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X-ray Crystallographic and Mass Spectrometric Probing of the Conformational and Ionophoric Properties of Stereoisomeric Hexatetrahydrofuranylhexane Segments

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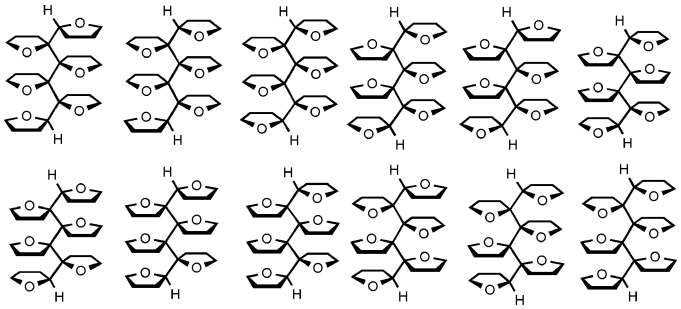

A full account of the synthesis of the 12 hexacyclic tetrahydrofuran isomers represented by the nearby formulas is first provided. The key steps involved in further elaboration of the spiro ethers **12**, **15**, **28**, and **45** include controlled ozonolysis, 1,2-addition of the Normant reagent, and heterocyclization. Eight of the end products proved to be sufficiently crystalline to enable X-ray analysis and determination of their solid-state conformational features. The alkali metal ion selectivities of the 12 hexamers were evaluated by a picrate extraction method and by electrospray ionization mass spectrometry (ESI-MS) which indicated that small, but significant, selectivity differences exist within the groups of diastereomers. These results revealed that each hexamer demonstrated a preference for lithium ion complexation relative to sodium or potassium ion complexation. Stereoisomeric classification of the hexamers was based on the competition between two dissociation routes promoted by collision-induced dissociation. The preference for each of the two dissociation pathways, both of which involved cleavage at the midpoint of the hexamer, correlated with the stereochemical configurations (syn versus anti) of the THF groups near the termini.

Introduction

The capability of the cyclohexane ring to function as a serviceable probe of substituent effects is well appreciated.[1] For monosubstituted systems, the operation of chair−chair interconversion allows for competing occupancy of either an axial or equatorial site. The resulting preference is readily amenable to quantification in the form of *A* values.[1,2] However, conformational energetics involving more than one substituent can be problematical. For groups positioned in a 1,4-relationship, the effects are expectedly close to additive.[3,4] Some breakdown of this phenomenon is already seen for groups oriented 1,3 to each other, and summation effects are totally lost in most vicinal 1,2-disubstitution examples.[5] Despite the existence of this

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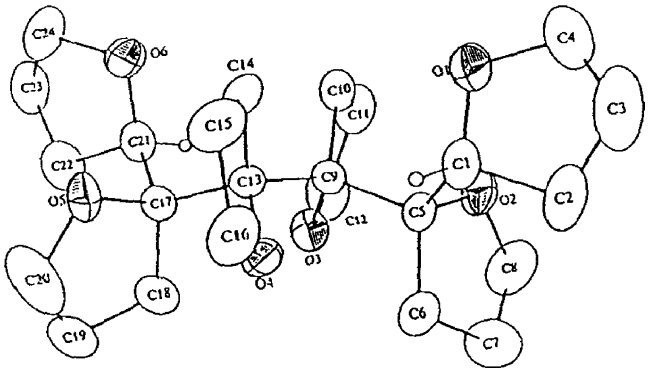
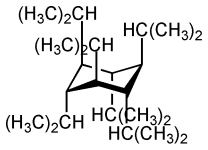


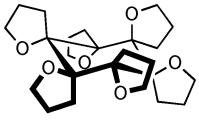
FIGURE 1. ORTEP plot of the final X-ray model of **18** with hydrogens omitted for clarity.[19]

leveling effect,[6] more extreme degrees of substitution have revealed that directed orientation can make a return and provide important structural insight. Several classical examples have now been reported. The excessive steric strain on the periphery of hydrocarbon **1** is best accommodated by adoption of the all-axial conformation, with directed orientation of the isopropyl methane hydrogens toward the cyclohexane core.[7] In contrast, both the all-*trans* hexaethyl (**2a**)[7] and hexamethoxy (**2b**) derivatives[8] assume the all-equatorial arrangement depicted in the structural formulas. The preference of multiple C−O sigma bonds for maximum equatorial occupancy is general, barring overriding steric effects, as reflected in the preferred conformation adopted by **3**[9] and most especially the $\mathbf{D}_{3d}$-symmetric hexa-(spirotetrahydrofuranyl)cyclohexane **4**.[10]



1

2a, X = CH_2
b, X = O



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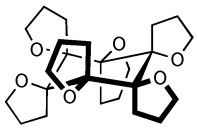
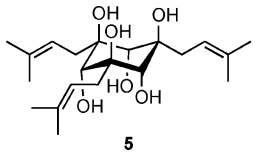


4

The significant conformational bias exhibited by **2b** and **4** has been attributed to two factors operating in the same direction.[10c] The six gauche stabilizing interactions that materialize when the C−O bonds are projected equatorially are partially responsible. However, these contributions can account for only a portion of the >20 kcal/mol energy imbalance separating the two conformations.[11] Also contributing to the elevated energy cost is the electrostatic repulsion that would arise were the C−O bonds all projected axially on the cyclohexane scaffold. These interactions are estimated to be about 2 kcal/mol larger between each pair of alkoxy substituents than between alkyl groups.

Steric factors arising from nonbonded interactions around the periphery of the chair can also be conformationally defining. Thus, in contrast to *scyllo*-inositol which exists in the all-equatorial form,[12] the stable arrangement for the natural product muellitol (**5**) is that in which its six hydroxyls are disposed in *syn*-axial fashion as a consequence of the three added prenyl substituents.[13] On the other hand, the acid-catalyzed cyclization product of **5** known as isomuellitol (**6**) exhibits a reversal in conformational bias.



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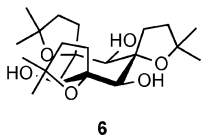
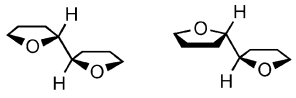
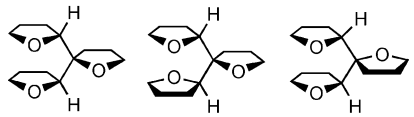


6

In the light of this information, the timeliness of an investigation into the interplay of electronic and steric influences in *open-chain* ethers was deemed appropriate. The adoption by 1,2-dimethoxyethane[15] and polyoxyethylene, $(OCH_2CH_2)_n$,[16] of a gauche rather than a perfectly staggered spatial arrangement has long been recognized.[2] More recently, computational assessment has been made of the preferred conformations adopted by the polycyclic bis- and tris-tetrahydrofuran systems **7**−**11**.[17]



7 **8**



9 **10** **11**

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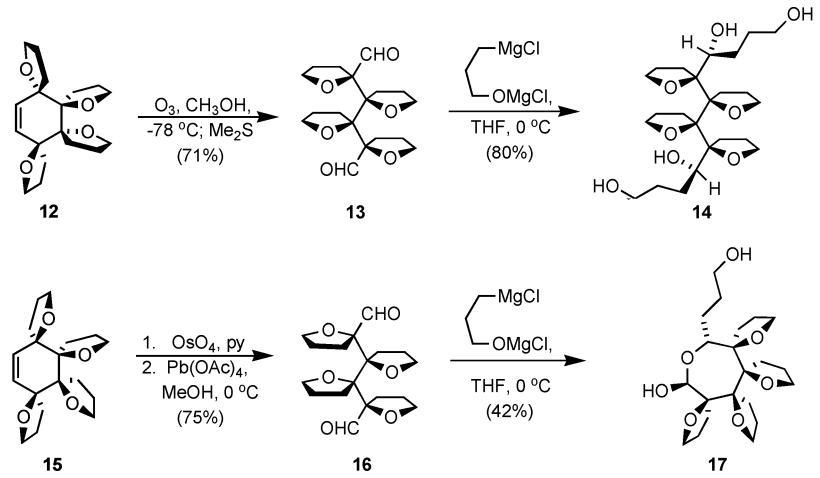
SCHEME 1. Ring Cleavage and Capping of 12 and 15



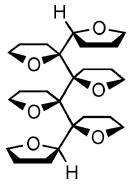
As enticing as these structurally novel oligomeric assemblies are, their ladder-like arrays can be regarded as too abbreviated to provide a sufficiently detailed profile of the global energetic factors involved. These considerations have led us to synthesize a comprehensive selection of stereoisomeric hexamers more directly related to **3** and **4**, and to ascertain by X-ray crystallographic analysis the specific conformation populated in the solid state in many examples. In addition, the capacity of these molecules to enter into complexation with alkali metal ions in both solution phase and gas phase has been evaluated.

The present report deals with 12 stereoisomers. There are six chiral centers and hence 64 stereochemical perturbations of these centers. Many of these are, of course, identical or chiral pairs. The symmetry properties of the poly-THF molecules prepared herein are the same as those of the Fischer aldaric acids, and the structural permutations can be derived in the same way. In short, for six chiral centers, there are 20 compounds potentially distinguishable by achiral methods and 36 distinguishable by chiral methods.

Background Developments

The adoption of a universal strategy for the elaboration of the targeted hexacyclic structural units was based in large part on adventitious use of the appreciable stereocontrol levels attainable with cyclohexane rings as scaffolds.[10b,18] In a preliminary study, we demonstrated that both **12** and **15**, available on the basis of this chemistry, were amenable to cleavage of their endocyclic double bonds with formation of the dialdehydes **13** and **16**, respectively (Scheme 1).[19] Differences in the chemical reactivity of these diastereomeric subsets were already surfacing at this point. Thus, comparative experiments revealed the hindered double bond in **12** to respond satisfactorily to ozonolysis conditions, which was not the case with **15**. However, the latter underwent smooth conversion to **16** via OsO_4-promoted dihydroxylation followed by exposure to lead tetraacetate. Beyond this, the different stereodisposition of the oxygen atoms in **13** and **16** was seen to induce a rather different reactivity pattern toward the Normant reagent[20] at 0 °C.

Following the acquisition of tetrol **14**, it was an easy matter to tosylate its two primary hydroxyl groups selectively and to "cap" the termini of the chain via intramolecular cyclization.[21] The generation of **18** in this manner provided a substance whose high crystallinity made possible the definition of its three-dimensional features by X-ray diffraction methods (Figure 1). This open-chain polyether lacks the conformational constraint provided by a central ring (as in **3** and **4**) and is now free to rotate along its carbon backbone to relieve intramolecular strain. As seen from the compilation of O−C−C−O torsion angles in Table 1, the oxygen atoms in **18** are predominantly in gauche arrangements. Proper discussion of these and other relevant elements of structural organization are deferred to a later section of this paper where suitable comparison with other hexacyclic diasteroisomers is possible.



18

Execution of the Synthetic Plan

Optimization of the syntheses of **14** and **17** gave a 71% yield of **13** and showed that larger scale allowed the capping of all three diasteromeric tetrols resulting from 2-fold addition of the Normant reagent to **13** (Scheme 2). At this level, chromatography on silica gel enables their separation and identification. The major constituent was unmistakably the predescribed **18**. The remaining pair of isomers proved to be spectroscopically distinguishable, since **20** is a symmetrical molecule and **19** is not.

