Vicinal Tetrahydrofuranyl Substitution of Alkyl Chains. Tetra-, Penta-, and Hexafunctionalized Arrays

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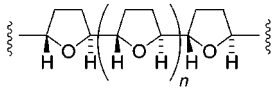
The tetrakis (tetrahydrofuranyl) dialdehydes **14** and **19** are accessible by oxidative cleavage of extensively substituted cyclohexenes, which have in turn been assembled in a stereocontrolled manner. Reaction of **14** with an excess of the Normant reagent followed by ring closure resulted in conversion to the hexafunctionalized polyether **15**. Allylindation of the same dialdehyde gave rise to lactol **16**, a reactivity pattern that was essentially duplicated when **19** was treated with the Normant reagent. Attempts to add allylmagnesium bromide to **19** resulted in operation of a Tishchenko reaction with formation of lactone **23**. By means of X-ray diffraction analysis, it was possible to ascertain the conformation adopted by **20** and **23** in the solid state. In addition, **15** was shown to populate a conformation in which the oxygen are very predominantly in gauche arrangements, this structural preorganization taking place in the absence of any metal ions.

Numerous methods have been devised for the stereocontrolled synthesis of oligo-2,5-linked tetrahydrofurans (**1**)[1−3] as a result of their direct relevance to the Annonaceous acetogenins,[4] naturally occurring polyether antibiotics,[5] and artificial ion channels.[6] In contrast, polycyclic ethers exemplified by *threo*-**2** and *erythro*-**3** have not previously come under scrutiny. These structurally unusual oligo tetrahydrofurans are enticing for a number of similar reasons. In particular, the ladder-like arrays of oxygen atoms are in principle amenable to binding to cations, thus enabling their transport across lipid bilayers. In doing so, appropriate conformations need to be adopted. To the extent that the illustrated conformation of **2** can be maintained, the termini of the chain continue to be projected in opposite in-plane directions. Similar alignment of the oxygen centers in **3** results in twisting of the chain such that a helical conformation develops (not shown). In this case, both termini are properly oriented to propagate the coiling.



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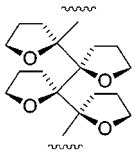

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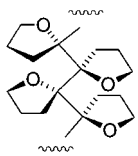

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The analysis presented above is highly conjectural and does not give consideration to the myriad of factors involved. Since experimentation is mandatory, we have initiated investigation of the synthesis of molecules related to **2** and **3** and herein record a number of initial observations.

Background

Prior to 1999, acyclic 1,1-linked polycycloalkanes remained an unknown, topologically interesting class of hydrocarbons. Last year, the Fitjer group succeeded in developing a viable approach to the tetracyclobutane **4** and acyl derivatives thereof as defined by **5**.[7] Almost concurrently, Kelly and Nally reported their stereochemically unambiguous synthesis of racemic *threo*-**6** and *meso-erythro*-**7**.[8] Unfortunately, their route, which proceeds via the oxidative cleavage of 1,5-cyclooctadiene monoepoxide and 2-fold oxygen-centered S_N2-type ring closure does not hold generality for higher homologues.

Belted mono- and bifacial ionophores[9] featuring poly(spirotetrahydrofuranyl) rings fitted around a cyclohexane core[10−14] have been a source of continuing interest

