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Synthesis of, and Structural Assignments to the Stereoisomers of Bis (2,2′)- and Tris (2,2′,2″)-Tetrahydrofurans: Conformational Features and Ionic Binding Capacities of These Gateway Polycyclic Networks

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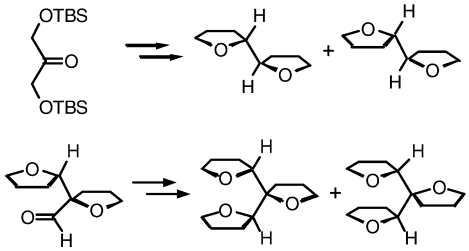

Construction of the polytetrahydrofuranyl building blocks **6**−**10** from the common bissiloxyacetone precursor **11** is detailed. The approach is concise and, for the bis-(THF) pair, capitalizes on the full retention of configuration observed during the rhodium-promoted decarbonylation of aldehydes **18** and **19**. The capability of the title compounds to associate with alkali metal ions in solution and the gas phase has demonstrated a preference for Li^+ over Na^+ and K^+ in all cases, with **6** and **7** exhibiting somewhat higher binding selectivities than **8**−**10**. The relative energy orderings of attainable conformations with the bis-THF and tris-THF series were explored computationally. The various envelope arrangements present in the individual THF units are shown to play a significant role alongside prevailing gauche interactions. The "gauche effect" is shown computationally not to be an accurate predictor of the lowest energy conformer.

In more advanced studies of conformational analysis, a key point of investigation involves molecules in which unshared electron pairs and/or polar bonds are linked to adjacent carbons.[1−5] Although several small, electronegative groups (e.g., CN, OCH_3, F) share in the unusual consequences of their vicinal arrangement, the greatest level of attention has been accorded to ethers because of their unique ligating features[6] and chemical

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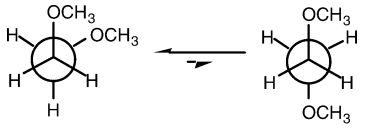
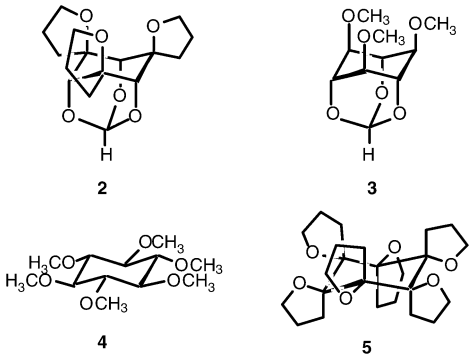
relevance.[7] Thus, 1,2-dimethoxyethane (**1**) is well recognized to adopt a gauche rather than a perfectly staggered spatial arrangement.[8] Polyoxyethylene, $(OCH_2CH_2)_n$, exhibits the same energetic bias and, as a consequence, assumes an overall helical conformation.[9] Such compounds provide a logical starting point for the development of a class of open-chain molecules having defined spatial arrangements.



1 *gauche* **1** *anti*

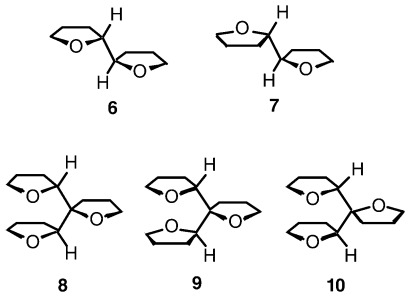
The progression from an acyclic ether to one cyclic in nature (e.g., diethyl ether to tetrahydrofuran) has profound consequences. For example, miscibility with water and intrinsic basicity differ strikingly, with the ring compound exhibiting greater hydrogen-bonding capability[10] and enhanced gas-phase proton affinity.[11] Faster rates of proton attachment in solution also fit this pattern.[12] Such factors are recognized to offer contrasting properties, although this need not necessarily be the case. Two illustrative examples follow. Whereas **2** is an impressively selective ligand for lithium ions, **3** is not at all conducive to binding to any alkali metal ion in solution.[13] On the other hand, both the hexamethyl ether of *scyllo*-inositol (**4**)[14] and *all-trans*-hexaspiro(THF)cyclohexane (**5**)[15,16] display a strong inherent preference for adoption of the all-equatorial oxido conformer. This overwhelming predilection for equatorial *O*-alkyl occupancy interesting for theoretical reasons and has been examined computationally.[17,18]

In light of these developments, it is striking that the properties of *threo*-(**6**) and *erythro*-bis(2,2′)-tetrahydrofuran (**7**) have not



2 **3** **4** **5**

yet been fully documented. This fact is in large part attributable to the absence until recently of a synthetic route amenable to unambiguously distinguishing the two diastereomers from each other.[19] An enantioselective synthesis of **7** was disclosed in 2004.[20] Because the **6**/**7** isomer pair as well as the three tris(THF) homologues **8**, **9**, and **10** constitute an important subset of reference compounds, we have pursued the development of



6 **7** **8** **9** **10**

a scheme capable of delivering in unequivocal fashion, pure samples of each member in preparative amounts.[21] This full complement of short-chain polytetrahydrofuranyl networks has come to be regarded as gateway molecules central to our fuller appreciation of the prospects anticipated for longer-chain polyether entities. All segments can partake of conformational flexibility. Rotation about the interconnective C−C bonds is, of course, an energetically inexpensive way to relieve intramolecular conformational effects.

