetate in hexanes) to afford 2.34 g (90%) of the spiro ether **11** and its HCl complex **12** (ratio 1.9:1) as a colorless oil.

The above material (3.50 g, 8.05 mmol) and 10% palladium on carbon (500 mg) in ethyl acetate (20 mL) was hydrogenolyzed under 40−50 psi of hydrogen for 8 h. The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 10−25% ethyl acetate in hexanes) to furnish 1.63 g (59%) of **11** and 0.96 g (31%) of **12**, both as white solids.

For **11**: mp 133−135 °C (from 5% CH_2Cl_2 in hexanes); IR (film, cm^{-1}) 3459, 1463, 1461, 1257, 1164; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (s, 1 H), 4.45−4.35 (m, 1 H), 4.20 (m, 1 H), 4.10−4.00 (m, 2 H), 3.94 (t, J = 6.7 Hz, 2 H), 3.82 (m, 1 H), 3.67 (m, 1 H), 2.29 (t, J = 7.4 Hz, 2 H), 1.96 (m, 2 H), 0.92 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.5, 81.7, 76.8, 74.5, 71.7, 70.0, 68.3, 62.1, 34.7, 25.9, 24.6, 18.3, −4.70, −4.73; HRMS m/z (M^+ − *t*-Bu) calcd 287.0951, obsd 287.0932.

For **12**: mp 133−135 °C (from 5% CH_2Cl_2 in hexanes); IR (film, cm^{-1}) 3331, 1470, 1415, 1245, 1162; ^1H NMR (300 MHz, $CDCl_3$) δ 5.44 (s, 1 H), 4.57 (s, 1 H), 4.30 (m, 1 H), 4.15−4.05 (m, 2 H), 3.93 (m, 1 H), 3.76 (m, 1 H), 3.59 (t, J = 6.3 Hz, 2 H), 2.25−2.05 (m, 1 H), 2.05−1.85 (m, 3 H), 0.93 (s, 9 H), 0.14 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.1, 77.0, 73.9, 71.8, 70.5, 67.9, 61.5, 44.9, 33.0, 25.7, 25.2, 18.2, −4.91, −4.95; HRMS m/z (M^+- *t*-Bu•HCl) calcd 287.0951, obsd 287.0924; FAB-MS m/z (M^+ + 1) calcd 381.15, obsd 381.00.

Anal. Calcd for $C_{16}H_{28}O_6Si$·HCl: C, 50.44; H, 7.41. Found: C, 50.28; H, 7.48.

Conversion of 12 into 11. A CH_2Cl_2 solution (20 mL) of **12** (1.00 g, 2.63 mmol), pyridine (0.94 mL, 11.6 mmol), acetic anhydride (0.55 mL, 5.8 mmol), and DMAP (20 mg) was stirred for 5 h at room temperature. The reaction mixture was diluted with 1 N HCl solution and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 10−25% ethyl acetate in hexanes) to afford the acetate. A THF (10 mL) solution of this acetate was treated with 1 N TBAF (5.80 mL, 5.80 mmol) for 2 h. The solvent was evaporated, and the residue was purified chromatographically on silica gel (elution with 50% ethyl acetate in hexanes containing 10% MeOH) to afford the alcohol.

To a CH_2Cl_2 solution (20 mL) of this alcohol and imidazole (791 mg, 11.6 mmol) was added *tert*-butyldimethylchlorosilane (875 mg, 5.80 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 15 h, diluted with saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried and concentrated in vacuo to leave a residue that was purified by chromatography on silica gel (elution with 10−25% ethyl acetate in hexanes) to afford the product which was treated with $LiAlH_4$ (500 mg, 13.2 mmol) in THF (20 mL) for 1 h at room temperature. The reaction mixture was quenched with 1 N NaOH solution, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 10−25% ethyl acetate in hexanes) to afford 0.53 g (59%) of **11**, identical in all respects to the material prepared above.

***tert*-Butyldimethyl[[(1′α,5′α,6′*β*,7′α,8′*β*,9′α)-tetrahydrodispiro[furan-2(3*H*),6′-[2,4,10]trioxaadamantane-8′,2″(3″*H*)-furan]-9′-yl]oxy]-silane (13).** To a cooled (0 °C) CH_2Cl_2 solution (100 mL) of **11** (3.29 g, 9.55 mmol) was added the Dess−Martin periodinane reagent (8.10 g, 19.1 mmol). After being warmed to room temperature for 15 h, the reaction mixture was filtered through a short silica gel plug and concentrated. The residue was purified by chromatography on silica gel (elution with 50% ethyl acetate in hexanes) to afford 3.30 g of the ketone as a white solid.

To a cooled (0 °C) solution of the above ketone in THF (100 mL) was added 0.26 N Normant reagent (75 mL, 19.5 mmol). The reaction mixture was warmed to room temperature for 2 h, quenched with saturated NH_4Cl solution, and filtered. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (elution with 50% ethyl acetate in hexanes) to afford the diol as a colorless liquid.