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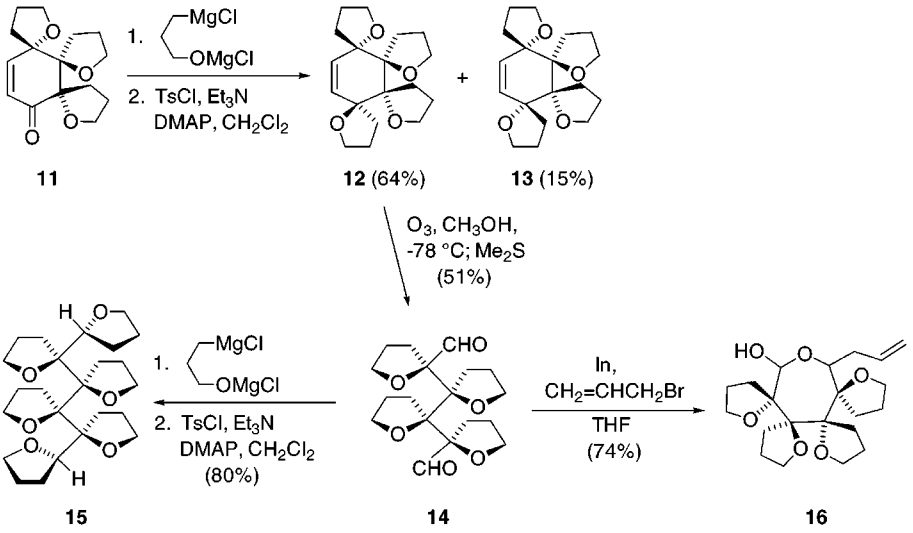
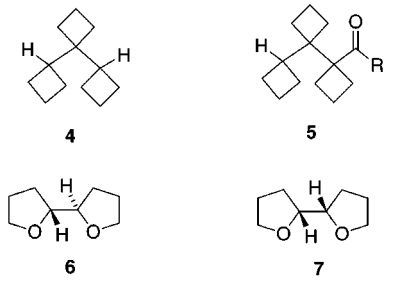
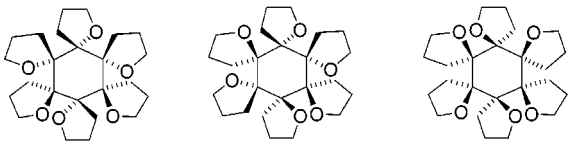
Scheme 1





in this laboratory as a consequence of their ability to bind alkali metal ions, most notably Li^+,[15−17] and to do so far more effectively than equivalently positioned methoxyl groups.[16] The development of rational strategies to such structurally preorganized hosts as **8**, **9**, and **10** has resulted in our elucidation of methods for the stereodefined serial elaboration of vicinal spirotetrahydrofuran structural units.[12,18,19] To take advantage of the high level of stereocontrol attainable with cyclohexane rings as scaffolds, we have opted to craft tetraspiroannulated systems in a manner that would allow for subsequent ring cleavage and appropriate structural modification.



Synthetic Considerations

The diol mixture produced by treatment of the previously described enone **11**[11] with the Normant reagent[20] was directly cyclized with *p*-toluenesulfonyl chloride and triethylamine in order to generate the chromatographically separable tetracyclic ethers **12** (64%) and **13** (15%) (Scheme 1). Ozonolysis of the more predominant C_2-symmetric diastereomer **12** afforded the dialdehyde **14** as a white crystalline solid. Introduction of the two terminal heterocyclic rings at this stage was found to proceed optimally when recourse was again made to the Normant reagent. Through addition of slightly more than 2 equiv of this organometallic to **14** and subsequent ring closure, it was possible to generate the oligo ether **15** in 80% isolated yield. The directionality of nucleophilic attack, which is expectedly identical at both ends of the chain, leads to formation of that product in which the stereoarrangement of the two terminal rings is anti to that of the four interior rings. Corroboration of this structural assignment was realized by X-ray crystallographic analysis (see below).

In view of the considerable attention that has been accorded to stereoselective additions to carbonyl groups and the obvious broad utility of this process, additional exploratory studies involving this dialdehyde were undertaken. The response of **14** to allylmagnesium bromide was closely comparable to that seen earlier. Subsequent hydroboration and monotosylate-mediated ring closure of the initially formed diol likewise gave rise to **15** as the predominant product. When recourse was made instead to indium-promoted allylation in THF, the seven-membered lactol **16** was formed in good yield. This oily product arises due to kinetically favored intramolecular attack of the hydroxyl group of the monoadduct onto the remaining aldehyde carbonyl. The NMR spectra of **16** indicate it to be a single stereoisomer despite the introduction of two additional chiral centers. It has not been possible to infer with reasonable confidence the configuration at these sites from the data available at this time.