The Synthetic Route. Our comprehensive synthetic pathway was founded on the initial assembly of a pair of perhydrogenated

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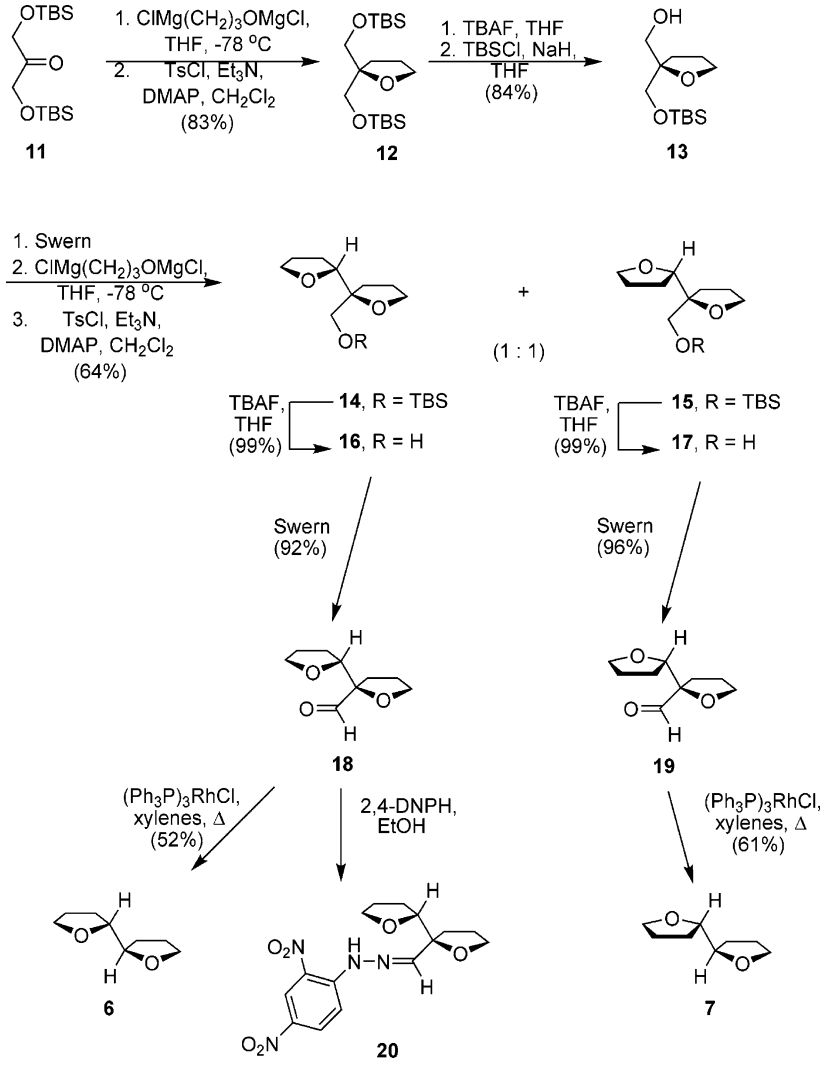
SCHEME 1



(2,2′)bifuranyls monofunctionalized in a manner that would allow simultaneously for the chromatographic separation of diastereomers and for crystallographic analysis to establish their relative configuration. Further, the reaction channel should be amenable to bifurcation, with one option leading simply and individually to **6** and **7**, and the other functioning as advanced scaffolding for the ultimate production of **8**−**10**. The level of functionality resident in the bissiloxyacetone **11**,[22] in combination with the Normant reagent,[23] proved adequate to address these issues concisely and efficiently.

Admixing of approximately equimolar amounts of these reactants in THF at −78 °C gave the expected 1,4-diol, thereby setting the stage for cyclization to **12** via the monotosylate[24] (Scheme 1). The symmetry inherent in **12** guarantees that it is the sole product of this reaction. To arrive at the monohydroxy derivative **13**, it proved most expedient to proceed via the two-step sequence involving treatment with excess TBAF in THF, followed by monosilylation. Clean conversion of **13** to the aldehyde by way of the Swern protocol laid the foundation for second-stage annulation. The absence of stereoselectivity, revealed in the 1:1 distribution of **14** and **15**, parallels the response customarily observed for the 1,2-addition of Grignard reagents to highly substituted aldehydes and offered no surprises. In fact, the absence of discernible chelation control was counted on to provide us with the maximum level of both products for more advanced synthetic applications. Of equivalent significance was the finding that **14** could be readily separated from **15** by chromatography on silica gel. The independent desilylation of **14** and **15** gave isomerically pure samples of alcohols **16** and **17**. From this point, the aldehydes **18** and **19** were made available by Swern oxidation. These carbonyl-functionalized intermediates were to play several important synthetic roles. Prior to this, it was mandatory that their relative configurations be unequivocally established. This objective was realized by the derivatization of **18** as its 2,4-dinitrophenylhydrazone **20** and X-ray crystallographic analysis of the latter. In this way, the detailed structures of both **18** and **19** were made known.

The elucidation of these details provided us with the insight needed to undertake the decarbonylation of these aldehydes.

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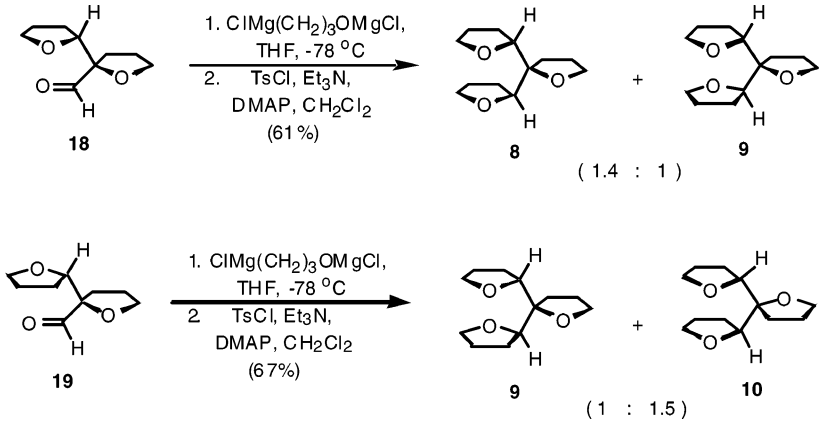
SCHEME 2



Walborsky and Allen reported in 1971 that optically active aldehydes bearing an adjacent stereogenic center are decarbonylated with retention of configuration in the presence of Wilkinson's catalyst.[26] This stereochemical outcome was realized irrespective of the particular hybridization of the carbon atom to which the carbonyl group is bonded. In the case of **18**, heating with $(Ph_3P)_3RhCl$ in xylene at 160 °C for 6 h gave rise to **6** in 52% yield. The analogous treatment of **19** provided **7** as the exclusive product (61% isolated). Although the ^{1}H NMR spectra of **6** and **7** hold many similarities, their ^{13}C NMR spectra are sufficiently distinctive to allow stereochemical assignment on this basis.

