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Vicinal Tetrahydrofuran Polysubstitution of Simulated Fatty Acids

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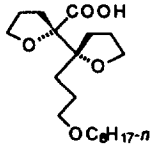
Abstract: Two groups of tetrahydrofuranyl-substituted long-chain carboxylic acids have been prepared under total stereochemical control. The diastereomeric ionophores were subsequently evaluated for their capability of binding alkali metal ions computationally by Amber force field calculations, experimentally by means of the picrate extraction method, and by mediating the transport of Li^+ and Na^+ through phospholipid bilayers. © 1997 Elsevier Science Ltd.

The ionophoric antibiotics have widespread biological action.[1] In continuation of a program focused on producing new and novel ionophoric materials designed to resemble to some degree the naturally occurring ionophoric antibiotics,[2] the carboxylic acids **1-6** were targeted for investigation. The incorporation of stereochemically defined networks of vicinal tetrahydrofuran rings in proximity to the head group of a long-chain carboxylic acid was considered to offer several advantages. The distribution of oxygen centers, particularly in the diastereomeric tris polyether subset **3-6**, promised to be adequate for partial solubility in both aqueous and lipid environments. Preliminary Amber force field calculations indicated that the efficacy of binding and membrane transport as a function of systematic stereoinversion in these ladder-like arrays would differ measurably. The structurally enforced adoption of different conformations could express itself quantitatively in conventional complexation scenarios as well as within the confines of a phospholipid bilayer.



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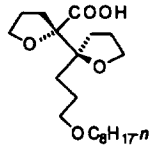

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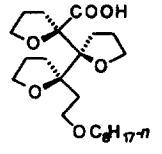

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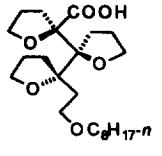

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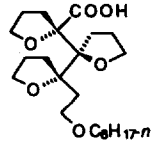

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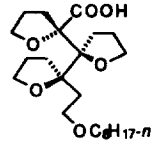
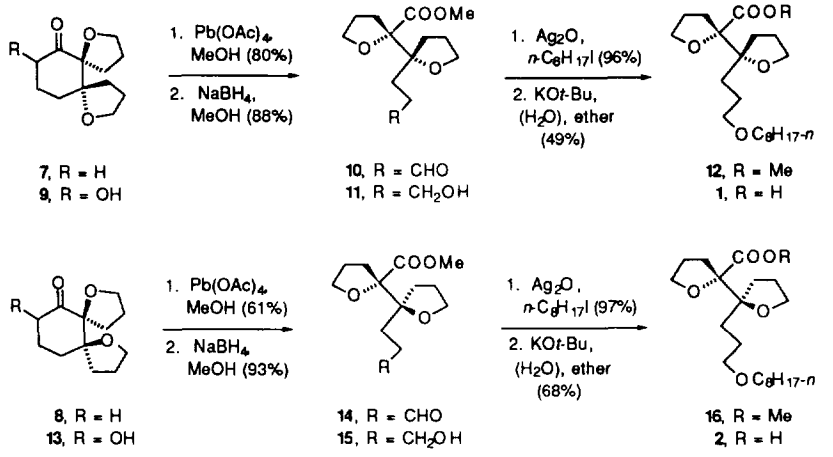


6

RESULTS

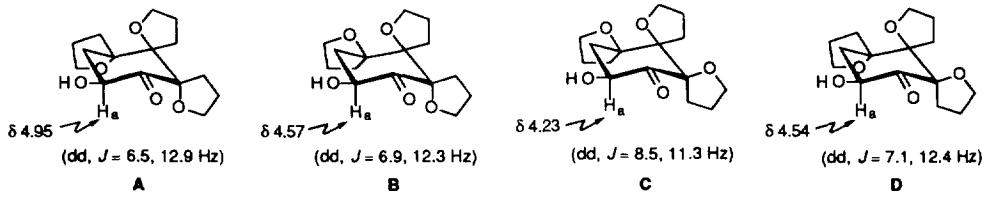
Stereocontrolled Molecular Construction. The known dispiro ketones **7** and **8**[2e,f] were α-hydroxylated,[2a] cleaved with lead tetraacetate in methanol,[3] and reduced with sodium borohydride at 0 °C[4] to give **11** and **15**, respectively (Scheme 1). As expected, conventional Williamson protocols such as the use of sodium hydride in THF containing 5-10% HMPA for formation of the *n*-octyl ether promoted intramolecular lactonization exclusively. Ultimately, the alternative use of 12.5 equivalents of Ag_2O and 20 equivalents of the iodide[4,5] routinely gave **12** and **16** in yields exceeding 95%. These methyl esters were best transformed into carboxylic acids **1** and **2** under the Gassman "anhydrous hydroxide" conditions.[6]