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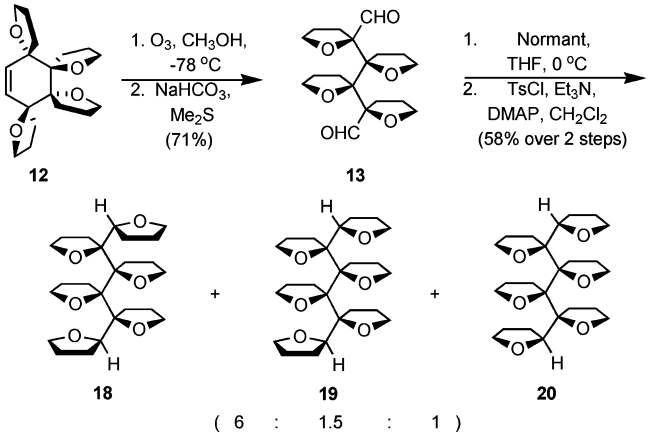
TABLE 1. O−C−C−O Torsion Angles (deg) for Select Hexaspirotetrahydrofuranylhexanes

compd	atoms	angle
18	O(1)−C(1)−C(5)−O(2)	60.1
	O(2)−C(5)−C(9)−O(3)	67.3
	O(3)−C(9)−C(13)−O(4)	**88.5**
	O(4)−C(13)−C(17)−O(5)	66.7
	O(5)−C(17)−C(21)−O(6)	54.8
23	O(1)−C(1)−C(5)−O(2)	**171.6**
	O(2)−C(5)−C(9)−O(3)	63.0
	O(3)−C(9)−C(13)−O(4)	−55.7
	O(4)−C(13)−C(17)−O(5)	−54.9
	O(5)−C(17)−C(21)−O(6)	−67.5
38	O(1)−C(1)−C(5)−O(2)	65.9
	O(2)−C(5)−C(9)−O(3)	57.9
	O(3)−C(9)−C(13)−O(4)	**95.3**
	O(4)−C(13)−C(17)−O(5)	74.5
	O(5)−C(17)−C(21)−O(6)	84.3
39	O(1)−C(1)−C(5)−O(2)	76.1
	O(2)−C(5)−C(9)−O(3)	−63.9
	O(3)−C(9)−C(13)−O(4)	**−97.4**
	O(4)−C(13)−C(17)−O(5)	−70.4
	O(5)−C(17)−C(21)−O(6)	−75.8
40	O(1)−C(1)−C(5)−O(2)	75.8
	O(2)−C(5)−C(9)−O(3)	−70.4
	O(3)−C(9)−C(13)−O(4)	**175.8**
	O(4)−C(13)−C(17)−O(5)	59.9
	O(5)−C(17)−C(21)−O(6)	−59.5
51	O(1)−C(1)−C(5)−O(2)	−58.2
	O(2)−C(5)−C(9)−O(3)	**179.0**
	O(3)−C(9)−C(13)−O(4)	57.8
	O(4)−C(13)−C(17)−O(5)	−68.7
	O(5)−C(17)−C(21)−O(6)	−60.6
52	O(1)−C(1)−C(5)−O(2)	−59.9
	O(2)−C(5)−C(9)−O(3)	**−179.8**
	O(3)−C(9)−C(13)−O(4)	54.5
	O(4)−C(13)−C(17)−O(5)	−71.5
	O(5)−C(17)−C(21)−O(6)	76.4
53	O(1)−C(1)−C(5)−O(2)	−75.8
	O(2)−C(5)−C(9)−O(3)	65.8
	O(3)−C(9)−C(13)−O(4)	**92.8**
	O(4)−C(13)−C(17)−O(5)	84.6
	O(5)−C(17)−C(21)−O(6)	77.2

SCHEME 2. Acquisition of 18−20



In a related context, lowering of the temperature at which the Normant addition to **16** is performed from 0 °C to −78 °C was found to deliver **21** in the absence of **17** (Scheme 3). As a result, access to **22** and **23** was now conveniently realized. Although **22** and **23** were solids, only where the symmetric **23** is concerned did it prove possible to prompt crystallization in a habit suited to X-ray analysis (Figure 2).

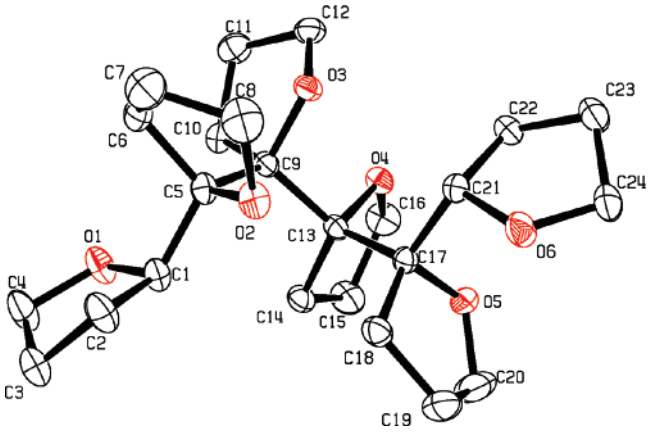
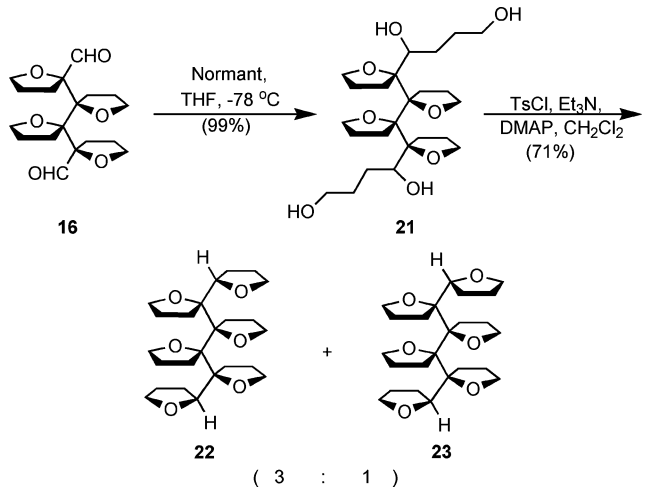


FIGURE 2. ORTEP plot of the final X-ray model of **23** with hydrogens omitted for clarity. The anisotropic ellipsoids have been drawn at the 50% probability level.

SCHEME 3. Arrival at 22 and 23



The C_2-symmetric cyclohexene **29**, available in four steps from **24**,[18] was next to be investigated. The heteroatomic arrangement resident in this isomer proved to be contributory to a remarkably recalcitrant rate of ozonolytic cleavage of the associated double bond. Evidently, the facial bias available to the O_3 reagent is not conducive to normal reactivity. This conclusion is reinforced by the fact that aldehydo acid **30**, formed in only 25% yield, eventually emerged as the sole characterizable product (Scheme 4). The ozonolytic conversion of cyclic alkenes to terminally differentiated products under various circumstances has earlier been reported.[22,23]

The cleavage to form aldehydo carboxylic acids is likely achieved via deprotonation of the intermediate ozonide by the $NaHCO_3$, as in **A**. This pathway does not result in the bonding of an oxygen atom to the customary reducing agent (Me_2S), thus resulting in the overoxidation of one of the original olefinic centers.

The inefficiency with which **31** was produced prompted us to abandon this option and to give consideration instead to the

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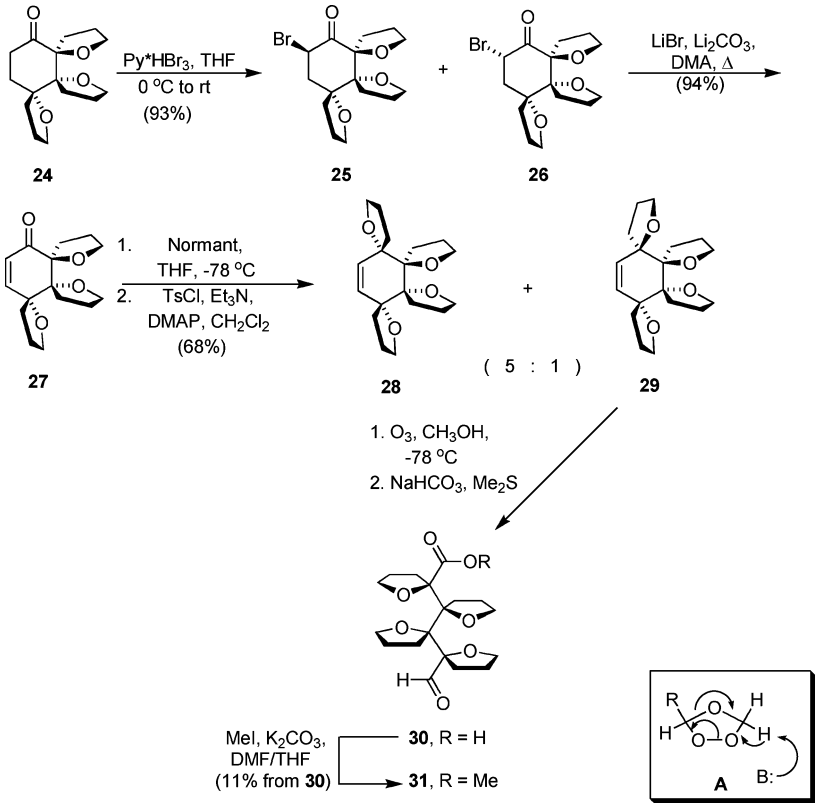
SCHEME 4. Pathway to 31



preparation of **33**−**41** (Scheme 5). When our attention became directed at **28**,[19] it was immediately evident that this cyclohexene was more responsive than **29** toward ozone. Moreover, the conversion to aldehydo ester **33** could be realized in a preparatively useful 73% yield. Chemospecific "capping" of this intermediate proceeded without incident to deliver a chromatographically separable 5.6:1 mixture of **34** and **35**. Should chelation control be operative at a modest level during this homologation as it is in simpler examples[24] as well as in the **13** → **18** conversion,[25] the emergence of **35** as the predominant product would be expected. However, once **38**−**41** subsequently became available, three of these end-products were subjected to X-ray crystallographic analysis (Figures 3−5), thus leaving no opportunity for structural misassignment. This expanse of data revealed that neither **33** nor **37** reacts predominantly via the customary chelated transition state. Presumably, these substrates are sterically inhibited from adopting that conformation properly conducive to coordination involving the Normant reagent and the α-spirocyclic ether.

The multiple cyclizations defined in Scheme 6 constitute a notably informative contrast in stereoselectivity. In the course of coupling the Normant reagent to **46**, **49**, and **50**, the resulting pairs of products proved invariably to be populated to a greater degree (3.1−6:1) by the anti isomers, thus providing indication that the chelate control alternative was kinetically favored across this series. Accordingly, the particular configurational alignment of the multiple ethereal C−O bonds does play a central note in defining the directionality of C−C bond formation at the carboxaldehyde terminus. Solid-state structural analysis, performed on both **51**, **52**, and **53**, in tandem with the realization that **52** is also produced in the course of the annulations of both **49** and **50**,[26] once again allowed the prevailing disposition of the oxygen atoms to be defined (Table 1, Figures 6−8).

Solid-State Conformational Biases

The hexacyclic ethers **18**, **23**, **38**−**40**, and **51**−**53** were subjected to X-ray crystallographic analysis, and the resulting perspective drawings are depicted in Figures 1−8. These structural data provided for determination of the respective O−C−C−O dihedral angles, which number five per molecule (Table 1). Quite strikingly, gauche effects proved not to be universally operative.

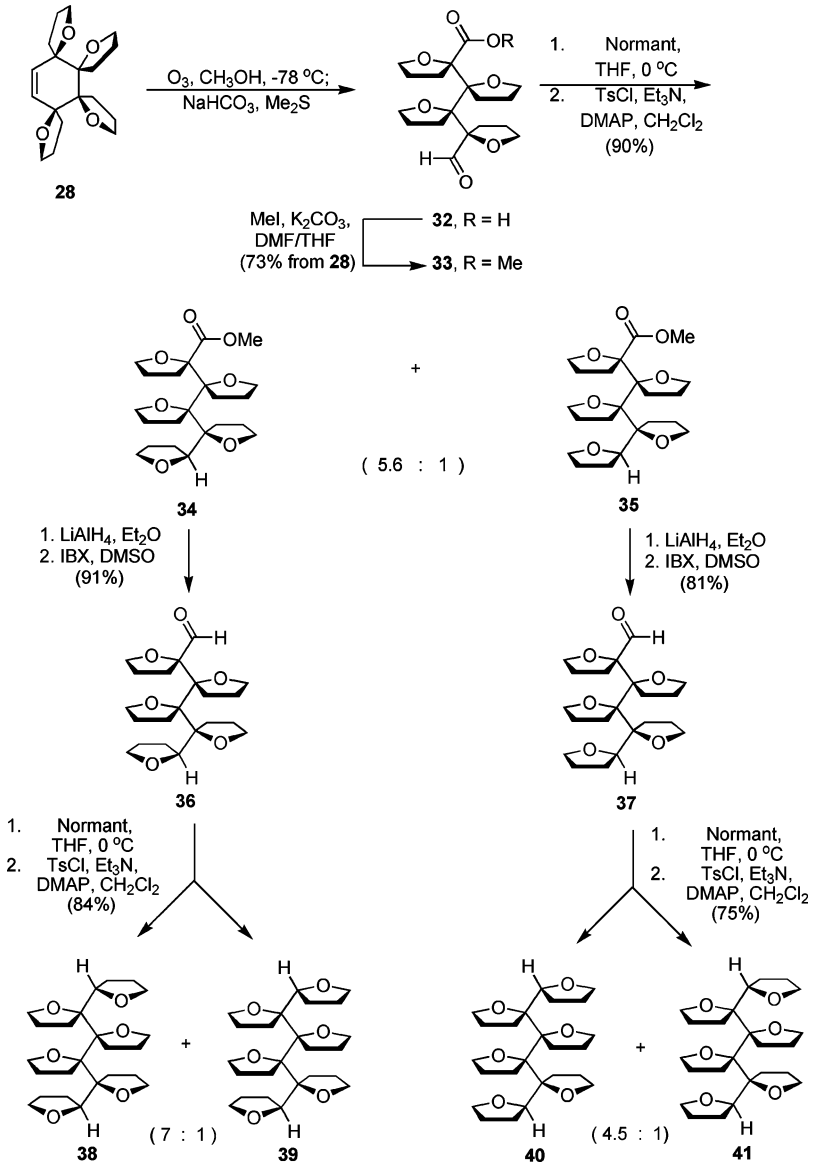
Instead, all eight diastereomers studied here display one serious deformation from the ideal gauche angle, most often in the central region of the chain. The previously described polyether **18** exhibits at 89° a relatively small central O(3)−C(9)−C(13)−O(4) dihedral angle. Its diastereomers **38**, **39**, and

(24) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Part A, Chapter 5.