The processing of **18** through a third-stage annulation afforded two tris(THF) stereoisomers, which proved readily amenable to chromatographic separation on silica gel. The structural assignments to these products awaited the comparable chemical modification of **19** (Scheme 2). Once this was accomplished, it was made clear that the minor product (1.4:1) of the first reaction sequence was chemically identical to the minor product (1:1.5) of the second. Since the only common isomer can be **9**, the stereochemical features of all three isomers are made unequivocally apparent.[27]

Solution-Phase Complexation Studies. The three tris-(2,2′,2″)-tetrahydrofuran isomers were subjected to picrate extraction involving water/chloroform mixtures according to the procedure laid out by Cram and co-workers.[28] The objective was to determine to what degree alkali metal binding would occur through the coordination of picrate salts by these potentially specific host molecules. ^{13}C NMR titrations involving the syn/syn isomer **8** and its anti/anti counterpart **10** with lithium perchlorate in 1:1 CH_3CN:$CDCl_3$ proved inconclusive.[29] On this basis, high levels of binding were not anticipated. As seen in Table 1, alkali metal ions are in fact not particularly well accommodated. As expected, a general trend can be noted wherein higher K_a values are seen for all isomers with the lithium cation. The lowest values are associated with the larger potassium ion. While the data for the two symmetric tris-(THF) isomers are closely comparable, the asymmetric **9** exhibits 1.5 times the K_a value for all three metal ions.

TABLE 1. Association Constants (K_a) Determined by Picrate Extraction from $CHCl_3$

ligand	Li^+	Na^+	K^+
15-crown-5[a]	9.4×10^4	6.3×10^6	1.1×10^6
syn/anti **8**	2.9×10^4	1.6×10^4	1.3×10^4
syn/anti **9**	4.3×10^4	2.7×10^4	1.7×10^4
syn/anti **10**	2.7×10^4	1.9×10^4	1.2×10^4

[a] For calibration purposes; see Paquette, L. A.; Tae, J.; Hickey, E. R.; Rogers, R. D. *Angew. Chem. Int. Ed.* **1999**, *38*, 1409.

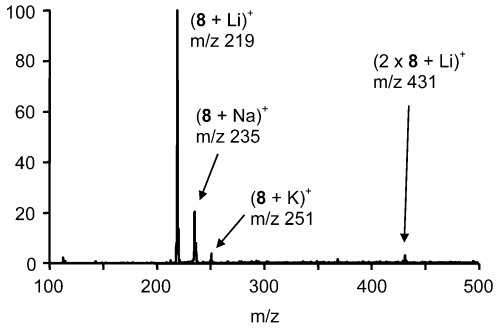


FIGURE 1. Positive ion mode MS spectrum of a solution containing ligand **8** (10 μM) and LiCl, NaCl, and KCl (100 μM each).

Electrospray Ionization−Mass Spectrometry Measurements. Electrospray ionization mass spectrometry (ESI−MS) was used to evaluate the alkali metal ion selectivities of the ligands.[30] A typical mass spectrum obtained upon electrospray ionization of one of the ligands in methanol in the presence of excess alkali metals is shown in Figure 1. A summary of the metal selectivities, in terms of the distribution of lithium, sodium, and potassium complexes obtained from the abundances of complexes in the ESI−mass spectra for each ligand, is shown in Table 2. For all of the ligands, the lithium-cationized complexes had the greatest abundances, and the abundances of

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(27) The title compounds have been universally depicted with 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 (see the sequel). 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.

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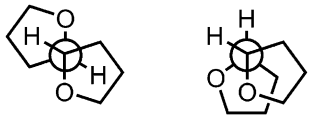
TABLE 2. ESI−MS Metal Ion Selectivities of Bis- and Tris-(THF) Ligands[a]

ligand	Li (%)	Na (%)	K (%)
6	94	6	<1
7	96	4	<1
8	81	16	3
9	87	11	2
10	77	20	3

[a] Percentage of Li, Na, and K complexes obtained from the ESI−mass spectrum of solutions containing one ligand and a mixture of all three alkali metals in methanol.

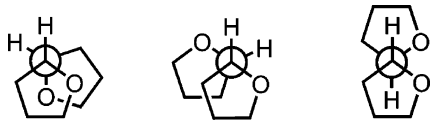
TABLE 3. *Meso* Conformers and Calculated Energies



A **B**

RHF/6-31G(d)	0−0.5	2.1−2.5 kcal/mol
B3LYP/6-31G*	0.00	0.9 kcal/mol
B3LYP/6-31+G**	0.00	1.5 kcal/mol

TABLE 4. *Rac* Conformers and Calculated Energies

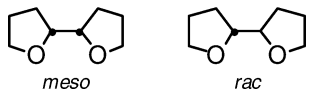


C **D** **E**

RHF/6-31G(d)	0−0.3	1.5−1.7	2.4 kcal/mol
B3LYP/6-31G*	0.00	2.0	2.6 kcal/mol
B3LYP/6-31+G**	0.00	1.5	2.5 kcal/mol

the potassium complexes were very low. The differences in lithium versus sodium selectivity within each series of bicyclic or tricyclic ligands were not deemed significant based on the precision of the measurements. The ESI−MS method affords a rapid way to screen the metal selectivities of these ligands and reveals that all favor complexation with lithium over the larger alkali metals, thus mirroring the trend obtained from the picrate extraction results.