Dehydration of the known alcohol **17**[21] with the Martin sulfurane reagent[22] resulted in smooth conversion to the cyclohexene **18** (Scheme 2). The sterically hindered

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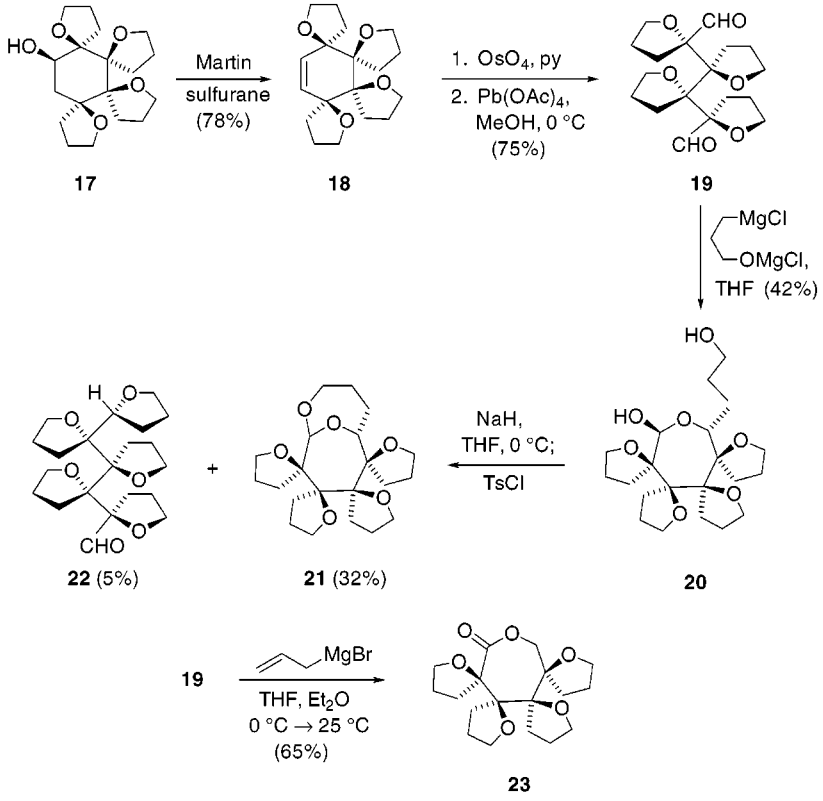
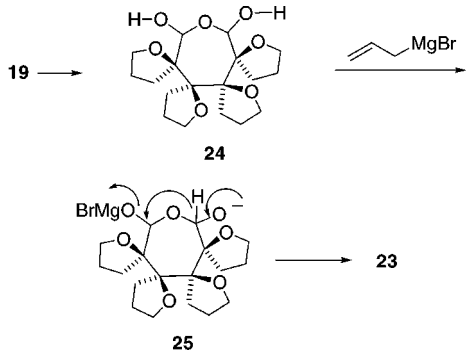
Scheme 2



nature of the double bond in this cyclic olefin proved to be a deterrent to OsO_4-promoted dihydroxylation under the customary catalytic conditions. However, a sufficiently rapid reaction rate was realized when stoichiometric quantities of this oxidant were employed. Direct cleavage of the resultant diols with lead tetraacetate provided dialdehyde **19**. The entirely different stereodisposition of the oxygen atoms in **19** relative to its diastereomer **14** was seen to induce an entirely different reactivity pattern toward Grignard reagents. For

example, exposure of **19** to the Normant reagent resulted in the isolation of lactol **20** in modest yield. No evidence was found for the generation of one or more double addition products. The crystallinity of **20** made possible the definition of its stereochemical features by X-ray diffraction methods (see below). When this lactol was deprotonated with sodium hydride and subsequently treated with *p*-toluenesulfonyl chloride, the cyclic acetal **21** was formed alongside a minor product believed to be the pentafunctionalized aldehyde **22**.

Irrespective of whether **19** was treated with aged or freshly prepared solutions of allylmagnesium bromide, no 1,2-addition was observed. Instead, a crossed Tishchenko reaction was seen to operate with the formation of lactone **23**. Metal alkoxides have previously been recognized to be effective promoters of the conversion of aldehydes into esters,[23−25] with effective reduction of one carbonyl and oxidation of the other. In the present instance, it is conceivable that effective chelation of the metal center in the Grignard reagent to multiple tetrahydrofuranyl oxygens[26] acts to curtail the rate of 1,2-addition. With the adventitious buildup of magnesium alkoxides and hydroxides comes the opportunity for Cannizzaro-type chemistry,[27] since neither aldehyde is enolizable. Alternatively, the possibility exists that the hydrated form of **19** shown as **24** is involved and that this acetal experiences 1,3-hydride shift via **25**. Wu has recently reported a Lewis acid-promoted hydride rearrangement of acetals.[28] In any event, the two previously identical aldehyde functionalities in **19** can be chemically differentiated with relative ease.