This diol in CH_2Cl_2 (50 mL) was treated with *p*-toluenesulfonyl chloride (3.67 g, 19.3 mmol), triethylamine (5.37 mL, 38.5 mmol), and DMAP (50 mg) at room temperature for 15 h and refluxed for 3 d. The reaction mixture was washed with water, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic solutions were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 5−25% ethyl acetate in hexanes) to afford 3.20 g (84%) of the separable product mixture **13** and **14** (1.1:1).

For **13**: mp 163−165 °C (from 5% CH_2Cl_2 in hexanes); IR (film, cm^{-1}) 1462, 1249, 1157, 1079; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (s, 1 H), 4.30 (m, 1 H), 4.00−3.85 (m, 4 H), 3.62 (m, 2 H), 3.46 (m, 1 H), 2.45−2.30 (m, 2 H), 2.25−2.10 (m, 2 H), 1.95−1.85 (m, 4 H), 0.91 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.0, 80.7, 77.5, 76.1, 69.6, 63.8, 34.9, 25.9, 24.4, 18.3, −4.7; HRMS m/z (M^+ − *t*-Bu) calcd 327.1264, obsd 327.1279.

Anal. Calcd for $C_{19}H_{32}O_6Si$·$0.5CH_2Cl_2$: C, 54.85; H, 7.79. Found: C, 54.55; H, 7.84.

For **14**: colorless oil; IR (film, cm^{-1}) 1463, 1416, 1361, 1255, 1163; ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (s, 1 H), 4.71 (s, 1 H), 4.25 (m, 1 H), 3.97 (t, J = 6.7 Hz, 2 H), 3.73 (m, 1 H), 3.65 (m, 1 H), 3.57(m, 1 H), 3.51 (m, 1 H), 2.45−2.25 (m, 2 H), 2.20−1.90 (m, 6 H), 0.93 (s, 9 H), 0.13 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.6, 81.7, 77.0, 76.3, 74.0, 71.1, 70.2, 62.9, 45.3, 34.8, 32.9, 25.9, 24.6, 18.4, −4.62, −4.67; HRMS m/z (M^+ − *t*-Bu·HCl) calcd 327.1264, obsd 327.1279.

Anal. Calcd for $C_{19}H_{33}ClO_6Si$: C, 54.21; H, 7.66. Found: C, 54.67; H, 7.85.

(1′α,5′α,6′*β*,7′α,8′*β*,9′α)-Tetrahydrodispiro[furan-2(3*H*),6′-[2,4,-10]trioxaadamantane-8′,2″(3″*H*)-furan]-9′-ol (15). A. From 13. A

THF solution (20 mL) of **13** (1.44 g, 3.74 mmol) was treated with 1 N TBAF (7.49 mL, 7.49 mmol) for 15 h. The solvent was concentrated, and the residue was purified by chromatography on silica gel (elution with 50% ethyl acetate in hexanes containing 10% MeOH) to afford 1.01 g (100%) of **15** as a white solid, mp 192−194 °C (from 5% CH_2Cl_2 in hexanes); IR (film, cm^{-1}) 3550, 1455, 1246, 1140; ^1H NMR (300 MHz, $CDCl_3$) δ 5.41 (s, 1 H), 4.17−4.10 (m, 1 H), 4.05−3.85 (m, 4 H), 3.73 (m, 2 H), 3.50 (m, 1 H), 3.20 (d, J = 11.8 Hz, 1 H), 2.45−2.30 (m, 2 H), 2.25−2.10 (m, 2 H), 2.00−1.85 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.1, 80.2, 77.4, 75.8, 69.6, 63.5, 34.9, 24.4; HRMS m/z ($M^+ + 1$) calcd 271.1181, obsd 271.1180.

Anal. Calcd for $C_{13}H_{18}O_6 \cdot 0.6CH_2Cl_2$: C, 50.85; H, 6.02. Found: C, 50.98; H, 6.22.

B. From 14. A THF solution (10 mL) of **14** (1.00 g, 2.38 mmol) was treated with 1 N TBAF (5.20 mL, 5.20 mmol) for 2 h. The solvent was evaporated, and the residue was purified by chromatography on silica gel (elution with 50% ethyl acetate in hexanes containing 10% MeOH) to afford 527 mg (82%) of **15**, which proved spectroscopically identical to the compound isolated in part A.