Scheme 1



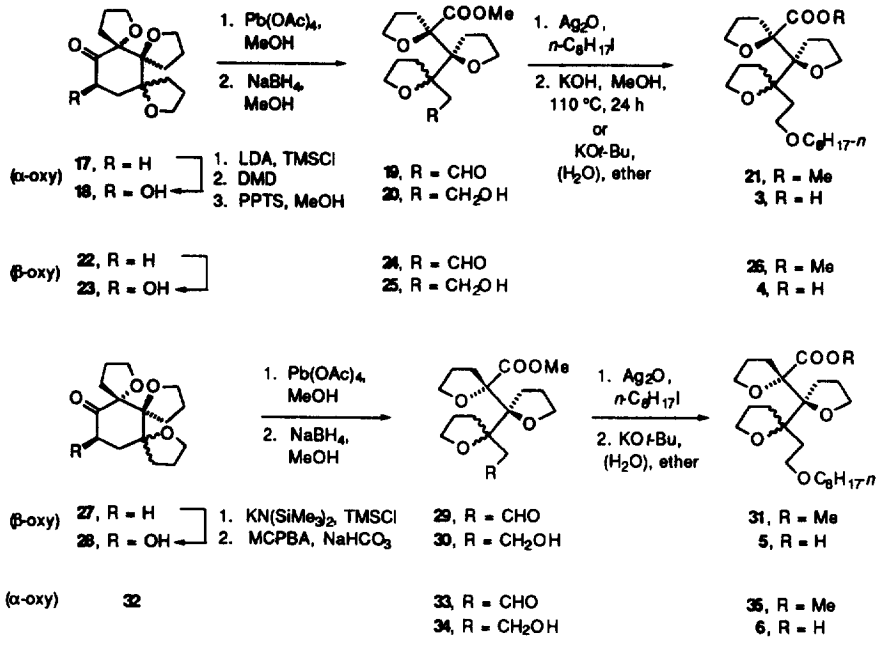
Extension of this chemistry to the generation of homologs **3-6** was undertaken without complications (Scheme 2). The stereochemistry of the individual α-hydroxy ketone epimers follows reliably from the chemical shift and multiplicity of their carbinol proton. The notably downfield resonance of this proton in **18** (at δ 4.95 in $CDCl_3$) convincingly points to its 1,3-diaxial relationship with *two* ethereal oxygens as in **A**. Beyond that, Ha is clearly coupled in $J_{ax\text{-}ax}$ and $J_{ax\text{-}eq}$ fashion to the neighboring methylene protons.

The appearance of the carbinol proton in **23** as a doublet of doublets at δ 4.57 is viewed as clearly indicative of its axial disposition in close proximity to a *single* ethereal oxygen as in **B**. In fact, the spectral data for **23** parallels exceptionally closely those recorded earlier for **32** and to which conformation **D** had been assigned.[2a] The carbinol proton for **28** appears at highest field (δ 4.23) and must also be oriented axially. This upfield shift signifies that it is not deshielded by a proximate hetero atom in accord with conformation **C**.



The uniformly strong bias for orienting the methylene carbons and not the oxygen atoms of cyclohexyl systems substituted with five or six spirotetrahydrofuran rings axially in the solid state[2b] is not at all evident in **A-D** where the effect is actually reversed in the first of these molecules. This is because the presence of the trigonal carbonyl carbon flattens the chair to some degree while engaging the neighboring hydroxyl in hydrogen bonding.

Scheme 2



Molecular Modeling Studies. Monte Carlo conformational analyses were carried out using MacroModel[7] with the Amber force field.[8] The *n*-octyl substituent was replaced with a methyl group in order to remove conformational differences due only to this side chain. The total and relative energies of the lithium, sodium, and potassium carboxylates of acids **1-6** generated by this procedure are compiled in Table 1.

Table 1. Energies of the Alkali Metal Carboxylates of **1-6** as Generated by the Monte-Carlo Protocol in MacroModel using the Amber Force Field.[a]

	Li^+		Na^+		K^+	
acid	total energy	relative energy	total energy	relative energy	total energy	relative energy
1	-30.57	0	-28.03	0	-10.08	0
2	-29.30	1.27	-27.15	0.88	-9.49	0.59
3	-18.70	0.37	-16.54	0.06	1.29	0.12
4	-17.62	1.45	-15.47	1.13	2.07	0.90
5	-19.07	0	-16.59	0.01	3.46	2.29
6	-18.75	0.32	-16.60	0	1.17	0

[a] All values are in kcal/mol.