(25) Depiction of the target molecules in a zigzag conformation positions the geminal oxygen atoms at the site of reaction in a distinctive anti arrangement when chelation control is operative during 1,2-addition of the Normant reagent. Otherwise, a syn relationship materializes.

(26) The title compounds have been universally depicted in a zigzag conformation of their backbone carbon chains. The resulting conformational representations are not intended to imply that the all-anti arrangements are thermodynamically more stable. All of the polycyclics are either meso or racemic in nature. Despite the indicated standardization, visualization remains less than obvious in certain cases. The pair of formulas presented below illustrates the problem, which is reminiscent of that associated with the use of Fisher projections.

SCHEME 5. Generation of 32−41



53 partake of related deformations in the range of 93−97° at the same core position. Conformational consequences of far greater magnitude are seen in the remaining examples. Of these, angle widenings to 176−180° occur again along O(3)−C(9)−C(13)−O(4) in three examples (**40**, **51**, and **52**). The unique departure from this pattern operates in **23** where a 172° dihedral is adopted within the O(1)−C(1)−C(5)−O(2) domain *at one end of the chain*. At the same time, its most central dihedral angle is contracted to a record-low value of 56°. Should these deviations be sterically enforced to some significant degree as we anticipate, tracking the stereochemical ordering along the hexane backbone holds promise of harboring information of predictive and explanatory value. The analysis that follows is based on favored adoption by these hexa(THF) systems of a staggered zigzag conformation. Figures 1−8 reveal the deviations from this norm that we have indicated above.

In all of the polyethers reported herein except **53**, the departure from regularity materializes at the site where two THF rings have a syn relationship. When this structural feature is present and the two rings in question are flanked by an additional syn THF unit, an average deviation of 96° is realized (e.g., **38** and **39**). If instead at least one of the flanking rings is anti oriented, the dihedral deviation is distinctively large and approaching 180° (e.g., **51** and **52**). This feature is exhibited as well by **23** whose terminal pair of syn-oriented THF rings is flanked by a single anti heterocycle. This analysis, however, is not extendable to **18** and **40**. These latter substrates feature a dihedral angle of approximately 175° between O(3) and O(4), but is flanked by a syn and anti THF ring in a manner comparable to **38** and **39** (∼90° for either isomer). Where **19** is concerned, the central 88° dihedral angle is positioned between two syn THF cycles. No other "syn/syn"-flanked isomers are presently available for comparative analysis. Also, unlike its relative, **53** exhibits a less dramatically widened dihedral angle that is located between two THF rings that have an anti relationship. When this stereochemical pattern is extended to all four THF rings as in **23**, an anomalous O−C−C−O dihedral angle of 172° makes its appearance at one end of the chain but not the other.

To recapitulate, an attempt has been made to relate structure and stereochemistry in eight isomeric hexa(THF) polycyclics. Changes in relative configuration are expectedly manifested in

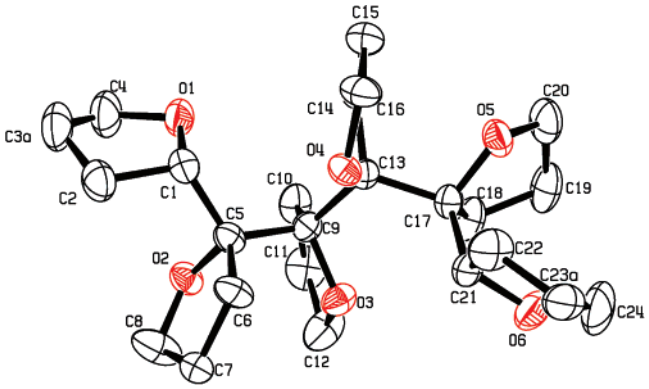


FIGURE 3. ORTEP plot of the final X-ray model of **38** with hydrogens omitted for clarity. The anisotropic ellipsoids have been drawn at the 50% probability level.

TABLE 2. Association Constants (K_a) Determined for the Hexaspirotetrahydrofuranylhexanes by Picrate Extraction into Chloroform at 20 °C[a]

ionophore	Li^+	Na^+	K^+
15-crown-5	8.36×10^4	6.13×10^6	9.23×10^5
anti/syn/syn/syn/anti **18**	2.71×10^4	1.94×10^4	1.6×10^4
syn/syn/syn/syn/anti **19**	8.8×10^4	4.8×10^4	4.6×10^4
syn/syn/syn/syn/syn **20**	7.0×10^4	4.1×10^4	3.7×10^4
syn/anti/anti/anti/anti **22**	3.4×10^4	1.2×10^3	3.75×10^3
syn/anti/anti/anti/syn **23**	7.9×10^4	4.1×10^4	3.8×10^4
anti/syn/syn/anti/syn **38**	5.8×10^4	4.0×10^4	3.1×10^4
syn/syn/syn/anti/syn **39**	4.0×10^4	1.9×10^4	2.0×10^4
syn/syn/syn/anti/anti **40**	7.0×10^4	4.5×10^4	3.0×10^4
anti/syn/syn/anti/anti **41**	1.4×10^4	6.1×10^3	4.8×10^3
anti/syn/anti/syn/anti **51**	3.9×10^4	2.1×10^4	2.0×10^4
anti/syn/anti/syn/syn **52**	9.7×10^4	5.6×10^4	4.0×10^4
syn/syn/anti/syn/syn **53**	1.1×10^5	6.6×10^4	4.5×10^4

[a] The method developed by Koenig, K. E.; Lein, G. M.; Struckler, P.; Kaneda, T; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553 was utilized.

the overall molecular shape adopted by each system. A limited set of trends has been noted, suggesting that long-range steric interactions likely exert major consequences that are capable of overriding gauche effects.

Another interesting phenomenon involves the overall flexibility of these structures as observed by NMR spectroscopy. Compounds **18**, **19**, **20**, **41**, and **51** demonstrate ideal behavior in both ^1H and ^{13}C NMR, producing sharp spectra and therefore displaying either fast rotation, or more likely, conformational rigidity on the NMR time scale. The remaining polyethers **22**−**23**, **38**−**40**, and **52**−**53** show minor to major line broadening in their NMR spectra. The majority of these samples required heating to 60−70 °C in order to sharpen the spectral lines. These trends indicate that certain stereoisomers are less flexible than their acyclic hexane backbones would suggest. Others enjoy the capability for exhibiting a modest level of dynamic exchange. At issue is whether these parameters can be made utilitarian with respect to metal ion binding capability and other tailored properties.

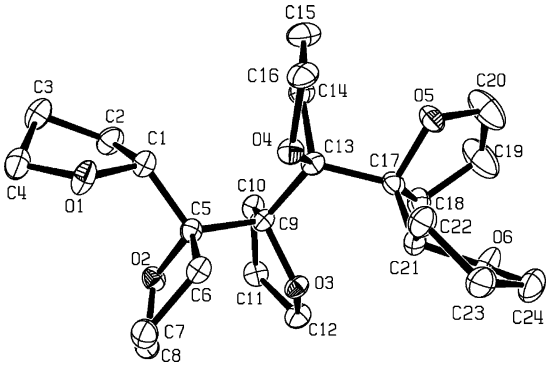


FIGURE 4. ORTEP plot of the final X-ray model of **39** with hydrogens omitted for clarity. The anisotropic ellipsoids have been drawn at the 50% probability level.

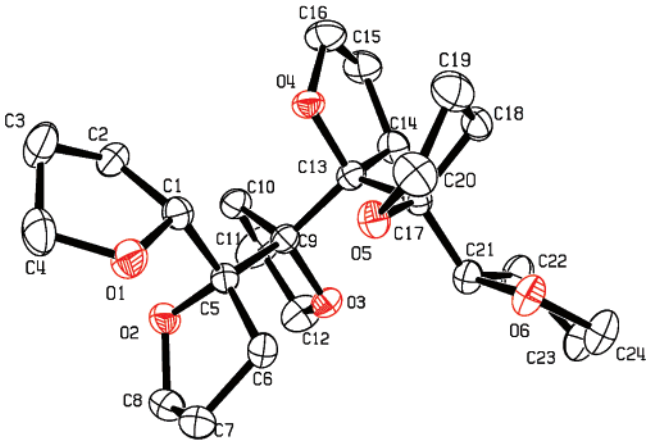


FIGURE 5. ORTEP plot of the final X-ray model of **40** with hydrogens omitted for clarity. The anisotropic ellipsoids have been drawn at the 50% probability level.

TABLE 3. Alkali Metal Selectivity of the Hexamers as Measured by ESI-Mass Spectrometry[a]

hexamer	Li %	Na %	K %
22	96.5 (0.3)	2.9 (0.3)	0.6 (0.2)
19	95 (2)	5 (1)	0.8 (0.7)
51	94 (3)	5 (2)	1.2 (0.7)
18	93 (4)	6 (3)	1.4 (1.2)
23	91 (5)	8 (5)	0.3 (0.1)
41	89 (4)	9 (3)	1.5 (0.1)
53	89 (2)	9 (2)	2.2 (0.6)
20	88 (4)	11 (3)	1.6 (0.9)
39	88 (4)	11 (4)	1.7 (0.9)
38	86 (2)	13 (1)	1.9 (0.6)
52	81 (5)	15 (3)	4.3 (1.3)
40	78 (5)	15 (3)	7 (2)

[a] Relative abundances of lithium, sodium, and potassium complexes are shown as averages of four experiments. Percentages may not add up to 100 due to rounding. Standard deviations are given in parentheses.

Alkali Metal Ion Binding Studies

Picrate extraction studies were initially undertaken in order to gain insight into the solution-phase alkali metal ion coordination capacities of the 12 stereoisomeric hexamers. The association constants (K_a) determined in this manner revealed little to no selectivity (Table 2). In all cases, Li^+ coordination was found

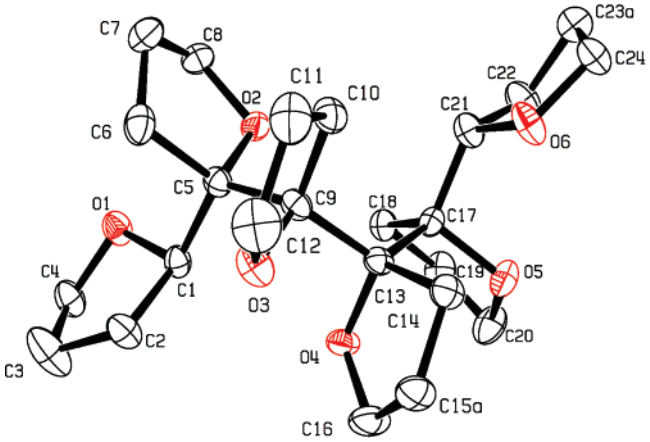


FIGURE 6. ORTEP plot of the final X-ray model of **51** with hydrogens omitted for clarity. The anisotropic ellipsoids have been drawn at the 50% probability level.

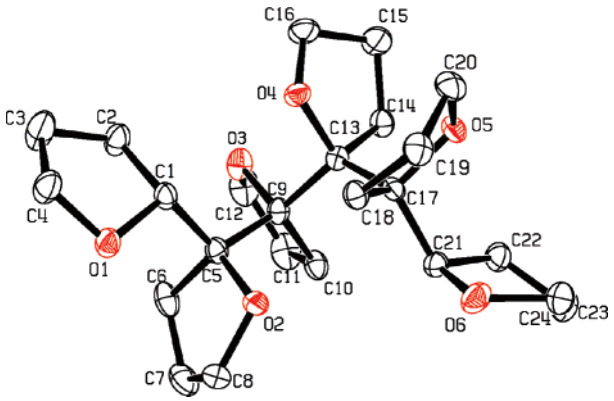


FIGURE 7. ORTEP plot of the final X-ray model of **52** with hydrogens omitted for clarity. The anisotropic ellipsoids have been drawn at the 50% probability level.

to be favored, although the selectivity over Na^+ and K^+ was no more than 2-fold in the majority of examples. A limited number of isomers such as **53** did exhibit reasonable binding abilities on the order of 10^5.