(1′α,5′α,6′*β*,7′α,8′*β*)-Tetrahydrodispiro[furan-2(3*H*),6′-[2,4,10]trioxaadamantane-8′,2″(3″*H*)-furan]-9′-one (16). To a cooled (−78 °C) CH_2Cl_2 solution (50 mL) of oxalyl chloride (0.86 mL, 9.86 mmol) were added DMSO (1.11 mL, 15.6 mmol) in CH_2Cl_2 (5 mL) and **15** (1.01 g, 3.74 mmol) dissolved in CH_2Cl_2 (15 mL) within 5 min. The mixture was stirred for 2 h at −78 °C, treated with triethylamine (2.72 mL, 19.5 mmol), and warmed to room temperature for 1 h before being washed with water and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried and concentrated in vacuo to leave a residue that was purified by chromatography on silica gel (elution with 50% ethyl acetate in hexanes containing 5% MeOH). There was isolated 974 mg (97%) of **16** as a white solid, mp 244−246 °C (from 5% CH_2Cl_2 in hexanes); IR (film, cm^{-1}) 1767, 1462, 1378, 1267; ^1H NMR (300 MHz, $CDCl_3$) δ 5.61 (s, 1 H), 4.05−3.90 (m, 6 H), 3.70 (m, 1 H), 2.55−2.40 (m, 2 H), 2.30−2.15 (m, 2 H), 2.05−1.85 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 102.5, 82.9, 80.1, 78.4, 70.0, 34.9, 24.3; HRMS m/z (M^+) calcd 268.0947, obsd 268.0924.

(1α,5α,6α,7α,8*β*,9*β*)-Hexahydrotrispiro[2,4,10-trioxaadamantane-6,2′(3′H);8,2″(3″H);9,2‴(3‴H)-trisfuran] (17). To a cooled (−78 °C) solution of 16 (112 mg, 0.418 mmol) in THF (10 mL) was added 0.26 N Normant reagent (3.2 mL, 0.83 mmol). The reaction mixture was warmed to room temperature for 2 h, quenched with saturated NH4Cl solution, and filtered. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (elution with 25% ethyl acetate in hexanes) to afford the diol (∼10:1) as a colorless liquid.

This diol in CH_2Cl_2 (10 mL) was treated with *p*-toluenesulfonyl chloride (159 mg, 0.834 mmol), triethylamine (0.23 mL, 1.6 mmol), and DMAP (10 mg) at room temperature for 15 h and refluxed for 1 d. The reaction mixture was concentrated in vacuo, and the residue was purified by chromatography on silica gel (elution with 50% ethyl acetate in hexanes) to afford 58 mg (45%) of 17 as a colorless oil; IR (film, cm-1) 1434, 1372, 1280, 1157; 1H NMR (300 MHz, CDCl3) δ 5.36 (s, 1 H), 4.05−3.85 (m, 4 H), 3.75−3.60 (m, 4 H), 3.55 (m, 1 H), 2.45−2.25 (m, 2 H), 2.25−2.15 (m, 2 H), 2.10−2.00(m, 2 H), 2.00−1.85 (m, 4 H), 1.80−1.70 (m, 2 H); 13C NMR (75 MHz, CDCl3) δ 102.1, 80.8, 76.6, 74.4, 71.0, 69.2, 63.2, 35.9, 33.3, 25.8, 23.9; HRMS m/z (M^+) calcd 310.1416, obsd 310.1430.

(1α,5α,6*β*7α,8*β*,9*β*)-Hexahydrotrispiro[2,4,10-trioxaadamantane-6,2′(3′H);8,2″(3″H);9,2‴(3‴H)-trisfuran] (3). To a cooled (−78 °C) solution of 16 (170 mg, 0.634 mmol), which was precomplexed with LiClO4 (337 mg, 3.17 mmol) in THF (10 mL) for 2 h at room temperature, was added 0.26 N Normant reagent (7.3 mL, 1.90 mmol). The reaction mixture was warmed to room temperature for 15 h, quenched with saturated NH4Cl solution, and filtered. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (elution with 50% ethyl acetate in hexanes containing 5% MeOH) to afford the diol.

This diol in CH_2Cl_2 (10 mL) was treated with *p*-toluenesulfonyl chloride (255 mg, 1.34 mmol), triethylamine (0.37 mL, 2.7 mmol), and DMAP (10 mg) at room temperature for 15 h. The reaction mixture was concentrated in vacuo, and the residue was purified by chromatography on silica gel (elution with 20−50% ethyl acetate in hexanes) to afford 262 mg of the monotosylate as a white solid.

To a benzene (10 mL) solution of the monotosylate was added 0.5 N potassium hexamethyldisilazide (2.2 mL, 1.1 mmol) at 0 °C. After 30 min, the reaction mixture was warmed to room temperature, stirred for 15 h, quenched with deionized H_2O (10 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with deionized H2O (10 mL) and concentrated in vacuo without drying to give 144 mg (73% for 3 steps) of 3 as a white solid, mp >280 °C (from 10% CH2Cl2 in hexanes); IR (film, cm-1) 1440, 1350, 1250, 1125; 1H NMR (300 MHz, CDCl3) δ 5.37 (s, 1 H), 3.95 (t, J = 6.8 Hz, 6 H), 3.51 (s, 3 H), 2.26 (t, J = 7.3 Hz, 6 H), 1.91−1.80 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.4, 80.0, 75.9, 69.4, 36.3, 23.9; HRMS m/z (M^+) calcd 310.1416, obsd 310.1427.

Anal. Calcd for $C_{12}H_{22}O_6$: C, 61.92; H, 7.14. Found: C, 61.68; H, 7.06.