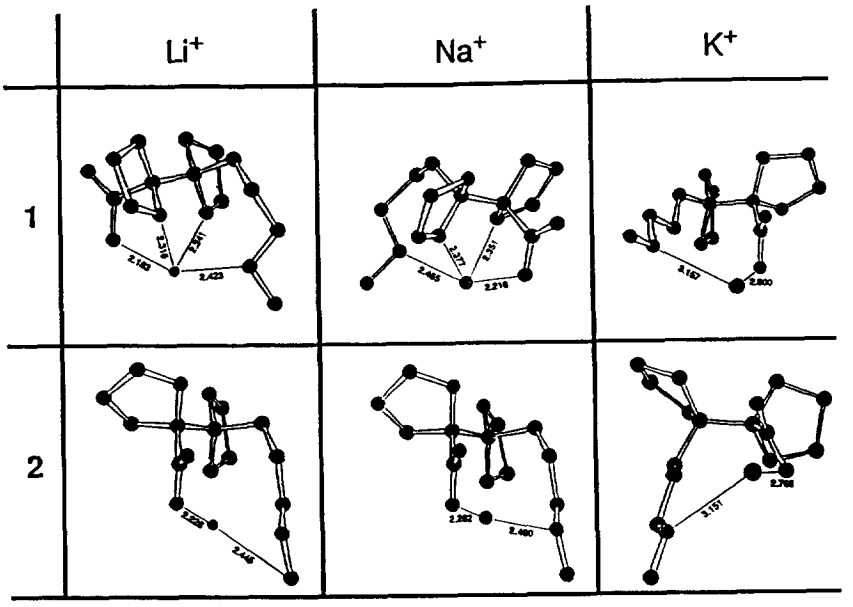


Figure 1. Lowest Energy Conformations of **1** and **2** with Li^+, Na^+, and K^+ as Optimized by Amber Force Calculations.

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

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

	K_a		
host	Li^+	Na^+	K^+
1	5.4×10^3	2.0×10^3	1.0×10^3
2	2.3×10^3	3.2×10^4	3.0×10^4
3	1.4×10^3	3.4×10^4	4.5×10^4
4	1.2×10^3	4.9×10^4	1.8×10^4
5	3.2×10^2	9.4×10^4	5.6×10^4
6	3.9×10^3	2.5×10^4	3.2×10^4
21			2.1×10^4
26		5.5×10^3	1.4×10^4
31		2.0×10^3	1.5×10^4

[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.

In the bis series, the lowest energy conformation of **1** in the presence of each metal ion was calculated to be more stable than that of **2**, which is consistent with our experimental findings (Figure 1). The lowest energy conformations determined for **3-6** are depicted in Figure 2. The calculations involving **5**-Li^+ and **5**-Na^+ are noteworthy. The stability associated with this pair of complexes emanates from the capability of four of the five oxygen atoms to enter into the coordination sphere of the metal ion (2.174-2.443 Å for Li^+; 2.204-2.485 Å for Na^+).

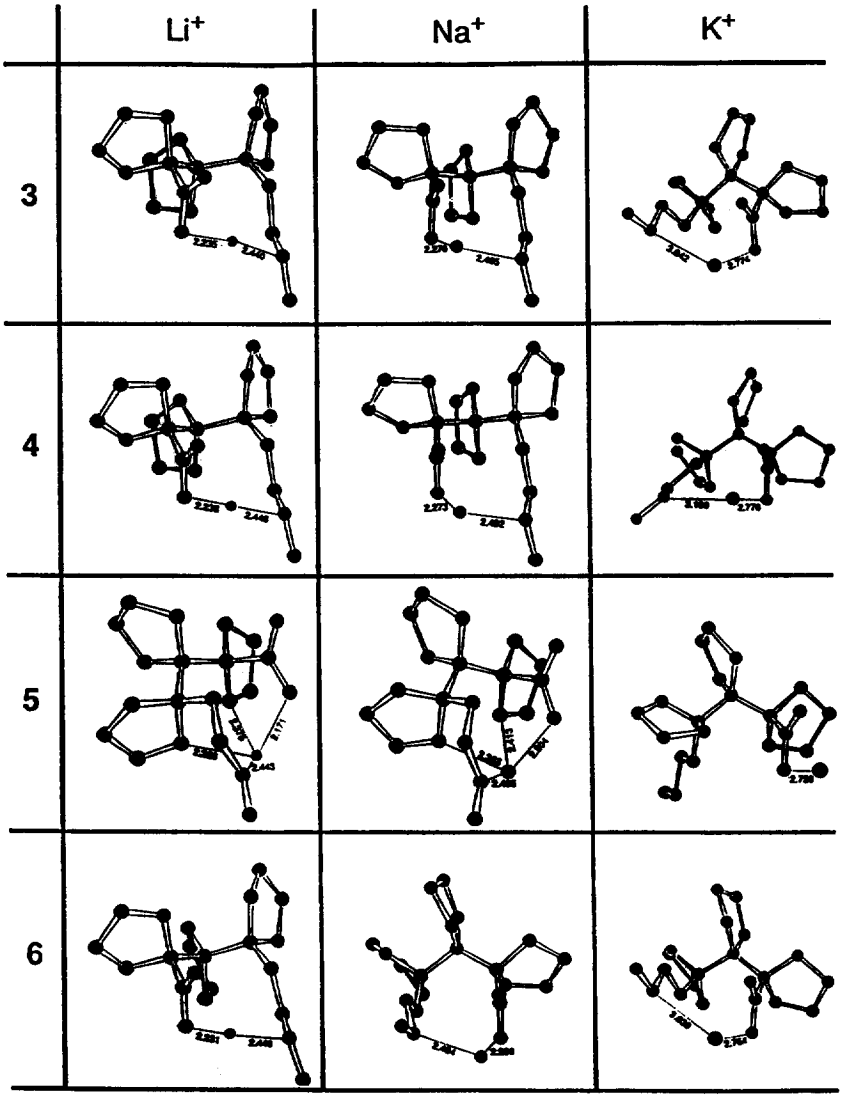


Figure 2. Lowest Energy Conformations of **3-6** with Li^+, Na^+, and K^+ as Optimized by Amber Force Calculations.