Conformational Analysis of the Bis-Tetrahydrofurans. Conformers of the *meso* and *rac* diastereomers of 2,2′-bis-tetrahydrofurans (−THF's) were first explored by a Monte Carlo conformational search using the MMFF94 force field in Macromodel.



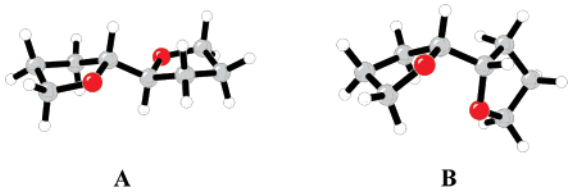
meso *rac*

The resulting 16 lowest energy conformers were then reoptimized by RHF/6-31G(d) calculations, which maintain the same relative energy order but reduce the energy differences. The lowest energy conformers of the *meso* and *rac* diastereomers were also reoptimized by B3LYP/6-31G* and B3LYP/6-31+G**. Their designations and relative conformational preferences are given in Tables 3 and 4, and their energies are listed in Table 5.

For the *meso* diastereomer, there are two families of unique low energy conformers. The family of conformers, **A**, containing an anti OCCO, an anti CCCC, and two gauche OCCC interactions, is the lowest in energy and differs within the family only by the specific envelope conformations of the THF rings. The second family of conformers, **B**, containing a gauche OCCO, a gauche CCCC, a gauche OCCC, and an anti OCCC interaction, is higher in energy by each type of calculation. The lowest energy conformers of **A** and **B** are shown in Figure 2.

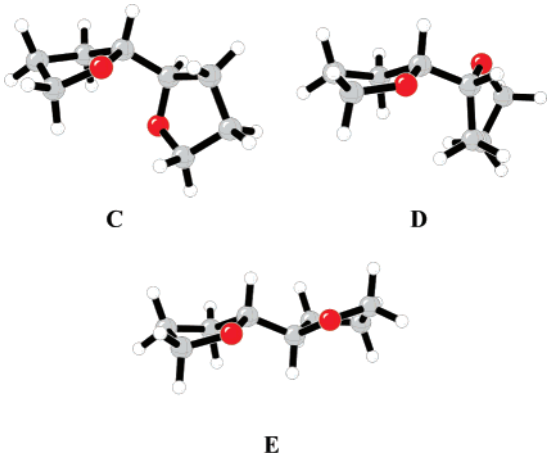
TABLE 5. Relative RHF/6-31G(d) Energies of Lowest Energy Conformers of bis-THF

Meso conformer	E+ZPE (kcal/mol)	*Rac* conformer	E+ZPE (kcal/mol)
A	0	**C**	0
	0.2		0.2
	0.5		0.3
B	2.1	**D**	1.5
	2.1		1.6
	2.5		1.7
	2.5	**E**	2.4
			2.4
			2.4



A **B**

FIGURE 2. B3LYP/6-31+G** optimized structures of lowest energy conformers of **A** and **B**.



C **D** **E**

FIGURE 3. B3LYP/6-31+G** optimized structures of lowest energy conformers of **C**, **D**, and **E**.

For the *rac* diastereomer, there are three families of low energy conformers. The lowest energy family, **C**, contains a gauche OCCO, an anti CCCC, and two gauche OCCC interactions; the intermediate energy family, **D**, contains an anti OCCO, a gauche CCCC, and two gauche OCCC interactions; and the highest energy family, **E**, contains a gauche OCCO and gauche CCCC interactions. Again, each energy family differs in the conformations about the THF cycles. Each basis set and method applied give the same relative trend in energies. The lowest energy conformers of **C**, **D**, and **E** are shown in Figure 3.

Given the energetic preference for electronegative atoms to be gauche rather than anti, generally known as the gauche effect,[31] the anti OCCO conformations are expected to be

(31) Wolfe, S. *Accounts Chem. Res.* **1972**, *5*, 102.

relatively less stable than the gauche. However, the anti OCCO conformer is the minimum in the *meso* and of intermediate energy in the *rac* diastereomer, respectively.

We explored whether additive effects of conformational preferences in acyclic molecules could explain the relative conformational preference of these polar acyclic molecules, similar to the additivity[32] used in the conformational analysis of hydrocarbon acyclic systems. The three types of gauche interactions that can occur between vicinal groups, involving OCCO, OCCC, and CCCC dihedral angles, were analyzed to determine if the relative preferences of these would explain the conformational preference of each diastereomer. The simple component, 1,2-dimethoxyethane, was chosen as a model system to establish the OCCO preference, 1-propanol for the OCCC preference, and *n*-butane for the CCCC preference.

The origin of the gauche preference in 1,2-dihydroxyethane has been the subject of much debate in recent years. A number of theoretical[33] and experimental[34] studies have been conducted to elucidate the nature of the gauche effect in 1,2-dihydroxyethane (ethylene glycol), some citing the possibility of intramolecular H-bonding adding to the preference due to stereoelectronic effects. In all studies, the three dihedral angles making up the molecular backbone are important in determining the conformational preference. For three single bonds, there are 27 possible conformers of which 10 are unique. The dihedral angles are designated as g^+, t, and g^-, respectively, for gauche clockwise, anti, and gauche counterclockwise torsions about C−O, and G^+, T, and G^- for torsions about C−C. Thus, the all anti conformer would be designated tTt. Whereas the gauche C−C conformations of 1,2-dihydroxyethane predominate over the anti conformations, the reverse is true of 1,2-dimethoxyethane; the tTt conformer is the global minimum, 0.5 kcal/mol lower than the tGt and tGg^- conformers.[35] A 0.5 kcal/mol preference for anti OCCO over gauche OCCO was adopted as the reference.