(1α,5α,6*β*,7α,8*β*,9*β*)-6,8,9-Trimethoxy-2,4,10-trioxaadamantane (19). Alcohol **18**[11] (5.26 g, 14.2 mmol) was treated with 80% sodium hydride (852 mg, 28.4 mmol) and an excess of methyl iodide (1.77 mL) in THF (50 mL) for 15 h at room temperature. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried and concentrated. The residue was purified by chromatography on silica gel (elution with 25% ethyl acetate in hexanes) to afford the monomethyl ether.

The above unpurified product in EtOH (20 mL) was hydrogenolyzed over 10% palladium on carbon (1.00 g) under 1 atm of hydrogen for 15 h. The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was used directly in the next step.

The diol was treated with 80% sodium hydride (1.70 g, 56.8 mmol) and an excess of methyl iodide (4.0 mL) in THF (50 mL) for 2 h at room temperature. The reaction solution was quenched with water and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried and evaporated. The residue was purified by chromatography on silica gel (elution with 50% ethyl acetate in hexanes) to afford 2.51 g (76% over 3 steps) of **19** as a colorless crystalline solid, mp 177−179 °C (from 5% CH_2Cl_2 in hexanes); IR (film, cm^{-1}) 1452, 1224, 1192, 1147; ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (s, 1 H), 4.45 (m, 3 H), 4.03 (m, 3 H), 3.44 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.9, 75.0, 67.7, 58.2; HRMS m/z (M^+) calcd 232.0947, obsd 232.0936.

Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.97; H, 6.93.

(5α,6*β*,7α,12*β*,13α,18*β*)-6,12,18-Trimethoxy-1,8,14-trioxatrispiro-[4.1.4.1. 4.1]octadecane (24). A solution of **3** (200 mg, 0.644 mmol) in 25 mL of 1:2 HCl−MeOH was refluxed for 30 min and evaporated to give the triol, which was treated with 80% sodium hydride (200 mg, 6.67 mmol) and an excess of methyl iodide (1.5 mL) in DMF for 1 h at room temperature. The reaction mixture was quenched with water at 0 °C and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 20% ethyl acetate in hexanes) to afford 195 mg (88%) of **24** as a colorless crystalline solid, mp 130−132 °C (from 5% CH_2Cl_2 in hexanes); IR (film, cm^{-1}) 1445, 1375, 1250, 1170; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (t, J = 6.5 Hz, 6 H), 3.54 (s, 9 H), 3.31 (s, 3 H), 2.00−1.90 (m, 6 H), 1.90−1.80 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 89.0, 88.1, 67.5, 62.0, 29.0, 24.4; HRMS m/z (M^+) calcd 342.2042, obsd 342.2047.

Anal. Calcd for $C_{18}H_{30}O_6$: C, 63.14; H, 8.83. Found: C, 62.99; H, 8.75.

(1α,5α,6α7α,8*β*,9*β*)-3-[(*p*-Methoxyphenoxy)methyl]-2,4,10-trioxaadamantane-6,8,9-triol (26). Into an ethanol solution (22 mL, 0.38 mmol) of (*p*-methoxy)phenoxyacetonitrile[23] (62 g, 0.38 mmol) was bubbled dry hydrogen chloride for 1 h with mechanical stirring to give a yellowish solid that was stored for 1 d at 0 °C. The resulting imidate was dried in vacuo for 2 h, taken up in 500 mL of 1:1 EtOH−Et_2O, and refluxed for 2 d. The solid residue was separated by filtration, and the filtrate was evaporated in vacuo. The residue taken up in 500 mL of 20% EtOAc−hexanes, and the resulting solid was filtered. The filtrate was concentrated in vacuo to give ortho ester **25**, which was used without further purification.

The crude ortho ester **25**, *myo*-inositol (30 g, 166.6 mmol) and *p*-toluenesulfonyl chloride (3 g) in DMF (250 mL) were heated at 100

°C for 24 h. After cooling, 3 g of $NaHCO_3$ was added, and the unreacted inositol (12 g) was separated by filtration. Next, the DMF was evaporated in vacuo to give a gummy solid, which was triturated with CH_2Cl_2 and filtered to give **26** as a white solid. The filtrate was concentrated and purified by chromatography on silica gel (elution with 30% *i*-PrOH in hexanes) to afford additional **26** (combined 31 g, 57%, 95% based on recovered **5**), mp 179−181 °C (from 50% MeOH in CH_2Cl_2); IR (film, cm^{-1}) 3210, 1495, 1430, 1215; ^1H NMR (300 MHz, DMSO-d_6) δ 6.95−6.75 (m, 4 H), 5.47 (d, J = 6.2 Hz, 2 H), 5.26 (d, J = 6.2 Hz, 1 H), 4.32 (s, 2 H), 4.20−4.00 (m, 4 H), 3.84 (s, 2 H), 3.68 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ153.8, 152.5, 116.1, 114.7, 106.4, 75.3, 70.1, 69.7, 67.3, 58.2, 55.5; HRMS m/z (M^+) calcd 326.1001, obsd 326.1016.

Anal. Calcd for $C_{15}H_{18}O_8$: C, 55.21; H, 5.56. Found: C, 55.13; H, 5.64.