Complexation Studies and Ion Transport. [9,14] The binding properties of **1-6** were determined relative to lithium, sodium, and potassium picrate in water-chloroform mixtures by means of Cram's extraction method (Table 2). No corrections were made for the possible low aqueous solubility of the spirotetrahydrofuran hosts. The K_a values realized, although modest in an absolute sense, are construed to be rather respectable for the limited number of oxygen atoms available for complexation by these open-chain systems. The chelating capacity of **1-6** is lower when membrane transport is involved. The slow exchange technique involving ^{7}Li and ^{23}Na exchange was used. Passive exchange rates of Na^+ with Li^+ varied from experiment to experiment and in the range 1-5 x 10^{-4} s^{-1} and increased only slightly after addition of the synthesized material.

EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at the indicated field strengths. High resolution mass spectra were obtained at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark and at Atlantic Microlab, Inc., Norcross, Georgia. All separations were effected under flash chromatography on Merck silica gel HG_{254}. The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in many cases dried before use.

Methyl (2R,2'S*)-2'-(2-Formylethyl)hexahydro[2,2'-bifuran]-2(3H)-carboxylate (**10**).* To a cold (0 °C), magnetically stirred solution of **9** (72% α, 28% β) (820 mg, 3.63 mmol) in methanol (40 mL) was added lead tetraacetate (3.6 g, 8.1 mmol). The reaction mixture was allowed to warm slowly to rt and after 2 h partitioned between water (50 mL) and ether (50 mL). The separated aqueous phase was extracted with ether (3 x 50 mL), and the combined organic solutions were washed with water (2 x 25 mL), dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 15% ether in hexanes) gave **10** as a colorless oil (740 mg, 80%); IR (neat, cm^{-1}) 1730, 1450, 1270, 1080; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (t, J = 1.4 Hz, 1 H), 3.78-3.51 (m, 7 H), 2.34-1.50 (series of m, 11 H), 1.48-1.43 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 201.5, 173.8, 923, 86.7, 69.5, 68.9, 51.9, 38.3, 31.3, 31.2, 29.4, 26.7, 25.7; MS *m/z* (M^++1) calcd 257.1383, obsd 257.1372.

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.91; H, 7.87. Found: C, 60.94; H, 7.90.

Methyl (2R,2'R*)-Hexahydro-2'-(3-hydroxypropyl)[2,2'-bifuran]-2(3H)-carboxylate (**11**).* To a cold (0 °C) solution of **10** (740 mg, 2.89 mmol) in methanol (15 mL) was added sodium borohydride (1.0 g, 26 mmol) in several portions. After 45 min, the reaction mixture was poured into 1 M HCl (50 mL) and ether (50 mL), and the aqueous phase was extracted with ether (3 x 25 mL). The combined organic layers were dried and concentrated to leave a residue that was purified by chromatography on silica gel (elution with 50-100% ethyl acetate in petroleum ether) to give **11** as a faintly yellow oil (650 mg, 88%); IR (neat, cm^{-1}) 3470, 1735, 1280, 1245, 1200, 1060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95-3.78 (m, 4 H), 3.73 (s, 3 H), 3.68-3.59 (m, 2 H), 2.50-2.21 (m, 3 H), 2.06-1.55 (series of m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.4, 92.9, 87.6, 70.2, 69.2, 63.3, 52.3, 33.3, 31.3, 31.2, 27.3, 26.7, 26.2; MS *m/z* (M^+) calcd 258.1467, obsd 258.1451.

Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.43; H, 8.59. Found: C, 60.13; H, 8.85.