Improvement in sensitivity was achieved by conducting competitive metal binding experiments involving a series of solutions containing one of the hexamers with lithium, sodium, and potassium salts, analyzed by electrospray ionization mass spectrometry (ESI-MS). Table 3 summarizes the alkali metal selectivities in terms of the distribution of lithium, sodium, and potassium complexes obtained from the ion abundances in the ESI mass spectra for each solution. For all of the hexamers, the lithium complexes had the greatest abundances, and the abundances of the potassium complexes were relatively low. Small but significant selectivity differences were observed between the diastereomers, with the preference for lithium ranging from a high of 96% for **22** to a low of 78% for **40**.

In an effort to assess the ability to differentiate the 12 hexatetrahydrofuranylhexane isomers, tandem mass spectrometry via collision-induced dissociation (CID) was undertaken on each of the 12 protonated hexamers. Each protonated molecule yielded a similar array of fragment ions. A typical CID mass spectrum is shown in Figure 9. The main fragment ions appear at intervals of 70 Da, which corresponds to the mass of the tetrahydrofuranyl group (C_4H_6O) that makes up the repeat unit of the hexamers. Losses of from one to four of the

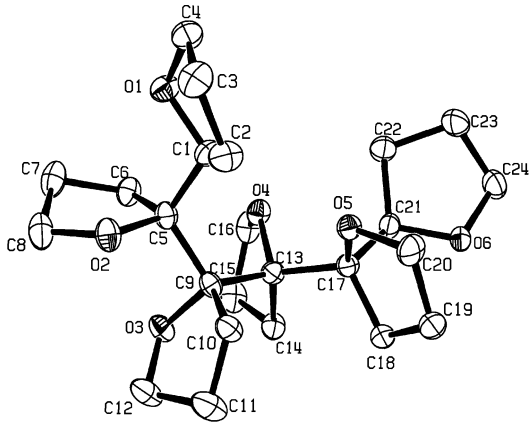


FIGURE 8. ORTEP plot of the final X-ray model of **53** with hydrogens omitted for clarity. The anisotropic ellipsoids have been drawn at the 50% probability level.

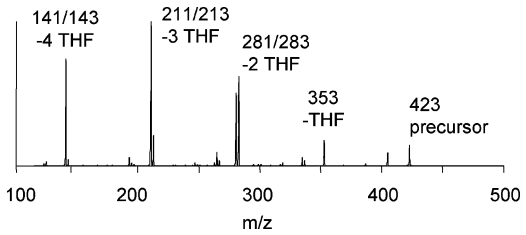


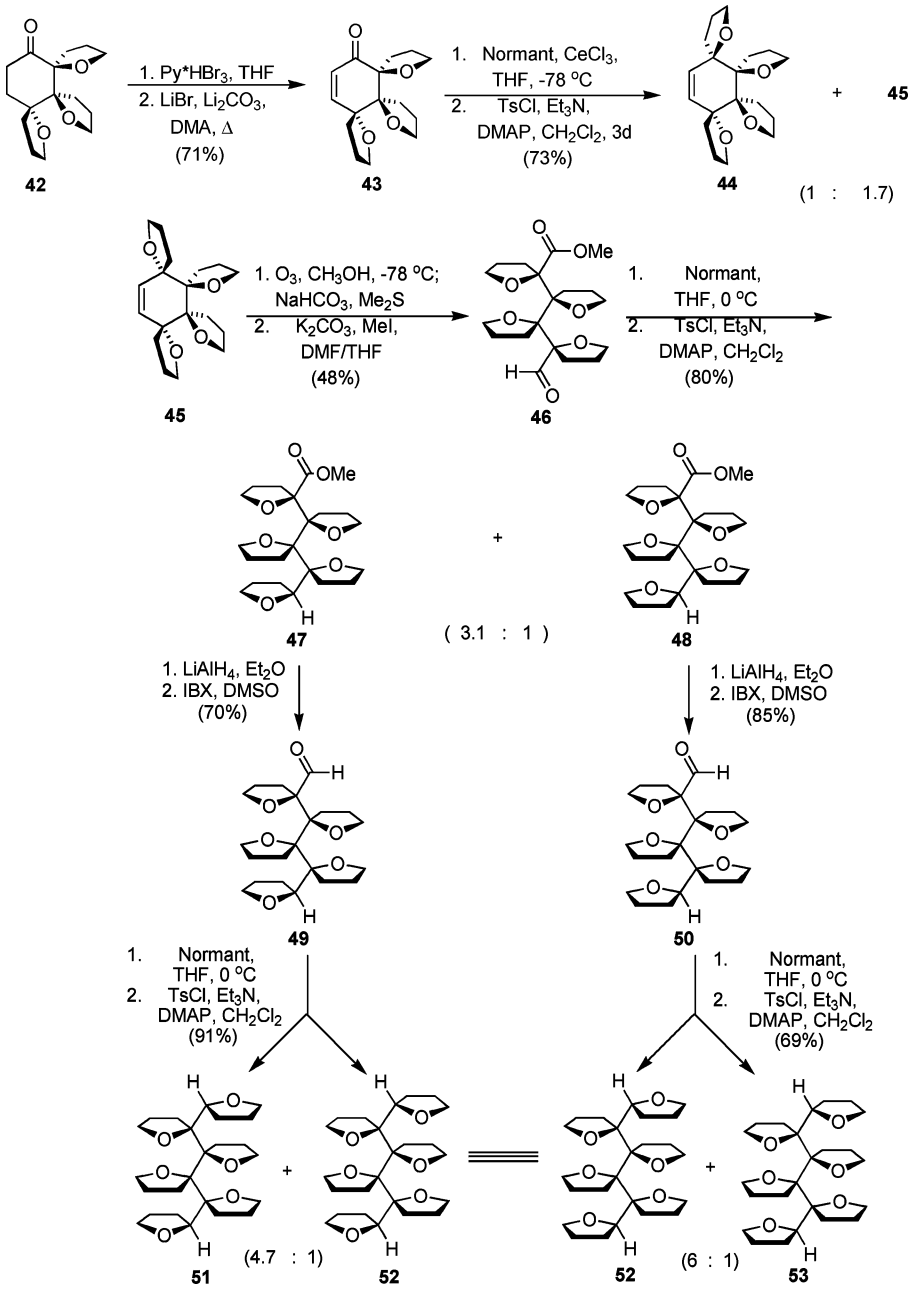
FIGURE 9. MS/MS spectrum of protonated hexamer **51**.

tetrahydrofuranyl groups are typically observed in the CID mass spectra of each of the protonated hexamers. These losses of tetrahydrofuranyl groups may occur in conjunction with a transfer of one hydrogen to or from the portion lost during the dissociation process, thus giving two series of fragment ions that differ in mass by 2 Da. Examples of the types of fragment ions that would result from these parallel pathways are shown in Scheme 7. The specific protonation site is not known, but initial localization of the proton on one of the oxygen atoms is expected, and the charge site may be further stabilized via intramolecular hydrogen-bond formation involving a second oxygen atom. Upon collisional activation, the proton may be mobile and migrate to other sites, thus facilitating several competing fragmentation processes. In general, the series of fragment ions involving the multiple losses of the tetrahydrofuranyl groups are highly characteristic of the hexatetrahydrofuranylhexane structures but do not allow specific stereoisomer differentiation.

The dissociation patterns of the lithium and sodium complexes by tandem mass spectrometry were also explored, revealing an interesting stereochemical−structural correlation discussed below that was not observed for the dissociation of the protonated hexamers. Figure 10 shows several representative CID mass spectra for the lithium and sodium complexes. One ubiquitous fragmentation pathway stems from the loss of 142 Da, which corresponds to the loss of two THF groups with one hydrogen migration ($-C_8H_{14}O_2$). This dissociation route is observed for all of the lithium and sodium complexes and is not stereochemically diagnostic.

The dominant fragmentation pathways for both the lithium and sodium complexes result in the loss of three THF groups, either with or without a hydrogen migration and thus constituting the loss of 212 or 210 Da, similar to the neutral losses shown in Scheme 7 for the protonated hexamer. It is the distribution

SCHEME 6. Route Leading to 51−53



of the resulting fragment ions (*m*/*z* 217 or 219 for the lithium complexes, and *m*/*z* 233 and 235 for the sodium complexes) that allows the stereoisomeric classification of the hexamers, as summarized in Table 4. For example, based on the CID mass spectra of the lithium adducts, the hexamers can be divided into three categories. Group I, consisting of **18**, **41**, and **51**, has THF groups in the anti configuration at both ends of each hexamer. Dissociation of the lithium complexes of this group favors the loss of 210 Da over the loss of 212 Da, as shown by the example of the CID mass spectrum for **18** in Figure 10. The fragment ion due to loss of 212 Da is consistently about half of the abundance of the fragment ion due to loss of 210 Da, giving a ratio of −212/−210 that averages 0.5 for Group I (anti,anti). Group II consists of **19**, **22**, **38**, **40**, and **52**. In this group, the two THF rings at one terminus are in the syn configuration, while the pair of THF rings at the other terminus is in the anti configuration. The lithium complexes of these compounds show nearly equal preference for the two competing fragmentation pathways although the loss of 212 Da is always slightly favored, as illustrated by the CID mass spectrum of **19** in Figure 10. The ratio of −212/−210 averages 1.2 for Group II (syn,anti). Group III consists of **20**, **23**, **39**, and **53**. The common structural feature of this group of hexamers is that the pairs of THF rings at both ends of each molecule are in the syn configuration. The lithium complexes of these four diastereomers favor the loss of 212 Da over the loss of 210 Da in a ratio of about 2:1 for Group III (syn,syn). An example of this pattern is shown in Figure 10 for **20**. The sodium complexes yield analogous results for the preference for the loss of 210 versus 212 Da based on the stereochemical category of the hexamer (i.e., anti,anti; syn,-anti; syn,syn).

These results demonstrate that the presence of a lithium or sodium ion allows discrimination between the stereochemical configurations of the THF rings near the two termini of the

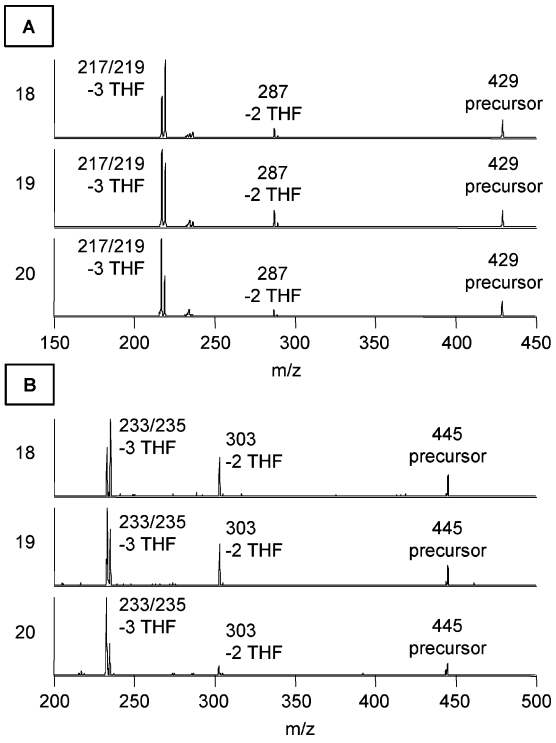
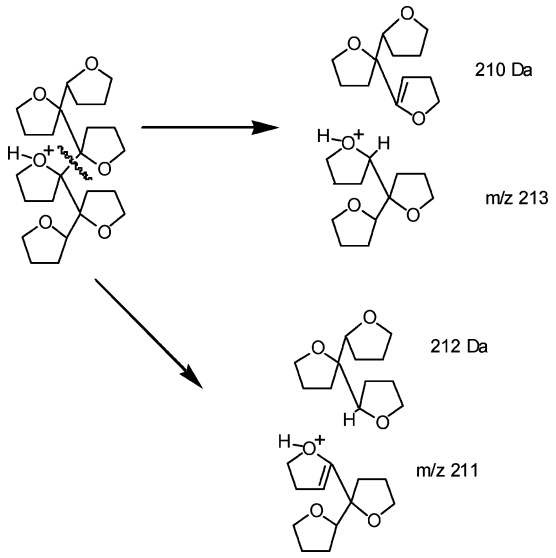


FIGURE 10. MS/MS spectra of (A) lithium complexes and (B) sodium complexes of selected hexamers.