Stereoselectivity Issues

The very appreciable stereoselectivity associated with the capture by **14** of the Normant and allylmagnesium bromide reagents is compatible either with kinetically

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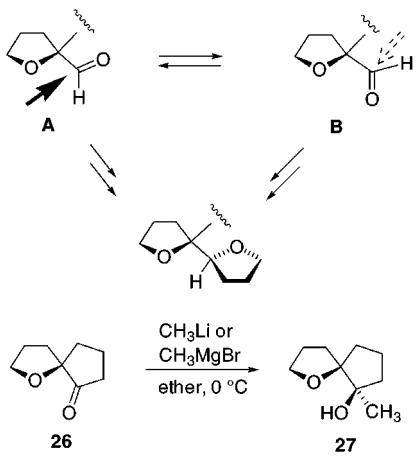
Scheme 3



preferred frontside attack on conformer **A** or rearside approach on conformer **B** (Scheme 3).

Since the interconversion of **A** and **B** likely operates across a relatively low energy barrier, it is not possible to distinguish reliably between operation of the Cram chelate model[29] or adherence to the Felkin−Anh transition state[30] or Cieplak's hyperconjugation hypothesis.[31] Although a direct parallelism with the exclusiveness exhibited by **26** for conversion to **27**[32] can be drawn, the haptophilic properties of the tetrahydrofuran ring are sufficiently well delineated[33−35] that the possibility of chelate control cannot be dismissed. It is clear, however, that product composition profits significantly from the possible operation of different effects having an identical stereochemical outcome.

Conformational Biases

Hexa-O-methyl-*scyllo*-inositol (**28**),[36] the all-trans hexa(spirotetrahydrofuranyl) cyclohexane **29**,[14] and closely related molecules[10] are now recognized to display a strong preference for equatorial orientation of the maximum number of C−O bonds, presumably as a result of electrostatic factors. On this basis, the picture that has emerged is a set of six eclipsed C−O bonds around the ring that are continuously changing their dihedral angle relationship between rather modest limits.

In **20** and **23**, the all-cis relationship of the four pendant heterocyclic rings does not accommodate the universal adoption by their oxygen atoms of equatorial sites. Consequently, the conformations adopted by these compounds in the solid state holds interest. As shown in Figure 1, the oxepane core of **20** adopts a more or less classical tub geometry in which the lactol hydroxyl and

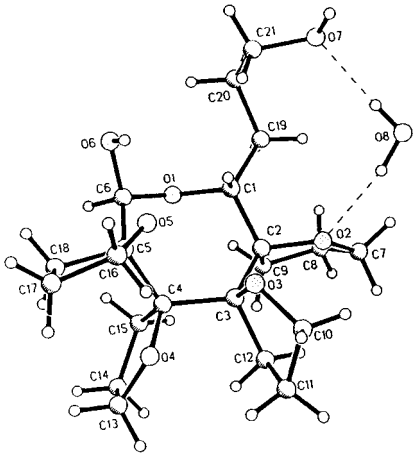


Figure 1. Computer-generated perspective drawing of the final X-ray model of **20**.

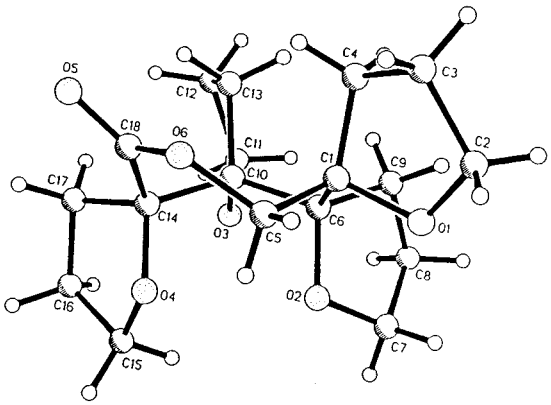
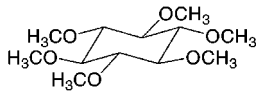


Figure 2. Computer-generated perspective drawing of the final X-ray model of **23**.