Methyl (2R,2'R*)-Hexahydro-2'-[3-(octyloxy)propyl][2,2'-bifuran]-2(3H)-carboxylate (12).* A stirred solution of **11** (430 mg, 1.67 mmol) in *n*-octyl iodide (12.24 g, 51 mmol) was treated with silver oxide (4.83 g, 20.8 mmol) and heated at 90 °C for 60 h. After being cooled, the mixture was filtered and concentrated under reduced pressure to leave a residue which was purified by chromatography on silica gel. Gradient elution with 0-50% ether in petroleum ether afforded **12** as a colorless oil (570 mg, 96%); IR (neat, cm^{-1}) 1740, 1465, 1370, 1275, 1240, 1100, 925, 740; ^1H NMR (300 MHz, $CDCl_3$) δ 3.90-3.72 (m, 4 H), 3.69 (s, 3 H), 3.39-3.30 (m, 4 H), 2.45-2.16 (m, 3 H), 1.96-1.46 (series of m, 11 H), 1.40-1.24 (m, 10 H), 0.87-0.82 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.3, 92.9, 87.6, 71.2, 70.9, 70.0, 69.1, 52.1, 33.2, 31.8, 31.2, 31.0, 29.7, 29.4 (2 C), 29.2, 27.3, 26.2, 23.9, 22.6, 14.0; MS *m/z* (M^+) calcd 370.2719, obsd 370.2698.

Anal. Calcd for $C_{21}H_{38}O_5$: C, 68.07; H, 10.34. Found: C, 68.22; H, 10.19.

(2R,2'R*)-Hexahydro-2'-[3-(octyloxy)propyl][2,2'-bifuran]-2(3H)-carboxylic Acid (1).* A cold (0 °C), magnetically stirred slurry of potassium *tert*-butoxide (1.5 g, 13 mmol) in ether (15 mL) was treated with water (0.1 mL). After 5 min, **12** (570 mg, 1.6 mmol) dissolved in ether (10 mL) was added, the cooling bath was removed, and stirring was continued overnight prior to the addition of water (50 mL). The aqueous phase was acidified with 12 M HCl and extracted with ether (5 x 25 mL). The combined ethereal extracts were dried and concentrated. Purification of the residue by chromatography on silica gel (elution with 10% methanol in CH_2Cl_2) furnished oily **1** (270 mg, 49%); IR (neat, cm^{-1}) 3220, 2860, 1730, 1460, 1365, 1185, 1085, 910, 730; ^1H NMR (300 MHz, $CDCl_3$) δ 4.06 (ddd, J = 7.8, 7.8, 4.1 Hz, 1 H), 3.95-3.78 (m, 3 H), 3.48-3.31 (m, 4 H), 2.38-1.49 (series of m, 25 H), 0.89-0.82 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.5, 92.6, 88.0, 71.1, 71.0, 70.2 (2 C), 32.4, 31.8, 31.7, 31.2, 29.7, 29.4, 29.2, 26.9, 26.2, 26.0, 23.9, 22.6, 14.0; MS *m/z* (M^+) calcd 356.2563, obsd 356.2563.

Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.01; H, 10.17.

Methyl (2R,2'R*)-2'-(2-Formylethyl)hexahydro[2,2'-bifuran]-2(3H)-carboxylate (14).* Oxidation of **13** (100% β) (2.75 g, 11.37 mmol) in methanol (120 mL) with lead tetraacetate (6.00 g, 13.53 mmol) at 0-25 °C as before afforded 1.79 g (61%) of **14** as a colorless oil; IR (neat, cm^{-1}) 1725, 1440, 1270, 1230, 1190, 1085; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (t, J = 1.1 Hz, 1 H), 3.99-3.95 (m, 2 H), 3.89-3.77 (m, 2 H), 3.74 (s, 3 H), 2.54-2.14 (series of m, 5 H), 2.02-1.66 (series of m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.4, 174.4, 93.0, 87.4, 69.8, 69.4, 52.4, 38.9, 32.6, 32.4, 29.4, 26.6, 25.0; MS *m/z* (M^+) calcd 256.1311, obsd 256.1322.

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.91; H, 7.87. Found: C, 60.82; H, 7.81.

Methyl (2R,2'S*)-Hexahydro-2'-(3-hydroxypropyl)[2,2'-bifuran]-2(3H)-carboxylate (15).* Reduction of **14** (1.74 g, 6.80 mmol) in methanol (50 mL) with sodium borohydride (1.0 g, 26 mmol) at 0-25 °C provided 1.64 (93%) of **15** as a colorless oil; IR (neat, cm^{-1}) 3450, 1730, 1275, 1235, 1190, 1060; ^1H NMR (300 MHz, $CDCl_3$) δ 3.97-3.88 (m, 4 H), 3.72 (s, 3 H), 3.71-3.53 (m, 2 H), 2.30-2.12 (m, 2 H), 2.04 (s, 1 H), 2.02-1.47 (series of m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.5, 93.0, 88.1, 70.1, 69.2, 63.3, 52.3, 32.9, 32.5, 31.7, 27.0, 26.9, 25.1; MS *m/z* (M^+) calcd 258.1467, obsd 258.1451.