SCHEME 7. Proposed Fragmentation Pathways of Protonated Hexamers



hexamers. It is surmised that the metal ions promote a consistent conformational change among the hexamers that directs their dissociation pathways in a diagnostic stereochemically dependent manner. The presence of vicinal THF rings syn to each other at the terminus of the molecule promotes the loss of 212 Da, while vicinal THF groups in the anti configuration promote the loss of 210 Da. When the two termini differ in this regard (syn,-anti), both neutral losses are favored nearly equally. In fact, the −212/−210 Da ratio of the Group II compounds is approximately the average of the Group I and Group III compounds. One possible explanation is that when one terminus of the hexamer is in the syn configuration while the other is in the anti configuration, either of the two dissociation pathways may occur with near equal probability. Since the product ions that are observed correspond to the half of the molecule that retains the alkali metal ion, this suggests multiple binding sites for the metal ion, with lithium or sodium residing half the time on the syn half of the molecule and half the time on the anti half.

TABLE 4. Stereochemical Classification of Hexamers Based on Loss of 210 Da versus 212 Da for Lithium and Sodium Complexes[a]

hexamer	−212/−210 for $(M + Li)^+$	−212/−210 for $(M + Na)^+$
	Group I	
18	0.52 ± 0.05	0.58 ± 0.11
41	0.49 ± 0.02	0.54 ± 0.09
51	0.47 ± 0.03	0.48 ± 0.09
	Group II	
19	1.22 ± 0.04	1.36 ± 0.08
22	1.11 ± 0.04	1.32 ± 0.09
38	1.20 ± 0.03	1.25 ± 0.06
40	1.19 ± 0.06	1.36 ± 0.15
52	1.21 ± 0.01	1.35 ± 0.13
	Group III	
20	1.92 ± 0.04	2.52 ± 0.01
23	2.03 ± 0.10	2.61 ± 0.08
39	2.08 ± 0.12	2.67 ± 0.02
53	1.83 ± 0.07	1.89 ± 0.06

[a] Ratios were calculated on the basis of the relative abundance of the fragment ions due to the loss of 212 Da or 210 Da; 90% confidence intervals were calculated on the basis of three replicate measurements.

In light of these observations, the X-ray crystallography data was re-examined for further correlation with the mass spectrometry data. For any hexamer with a terminal pair of THF groups in the anti configuration, the torsion angle between those two THF groups (as measured between the oxygen atoms) is always very close to the ideal gauche angle of 60° (or −60°). In contrast, the typical dihedral angle of terminal THF groups in the syn configuration is 76° or −76°, with a deviation of no more than 1.2°. The only exceptions are **23** and **38**, which have terminal syn groups with widely differing dihedral angles. This consistent correlation between the stereochemistry and conformation of the terminal THF groups may influence the coordination of the alkali metal ions and the favored dissociation pathway of the resulting complexes upon ESI-MS/MS analysis.

Finally we note that the lithium, sodium, and potassium association constants are highly correlated in the picrate studies. If compound **22** is removed from the correlation, R for Li^+/Na^+ increases to 0.96, that for Li^+/K^+ increases to 0.92, and that for Na^+/K^+ reduces to 0.88. The reduction in the Na^+/K^+ correlation occurs because the association constants for the Na^+ and K^+ are the lowest in the listing, and their removal therefore has a disproportionate effect on the correlation.

Also to be noted is the fact that compound **22** shows a 28-fold selectivity for lithium over sodium and 9-fold selectivity for lithium over potassium. This lithium/sodium selectivity is particularly significant. To put these numbers in perspective, the 15-crown-5 selectivity for lithium over sodium is 73-fold, but selectivity for lithium over potassium is 11-fold. This is all the more remarkable because the crown is macrocyclic, whereas the poly-THFs have a considerable entropic penalty upon binding.

Experimental Section

Dialdehyde 13. Cyclohexene **12** (500 mg, 1.62 mmol) was dissolved in MeOH (100 mL) and cooled to −78 °C. Ozone was bubbled through the solution for 45 min, followed by O_2 for 10

min. The mixture was then warmed to rt, treated with $NaHCO_3$ (500 mg), and Me_2S (5 mL). Following overnight stirring, the solvent was removed *in vacuo*, and column chromatography of the resulting oil on silica gel with 40% ether in hexanes afforded 394 mg (71%) of **13** as a solid. The spectral properties were identical to those previously reported.[19]

Hexa(THF) Ethers 18−20. The Normant reagent (8.3 mL, 0.40 M in THF) was added to a cold (0 °C) solution of **13** (0.47 g, 1.38 mmol) in THF (15 mL) under N_2. After 1 h, the mixture was quenched with 5% HCl solution, and the separated aqueous phase was extracted with CH_2Cl_2 (4×) and dried. The combined organic phases were dried, filtered, and concentrated by rotary evaporation. After being placed under high vacuum overnight, the crude diol was taken up in CH_2Cl_2 (50 mL) under N_2. Triethylamine (0.87 mL, 4.5 mmol) and DMAP (50 mg) were added, the solution was cooled to 0 °C, and TsCl (0.58 g, 3.04 mmol) was introduced. After overnight stirring at rt, an additional 50 mg of TsCl was added, and stirring was maintained an additional 24 h. The reaction mixture was then washed with 10% HCl solution, the separated aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic phases were dried. Filtration and solvent removal resulted in an oil that was chromatographed on silica gel with 20% ether in hexanes to afford 40 mg (7%) of **20** and 300 mg of a mixture of **18** and **19**, which were subsequently separated by column chromatography on silica gel with 10% ether in CH_2Cl_2 to yield 240 mg (41%) of **18** and 60 mg (10%) of **19**.

For **20**: white solid, mp 134−135 °C; (IR neat, cm^{-1}) 2970, 2870, 1059; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.95−3.80 (m, 8H), 3.83 (q, J = 7.3 Hz, 2H), 3.60−3.55 (m, 4H), 2.95−2.85 (m, 2H), 2.73−2.64 (m, 2H), 2.41−2.30 (m, 2H), 2.21−2.05 (m, 6H), 1.90−1.80 (m, 2H), 1.69−1.50 (series of m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 96.4, 94.5, 82.8, 69.8, 68.7, 66.5, 33.4, 28.0, 27.6, 26.0; ES HRMS m/z $(M + Na)^+$ calcd 445.2566, obsd 445.2574.

For **18**: white solid, known compound with spectroscopic data identical to that previously reported.[19]

For **19**: colorless oil; (IR neat, cm^{-1}) 2964, 2871, 1059; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.03−3.82 (m, 8H), 3.75 (q, J = 7.7 Hz, 3H), 3.65−3.55 (m, 3H); 3.03−2.89 (m, 2H), 2.73−2.64 (m, 2H), 2.51−2.19 (series of m, 4H), 2.01−1.52 (series of m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 97.8, 97.1, 95.1, 93.8, 83.0, 82.8, 70.3, 69.8, 69.6, 68.7, 68.3, 66.7, 34.2, 33.8, 33.5, 31.6, 28.2, 28.1, 27.8, 27.7, 27.1, 26.6, 26.3, 25.5; ES HRMS m/z $(M + Na)^+$ calcd 445.2566, obsd 445.2559.

Hexa(THF) Ethers 22 and 23. The Normant reagent (10.5 mL, 0.40 M in THF) was added to a cold (−78 °C) solution of **16** (140 mg, 0.41 mmol) in THF (20 mL) under N_2. After 1 h, the mixture was quenched with 5% HCl solution, extracted with CH_2Cl_2 (15×), dried, and concentrated by rotary evaporation. After being placed under high vacuum overnight, the crude diol **21** was taken up in CH_2Cl_2 (20 mL) under N_2. Triethylamine (0.35 mL, 2.5 mmol) and DMAP (20 mg) were added, and the solution was cooled to 0 °C. Tosyl chloride (240 mg, 1.26 mmol) was introduced, and the mixture was allowed to stir at rt overnight. The following day, an additional 40 mg of TsCl was added, and after an additional 24 h, the reaction mixture was washed with 10% HCl solution, and the separated aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phases were dried and freed of solvent. The resulting oil was chromatographed on silica gel with 10% ether in CH_2Cl_2 to afford 32 mg (18%) of **23** and 99 mg (57%) of **24**.

For **23**: white solid, mp 153−154 °C; (IR neat, cm^{-1}) 2960, 2876, 1069; ^1H NMR (C_6D_6, 500 MHz, 70 °C) δ 4.61−4.50 (m, 2H), 4.08−3.97 (m, 4H), 3.89 (t, J = 6.4 Hz, 4H), 3.75 (q, J = 7.5 Hz, 2H), 3.63 (q, J = 6.1 Hz, 2H), 2.48−2.21 (br m, 2H), 2.21−2.08 (m, 6H), 2.03−1.61 (series of m, 16H); ^{13}C NMR (C_6D_6, 125 MHz, 70 °C) δ 100.8, 94.6, 84.0, 70.0, 69.3, 67.6, 32.3, 29.5, 27.7, 27.5, 27.3, 26.4; ES HRMS m/z ($C_{24}H_{38}O_6Na^+$) calcd 445.2566, obsd 455.2566.

For **22**: white solid, mp 149−150 °C; (IR neat cm^{-1}) 2967, 2872, 1068; ^1H NMR (C_6D_6, 500 MHz, 60 °C) δ 4.93 (t, J = 7.3 Hz, 1H), 4.18−4.10 (m, 2H), 4.08−4.03 (m, 3H), 3.96 (q, J = 7.4 Hz, 1H), 3.81−3.68 (series of m, 5H), 3.64 (q, J = 7.9 Hz, 1H), 3.56 (q, J = 5.3 Hz, 1H), 2.90−2.80 (m, 1H), 2.57−2.51 (m, 1H), 2.36−2.28 (m, 1H), 2.19−1.52 (series of m, 20 H), 1.48−1.39 (m, 1H); ^{13}C NMR (C_6D_6, 125 MHz, 60 °C) δ 101.2, 100.1, 96.4, 94.4, 85.7, 83.9, 70.9, 70.6, 69.7, 69.1, 67.2, 66.9, 34.5, 33.4, 32.4, 30.4, 30.1, 28.2, 28.0, 27.9, 27.8, 27.5, 27.1, 26.7; ES HRMS m/z ($C_{24}H_{38}O_6Na^+$) calcd 445.2566, obsd 445.2572.

α-Bromocyclohexanones 25 and 26. Ketone **24** (0.40 g, 1.5 mmol), dissolved in THF (10 mL) under N_2, was cooled to 0 °C and treated with HBr_3·Py (0.53 g, 1.65 mmol) in 15 mL of THF via syringe. After 15 min, the reaction mixture was warmed to rt, diluted with Et_2O (20 mL), and treated with 10% sodium thiosulfate solution after 30 min. The two layers were vigorously mixed and separated, followed by washing of the organic phase with H_2O and brine. The ethereal solution was dried, concentrated, and chromatographed on silica gel with 20% EtOAc in hexanes to afford **25** and **26** as 0.28 g (54%) of solid and 0.20 g (39%) of an oil, respectively.

For the less polar isomer: white solid, mp 124 °C; (IR neat, cm^{-1}) 1735, 1084, 1063; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.11 (dd, J = 6.3, 13.5 Hz, 1H), 3.98−3.72 (m, 5H), 3.74 (q, J = 6.5 Hz, 1H), 2.76−2.70 (m, 1H), 2.40 (dd, J = 6.3, 13.5 Hz, 1H), 2.20−1.60 (series of m, 11H), 1.51−145 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.6, 95.1, 91.1, 87.5, 71.2, 69.2, 68.1, 50.7, 44.6, 32.8, 32.5, 32.3, 26.7, 26.0, 25.3; ES HRMS m/z ($C_{15}H_{21}BrO_4Na^+$) calcd 367.0515, obsd 367.0511.

For the more polar isomer: colorless oil; (IR neat, cm^{-1}) 2952, 2875, 1735; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.12 (dd, J = 6.2, 13.8 Hz, 1H), 3.92−3.68 (m, 5H), 3.63 (q, J = 8.4 Hz, 1H), 2.65 (quintet, J = 6.4 Hz, 1H), 2.55 (t, J = 12.9 Hz, 1H), 2.31 (quintet, J = 6.2 Hz, 1H), 2.20−1.73 (series of m, 10H), 1.65−1.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.5, 92.4, 90.7, 88.1, 70.1, 69.6, 67.7, 50.7, 44.0, 32.8, 28.1, 27.6, 27.1, 26.1, 25.4; ES HRMS m/z ($C_{15}H_{21}BrO_4Na^+$) calcd 367.0515, obsd 367.0507.