(1α,5α,6*β*,7α,8*β*,9α)-9-(*tert*-Butyldimethylsiloxy)-3-[(*p*-methoxyphenoxy)methyl]-2,4,10-trioxaadamantane-6,8-diol (27). To a DMF solution (50 mL) of **26** (17.7 g, 54.2 mmol) and imidazole (4.43 g, 65.1 mmol) was added *tert*-butyldimethylchlorosilane (8.18 g, 54.2 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 15 h, diluted with saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried and concentrated in vacuo. The solid product was filtered, and the oily filtrate was purified by chromatography on silica gel (elution with 20−50% ethyl acetate in hexanes) to afford a combined 12.3 g of **27** as a white solid (55%, 82% based on recovered **26**), the bissilylated product (4.66 g), and **26** (5.82 g).

For **27**: mp 115−117 °C (from 10% CH_2Cl_2 in hexanes); IR (film, cm^{-1}) 3420, 1495, 1425, 1215; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95−6.75 (m, 4 H), 4.55 (m, 2 H), 4.30−4.20 (m, 4 H), 3.95 (s, 2 H), 3.91 (d, J = 7.6 Hz, 2 H), 3.75 (s, 3 H), 0.94 (s, 9 H), 0.14 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 152.7, 116.4, 114.5, 106.6, 75.5, 70.8, 69.1, 68.2, 59.9, 55.7, 25.8, 18.3, −4.6; HRMS m/z (M^+) calcd 440.1866, obsd 440.1831.

Anal. Calcd for $C_{21}H_{32}O_8Si$: C, 57.25; H, 7.32. Found: C, 57.34; H, 7.27.

(1α,5α,7α,8*β*,9α)-8-(Benzyloxy)-9-(*tert*-butyldimethylsiloxy)-3-[(*p*-methoxyphenoxy)methyl]-2,4,10-trioxaadamantan-6-one (29). To a sodium hydride (80%, 484 mg, 16.1 mmol) in DMF (10 mL) was added **27** (6.46 g, 14.7 mmol) in DMF (10 mL) followed by benzyl bromide (1.74 mL, 14.7 mmol) at 0 °C. After 30 min, the reaction mixture was warmed to room temperature, stirred for additional 2 h, quenched with saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 10−25% ethyl acetate in hexanes) to afford the monobenzyl ether **28** (4.32 g, 56%, 86% based on recovered **27**) as a colorless liquid alongside the dibenzyl ether (2.87 g) and unreacted **27** (2.30 g).

To a cooled (0 °C) CH_2Cl_2 solution (75 mL) of **28** (4.32 g, 8.14 mmol) was added the Dess−Martin periodinane reagent (5.18 g, 12.2 mmol). After being warmed to room temperature for 15 h, the reaction mixture was filtered through a short silica gel plug and concentrated. The residue was purified by chromatography on silica gel (elution with 25% ethyl acetate in hexanes) to afford **29** as colorless oil (3.74 g, 87%); IR (film, cm^{-1}) 1750, 1490, 1440, 1210; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5 H), 6.95−6.75 (m, 4 H), 4.66 (d, J = 11.9 Hz, 1 H), 4.51 (d, J = 11.9 Hz, 1 H), 4.50−4.25 (series of m, 4 H), 4.10−3.95 (m, 1 H), 4.04 (s, 2 H), 3.75 (s, 3 H), 0.94 (s, 9 H), 0.129 (s, 3 H), 0.122 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 154.4, 152.7, 136.5, 128.7, 128.4, 127.9, 116.3, 114.5, 107.7, 82.4, 77.5, 73.7, 71.9, 70.5, 70.2, 65.5, 55.6, 25.7, 18.1, −4.69, −4.78; HRMS m/z (M^+) calcd 528.2179, obsd 528.2191.

(1′α,5′α,6′*β*,7′α,8′*β*,9′α)-9′-(*tert*-Butyldimethylsiloxy)dihydro-3′-[(*p*-methoxyphenoxy)methyl]spiro[furan-2(3*H*),6′-[2,4,10]trioxaadamantan]-8′-ol (30). To a cooled (0 °C) solution of **29** (7.00 g, 13.2 mmol) in THF (100 mL) was added 0.26 N Normant reagent (76 mL, 19.9 mmol). The reaction mixture was warmed to room temperature for 2 h, quenched with saturated NH_4Cl solution, and filtered. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (elution with 25% ethyl acetate in hexanes) to afford the diol as a colorless liquid.

This diol in CH_2Cl_2 (100 mL) was treated with *p*-toluenesulfonyl chloride (5.05 g, 26.5 mmol), triethylamine (7.38 mL, 52.9 mmol), and DMAP (50 mg) at room temperature for 15 h and refluxed for 2 d. The reaction mixture was washed with water, and the aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). The combined organic phases were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 10−25% ethyl acetate in hexanes) to afford the monospiro ether and its HCl complex product as a colorless oil.