Methyl (2R,2'S*)-Hexahydro-2'-[3-(octyloxy)propyl][2,2'-bifuran]-2(3H)-carboxylate (16).* A

solution of **15** (330 mg, 1.28 mmol) in *n*-octyl iodide (7.07 g, 29.4 mmol) containing silver oxide was heated at 80 °C for 48 h and processed in the predescribed manner to give 440 mg (97%) of **16** as a colorless oil; IR (neat, cm-1) 1735, 1460, 1370, 1270, 1230, 1195, 1100; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94-3.84 (m, 4 H), 3.68 (s, 3 H), 3.40-3.23 (m, 4 H), 2.26-2.08 (m, 2 H), 1.90-1.15 (series of m, 22 H), 0.82 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.5, 92.9, 88.1, 71.1, 70.8, 70.0, 69.1, 52.1, 32.9, 32.3, 31.7, 31.3, 29.6, 29.3, 29.1, 26.8, 26.1, 25.1, 24.1, 22.5, 13.9; MS *m/z* (M^+) calcd 370..2719, obsd 370.2722.

Anal. Calcd for $C_{21}H_{38}O_5$: C, 68.07; H, 10.34. Found: C, 68.14; H, 10.62

Methyl (2R,2'S*)-Hexahydro-2'-[3-(octyloxy)propyl][2,2'-bifuran]-2(3H)-carboxylic Acid (2).* Hydrolysis of **16** (440 mg, 1.24 mmol) with potassium *tert*-butoxide (1.20 g, 10.7 mmol) in ether (20 mL) and water (0.05 mL) afforded 300 mg (68%) of oily **2**; IR (neat, cm^{-1}) 3200, 2870, 1460, 1370, 1305, 1245, 1200, 1100; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99-3.88 (m, 4 H), 3.45-3.25 (m, 4 H), 2.54-2.46 (m, 1 H), 2.20-1.08 (series of m, 24 H), 0.86 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.2, 92.4, 88.5, 70.8, 70.5, 69.7, 33.1, 31.7, 31.1, 30.3, 29.6, 29.4, 29.3, 29.2, 27.0, 26.1, 25.9, 23.8, 22.6, 14.0; MS *m/z* (M^+) calcd 356.2563, obsd 356.2560.

Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.69; H, 10.53.

(5R,6S*,11R*,17R*)-17-Hydroxy-1,7,12-trioxatrispiro[4.0.4.0.4.3]-octadecan-16-one (18).* To a cold (-78 °C), stirred solution of LDA [generated from diisopropylamine (910 mg, 8.99 mmol) in THF (100 mL)] was added **17** (1.6 g, 6.0 mmol) followed by chlorotrimethylsilane (0.98 g, 9.02 mmol) 3 h later. The reaction mixture was slowly warmed to rt, stirred overnight, and quenched with saturated $NaHCO_3$ solution (50 mL). The separated aqueous phase was extracted with ether (3 x 50 mL) and the combined organic layers were dried and evaporated. The resulting yellow oil was dissolved in CH_2Cl_2 (50 mL), cooled to -78 °C, treated with an acetone solution of dimethyldioxirane [prepared from 205 g (0.333 mmol) of oxone], allowed to warm slowly to rt during 8 h, decanted 1 h later, and concentrated. The residue was dissolved in methanol (50 mL), treated with pyridinium *p*-toluenesulfonate (1.0 g), stirred overnight, concentrated, and purified by chromatography on silica gel (elution with 50 → 95% ether in petroleum ether) to give recovered **17** (0.49 g) and the desired product **18** (0.93 g, 68%) as a viscous, colorless oil; IR (neat, cm^{-1}) 3500, 1740, 1075; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (dd, J = 6.5, 12.9 Hz, 1 H), 4.05-3.85 (m, 5 H), 3.66-3.61 (m, 1 H), 3.25 (br s, 1 H), 2.67-2.59 (m, 1 H), 2.31 (dd, J = 6.5, 13.1 Hz, 1 H), 2.20-1.45 (series of m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.7, 93.8, 91.2, 86.9, 70.5, 69.9, 69.1, 68.6, 42.5, 34.2, 27.9, 27.1, 26.9, 24.8, 24.5; MS *m/z* (M^+) calcd 282.1467, obsd 282.1455.

Methyl (2R,2'S*,2"R*)-2"-(Formylmethyl)octahydro[2,2':2'(3'H),2"-terfuran]-2(3H)-carboxylate (19).* Treatment of a cold (0 °C) solution of **18** (180 mg, 0.64 mmol) in methanol (30 mL) with lead tetraacetate (530 mg, 1.19 mmol) for 30 min and the normal ensuing workup including chromatographic purification on silica gel (elution with 50% ether in petroleum ether) afforded 210 mg (100%) of **19** as a colorless oil; IR (neat, cm^{-1}) 1740, 1465, 1315, 1280, 1245, 1210, 1190, 1080, 1030, 945; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (t, J = 1.0 Hz, 1 H), 3.95-3.73 (m, 6 H), 3.63 (s, 3 H), 2.45-2.25 (m, 5 H), 2.20-2.03 (m, 1 H), 2.00-1.50 (series of m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 201.1, 173.9, 93.9, 91.0, 90.2, 70.0, 69.0, 68.7, 52.0, 50.1, 33.7, 33.0, 32.0, 26.4, 25.2, 24.6; MS *m/z* (M^++1) calcd 313.1651, obsd 313.1560.

Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.75. Found: C, 61.07; H, 7.85.

(2R,2'S*,2"R*)-Octahydro-2"-[2-(octyloxy)ethyl][2,2':2'(3'H),2"-terfuran]-2(3H)-carboxylic Acid (3).* Reduction of **19** (480 mg, 1.54 mmol) with sodium borohydride (350 mg, 9.3 mmol) in methanol (30 mL) at 0 °C furnished **20** (530 mg, 98%) as a colorless oil following chromatography on silica gel (gradient elution with 50-95% ethyl acetate in petroleum ether); IR (neat, cm^{-1}) 3500, 1740, 1455, 1280, 1245, 1200, 1080, 950; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95-3.55 (m, 8 H), 3.70 (s, 3 H), 3.06 (s, 1 H), 2.55-2.40 (m, 4 H), 2.13-1.56 (series of m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.4, 94.6, 92.6, 92.5, 70.3, 69.0, 68.8, 60.0, 52.2, 38.9, 33.6, 32.3, 31.6, 28.0, 27.0, 24.0; MS *m/z* (M^+) calcd 315.1807, obsd 315.1780.

A mixture of **20** (230 mg, 0.73 mmol), *n*-octyl iodide (3.99 g, 16.7 mmol), and silver oxide (2.0 g, 8.6 mmol) was heated at 80 °C for 48 h, cooled, filtered, and chromatographed (silica gel, gradient elution with 20-95% ether in petroleum ether) to give **21** (270 mg, 89%) as a colorless oil; IR (neat, cm^{-1}) 1735, 1460, 1380, 1270, 1230, 1190, 1175, 1105, 1070; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95-3.73 (m, 4 H), 3.71 (s, 3 H), 3.68-3.52 (m, 2 H), 3.48 (t, J = 7.4 Hz, 2 H), 3.37 (ddd, J = 1.9, 6.7 Hz, 2 H), 2.50-2.31 (m, 1 H), 2.28 (dd, J = 7.8, 7.8 Hz, 1 H), 2.15-1.46 (series of m, 10 H), 1.41-1.16 (m, 14 H), 0.87 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.4 , 94.7, 90.0, 71.2, 70.2, 69.0, 68.7, 67.5, 52.1, 37.3, 33.7, 32.8, 31.9, 31.8, 31.6, 29.8, 29.4, 29.2, 27.5, 27.0, 26.2, 25.7, 24.1, 14.0; MS *m/z* (M^++1) calcd 427.3048, obsd 427.3028.

Anal. Calcd for $C_{24}H_{42}O_6$: C, 67.57; H, 9.93. Found: C, 67.27; H, 10.06.

The above ester (110 mg, 0.27 mmol) was hydrolyzed with 50% potassium hydroxide solution (20 mL) in methanol (20 mL). After being heated at 110 °C for 24 h, the reaction mixture was cooled and concentrated. The remaining aqueous layer was acidified with 12 M HCl and extracted with ethyl acetate (5 x 30 mL). The combined organic layers were dried and freed of solvent to leave a residue that was purified by chromatography on silica gel (elution with ethyl acetate followed by 10% methanol in CH_2Cl_2) to give **3** as a foam (40 mg, 38%); IR (neat, cm^{-1}) 1740, 1470, 1385, 1340, 1310, 1190, 1110, 1075, 940; ^1H NMR (300 MHz, $CDCl_3$) δ 4.18-4.13 (m, 1 H), 4.11-3.94 (m, 3 H), 3.85-3.75 (m, 2 H), 3.51 (t, J = 7.3 Hz, 2 H), 3.378 (dd, J = 6.6, 6.7 Hz, 1 H), 3.376 (dd, J = 6.7, 6.7 Hz, 1 H), 2.58-2.45 (m, 1 H), 2.33 (dd, J = 7.5, 7.5 Hz, 1 H), 1.27 (br envelope, 25 H), 0.87 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.4, 94.9, 90.1, 71.3, 70.7, 70.0, 67.3, 37.3, 33.8, 33.6, 33.4, 31.8, 31.6, 31.1, 29.8, 29.4, 29.2, 26.4, 26.2, 24.7, 24.0, 22.6, 14.1; MS *m/z* (M^+) calcd 412.2825, obsd 412.2857.

Anal. Calcd for $C_{23}H_{40}O_6$: C, 66.96; H, 9.78. Found: C, 66.68; H, 9.90.

Alternatively, the ester (280 mg, 0.674 mmol) was stirred as before with potassium *tert*-butoxide (640 mg, 5.71 mmol) in ether (12 mL) containing H_2O (0.15 mL) for 24 h to give **3** in 96% yield.