The simple four atom backbone molecules, 1-propanol and butane, were used as models for the other vicinal interactions across the THF linkage. The gauche conformer of 1-propanol is known[36] to be preferred by 0.4 kcal/mol over the anti conformer; therefore, a 0.4 kcal/mol preference was adopted for gauche OCCC over anti OCCC. The well-known[32] 0.9 kcal/mol preference of anti butane over gauche butane was used.

For the *meso* diastereomer, the standard values described in the previous paragraph predict a 1.8 kcal/mol difference between the two diastereomers, whereas the full B3LYP/6-31+G** computations predict a difference of 1.5 kcal/mol. For the *rac* diastereomer, the standard values predict relative B3LYP/6-31+G** energies of 0, 0.4, and 1.7 kcal/mol versus the computed values of 0, 1.5, and 2.5 kcal/mol. Although the order is correct, the quantitative values deviate substantially.

The conformational preference of OCCO torsions is very sensitive to the torsions about the peripheral O−C bonds.[33] In the 2,2′-bis-THF diastereomers, the five-membered ring holds the COCC moiety in nearly an eclipsing conformation, whereas the standard values are appropriate for staggered conformations. Consequently, energies of the (C)OCCO(C) conformers when the CCO(C) is eclipsed were studied. The torsional angles about the COCC, OCCO, and CCOC bonds from the optimized structures of the 2,2′-bis-THF's were determined; subsequently, 1,2-dimethoxyethane with its dihedrals locked in the same angles was optimized with B3LYP/6-31G*. The same analysis was performed on *n*-hexane to determine how conformational constraint to a geometry appropriate for 2,2′-bis-THF's better influences the standard values. These results are summarized in Table 6, where e^- and e^+ refer to eclipsing counterclockwise and eclipsing clockwise, respectively.

In the 1,2-dimethoxyethane model, both anti OCCO conformations are lower in energy than the gauche OCCO conformations; however, the two anti conformers differ by 0.7 kcal/mol, and the three gauche conformations range across 1.7 kcal/mol in energy. This effect is even more pronounced in the case of hexane, where the global minimum has a CCCC anti conformation, as expected, but another anti arrangement, **C**, is 1.4 kcal/mol higher in energy.

These larger deviations from standard acyclic conformational preferences arise from steric and electronic interaction of the terminal methyls and oxygen lone pairs. These interactions are also important in cyclic systems where vicinal groups are constrained.

Regardless of the exact energetic differences, it is clear that *meso* conformer **B** is higher in energy than conformer **A** due mainly to the unfavorable gauche CCCC interaction across the central linkage; the gauche OCCO conformation is also unfavorable. For the *rac*-isomer, conformer **D** experiences mainly destabilizing gauche CCCC interactions, while conformer **E** has gauche CCCC and rather severe gauche OCCO repulsions since the lone pairs are aimed at each other.

Conformational Evaluation of the Tris-Tetrahydrofurans. Conformations of the tris-THF's were explored in a similar fashion. There are two diastereoisomers, having up to 21 conformers within 3 kcal/mol of the lowest energy conformation at the RHF/6-31G(d) level. The lowest energy conformers from RHF/6-31G(d) optimizations are shown in Figure 4 for each of the two diastereomers (RR or SS (the center carbon is not a stereogenic center), and RRS or SSR). The many different conformers with slightly different energies vary in the envelope conformations of the individual THF units.

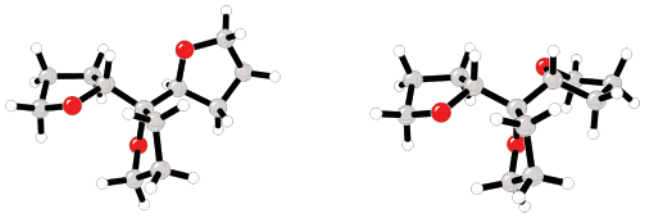


FIGURE 4. RHF/6-31G(d) optimized structures of lowest energy conformers **F** and **G**.

Summary. Synthetic protocols that allow unequivocal access to the bis- and tris-tetrahydrofurans **6**−**10** have been successfully devised. All issues surrounding the individual assignment of configuration to this group of polycyclic ethers have been fully clarified. The ability of **6**−**10** to complex to alkali metal ions was evaluated in solution as well as in the gas phase. In

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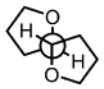
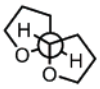
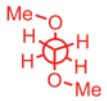
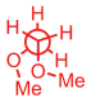
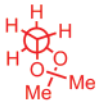
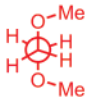
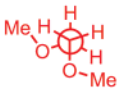
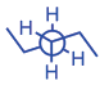
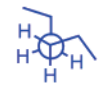
TABLE 6. Acyclic Conformational Analysis Based on 1,2-dimethoxyethane (red) and *n*-hexane (blue) Constrained Across Three Dihedral Angles (degrees) as Determined by the *Meso* and *Rac* Conformers

	A	B	C	D	E
Meso and rac structures					
ΦCOCC [1]	-140	-111	-122	-143	-136
ΦOCCO [2]	180	70	65	-173	-64
ΦCCOC [1]	138	140	-122	-148	-136
ΦCCCC [1]	-151	-154	143	113	152
ΦCCCC [2]	180	69	-175	-52	59
ΦCCCC [1]	151	132	143	156	152
1,2-dimethoxy-ethane acyclic model system					
E (kcal/mol) [3] B3LYP/6-31G*	0.7	1.0	0.7	0	2.4
n-hexane acyclic model system					
E (kcal/mol) [3] B3LYP/6-31G*	0	1.7	1.4	2.8	0.5

[1] Optimized dihedral angle along the periphery of the central bond. [2] Optimized dihedral angle along the central bond. [3] Energies optimized with the shown dihedral angles restricted.

particular, ESI−MS has allowed the rapid assessment of relative alkali metal binding selectivities involving these fascinating structural networks. All five polycyclic tetrahydrofurans prefer to associate with lithium ions over sodium and potassium, and the two bis isomers exhibit slightly higher selectivities for lithium than the three tris isomers. Conformational searches with force field methods and optimizations with HF or B3LYP indicate that these molecules have a large number of readily accessible conformations, both with respect to the conformations of individual tetrahydrofuran rings and with respect to rotation about the CC bonds connecting these rings. Preferred geometries are explained by a combination of steric and electronic effects.