The above products and 10% palladium on carbon (500 mg) in ethyl acetate (20 mL) were hydrogenolyzed under 40−50 psi of hydrogen pressure for 15 h. The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 10% to 25% ethyl acetate in hexanes) to elute 3.56 g (55%) of **30** and **31** (ratio 1.9:1) as colorless oils.

For **30**: IR (film, cm^{-1}) 3455, 1435, 1210; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95−6.75 (m, 4 H), 4.44 (m, 1 H), 4.20 (s, 2 H), 4.10−3.90 (series of m, 6 H), 3.80−3.75 (m, 1 H), 3.74(s, 3 H), 2.40−2.30 (m, 2 H), 2.10−1.90 (m, 2 H), 0.94 (s, 9 H), 0.132 (s, 3 H), 0.127 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 152.9, 116.2, 114.4, 106.8, 81.5, 77.7, 75.3, 72.2, 70.6, 70.1, 68.1, 61.4, 55.6, 34.7, 25.8, 24.6, 18.3, −4.60, −4.63; HRMS m/z (M^+) calcd 480.2215, obsd 480.2166.

Anal. Calcd for $C_{24}H_{36}O_8Si$: C, 59.98; H, 7.55. Found: C, 59.87; H, 7.55.

For **31**: IR (film, cm^{-1}) 3400, 1420, 1210; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95−6.75 (m, 4 H), 4.64 (s, 1 H), 4.29 (s, 1 H), 4.19 (m, 1 H), 4.15−3.85(seires of m, 5 H), 3.75(s, 3 H), 3.59 (t, J = 6.3 Hz, 2 H), 2.25−1.90 (m, 4 H), 0.94 (s, 9 H), 0.13 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 152.7, 116.3, 114.5, 106.6, 78.0, 74.9, 71.9, 71.3, 70.5, 68.0, 60.9, 55.7, 45.2, 33.2, 25.8, 25.5, 18.3, −4.59, −4.62; HRMS m/z (M^+ − HCl) calcd 480.2215, obsd 480.2167; FAB MS m/z (M^+ + 1) calcd 517.20, obsd 517.08.

Conversion of 31 into 30. A CH_2Cl_2 solution (40 mL) of **31** (3.21 g, 6,21 mmol), pyridine (2.22 mL, 27,4 mmol), acetic anhydride (1.30 mL, 13.7 mmol), and DMAP (20 mg) was stirred for 5 h at room temperature. The reaction mixture was diluted with 1 N HCl solution and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried and concentrated in vacuo to leave a residue that was purified by chromatography on silica gel (elution with 10−25% ethyl acetate in hexanes) to afford the acetate. A THF solution (20 mL) of this acetate was treated with 1 N TBAF (13.7 mL, 13.7 mmol) for 2 h. The solvent was evaporated and the residue was purified chromatographically on silica gel (elution with 50% ethyl acetate in hexanes containing 10% MeOH) to afford the alcohol.

To a CH_2Cl_2 solution (40 mL) of this alcohol and imidazole (1.87 g, 27.4 mmol) was added *tert*-butyldimethylchlorosilane (2.07 g, 13.7 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 15 h, diluted with saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 10−25% ethyl acetate in hexanes) to afford the product, which was treated with $LiAlH_4$ (1.18 g, 31.2 mmol) in THF (40 mL) for 1 h at room temperature. The reaction mixture was quenched with 1 N NaOH solution, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 10−25% ethyl acetate in hexanes) to give **30** (2.00 g, 67%).

(1′α,5′α,6′*β*,7′α,8′*β*,9′α)-Tetrahydro-3′-[(*p*-methoxyphenoxy)methyl] dispiro[furan-2(3*H*),6′-[2,4,10]trioxaadamantane-8′,2″(3″*H*)-furan]-9′-ol (32). To a cooled (0 °C) CH_2Cl_2 solution (50 mL) of **30** (1.76 g, 3.66 mmol) was added the Dess−Martin periodinane reagent (2.33 g, 5.49 mmol). After being warmed to room temperature for 2 h, the reaction mixture was filtered on a short silica gel plug and concentrated. The residue was purified by chromatography on silica gel (elution with 50% ethyl acetate in hexanes) to afford the ketone as a colorless oil.

To a cooled (0 °C) solution of the ketone in THF (30 mL) was added 0.26 N Normant reagent (29.0 mL, 7.54 mmol). The reaction mixture was warmed to room temperature for 2 h, quenched with saturatd NH_4Cl solution, and filtered. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (elution with 50% ethyl acetate in hexanes) to afford the diol as a colorless liquid.

This diol in CH_2Cl_2 (50 mL) was treated with *p*-toluenesulfonyl chloride (1.40 g, 7.34 mmol), triethylamine (2.04 mL, 14.6 mmol), and DMAP (50 mg) at room temperature for 15 h and refluxed for 2 d. The reaction mixture was washed with water, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 5−25% ethyl acetate in hexanes) to afford the product as a colorless oil.