α,β-Unsaturated Ketone 27. A mix of bromides **25** and **26** (3.3 g, 14.2 mmol) was dissolved in dimethylacetamide (150 mL) along with LiBr (3.3 g, 56.8 mmol) and Li_2CO_3 (2.9 g, 56.8 mmol) under N_2. The mixture was refluxed for 4 h and cooled. Removal of solvent *in vacuo* was followed by column chromatography on silica gel with 30% EtOAc in hexanes to afford 2.5 g (94%) of **27** as a white solid, mp 65−66 °C; (IR neat, cm^{-1}) 2958, 2874, 1689; ^1H NMR (DMSO-d_6, 500 MHz, 90 °C) δ 6.75 (d, J = 10.1 Hz, 1H), 5.96 (d, J = 10.1 Hz, 1H), 3.93 (t, J = 5.3 Hz, 1H), 3.83−3.71 (m, 5H), 2.39−2.30 (m, 1H), 2.20−2.15 (m, 1H), 1.98−1.70 (series of m, 10H); ^{13}C NMR too broad even at 90 °C in DMSO-d_6; ES HRMS m/z ($C_{15}H_{20}O_4Na^+$) calcd 287.1254, obsd 287.1258.

Tetra(THF) Ethers 28 and 29. The Normant reagent (32.6 mL, 0.40 M) was added to a cooled (−78 °C) solution of **27** (2.3 g, 8.7 mmol) in THF (150 mL) under N_2 via syringe pump over 30 min, and warmed to rt after an additional 2 h. The mixture was quenched with saturated NH_4Cl solution, extracted with CH_2Cl_2 (3×), dried, and evaporated. After removal of excess solvent under high vacuum (0.5 mmHg) overnight, the crude diol was taken up in CH_2Cl_2 (150 mL) under N_2 and treated with triethylamine (2.4 mL, 17.0 mmol) and DMAP (50 mg). The solution was cooled to 0 °C, *p*-toluenesulfonyl chloride (1.4 g, 7.4 mmol) was added, and the mixture was stirred at rt for 2 d, washed with 10% HCl, water, and brine and then dried. Filtration and solvent removal gave an oil that was chromatographed on silica gel with 20% EtOAc in hexanes to afford 1.6 g (60%) of **28** and 300 mg (8%) of **29**.

For **28**: see ref 19.

For **29**: colorless oil; (IR neat, cm^{-1}) 2957, 2869, 1048; ^1H NMR (C_6D_6, 500 MHz) δ 5.43 (s, 2H), 3.90−3.86 (m, 2H), 3.81−75 (m, 6H), 3.02−2.98 (m, 2H), 2.08−2.01 (m, 2H), 1.86−1.75 (m, 2H), 1.72−1.64 (m, 4H), 1.62 (m, 6H); ^{13}C NMR (C_6D_6, 125 MHz) δ 131.9, 91.3, 87.0, 69.1, 68.4, 35.1, 31.5, 28.3, 26.7; ES HRMS m/z ($C_{18}H_{26}O_4Na^+$) calcd 329.1723, obsd 329.1729.

Aldehydo Ester 31. Cyclohexene **29** (190 mg, 0.62 mmol) was dissolved in MeOH (5 mL) and cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted. Following treatment with $NaHCO_3$ (50 mg), the mixture was warmed to rt, Me_2S (0.5 mL) was added, and the solution was stirred overnight. The solvent was removed *in vacuo*, and column chromatography on silica gel with 50% EtOAc in hexanes to 50% EtOAc in hexanes containing 5% MeOH afforded 61 mg of the crude aldehydo acid **30**.

The acid (105 mg, 0.30 mmol) was then dissolved in a 3:2 THF/DMF solution (3 mL) with K_2CO_3 (102 mg, 0.75 mmol) under N_2. MeI (0.18 mL, 2.96 mmol) was added, the mixture was stirred for 4 h, and saturated NH_4Cl solution and CH_2Cl_2 were introduced. The separated aqueous phase was extracted with CH_2Cl_2 (2×), and the combined organic phases were dried and concentrated. The resulting oil was chromatographed on silica gel with 50% EtOAc in hexanes to provide 45 mg (11% over two steps) of **31** as a colorless oil; (IR neat, cm^{-1}) 2948, 1723, 1069; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.45 (s, 1H), 3.98−3.73 (m, 3H), 3.70−3.60 (m, 4H), 3.58 (s, 3H), 3.54 (q, J = 9.8 Hz, 1H), 2.45−2.36 (m, 1H), 2.28−2.15 (m, 2H), 2.13−2.08 (m, 3H), 2.00−1.72 (m, 9H), 1.52−1.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.3, 174.1, 95.4, 94.6, 92.7, 91.5, 70.2, 69.2, 68.8, 67.1, 51.9, 33.4, 33.3, 30.7, 27.4, 27.0, 26.3, 26.2, 25.2; ES HRMS m/z $(M + Na)^+$ calcd 391.1733, obsd 391.1746.

Aldehydo Acid 33. Cyclohexene **28** (1.3 g, 4.2 mmol) was dissolved in MeOH (55 mL) and cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted, and the mixture was treated with $NaHCO_3$ (1.0 g). After warming to rt, Me_2S (5 mL) was added, and the solution was stirred overnight. Solvent was removed *in vacuo*. Column chromatography of the residue on silica gel with 50% EtOAc in hexanes containing 5% MeOH afforded 1.17 g (79%) of **32** as a white solid, mp 148−149 °C; (IR neat, cm^{-1}) 1762 (s), 1720 (s), 1066 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.49 (s, 1H), 4.28−4.20 (m, 1H), 4.02 (t, J = 6.5 Hz, 2H), 3.98−3.88 (m, 3H), 3.78 (q, J = 7.7 Hz, 1H), 3.69−3.61 (m, 1H), 2.31−1.75 (series of m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.1, 173.4, 96.7, 95.1, 94.6, 91.7, 71.6, 70.0, 69.4, 67.2, 32.8, 31.8, 30.6, 27.0, 26.8, 25.6, 25.5, 23.9; ES HRMS m/z ($C_{18}H_{26}O_7Na^+$) calcd 377.15707, obsd 377.1555.

The acid **32** (115 mg, 0.32 mmol) was dissolved in a 3:2 THF/DMF solution (5 mL) with K_2CO_3 (111 mg, 0.8 mmol) under N_2. MeI (0.2 mL, 3.2 mmol) was added, and the mixture stirred for 4 h, after which saturated NH_4Cl solution and CH_2Cl_2 were introduced. The separated aqueous phase was extracted with CH_2Cl_2 (2×), and the combined organic phases were dried and concentrated. The resulting oil was chromatographed on silica gel with 50% EtOAc in hexanes to afford 108 mg (92%) of **33** as a solid, mp 125−126 °C; (IR neat, cm^{-1}) 2950, 2886, 1730, 1066; ^1H NMR (C_6D_6, 500 MHz, 70 °C) δ 9.79 (s, 1H), 4.08−4.02 (m, 1H), 3.99−3.90 (m, 1H), 3.74 (dt, J = 5.1, 8.1 Hz, 1H), 3.68 (q, J = 6.1 Hz, 1H), 3.60 (q, J = 6.5 Hz, 1H), 3.56−3.49 (m, 3H), 3.41 (s, 3H), 2.75−2.68 (m, 1H), 2.46−2.40 (m, 1H), 2.28−2.20 (m, 3H), 1.92−1.74 (series of m, 6H), 1.68−1.39 (series of m, 5H); ^{13}C NMR (C_6D_6,125 MHz, 70 °C) δ 193.3, 172.6, 95.7, 95.6, 92.9, 92.6, 70.9, 69.1, 68.3, 67.2, 50.9, 33.2, 32.5, 32.1, 27.5, 27.0, 25.9, 25.87, 25.5; ES HRMS m/z ($C_{19}H_{28}O_7Na^+$) calcd 391.1727, obsd 391.1728.

Penta(THF) Ethers 34 and 35. The Normant reagent (1.76 mL, 0.40 M) was added to a cooled (0 °C) solution of **33** (200 mg, 0.54 mmol) in THF (18 mL) under N_2 and stirred for 1 h. The mixture was quenched with saturated NH_4Cl solution, the separated aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic solutions were dried and concentrated by rotary evaporation. After removal of excess solvent under high vacuum overnight, the crude diol was taken up in CH_2Cl_2 (150 mL) under N_2. Triethylamine (0.25 mL, 1.8 mmol) and DMAP (10 mg) were added, and the reaction mixture was cooled to 0 °C prior to the addition of TsCl (160 mg, 0.84 mmol). The mixture was stirred at rt for 2 d before treatment with 10% HCl solution, water, and brine. The combined organic phases were dried and concentrated to give an oil that was chromatographed with 25% EtOAc in hexanes to provide 168 mg (76%) of **34** and crude **35** as a solid and oil, respectively. Compound **35** was further purified by column chromatography with 2% Et_2O in CH_2Cl_2 to remove a UV-active impurity (14%).

For **34**: white solid, mp 109−110 °C; (IR neat, cm^{-1}) 2948, 2882, 1734, 1067; ^1H NMR (C_6D_6, 500 MHz, 70 °C) δ 5.06 (t, J = 8.0 Hz, 1H), 4.10−4.03 (m, 1H), 3.99−3.94 (m, 2H), 3.90−3.63 (series of m, 7H), 3.51 (s, 3H), 3.38 (t, J = 10.3 Hz, 1H), 2.86−2.78 (m, 1H), 2.61−2.53 (m, 2H), 2.45 (q, J = 8.4 Hz, 1H), 2.30−2.25 (m, 2H), 2.18−1.95 (series of m, 6H), 1.85−1.65 (series of m, 7H); ^{13}C NMR (C_6D_6, 125 MHz, 70 °C) δ 171.9, 97.4, 97.0, 95.2, 93.5, 84.9, 69.9, 69.7, 69.2, 68.5, 66.9, 50.7, 36.3, 34.3, 32.05, 32.0, 27.64, 27.6, 27.1, 27.0, 25.8, 25.7; ES HRMS m/z ($C_{22}H_{34}O_7Na^+$) calcd 433.2197, obsd 433.2202.

For **35**: colorless oil; (IR neat, cm^{-1}) 2952, 2880, 1730, 1066; ^1H NMR (C_6D_6, 500 MHz, 60 °C) δ 4.40−4.36 (m, 1H), 4.08−4.04 (m, 1H), 3.97−3.90 (m, 2H), 3.81−3.72 (m, 5H), 3.67−3.59 (m, 2H), 3.45 (s, 3H), 3.10−3.03 (m, 1H), 2.81−2.77 (m, 1H), 2.57−2.51 (m, 1H), 2.38−2.20 (m, 2H), 2.00−1.56 (series of m, 15H); ^{13}C NMR (C_6D_6, 125 MHz, 70 °C) δ 172.8, 97.5, 97.4, 94.9, 94.0, 84.4, 70.2, 70.0, 69.5, 68.0, 67.3, 50.8, 34.9, 34.0, 32.3, 30.5, 29.3, 26.9, 26.6, 26.4, 26.2, 26.0; ES HRMS m/z ($C_{22}H_{34}O_7Na^+$) calcd 433.2197, obsd 433.2202.

Aldehyde 36. $LiAlH_4$ (20 mg, 0.54 mmol) was added to **34** (110 mg, 0.27 mmol) dissolved in Et_2O (5 mL) and stirred for 1 h. Solid $Na_2SO_4 \cdot 10H_2O$ was added, the mixture was filtered, and the filtrate was concentrated by rotary evaporation. The crude alcohol was then taken up in DMSO (4 mL) and treated with IBX (113 mg, 0.41 mmol). After 4 h, H_2O and CH_2Cl_2 were added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phases were dried and concentrated *in vacuo*. The resulting oil was chromatographed on silica gel with 20% EtOAc in hexanes to afford 94 mg (92%) of **36** as a solid, mp 102−104 °C; (IR neat, cm^{-1}) 2948, 2882, 1734, 1067; ^1H NMR (C_6D_6, 500 MHz, 70 °C) δ 9.65 (s, 1H), 4.75 (t, J = 7.1 Hz, 1H), 4.00−3.81 (series of m, 5 H), 3.68−3.52 (series of m, 5H), 2.32−2.28 (m, 1H), 2.25−2.06 (m, 4H), 2.00−1.91 (m, 3H), 1.88−1.75 (m, 3H), 1.72−1.62 (m, 8H), 1.50−1.42 (m, 1H); ^{13}C NMR (C_6D_6, 125 MHz, 70 °C) δ 194.1, 97.4, 97.0, 94.5, 93.9, 84.8, 70.3, 69.7, 69.1, 68.9, 67.2, 33.63, 33.6, 31.4, 28.8, 28.0, 27.3, 27.2, 26.0, 25.4, 24.3; ES HRMS m/z ($C_{21}H_{32}O_6Na^+$) calcd 403.2091, obsd 403.2098.