Experimental Section

2,2-Bis(*tert*-butyldimethylsiloxymethyl)tetrahydrofuran (12). A cold (−78 °C) solution of **11** (5.85 g, 18.4 mmol) in dry THF (100 mL) was treated dropwise with the Normant reagent (55.0 mL of 0.4 M in THF, 22 mmol), stirred at low temperature for 1 h, quenched with saturated NH_4Cl solution, and allowed to warm to room temperature. After dilution with CH_2Cl_2, the aqueous phase was separated and extracted with CH_2Cl_2 (3×). The combined organic solutions were dried and evaporated. The residue was chromatographed on silica gel (elution with 35% ethyl acetate in hexanes) to afford the diol as a colorless oil (6.1 g, 86%).

The above diol was taken up in CH_2Cl_2 (250 mL), admixed with triethylamine (6.6 mL, 47 mmol) and DMAP (50 mg), and cooled to 0 °C. After the addition of tosyl chloride (1.72 g, 9.0 mmol), the reaction mixture was stirred at rt for 2 days and quenched with saturated NH_4Cl solution. The separated aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic phases were dried and evaporated. The residue was chromatographed on silica gel (elution with 10% ethyl acetate in hexanes) to afford 3.0 g of **12** along with 3.8 g of the tosylate intermediate. The latter was dissolved in benzene (100 mL), treated with KHMDS in toluene (18 mL of 0.5 M, 9.0 mmol) at 0 °C, stirred for 1 h, and worked up in the predescribed manner. There was isolated an additional 2.5 g of **12** (total yield 83%) as a colorless oil; IR (neat, cm^{-1}) 1471, 1255, 1096; ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 (t, $J = 6.5$ Hz, 2H), 3.56 (d, $J = 10.0$ Hz, 2H); 3.46 (d, $J = 10.0$ Hz, 2H), 1.89−1.73 (m, 4H), 0.88 (s, 18H), 0.04 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.5, 68.7, 65.5, 29.3, 26.1, 25.9, 18.3, −5.4; ES HRMS *m*/*z* $(M + Na)^+$ calcd 383.2414, obsd 383.2408.

2-(*tert*-Butyldimethylsiloxymethyl)-2-(hydroxymethyl)tetrahydrofuran (13). A solution of **12** (5.5 g, 15 mmol) in THF (36 mL) was cooled to 0 °C, treated with TBAF (36.0 mL of 1 M in THF, 36 mmol), and stirred for 2.5 h. After solvent evaporation, the residue was eluted through silica gel (50% ethyl acetate in hexanes) to deliver 1.95 g (97%) of the diol. This material (0.63 g, 4.5 mmol) was redissolved in THF (10 mL) and added dropwise to a cooled slurry of sodium hydride (0.19 g of 60% in oil, 4.7 mmol) in THF (25 mL). After 30 min, the reaction mixture was allowed to warm to rt prior to the addition of a solution of *tert*-butyldimethysilyl chloride (0.71 g, 4.9 mmol) in THF (5 mL). After 3 h, saturated $NaHCO_3$ solution and ether were introduced, and the separated aqueous phase was extracted with ether (3×). The combined organic phases were dried and evaporated, and the residue was chromato-

graphed on silica gel. Elution with 20% ethyl acetate in hexanes furnished 0.94 g (84% over two steps) of **13** as a colorless oil; IR (neat, cm^{-1}) 3432, 1254, 1091; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (t, J = 6.0 Hz, 2H), 3.62−3.40 (m, 4H), 2.26 (s, 1H), 1.97−1.71 (m, 4H), 0.88 (s, 9H), 0.46 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.8, 68.7, 66.2, 66.1, 29.9, 26.1, 25.8, 18.2, −5.5; ES HRMS m/z $(M + Na)^+$ calcd 269.1549, obsd 269.1544.

Oxidation and Spiroannulation of 13. A solution of oxalyl chloride (0.72 mL, 8.3 mmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C and treated slowly with a solution of DMSO (1.2 mL, 16 mmol) in the same medium (5 mL). After 15 min, **13** (1.35 g, 5.5 mmol) dissolved in CH_2Cl_2 (10 mL) was introduced via syringe. Following 30 min, the reaction mixture was charged with triethylamine (4.6 mL, 33 mmol), stirred for 1 h, warmed to rt, and diluted with water. The separated aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic phases were dried and evaporated to leave a residue that was chromatographed on silica gel. Elution with 10% ethyl acetate in hexanes afford 1.25 g (93%) of the oily aldehyde that was immediately taken up in THF (40 mL), cooled to −78 °C, and treated dropwise with the Normant reagent (19.2 mL of 0.4 M in THF, 7.7 mmol). After 3 h of stirring in the cold, saturated NH_4Cl solution and CH_2Cl_2 were introduced, and the separated aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phases were dried and evaporated to leave an oil that was chromatographed on silica gel (elution with 10% methanol in 50% ethyl acetate/hexanes). There was isolated 1.2 g (77%) of the diol as a colorless oil that was directly taken up in CH_2Cl_2 (130 mL), treated with triethylamine (1.7 mL, 12 mmol) and DMAP (50 mg) prior to cooling to 0 °C and the addition of tosyl chloride (0.90 g, 4.7 mmol). After 48 h of stirring, the reaction mixture was diluted with saturated NH_4Cl solution, the separated aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic layers were dried and concentrated. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 0.51 g of **14** and 0.53 g of **15** (65%) over three steps.