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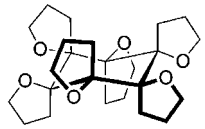

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3-hydroxypropyl side chain are projected pseudoequatorially. To accommodate the adoption of the requisite torsion angles, the spirotetrahydrofuran that flanks the hydroxyl has its oxygen (labeled as O(5)) projected axially. In contrast, O(2) is oriented approximately in the equatorial plane, thereby making possible hydrogen bonding to a water molecule also coordinated to O(7). The important picture that emerges is that the pentad O(2)−O(6) possesses an alternating *e,a,e,a,e* arrangement, any movement away from which presumably leads to an increase in ground-state energy.

For lactone **23**, the conformational status of the spirotetrahydrofuranyl subunits is closely comparable (Figure 2). Despite the absence of a three-carbon chain that likely has a determinative effect on the global structural characteristics of **20**, the oxepanone also is multidimensional in its orientation of O(1)−O(4), and in precisely the same way. Another distinctive feature is the rather large angle (125.8°) that materializes between the carbonyl group and C(14)−O(4).[37]

The open-chain hexafunctionalized ether **15** is not similarly constrained and can rotate along its carbon backbone to relieve intramolecular strain. As reflected

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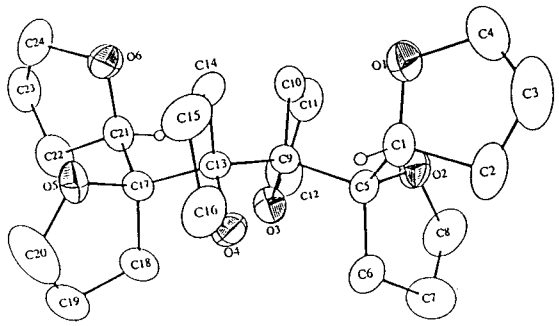

Figure 3. Computer-generated perspective drawing of the final X-ray model of **15**.

Table 1. Torsion Angles (deg) for 15

atoms	angle
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(23)- -O(4)	88.5
O(4)- - -C(13)- -C(17)- -O(5)	66.7
O(5)- - -C(17)- -C(21)- -O(6)	54.8

in Figure 3, this molecule is centrosymmetric. All eight O−C−C−O torsion angles are compiled in Table 1. As expected from the proclivity of 1,2-dimethoxyethane to adopt a gauche conformation in the gas phase,[38] the values range from 54.8° to 88.5. The greatest deviation (88.5°) occurs in the central sector of this molecule, indicating that steric parameters contribute to a significant widening of this angle. Otherwise, the average torsion angle is only 67.5°. Thus, the structural backbone of **15** populates closely related defined shapes controlled by the ether oxygen atoms, while maintaining full conformational flexibility. The preference shown can be considered to be an intrinsic property of such systems.[39]

In conclusion, some of the salient features of the present study are (a) the stabilizing effects of gauche O−C−C−O arrangements can be propagated repeatedly down a chain so as to give rise to a helical pattern of oxygen atoms about the extended carbon chain, (b) a difference in the reactivity of the diastereomeric dialdehydes **14** and **19** toward the Normant reagent, showing one consequence of stereochemical modulation in these systems, and (c) the fact that structural preorganization can be achieved in the absence of a metal ion to be bound.

Experimental Section

General Methods. Melting points are uncorrected. The column chromatographic separations were performed with Woelm silica gel (230−400 mesh). Solvents were reagent grade and in most cases dried prior to use. The purity of all compounds was shown to be >95% by TLC and high-field ^{1}H and ^{13}C NMR. The high-resolution and fast-atom-bombardment spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at Atlantic Microlab, Inc., Norcross, GA.

(2*R,2′*S**,2″*S**,2‴*R**)-Octahydro[2,2′:2′(3′*H*),2″:2″(3‴*H*),2‴-quaterfuran]-2,2‴(3*H*,3‴*H*)-dicarboxaldehyde (14).** A solution of **12**[11] (50 mg 0.16 mmol) in 15 mL of MeOH was cooled to −78 °C, ozonolyzed at this temperature for 45 min, freed of excess ozone by bubbling oxygen through for 15 min, and warmed to room temperature. Potassium carbonate (25 mg) was introduced, followed by 1 mL of dimethyl sulfide. After being stirred at room temperature overnight, the reaction mixture was filtered and concentrated. The reside was taken up in CH_2Cl_2, dried, and evaporated to leave a white solid, which was purified by MPLC (silica gel, elution with 40% ether in petroleum ether) to give 28 mg (51%) of **14** as a white, crystalline solid: mp 168−171 °C; IR (neat, cm^{-1}) 1710; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 2 H), 4.21 (m, 2 H), 3.96−3.56 (m, 6 H), 2.34 (m, 2 H), 2.18−1.70 (series of m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 95.8, 92.2, 71.0, 69.0, 31.1, 28.0, 25.6, 22.9; FAB MS *m*/*z* (M^+ + H) calcd 339.18, obsd 339.20.