A THF solution (10 mL) of the oil was treated with 1 N TBAF (7.32 mL, 7.32 mmol) for 2 h. The solvent was evaporated, and the residue was purified by chromatography on silica gel (elution with 50% ethyl acetate in hexanes containing 10% MeOH) to afford 1.25 g (79% over four steps) of **32**; IR (film, cm^{-1}) 3470, 1440, 1280, 1215; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95−6.75 (m, 4 H), 4.14 (d, J = 11.7 Hz, 1 H), 4.00−3.90 (m, 6 H), 3.84 (m, 2 H), 3.72(s, 3 H), 3.56 (s, 1 H), 3.16 (d, J = 11.7 Hz, 1 H), 2.45−2.35 (m, 2 H), 2.25−2.10 (m, 2 H), 2.00−1.85 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 152.2, 115.6, 113.9, 106.8, 79.6, 77.3, 76.1, 70.1, 69.2, 62.2, 55.1, 34.3, 23.8; HRMS *m*/*z* (M^+) calcd 406.1627, obsd 406.1626.

(1α,5α,6*β*,7α,8*β*,9*β*)-Hexahydro-3-[(*p*-methoxyphenoxy)methyl]-trispiro [2,4,10-trioxaadamantane-6,2′(3′*H*);8,2″(3″*H*);9,2‴(3‴*H*)-trisfuran] (33). To a cooled (−78 °C) CH_2Cl_2 solution (30 mL) of oxalyl chloride (0.67 mL, 7.68 mmol) were added DMSO (1.09 mL, 15.54 mmol) in CH_2Cl_2 (5 mL) and **32** (1.68 g, 3.87 mmol) in CH_2Cl_2 (15 mL) within 5 min. The mixture was stirred for 2 h at −78 °C and treated with triethylamine (2.69 mL, 19.2 mmol) and then warmed to room temperature for 1 h. The reaction mixture was washed with water, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 25−50% ethyl acetate in hexanes) to afford the ketone as a colorless oil.

To a cooled (−78 °C) solution of the ketone, which was precomplexed with dry $LiClO_4$ (2.06 g, 19.4 mmol) in THF (50 mL) for 2 h at room temperature, was added 0.26 N Normant reagent (45.0 mL, 11.7 mmol). The reaction mixture was warmed to room temperature for 15 h, quenched with saturated NH_4Cl solution and filtered. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (elution with 50% ethyl acetate in hexanes containing 5% MeOH) to afford the diol.

This diol in CH_2Cl_2 (100 mL) was treated with *p*-toluenesulfonyl chloride (1.47 g, 7.71 mmol), triethylamine (2.16 mL, 15.5 mmol), and DMAP (50 mg) at room temperature for 15 h and refluxed for 2 d. The reaction mixture was quenched with deionized H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were concentrated in vacuo without drying, and the residue was purified by chromatography on silica gel (gradient elution with 50% ethyl acetate in hexanes to 5% MeOH in CH_2Cl_2) to afford 1.35 g (78%) of **33** as a white solid, mp 189−191 °C (from 10% CH_2Cl_2 in hexanes); IR (film, cm^{-1}) 1440, 1220, 1060, 1020; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84−6.70 (m, 4 H), 3.93 (t, J = 6.8 Hz, 6 H), 3.86 (s, 2 H), 3.69 (s, 3 H), 3.91 (s, 3 H), 2.26 (t, J = 7.6 Hz, 6 H), 1.83 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ154.2, 152.8, 115.9, 114.4, 106.8, 80.0, 76.3, 70.3, 69.5, 55.5, 36.2, 23.9; HRMS *m*/*z* (M^+) calcd 446.1940, obsd 446.1958.

Anal. Calcd for $C_{24}H_{30}O_8CH_2Cl_2$: C, 56.50; H, 6.07. Found: C, 56.06; H, 5.82.

(1α,5α,6*β*,7α,8*β*,9*β*)-3-Ethynylhexahydrotrispiro[2,4,10-trioxaadamantane-6,2′(3′*H*);8,2″(3″*H*);9,2‴(3‴*H*)-trisfuran] (35). To a cold solution (0 °C) of **33** (328 mg, 0.735 mmol) in 10 mL of 4:1 CH_3CN-H_2O was added ceric ammonium nitrate (1.01 g, 1.84 mmol). After 10 min, the reaction mixture was quenched with deionized water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over K_2CO_3, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (gradient elution with 55% ethyl acetate in hexanes to 5% MeOH in CH_2Cl_2) to afford 163 mg (69%) of **34** as a white solid.

To a cooled (−78 °C) CH_2Cl_2 (15 mL) solution of oxalyl chloride (0.22 mL, 2.52 mmol) were added DMSO (0.35 mL, 4.93 mmol) in CH_2Cl_2 (1 mL) and **34** (423 mg, 1.24 mmol) in CH_2Cl_2 (5 mL) within 5 min. The mixture was stirred for 1 h at −78 °C, treated with triethylamine (0.87 mL, 6.21 mmol), warmed to room temperature for 1 h, and washed with deionized water. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phases were dried over K_2CO_3 and concentrated in vacuo.