For **14**: IR (neat, cm^{-1}) 1463, 1255, 1083; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95 (t, J = 6.5 Hz, 1H), 3.86−3.72 (m, 4H), 3.53 (d, J = 10.0 Hz, 1H), 3.42 (d, J = 10.0 Hz, 1H), 1.94−1.65, (series of m, 8H), 0.88 (s, 9H), 0.38 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.2, 81.6, 69.2, 68.3, 66.7, 29.7, 26.5, 26.3, 26.2, 25.9, 18.2, −5.5; ES HRMS m/z $(M + Na)^+$ calcd 309.1862, obsd 309.1870.

For **15**: colorless oil; IR (neat, cm^{-1}) 1458, 1253, 1073; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92−3.79 (m, 4H), 3.76−3.68 (m, 1H), 3.61 (d, J = 10.0 Hz, 1H), 3.51 (d, J = 10.0 Hz, 1H), 1.93−1.77 (m, 6H), 1.71−1.60 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.7, 81.9, 69.5, 68.2, 66.5, 28.9, 26.6, 26.2, 26.0, 25.9, 18.2, −5.5; ES HRMS m/z $(M + Na)^+$ calcd 309.1862, obsd 309.1870.

Bicyclic Alcohol 16. A solution of **14** (0.41 g, 1.4 mmol) in THF (10 mL) was treated with tetrabutylammonium fluoride (2.1 mL of 1 M in THF, 2.1 mmol), stirred for 2 h, and concentrated on a rotary evaporator. Chromatography of the residue on silica gel (elution with 50% ethyl acetate in hexanes to 10% methanol in 50% ethyl acetate/hexanes) afforded 240 mg (99%) of **16** as a colorless oil; IR (neat, cm^{-1}) 3436, 1057; ^1H NMR (300 MHz, $CDCl_3$) δ 3.99−3.65 (m, 5H), 3.68 (d, J = 11.2 Hz, 1H), 3.44 (s, 1H), 1.90−1.70 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.8, 82.2, 68.9, 68.3, 66.1, 29.2, 26.6, 26.5, 25.9; ES HRMS m/z $(M + Na)^+$ calcd 195.0997, obsd 195.1005.

Bicyclic Alcohol 17. Desilylation of **15** (0.39 g, 1.4 mmol) dissolved in THF (10 mL) with TBAF (2.1 mL of 1 M in THF) in the predescribed manner afforded **17** (240 mg, 99%) as a colorless oil: IR (neat, cm^{-1}) 3429, 1062; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95−3.67 (series of m, 5H), 3.68 (s, 2H), 2.88 (s, 1H), 1.90−1.54 (series of m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.9, 82.6, 69.0, 68.3, 66.0, 29.4, 26.6, 26.0, 25.6; ES HRMS m/z $(M + Na)^+$ calcd 195.0997, obsd 195.0992.

Bicyclic Aldehyde 18. A solution of oxalyl chloride (0.076 mL, 0.87 mmol) in CH_2Cl_2 (5 mL) was cooled to −78 °C prior to the slow addition of DMSO (0.12 mL, 1.7 mmol). After 15 min, a solution of **16** (100 mg, 0.58 mmol) in CH_2Cl_2 (2 mL) was introduced via syringe. After 1 h of stirring, triethylamine (0.49 mL, 3.5 mmol) was admixed, and the reaction mixture was warmed to rt and diluted with water. Workup in the predescribed manner furnished 98 mg (92%) of **18** as a colorless oil; IR (neat, cm^{-1}), 1729, 1078; ^1H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H), 4.04 (t, J = 7.2 Hz, 1H), 4.00−3.82 (m, 2H), 3.77−3.66 (m, 2H), 2.14−2.05 (m, 1H), 2.00−1.65 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 90.6, 81.5, 69.7, 68.6, 29.6, 26.3, 25.9, 25.8; ES HRMS m/z $(M + Na)^+$ calcd 193.0841, obsd 193.0834.

The 2,4-dinitrophenylhydrazone derivative **20** consisted of yellow needles, mp 163−164 °C; IR (neat, cm^{-1}) 3297, 1614, 1589; ^1H NMR (300 MHz, $CDCl_3$) δ 11.0 (s, 1H), 9.12 (d, J = 2.6 Hz, 1H), 8.32 (dd, J = 2.6, 9.5 Hz, 1H), 7.90 (d, J = 9.5 Hz, 1H), 7.50 (s, 1H), 4.08 (t, J = 6.9 Hz, 1H), 3.95−3.78 (m, 4H), 2.48−2.38 (m, 1H), 2.03−1.72 (series of m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 147.9, 145.1, 130.0, 129.6, 123.4, 116.5, 86.7, 83.2, 70.2, 68.9, 31.0, 27.3, 27.1, 26.0; ES HRMS m/z $(M + Na)^+$ calcd 373.1124, obsd 373.1111.

Bicyclic Aldehyde 19. A 240 mg (1.4 mmol) sample of **17** was oxidized in the manner described above to afford 229 mg (96%) of **19** as a colorless oil; (IR, neat, cm^{-1}) 1732, 1068; ^1H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 4.12 (t, J = 7.0 Hz, 1H), 4.03−3.82 (m, 3H), 3.74 (q, J = 6.0 Hz, 1H), 2.24−2.10 (m, 1H), 1.95−1.65 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 90.7, 81.5, 70.1, 68.9, 29.6, 26.2, 25.7, 25.5; ES HRMS m/z $(M + Na)^+$ calcd 193.0841, obsd 193.0842.