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 64.35; H, 8.08.

(2*R,2′*S**,2″*R**,2‴*R**,2⁗*S**,2⁗′*R**)-Hexadecahydro[2,2′:2′(3′*H*),2″:2″(3″*H*),2‴:2‴(3‴*H*),2⁗:2⁗(3⁗*H*),2⁗′-sexifuran] (15).** To a solution of **14** (20 mg, 0.06 mmol) in 1 mL of THF at 0 °C was added the Normant reagent[20] (0.26 mL of 0.51 N, 0.13 mmol) dropwise via syringe. The reaction mixture was stirred at room temperature for 1 h, quenched by the addition of 1 N HCl, and diluted with CH_2Cl_2. The combined organics were dried and concentrated to give 27.5 mg (100%) of the tetrol as a clear colorless oil. This material was dissolved in 1 mL of CH_2Cl_2, cooled to 0 °C, treated with *p*-toluenesulfonyl chloride (25 mg, 0.13 mol), DMAP (ca 2 mg), and triethylamine (25 μL, 0.25 mmol) via syringe, and stirred at room temperature overnight prior to dilution with CH_2Cl_2, washing with 1 N HCl, drying, and concentration in vacuo to leave a pale yellow oil, which was purified by MPLC (silica gel, elution with 20% ether in petroleum) to deliver 20 mg (80%) of **15** as white needles: mp 131−132 °C (from ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (m, 2 H), 3.95−3.67 (series of m, 8 H), 3.57 (m, 4 H), 3.05 (m, 2 H), 2.62 (m, 2 H), 2.37 (m, 2 H), 2.18 (m, 2 H), 2.00−1.60 (series of m, 16 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.8, 92.7, 82.4, 69.8, 69.6, 67.6, 33.7, 31.2, 27.0, 26.6, 26.1, 24.0; FAB MS *m*/*z* (M^+ + H) calcd 423.28, obsd 423.38.

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 67.86; H, 9.03.

(5*R,6*S**,11*R**,16*S**)-23-Allyl-1,7,12,17,22-pentaoxatetraspiro[4.0.4.0.4.0.4.3]tricosan-21-ol (16).** Indium powder (55 mg, 0.47 mmol) was suspended in 1.5 mL of dry THF and allyl bromide (41 μL, 0.47 mmol) was introduced via microsyringe. The resulting mixture was heated briefly to reflux and recooled to room temperature prior to addition of **14** dissolved in 1 mL of THF via cannula. The reaction mixture was stirred overnight, diluted with CH_2Cl_2, washed with 0.5 N HCl, dried, and concentrated. Purification of the residue by MPLC (silica gel, elution with 40% ether in petroleum ether) gave 33 mg (74%) of **16** as a colorless oil: IR (neat, cm^{-1}) 3600, 1060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (m, 1 H), 5.15−5.00 (m, 2 H), 4.52 (d, J = 3.5 Hz, 1 H), 3.93−3.40 (series of m, 9 H), 2.60 (m, 2 H), 2.50−1.66 (series of m, 16 H), 1.43 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 116.6, 102.0, 95.1, 93.6, 92.5, 91.9, 86.7, 68.9, 68.6 (2 C), 68.5, 36.3, 36.2, 30.6, 30.5, 28.9, 28.5, 28.2, 27.7, 26.8; HRMS (EI) *m*/*z* (M^+) calcd 380.2199, obsd 380.2173.