This residue was dissolved with K_2CO_3 (344 mg, 2.49 mmol) in methanol (15 mL) and treated with dimethyl 1-diazo-2-oxypropylphosphonate[24] (286 mg, 1.49 mmol) for 6 h at room temperature. The reaction mixture was diluted with deionized water (20 mL) and CH_2Cl_2 (20 mL), and the separated aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over K_2CO_3 and concentrated in vacuo. The solid residue was washed with 50% EtOAc−hexane, and the remainder was dissolved in 10% MeOH−CH_2Cl_2. The solvent was removed in vacuo to give 135 mg (33% over two steps) of **35** as a white solid, mp >270 °C dec (from 5% MeOH in CH_2Cl_2); IR (film, cm^{-1}) 3400, 2100, 1615, 1255, 1040, 960; ^1H NMR (300 MHz, $CDCl_3$) δ 3.96 (t, J = 6.9 Hz, 6 H), 3.60 (s, 3 H), 2.53 (s, 1 H), 2.32 (t, J = 7.6 Hz, 6 H), 1.88 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 101.4, 79.2, 77.2, 77.0, 69.8, 69.3, 36.1, 23.6; HRMS *m*/*z* (M^+) calcd 334.1416, obsd 334.1430.

3,3‴-(Butadiynylene)bis[(1α,5α,6*β*,7α,8*β*,9*β*)-hexahydrotrispiro-[2,4,10-trioxaadamantane-6,2′(3′*H*);8,2″(3″*H*);9,2‴(3‴*H*)-trisfuran]] (36). To a CH_2Cl_2 solution (15 mL) of **35** (128 mg, 0.383 mmol) and TMEDA (0.144 mL, 0.766 mmol) was added CuCl (38 mg, 0.38 mmol) under dry air conditions with protection by means of a $CaCl_2$ drying tube. After 4 h at room temperature, the reaction mixture was diluted with deionized water (20 mL), extracted with CH_2Cl_2 (4 × 30 mL), and dried over K_2CO_3. The concentrated filtrate was purified by chromatography on silica gel (elution with 5−10% MeOH in CH_2Cl_2) to afford 128 mg (100%) of the **36** as a white solid, mp >280 °C (from CH_2Cl_2); IR (film, cm^{-1}) 3418, 1633, 1462, 1264; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95 (t, J = 6.8 Hz, 12 H), 3.57 (s, 6 H), 2.25 (t, J = 7.6 Hz, 12 H), 1.87 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.3, 79.7, 77.7, 73.4, 69.8, 64.9, 36.6, 24.1; HRMS *m*/*z* (M^+) calcd 666.2676, obsd 666.2707.

Attempted Complexation of 36 with 37. To a CH_2Cl_2 solution (1.0 mL) of **36** (10 mg, 0.015 mmol) was added **37** (11 mg, 0.030 mmol) dissolved in CH_2Cl_2 (1.0 mL) dropwise. Solvent was allowed to evaporate during 12 h and the precipitate triturated with CH_2Cl_2 (1.0 mL). The solvent was decanted, and the residue was dried under vacuo to give **39** as a powdery white solid (15 mg), mp >280 °C; ESI-MS for **36**·Li^+, *m*/*z* (M^+ + 1) calcd 674.3, obsd 674.0 (intensity, 100%); for **36**·Li^+·**37**, *m*/*z* (M^+) calcd 925.4, obsd 925.9 (intensity, 20%); for **36**·Li^+·**36**, *m*/*z* (M^+) calcd 1339.5, obsd 1339.8 (intensity, 5%).

The decanted CH_2Cl_2 solution from the above reaction was concentrated to give 6 mg of recovered **37**.

Complexation of 36 to Lithium Tetrafluoroborate. To a CH_2Cl_2 solution (1.0 mL) of **36** (10 mg, 0.015 mmol) was added $LiBF_4$ (1.4 mg, 0.015 mmol) dissolved in CH_3CN (0.05 mL) dropwise. Solvent was allowed to evaporate during 12 h, and the precipitate was triturated with CH_2Cl_2 (1.0 mL) and CH_3CN (1.0 mL). The solvent was decanted, and the residue was dried under vacuo to give **40b** as a powdery white solid (11 mg), mp >280 °C.

Complexation of 36 to Lithium Picrate. To a CH_2Cl_2 solution (0.5 mL) of **36** (9.0 mg, 0.014 mmol) was added lithium picrate (6.3 mg, 0.027 mmol) dissolved in CH_3CN (2.0 mL) dropwise. Yellow crystals of **41** suitable for X-ray diffraction analysis were deposited from the solution.

Acknowledgment. This work was supported by the National Science Foundation. We are grateful to Professor Robin Rogers (University of Alabama) and Dr. Judith Gallucci for the X-ray crystallographic determinations, Dr. A. Daniel Jones (Penn State University) for the electrospray mass spectra, and Dr. Kurt Loening for assistance with nomenclature.

Supporting Information Available: Tables giving the crystal data and structure refinement information, bond lengths and bond angles, atomic and hydrogen coordinates, and isotropic and anisotropic displacement coordinates for **35** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA010103X