Hexa(THF) Ethers 38 and 39. The Normant reagent (0.47 mL, 0.40 M) was added to a cold (0 °C) solution of **36** (34 mg, 0.09 mmol) in THF (2 mL) under N_2 via syringe, and the mixture stirred for 1 h. The mixture was quenched with saturated NH_4Cl solution, and the separated aqueous phase was extracted with CH_2Cl_2 (3×). Subsequent drying and concentration left an oil which was placed under high vacuum overnight. The crude diol was taken up in CH_2Cl_2 (3 mL) under N_2. Triethylamine (37 μL, 0.27 mmol) and DMAP (2 mg) were added to the solution that was cooled to 0 °C prior to the addition of TsCl (32 mg, 0.18 mmol). The mixture was stirred at rt for 2 d and subsequently treated with 10% HCl solution. Following the separation of layers, the organic phase was washed with water and brine and then dried. Filtration and solvent removal gave an oil which was chromatographed on silica gel with 25% EtOAc in hexanes to give 28 mg (74%) of **38** and 4 mg (10%) of **39**.

For **38**: white solid, mp 140−142 °C; (IR neat, cm^{-1}) 2970, 2876, 1067; ^1H NMR (C_6D_6, 500 MHz, 70 °C) δ 5.08 (t, J = 8.1 Hz, 1H), 4.14 (q, J = 7.4 Hz, 1H), 3.99−3.90 (m, 2H), 3.88−3.74 (m, 4H), 3.715−3.69 (m, 2H), 3.65−3.59 (m, 4H), 3.53−3.45 (m, 1H), 2.78−2.66 (m, 2H), 2.43 (t, J = 11.3 Hz, 1H), 2.29−1.88 (series of m, 7H), 1.82−1.47 (series of m, 13H); ^{13}C (C_6D_6, 125 MHz, 70 °C) δ 99.0, 97.9, 96.2, 94.4, 85.2, 83.3, 70.1, 69.7, 69.5, 69.0, 68.4, 66.8, 35.4, 34.4, 32.9, 31.6, 27.9, 27.7, 27.6, 27.3, 27.26, 26.4, 25.7, 25.6; ES HRMS m/z ($C_{24}H_{38}O_6Na^+$) calcd 445.2561, obsd 445.2547.

For **39**: white solid, mp 118−119 °C; (IR neat, cm^{-1}) 2971, 2877, 1066; ^1H NMR (C_6D_6, 500 MHz, 60 °C) δ 5.04 (t, $J = 6.9$ Hz, 1H), 4.07−3.76 (series of m, 7H), 3.70−3.55 (m, 6H), 3.31−3.27 (m, 1H), 2.68−2.60 (m, 2H), 2.54−2.48 (m, 1H), 2.41−2.33 (m, 1H), 2.24−1.89 (m, 7H), 1.85−1.59 (series of m, 12H), ^{13}C (C_6D_6, 125 MHz, 70 °C) δ 97.7, 97.6, 95.4, 95.3, 94.6, 94.5, 69.8, 69.7, 68.9, 68.5, 66.8, 66.4, 34.5, 33.0, 31.1, 27.9, 27.8, 27.5, 27.3, 26.9, 26.8, 26.1, 26.0, 25.5; ES HRMS *m/z* ($C_{24}H_{38}O_6Na^+$) calcd 445.2561, obsd 445.2560.

Aldehyde 37. $LiAlH_4$ (5 mg, 0.13 mmol) was added to **35** (21 mg, 0.05 mmol) in Et_2O (2 mL) and stirred for 0.5 h. Solid $Na_2SO_4 \cdot 10H_2O$ was added, the mixture was filtered, and the filtrate was concentrated by rotary evaporation. The crude alcohol was then taken up in DMSO (2 mL) followed by the addition of IBX (28 mg, 0.1 mmol). After overnight stirring, the solvent was removed *in vacuo*, and the resulting oil was chromatographed on silica gel with 20% EtOAc in hexanes to afford 15.2 mg (80%) of **37** as a solid. This material was taken on directly into the next steps.

Hexa(THF) Ethers 40 and 41. The Normant reagent (0.2 mL, 0.40 M) was added to a cold (0 °C) solution of **37** (15 mg, 0.039 mmol) in THF (2 mL) under N_2 and stirred for 1 h. The mixture was quenched with saturated NH_4Cl solution, and the separated aqueous phase was extracted with CH_2Cl_2 (3×). After drying the organic phases, concentration resulted in an oil. Excess solvent was removed under high vacuum overnight. The crude diol was taken up in CH_2Cl_2 (2 mL) under N_2. Triethylamine (16 μL, 0.117 mmol) and DMAP (2 mg) were added to the solution and cooled to 0 °C prior to treatment with *p*-toluenesulfonyl chloride (18 mg, 0.094 mmol). After being stirred at rt overnight, the reaction mixture was washed with 10% HCl, water, and brine and then dried. Filtration and solvent removal gave an oil which was chromatographed on silica gel with 15% Et_2O in CH_2Cl_2 to give 10 mg (60%) of **40** and 2.5 mg (15%) of **41**.

For **40**: white solid, mp 157−159 °C; (IR neat, cm^{-1}) 2962, 2874, 1062; ^1H NMR (C_6D_6, 500 MHz, 60 °C) δ 4.75−4.65 (br m, 2H), 4.11 (q, $J = 7.2$ Hz, 1H), 3.98−3.94 (m, 1H), 3.85−3.69 (series of m, 7H), 3.66−3.60 (m, 3H), 2.94−2.87 (m, 2H), 2.64−2.58 (br m, 1H), 2.21−2.14 (m, 2H), 1.94−1.50 (series of m, 19H); ^{13}C NMR (C_6D_6, 125 MHz, 70 °C) δ 98.4, 98.2, 94.9, 94.8, 84.2, 83.7, 69.8, 69.7, 68.2, 68.1, 66.4, 66.3, 33.3, 33.0, 32.9, 32.8, 30.0, 29.4, 27.6, 27.2, 27.1, 26.8, 26.7, 26.6; ES HRMS *m/z* ($C_{24}H_{38}O_6Na^+$) calcd 445.2561, obsd 445.2540.

For **41**: colorless oil; (IR neat, cm^{-1}) 2960, 2876, 1063; ^1H NMR (C_6D_6, 300 MHz) δ 4.68−4.59 (m, 1H), 4.33−4.26 (m, 1H), 4.20−4.14 (m, 1H), 4.11 (q, $J = 4.6$ Hz, 1H), 4.02−3.96 (m, 1H), 3.86 (q, $J = 7.1$ Hz, 1H), 3.80−3.57 (series of m, 8H), 3.03−2.95 (m, 1H), 2.60−2.50 (m, 1H), 2.13−1.97 (series of m, 4H), 2.01−1.52 (series of m, 18H); ^{13}C NMR (C_6D_6, 75 MHz) δ 99.0, 98.6, 97.9, 94.3, 84.4, 83.3, 70.0, 69.6, 69.5, 69.3, 68.3, 67.0, 34.9, 34.3, 33.3, 29.5, 29.4, 27.7, 27.3, 27.0, 26.6, 26.4, 26.0, 25.7; ES HRMS *m/z* ($C_{24}H_{38}O_6Na^+$) calcd 445.2566, obsd 445.2589.

α,β-Unsaturated Ketone 43. Ketone **42** (1.9 g, 7.1 mmol) was dissolved in THF (100 mL) under N_2. After cooling to 0 °C, $HBr_3 \cdot$Py (2.97 g, 9.3 mmol) in 50 mL of THF was added via syringe and warmed to rt 15 min later. After 2.5 h, the solution was diluted with Et_2O (20 mL), and 10% sodium thiosulfate solution was added. The two layers were vigorously mixed, and the organic phase was washed with H_2O and brine. After drying of the organic phase, concentration provided an oil that was chromatographed on silica gel with 20% EtOAc in hexanes to afford 2.4 g of the bromide diastereomers as an oil.

The bromides were then dissolved in dimethylacetamide (100 mL) along with LiBr (2.3 g, 27.0 mmol) and Li_2CO_3 (2.0 g, 27.0 mmol) under N_2. The mixture was refluxed for 4 h and cooled. Removal of solvent by distillation at 0.5 mmHg followed by column chromatography on silica gel with 20% EtOAc in hexanes afforded 1.35 g (75%) of **43** as an oil; (IR neat, cm^{-1}) 1688, 1084, 1053; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.63 (d, $J = 8.2$ Hz, 1H), 5.86 (d, $J = 8.2$ Hz, 1H), 3.98−3.67 (series of m, 5H), 3.59−3.50 (br m, 1H), 2.85−2.78 (m, 1H), 2.40−2.30 (m, 1H), 2.20−1.63 (series of m, 9H), 1.45−1.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.0, 154.4, 124.6, 91.1, 89.3, 86.9, 71.1, 69.0, 68.0, 34.8, 32.3, 27.4, 26.3, 25.8, 24.8; ES HRMS *m/z* ($M + Na^+$) calcd 287.1259, obsd 287.1254

Tetra(THF) Ethers 44 and 45. $CeCl_3 \cdot 7H_2O$ (261 mg, 0.70 mmol) was dried overnight under high vacuum at 140 °C followed by stirring in THF (50 mL) for 1 h at rt. Ketone **43** (45 mg, 0.17 mmol) was added in THF (2 mL) and stirred for an additional hour. After cooling to −78 °C, the Normant reagent (1.75 mL, 0.40 M in THF) was added, and the reaction mixture was stirred for 2 h prior to quenching with 5% HCl solution. After extraction with CH_2Cl_2 (3×), the combined organic phases were dried, filtered, and concentrated. The resulting oil was chromatographed on silica gel with 40% CH_2Cl_2 in Et_2O to afford the crude diol containing some 1,4-addition product. This oil was then taken up in CH_2Cl_2 (3 mL) along with triethylamine (71 μL, 0.51 mmol) and DMAP (5 mg). The solution was cooled to 0 °C, treated with *p*-toluenesulfonyl chloride (75 mg, 0.30 mmol), and allowed to stir at rt for 2 d. The mixture was washed with 5% HCl, water, and brine and then dried. Filtration and solvent removal gave an oil that was chromatographed with 20% EtOAc in hexanes to afford of 24 mg (46%) of **45** and 14 mg (26%) of **44**.

For **45**: colorless oil; (IR neat, cm^{-1}) 2969, 2870, 1066; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.71 (d, $J = 10.1$ Hz, 1H), 5.34 (d, $J = 10.1$ Hz, 1H), 4.17 (q, $J = 7.5$ Hz, 1H), 3.98−3.52 (series of m, 7H), 2.95 (dt, $J = 8.1$, 16.1 Hz, 1H), 2.66−2.60 (m, 1H), 2.45−2.36 (m, 1H), 2.22 (sextet, $J = 9.0$ Hz, 1H), 2.06−1.96 (m, 3H) 1.93−1.45 (series of m, 9H); ^{13}C NMR (C_6D_6, 125 MHz) δ 133.8, 128.2, 92.5, 92.0, 87.8, 86.7, 70.0, 69.9, 69.1, 67.3, 34.8, 34.7, 32.6, 28.3, 27.8, 27.3, 27.2, 25.3; ES HRMS *m/z* ($M + Na^+$) calcd 329.1729, obsd 329.1720.

For **44**: colorless oil; (IR neat, cm^{-1}) 2966, 2868, 1054; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.48 (q, $J = 10.1$ Hz, 2H), 4.00−3.86 (m, 4H), 3.72−3.66 (m, 4H) 2.73−2.68 (m, 1H), 2.14−1.60 (series of m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.7, 128.3, 93.0, 90.9, 87.6, 86.8, 69.5, 69.2, 67.5, 66.9, 36.3, 34.6, 32.9, 27.6, 27.3, 27.1, 26.9, 26.7; ES HRMS *m/z* ($M + Na^+$) calcd 329.1729, obsd 329.1720.

Aldehydo Ester 46. Cyclohexene **45** (0.53 g, 1.73 mmol) and $NaHCO_3$ (500 mg) were dissolved in MeOH (50 mL) and cooled to −78 °C. Ozone was bubbled through the solution for 45 min, followed by O_2 for 10 min. The mixture was subsequently warmed to rt, Me_2S (4 mL) was added, and the solution was stirred overnight. The solvent was removed *in vacuo*, and column chromatography on silica gel with 50% EtOAc in hexanes to 50% EtOAc in hexanes containing 10% MeOH afforded 440 mg of the aldehydo acid as an oil.