(5*R,6*R**,11*S**,16*R**)-1,7,12,17-Tetraoxatetraspiro-[4.0.4.0.4.0.4.2]docos-21-ene (18).** Alcohol **17**[21] (353 mg, 1.09 mmol) in dry benzene (5 mL) was added to a solution of the Martin sulfurane[22] (150 g, 2.23 mmol) in the same solvent (5 mL) at room temperature. The mixture was stirred for 3 h, diluted with ethyl acetate, and poured into saturated $NaHCO_3$ solution. The separated aqueous phase was extracted with ethyl acetate (3x), and the combined organic layers were washed with water and brine prior to drying and solvent evaporation. The residue was purified by flash chromatography on silica gel (elution with 5% methanol in CH_2Cl_2) to furnish 259 mg (78%) of **18** as a colorless solid: mp 107−108 °C; IR (neat, cm^{-1}) 1050; ^{1}H NMR (300 MHz, C_6D_6, 350 K) δ 5.42 (s, 2 H), 3.96−3.65 (m, 8 H), 1.87−1.33 (series of m, 16 H); ^{13}C

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NMR (75 MHz, C_6D_6, 350 K) δ 131.1, 92.3, 86.6, 70.0, 68.2, 36.8, 31.6, 27.6, 26.9; HRMS *m/z* (M^+) calcd 306.1831, obsd 306.1867.

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.31; H, 8.42.

(2*R,2′*R**,2″*S**,2‴*S**)-Octahydro[2,2′:2′(3′*H*),2“:2”(3"*H*),2‴-quaterfuran]-2,2‴(3*H*,3‴*H*)-dicarboxaldehyde (19).** Osmium tetraoxide (1.0 g, 3.9 mmol) was added in one portion to a solution of **18** (740 mg, 2.4 mmol) in pyridine (10 mL). After the mixture had stirred overnight, the pyridine was removed in vacuo, the residue was taken up in CH_2Cl_2, saturated $NaHSO_3$ solution was introduced, and vigorous stirring was maintained for 2 h. The separated aqueous phase was extracted with CH_2Cl_2 (5×). The combined organic layers were dried and concentrated to give the diol (680 mg) suitable for direct oxidation.

The above material (209 mg, 0.61 mmol) was dissolved in methanol (10 mL), cooled to 0 °C, and treated with lead tetraacetate (420 mg, 0.95 mmol). The mixture was stirred for 30 min at 0 °C, at which point H_2O and CH_2Cl_2 were added. The separated aqueous layer was extracted with CH_2Cl_2 (2×), and the combined organic phases were dried and concentrated. Flash chromatography of the residue on silica gel (elution with 2% methanol in CH_2Cl_2) afforded **19** (187 mg, 75%) as a colorless solid: mp 126−128 °C; IR (neat, cm^{-1}) 1710; ^1H NMR (300 MHz, $CDCl_3$) δ 9.48 (s, 2 H), 3.99−3.85 (m, 8 H), 2.65−2.57 (m, 2 H), 2.21−1.67 (series of m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 94.9, 93.5, 70.9, 69.3, 31.5, 29.0, 25.5, 24.9; FAB MS *m/z* ($M^+ + H$) calcd 339.18, obsd 339.14.

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.67 H, 7.63.

(5*R,6*R**,11*R**,16*R**,21*R**,23*S**)-23-Hydroxy-1,7,12,17,-22-pentaoxatetraspiro[4.0.4.0.4.0.4.3]tricosane-21-propanol (20).** Addition of **19** (46 mg, 0.12 mmol) dissolved in dry THF (1 mL) to the Normant reagent (1.5 mL of 0.34 N) at 0 °C in the predescribed manner and subsequent purification by flash chromatography on silica gel (elution with 5% methanol in CH_2Cl_2) gave 20 mg (42%) of **20** along with 10 mg of an unknown compound.

For **20**: white crystals; mp 144−146 °C; IR (neat, cm^{-1}) 3415; ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (br s, 2 H), 4.33 (d, J = 10.4 Hz, 1 H), 4.17 (q, J = 7.8 Hz, 1 H), 4.08−4.02 (m, 2 H), 3.98−3.89 (m, 4 H), 3.80 (q, J = 8.2 Hz, 1 H), 3.64 (m, 3 H), 2.35−2.26 (m, 1 H), 2.21−1.54 (series of m, 18 H), 1.17 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.6, 95.6, 94.8, 93.7, 92.3, 72.3, 71.3, 71.0, 69.7, 69.1, 63.3, 34.4, 31.9, 30.4, 29.6, 27.8, 27.3, 26.7, 26.5, 24.4 (one C overlapped); FAB MS *m/z* ($M^+ + H$) calcd 399.2, obsd 399.18.