Decarbonylation of 18. The bicyclic aldehyde **18** (50 mg, 0.29 mmol) was dissolved in previously distilled xylenes (1.5 mL) and kept under N_2. Following the addition of Wilkinson's catalyst (270 mg, 0.29 mmol), the suspension was refluxed for 6 h and cooled. The reaction mixture was directly loaded onto a silica plug and eluted with 20% ether in hexanes. After careful evaporation of the solvent without heat, column chromatography (elution with 15% ether in CH_2Cl_2) provided the volatile **6** in 52% yield (21 mg) as a colorless oil; IR (neat, cm^{-1}) 2866, 1033; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91−3.73 (m, 6H), 2.00−1.75 (m, 6H), 1.65−1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.4, 68.4, 28.1, 25.9.

Decarbonylation of 19. The bicyclic aldehyde **19** (49 mg, 0.29 mmol) was dissolved in previously distilled xylenes (1.5 mL) and kept under N_2. Following addition of Wilkinson's catalyst (270 mg, 0.29 mmol), the suspension was refluxed for 6 h and cooled. The reaction mixture was directly loaded onto a silica column and gradient elution from hexanes to 10% ether in hexanes followed by careful solvent evaporation without heat provided the volatile **7** in 61% yield (25 mg) as a colorless oil; IR (neat, cm^{-1}) 2971, 2870, 1067; ^1H NMR (300 MHz, $CDCl_3$) δ 3.90−3.70 (m, 6H), 2.06−1.82 (m, 6H), 1.75−1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 81.0, 68.5, 28.2, 25.7.

Annulation of 18. Aldehyde **18** (85 mg, 0.50 mmol) was suspended in THF (5 mL) at −78 °C, stirred in the presence of the Normant reagent (1.9 mL of 0.4 M in THF, 2.7 mmol) for 3 h, quenched with 5% HCl, and diluted with CH_2Cl_2. The separated aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic solutions were dried and evaporated prior to being redissolved in CH_2Cl_2 (10 mL), charged sequentially at 0 °C with triethylamine (0.6 mL, 1.2 mmol), DMAP (25 mg), and tosyl chloride (90 mg, 0.47 mmol), and stirred overnight. Another 30 mg of tosyl chloride was added, and after another 24 h, the predescribed workup was applied. There was isolated 35 mg of **8** and 25 mg of **9** (61% over two steps) following chromatographic separation on silica gel (elution with 10% ethyl acetate in hexanes).

For **8**: colorless oil; IR (neat, cm^{-1}) 2975, 1071; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (t, J = 7.8 Hz, 2H), 3.82−3.66 (m, 6H), 1.95−1.72 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.1, 82.7, 69.5, 68.3, 28.9, 27.0, 26.5, 26.1; ES HRMS m/z $(M + Na)^+$ calcd 235.1310, obsd. 235.1309.

For **9**: colorless oil; IR (neat, cm^{-1}) 2968, 1064; ^1H NMR (300 MHz, $CDCl_3$) δ 3.96−3.70 (series of m, 8H), 2.01−1.71 (series of m, 11H), 1.61−1.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.9, 82.9, 82.5, 69.7, 68.1, 68.0, 28.0, 27.4, 26.8, 26.5, 26.3, 25.9; ES HRMS *m*/*z* $(M + Na)^+$ calcd 235.1310, obsd 235.1309.

Annulation of 19. A 95 mg (0.56 mmol) sample of **19** was processed in a manner analogous to that detailed above. Final chromatographic purification on silica gel (elution with 10% ethyl acetate in hexanes) provided 35 mg of **9** and 45 mg of **10** (67% over two steps).

For **10**: colorless oil; IR (neat, cm^{-1}) 2974, 1072; ^1H NMR (300 MHz, $CDCl_3$) δ 3.99−3.91 (m, 4H), 3.85 (t, $J = 6.8$ Hz, 2H), 3.75−3.69 (m, 2H), 1.93−1.75 (m, 8H), 1.70−1.64 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 88.0, 83.2, 70.0, 68.2, 28.1, 27.1, 26.5, 25.7; ES HRMS *m*/*z* $(M + Na)^+$ calcd 235.1310, obsd 235.1302.

Electrospray Ionization−Mass Spectrometry. The metal binding selectivities were assessed by dissolving a ligand in methanol at 10 μM and adding LiCl, NaCl, and KCl at 100 μM each. The high concentration of metal salts was necessary to minimize the contribution of environmental sodium. Analysis was performed on a quadrupole ion trap mass spectrometer equipped with an electrospray ionization source. The analyte solutions were directly infused into the mass spectrometer with a flow rate of 5 μL/min. Positive mode ionization was employed, using an ESI voltage of +5 kV and a heated capillary temperature of 150 °C. All other parameters were optimized on a daily basis for highest signal intensity. The selectivity of each ligand for the three alkali metals was calculated by summing the intensities of all ions containing a particular metal and dividing by the total intensity of all ions in the spectrum. Ions containing more than one ligand molecule were weighted accordingly. ESI−mass spectra were also recorded for each ligand with a single alkali metal salt instead of a mixture of all three alkali metals, and the abundances of the metal complexes in the resulting ESI−mass spectra were used to estimate ESI spray efficiencies. For these ligands, there were no significant differences noted in spray efficiencies.

Computational Details. A Monte Carlo conformational search[37] using the Schrödinger Maestro Macromodel Version 5.1.016 was performed with the following settings: Max#Iterations at 10000; Mixed MCMM/Low Mode; Automatic Setup; Converge on gradient; Force field MMFF94;[38] Energy window 50 kJ/mol. MMFF94 structures within ~3 kcal/mol above the global minimum were chosen for further geometry optimization and frequency calculations. Gas-phase optimized atoms were performed with Gaussian03 rev. B.05 at the RHF/6-31G(d), B3LYP/6-31G*, and B3LYP/6-31G** levels of theory.[39]

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Supporting Information Available: Spectroscopic (^1H/^{13}C NMR) characterization for all new compounds as well as crystallographic details for **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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