This acid was dissolved in a 2:1 THF/DMF solution (18 mL) along with K_2CO_3 (497 mg, 2.5 mmol) under N_2. MeI (0.90 mL, 14.4 mmol) was added, and the mixture was stirred for 4 h, after which saturated NH_4Cl solution and CH_2Cl_2 were introduced. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2×). The combined organic phases were dried and concentrated. The resulting oil was chromatographed on silica gel with 25% EtOAc in hexanes to afford 305 mg (48% over two steps) of **46** as an oil; (IR neat, cm^{-1}) 2953, 2886, 1725, 1073; ^1H NMR (C_6D_6, 300 MHz) δ 9.50 (s, 1H), 3.80−3.70 (m, 2H), 3.61 (sextet, $J = 7.9$ Hz, 2H), 3.50−3.40 (m, 7H), 3.18−3.10 (m, 1H), 2.72−2.62 (m, 1H), 2.60−2.52 (m, 1H), 2.49−2.08 (series of m, 5H), 2.05−1.85 (series of m, 4H), 1.61−1.48 (series of m, 4H); ^{13}C NMR (C_6D_6, 125 MHz) δ 192.5, 172.6, 94.6, 94.2, 93.3, 92.9, 69.8, 69.6 66.8, 66.6, 51.5, 32.0, 30.7, 30.6, 27.1, 26.8, 26.7, 26.6, 26.5; ES HRMS *m/z* ($M + Na^+$) calcd 391.1733, obsd 391.1742.

Penta(THF) Ethers 47 and 48. The Normant reagent (0.66 mL, 0.40 M) was added to a cooled (0 °C) solution of **46** (97 mg, 0.25 mmol) in THF (2 mL) and stirred for 1 h. The mixture was quenched with 5% HCl solution, extracted with CH_2Cl_2 (3×), dried, and concentrated by rotary evaporation. After removal of excess

solvent at high vacuum overnight, the crude diol was taken up in CH_2Cl_2 (5 mL) under N_2. Triethylamine (0.11 mL, 0.76 mmol) and DMAP (10 mg) were added to the solution and cooled to 0 °C. *p*-Toluenesulfonyl chloride (72 mg, 0.38 mmol) was introduced, and the mixture was allowed to stir at rt for 2 d. The reaction mixture was washed with 5% HCl, water, and brine and then dried. Filtration and solvent removal gave an oil that was chromatographed on silica gel with 25% EtOAc in hexanes to afford 62 mg (60%) of **47** and 20 mg (20%) of **48**.

For **47**: (IR neat, cm^{-1}) 2950, 2880, 1725; ^1H NMR (C_6D_6, 500 MHz, 60 °C) δ 3.94 (dd, J = 6.0, 8.6 Hz, 1H), 3.89−3.82 (m, 1H), 3.76 (quintet, J = 7.3 Hz, 2H), 3.75−3.65 (m, 4H), 3.59−3.53 (m, 2H), 3.47 (s, 3H), 3.47−3.40 (m, 1H), 3.39−3.30 (m, 1H), 2.61 (t, J = 7.3 Hz, 1H), 2.55−2.45 (m, 3H), 2.36−2.28 (m, 3H), 2.22−2.10 (m, 2H), 2.01−1.67 (series of m, 8H), 1.66−1.59 (m, 2H); ^{13}C NMR (C_6D_6, 125 MHz, 60 °C) δ 171.2, 95.8, 95.1, 94.0, 93.8, 83.6, 70.3, 68.7, 68.5, 67.0, 66.6, 50.9, 32.9, 30.8, 30.2, 28.3, 28.2, 28.0, 27.7, 27.3, 27.0, 26.6; ES HRMS m/z ($M + Na^+$) calcd 433.2202, obsd 433.2195.

For **48**: (IR neat, cm^{-1}) 2951, 2875, 1732, 1065; ^1H NMR (C_6D_6, 500 MHz, 60 °C) δ 4.27 (t, J = 7.1 Hz, 1H), 4.01−3.94 (m, 2H), 3.89−3.75 (series of m, 6H), 3.67−3.61 (m, 2H), 3.52 (s, 3H), 3.30−3.20 (br m, 1H), 3.14−3.08 (br m, 1H), 3.02−2.90 (br m, 1H), 2.34−2.23 (m, 2H), 2.02−1.49 (series of m, 15 H); ^{13}C NMR (C_6D_6, 125 MHz, 60 °C) δ 173.9, 100.6, 98.1, 92.7, 91.6, 82.8, 70.0, 69.6, 69.5, 68.4, 68.3, 51.0, 33.9, 32.5, 32.4, 29.8, 28.1, 28.0, 27.9, 27.6, 26.1, 25.2; ES HRMS m/z ($M + Na^+$) calcd 433.2202, obsd 433.2205.

Hexa(THF) Ethers 51 and 52. $LiAlH_4$ (36 mg, 0.95 mmol) was added to ester **47** (130 mg, 0.32 mmol) in Et_2O (5 mL) and stirred for 1 h. Solid $Na_2SO_4 \cdot 10H_2O$ was added, the mixture was filtered, and the filtrate was concentrated by rotary evaporation. The crude alcohol was then taken up in DMSO (5 mL) followed by the addition of IBX (62.5 mg, 0.80 mmol). After 4 h, H_2O and CH_2Cl_2 were added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phases were dried and concentrated *in vacuo*. The resulting oil was chromatographed on silica gel with 10% EtOAc in hexanes to afford 85 mg (70%) of **49** as a oil. The material was taken on directly into the next steps.

The Normant reagent (1.28 mL, 0.35 M) was added to a cooled (0 °C) solution of **49** (85 mg, 0.22 mmol) in THF (10 mL) via syringe and stirred for 1 h. The mixture was quenched with 5% HCl solution, extracted with CH_2Cl_2 (3×), dried, and concentrated by rotary evaporation. After removal of excess solvent by high vacuum overnight, the crude diol was taken up in CH_2Cl_2 (10 mL) under N_2. Triethylamine (0.12 mL, 0.88 mmol) and dimethylaminopyridine (10 mg) were added to the solution and cooled to 0 °C. *p*-Toluenesulfonyl chloride (63 mg, 0.33 mmol) was introduced and the mixture allowed to stir at rt for 3 d. The reaction mixture was washed with 10% HCl solution, and the separated aqueous phase was extracted with CH_2Cl_2 (3×) prior to drying and filtration. Solvent removal provided an oil which was chromatographed on silica gel with 20% EtOAc in hexanes to give 70 mg (75%) of **51** and 15 mg (16%) of **52**.

For **51**: white solid, mp 194−195 °C; (IR neat, cm^{-1}) 2954, 2870, 1062; ^1H NMR (C_6D_6, 300 MHz) δ 5.29−5.23 (m, 1H), 4.34−4.26 (m, 2H), 4.02 (q, J = 8.5 Hz, 1H), 3.95−3.60 (series of m, 10H), 3.39−3.30 (m, 1H), 3.22−3.09 (m, 2H), 2.33−2.29 (m, 1H), 2.06−1.49 (series of m, 20H); ^{13}C NMR (C_6D_6, 75 MHz) δ 100.1, 99.0, 94.3, 92.8, 86.2, 82.6, 70.1, 69.9, 69.8, 69.7, 68.2, 67.3, 34.2, 33.5, 30.4, 30.2, 29.5, 28.2, 28.1, 27.8, 27.7, 27.2, 26.8, 26.1; ES HRMS m/z ($M + Na)^+$ calcd 445.2566, obsd 445.2565.

For 52: white solid, mp: 162−164 °C; (IR neat cm^{-1}) 2954, 2868, 1060; ^1H NMR (C_6D_6, 500 MHz, 70 °C) δ 4.79−4.64 (m, 1H), 4.33 (t, J = 6.7 Hz, 1H), 4.05−3.97 (m, 1H), 3.91 (q, J = 7.3 Hz, 1H), 3.87−3.66 (series of m, 8H), 3.64−3.60 (m, 1H), 3.55 (q, J = 7.8 Hz, 1H), 2.79−2.68 (m, 2H), 2.55−2.30 (series of m, 2H), 2.23−2.19 (m, 1H), 2.05−1.64 (series of m, 19 H); ^{13}C NMR (C_6D_6, 125 MHz, 70 °C) δ 99.9, 99.8, 94.3, 93.7, 84.6, 83.0, 70.0, 69.6, 69.3, 69.0, 67.9, 67.2, 32.9, 32.8, 32.5, 31.5, 28.9, 28.4, 28.2, 28.0, 27.9, 27.5, 27.3, 26.3; ES HRMS m/z ($M + Na)^+$ calcd 445.2566, obsd 445.2588.

Hexa(THF) Ethers 52 and 53. $LiAlH_4$ (16 mg, 0.43 mmol) was added to ester **48** (70 mg, 0.17 mmol) in Et_2O (7 mL) and stirred for 0.5 h. Solid $Na_2SO_4 \cdot 10H_2O$ was added, the mixture was filtered, and the filtrate was concentrated by rotary evaporation. The crude alcohol was then taken up in DMSO (2.5 mL) followed by treatment with IBX (119 mg, 0.43 mmol). After overnight stirring, the solvent was removed *in vacuo*. The resulting oil was chromatographed on silica gel with 10% EtOAc in hexanes to afford 55 mg (85%) of **50** as a solid. This material was taken on directly into the next steps.

The Normant reagent (0.72 mL, 0.40 M) was added to a cooled (0 °C) solution of **50** (55 mg, 0.14 mmol) in THF (4 mL) and stirred for 1 h. The mixture was quenched with 5% HCl, extracted with CH_2Cl_2 (3×), dried, and concentrated by rotary evaporation. After column chromatography on silica gel with 50% EtOAc in hexanes containing 10% MeOH, the diol was obtained as an oil. This diol was taken up in CH_2Cl_2 (3 mL) and kept under N_2. Triethylamine (60 μL, 0.44 mmol) and DMAP (5 mg) were added to the solution and cooled to 0 °C prior to the introduction of *p*-toluenesufonyl chloride (36 mg, 0.19 mmol). After being stirred at rt overnight, the reaction mixture was washed with 10% HCl, and the separated aqueous phase was extracted with CH_2Cl_2 (3×) prior to drying. Solvent removal afforded an oil which was chromatographed on silica gel with 20% Et_2O in CH_2Cl_2 to provide 6 mg (10%) of **53** and 36 mg (59%) of **52**, respectively.

For **53**: white solid, mp 105−106 °C; (IR neat, cm^{-1}) 2972, 2865, 1056; ^1H NMR (C_6D_6, 500 MHz, 70 °C) δ 4.10−4.03 (m, 2H), 3.86−3.79 (m, 2H), 3.71−3.78 (m, 4H), 3.68 (q, J = 6.8 Hz, 2H), 3.61 (q, J = 7.8 Hz, 2H), 3.54 (q, J = 7.5 Hz, 2H), 2.49 (ddd, J = 3.2, 9.4, 12.4 Hz, 2H), 2.22−1.96 (series of m, 10H), 1.95−1.55 (series of m, 12H); ^{13}C NMR (C_6D_6, 125 MHz, 70 °C) δ 97.5, 95.2, 84.1, 69.1, 69.0, 67.0, 33.6, 27.8, 27.6, 27.3; ES HRMS m/z ($M + Na)^+$ calcd 445.2566, obsd 445.2579.

Electrospray Ionization-Mass Spectrometry. The alkali metal binding selectivity of each hexa(THF) compound was assessed by electrospray ionization mass spectrometry (ESI-MS). Solutions of each compound at the concentration of 10 μM were prepared in methanol, and 100 μM LiCl, NaCl, and KCl were added to each solution. The high concentration of metal salts was necessary to minimize the contribution from environmental sodium. The analyte solutions were directly infused into a ThermoFinnigan LCQ Duo quadrupole ion trap mass spectrometer (San Jose, CA) at a flow rate of 5 μL/min. Positive mode ionization was employed, using an ESI voltage of +5 V and a heated capillary temperature of 150 °C. All other parameters were optimized each day for highest signal intensity. The selectivity of each hexamer for Li, Na, and K was calculated by summing the abundances of all ions containing a particular metal and dividing by the total abundance of all ions in the spectrum. Ions containing more than one hexa(THF) molecule were weighted accordingly. All 12 diastereomers were assessed on the same day under identical tuning conditions, and replicate experiments were performed on different days.

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Supporting Information Available: High-field $^1H/^{13}C$ NMR spectra for all new compounds in addition to X-ray crystallographic details for hexamers **23**, **38**, **39**, **40**, **51**, **52**, and **53**. This material is available free of charge via the Internet at http://pubs.acs.org.

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