Anal. Calcd for $C_{21}H_{34}O_7$: C, 60.55; H, 8.71. Found: C, 60.58; H, 8.68.

(1*R,6*R**,7*R**,8*R**,9*R**,10*R**)Octahydrotetraspiro[2,11-dioxabicyclo[4.4.1]undecane-7,2′(3′*H*):8,2″(3″*H*):9,2‴-(3‴*H*):10,2⁗(3⁗*H*)-tetrakisfuran] (21) and (2*R**,2′*R**,-2″*R**,2‴*R**,2⁗*R**)-Dodecahydro[2,2′:2′(3′*H*),2″:2″(3"*H*),2‴:2‴(3‴*H*),2⁗-quinquefuran]-2(3*H*)-carboxaldehyde (22).** Sodium hydride (6.4 mg, of 60% in oil) was added to a solution of **20** (20 mg, 0.05 mmol) in dry THF (1 mL) at 0 °C. The mixture was stirred for 30 min at this temperature prior to the introduction of *p*-toluenesulfonyl chloride (12 mg, 0.06 mmol). After 6 h at room temperature, CH_2Cl_2 and saturated NH_4Cl solution were added, and the separated aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic solutions were dried and concentrated to leave a residue, which was subjected to flash chromatography on silica gel. Elution with 5% methanol in CH_2Cl_2 furnished 6.0 mg (32%) of **21** and 1.0 mg (5%) of **22**.

For **21**: white solid; mp 147−149 °C; IR (neat, cm^{-1}) 1453, 1055; ^1H NMR (300 MHz, $CDCl_3$) δ 4.84 (d, J = 11.2 Hz, 1 H), 4.58 (s, 1 H), 4.14−3.73 (series of m, 10 H), 2.23 (m, 1 H), 2.16−153 (series of m, 18 H), 1.24 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 101.3, 98.7, 96.5, 94.3, 90.9, 72.2, 71.3, 70.3, 70.1, 68.4, 65.6, 35.1, 32.5, 31.3, 29.8, 28.0, 27.7, 27.1, 26.5, 24.0; FAB MS *m/z* ($M^+ + H$) calcd 381.23, obsd 381.28.

For **22**: ^1H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 1 H), 4.14−3.88 (m, 4 H), 3.86−3.69 (m, 6 H), 3.48−3.44 (m, 1 H), 2.65 (m, 1 H), 2.30−1.58 (series of m, 19 H); FAB MS *m/z* ($M^+ + H$) calcd 381.23, obsd 381.26.

(5*R,6*R**,11*R**,16*R**)-1,7,12,17,22-Pentaoxatetraspiro-[4.0.4.0.4.0.4.3]tricosan-21-one (23).** Dialdehyde **19** (21 mg, 0.063 mmol) dissolved in dry THF (1 mL) was added to allylmagnesium bromide (0.25 mL of 1.0 M in ether) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, diluted with CH_2Cl_2 and saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3×). The combined organic layers were dried and concentrated. Purification of the residue by flash chromatography on silica gel (elution with 5% methanol in CH_2Cl_2) gave 14 mg (65%) of **23** as a white solid: mp 145−150 °C; IR (neat, cm^{-1}) 1725, 1065; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (d, J = 11.9 Hz, 1 H), 4.16−4.09 (m, 3 H), 4.00−3.91 (m, 3 H), 3.82−3.74 (m, 2 H), 3.63 (d, J = 11.9 Hz, 1 H), 2.53 (m, 1 H), 2.13−1.58 (series of m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 96.6, 96.1, 89.6, 88.4, 71.3 (2 C), 68.7, 67.6, 66.5, 32.4, 32.1, 30.5, 29.9, 26.9, 26.7, 26.2, 23.5; FAB MS *m/z* ($M^+ + H$) calcd 339.18, obsd 339.14.

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Supporting Information Available: Compilation of X-ray crystallographic data and refinement for **20**, **23**, and **15**, including tables of bond distances and angles, torsion angles, and final fractional coordinates, in addition to NMR spectra for **16**, **21**, and **22**. This material is free of charge via the Internet at http://pubs.acs.org.

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