(5R,6S*,11S*,17S*)-17-Hydroxy-1,7,12-trioxatrispiro[4.0.4.0.4.3]-octadecan-16-one (23).* To a cold (-78 °C), magnetically stirred solution of **22** (1.00 g, 3.76 mmol) in anhydrous THF (50 mL) was added potassium hexamethyldisilazide (14.91 mL of 0.5 M in toluene, 7.5 mmol) followed by chlorotrimethylsilane (1.04 g, 9.53 mmol) 3 h later. The reaction mixture was allowed to warm slowly to rt, stirred overnight, and quenched with saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with ether (3 x 75 mL), the combined organic solutions were dried and concentrated, and the resulting oil was taken up in CH_2Cl_2 (75 mL), and treated with $NaHCO_3$ (2.0 g, 24 mmol) and *m*-chloroperbenzoic acid (2.0 g of 90% purity, 10.5 mmol) in several portions. After being stirred for 24 h, this mixture was quenched with saturated Na_2SO_3

solution (30 mL). Thirty min later the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic solutions were dried and concentrated to leave a residue that was dissolved in methanol (75 mL) containing pyridinium *p*-toluenesulfonate (500 mg, 2.0 mmol), stirred for 2 h, and concentrated. Purification of the product by chromatography on silica gel (gradient elution with 50-95% ether in petroleum ether) provided **23** (530 mg, 50%) as a colorless crystalline solid, mp 89 °C; IR (neat, cm^{-1}) 3500, 1725, 1450, 1060; ^1H NMR (300 MHz, $CDCl_3$) δ 4.57 (dd, J = 6.9, 12.3 Hz, 1 H), 3.95-3.56 (series of m, 6 H), 3.29 (s, 1 H), 2.67-2.59 (m, 1 H), 2.30-1.53 (series of m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.3, 92.8, 90.0, 86.9, 70.1, 69.8, 69.3, 67.4, 41.4, 33.2, 28.0, 27.5, 26.2, 25.4 (one broadened signal not pinpointed); MS *m/z* (M^+) calcd 282.1461, obsd 282.1467.

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found: C, 64.01; H, 7.80.

Methyl (2R,2'S*,2"S*)-Octahydro-2"-(2-hydroxyethyl)-[2,2':2'(3'H),2"-terfuran]-2(3H)-carboxylate (25).* Oxidation of **23** (530 mg, 1.88 mmol) with lead tetraacetate (940 mg, 2.1 mmol) in methanol (50 mL) in the manner outlined above, followed by chromatography on silica gel (elution with 50% ether in petroleum ether) gave 400 mg (68%) of **24** as a colorless oil. This material was directly reduced with sodium borohydride (350 mg, 9.2 mmol) in several portions to furnish after chromatography (gradient elution with 50-95% ether in petroleum ether) 310 mg (77%) of colorless, oily **25**; IR (neat, cm^{-1}) 3500, 1735, 1450, 1375, 1250, 1200, 1065; ^1H NMR (300 MHz, $CDCl_3$) δ 4.06-3.60 (m, 8 H), 3.17 (br s, 1 H), 2.52-2.37 (m, 2 H), 2.17-1.54 (series of m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.4, 96.1, 71.0, 69.3, 68.7, 59.6, 52.2, 37.6, 33.0 (2 C), 30.8, 26.7, 26.5, 25.1; MS *m/z* (M^+-CH_3CO_2) calcd 255.1590, obsd 255.1596.

Methyl (2R,2'S*,2"S*)-Octahydro-2"-[2-(octyloxy)ethyl]-[2,2':2'(3'H),2"-terfuran]-2(3H)-carboxylate (26).* Analogous reaction of **25** (310 mg, 9.87 mmol) in *n*-octyl iodide (4.65 g, 19.4 mmol) with silver oxide (2.64 g, 11.4 mmol) at 90 °C for 48 h gave rise to 380 mg (90%) of **26**; colorless oil; IR (neat, cm^{-1}) 1730, 1450, 1100, 1070; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05-3.60 (series of m, 7 H), 3.71 (s, 3 H), 3.55-3.45 (m, 1 H), 3.40-3.28 (m, 1 H), 2.55-1.41 (m, 1 H), 2.27-2.14 (m, 1 H), 2.07-1.65 (m, 6 H), 1.60-1.49 (m, 3 H), 1.27 (br envelope, 16 H), 0.87 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.4, 96.2, 91.5, 89.9, 71.0, 69.3, 68.6, 67.6, 52.2, 36.4, 32.8, 33.7, 32.2, 31.8, 30.7, 29.9, 29.4, 29.3, 26.9, 26.7, 26.2, 25.5, 22.6, 14.1; MS *m/z* (M^+) calcd 426.2970, obsd 426.2984.

(2R,2'S*,2"S*)-Octahydro-2"-[2-(octyloxy)ethyl][2,2':2'(3'H),2"-terfuran]-2(3H)-carboxylic Acid (4).* Treatment of **26** (380 mg, 0.89 mmol) with potassium *tert*-butoxide (800 mg, 7.14 mmol) in ether (30 mL) and water (0.15 mL) as before afforded 300 mg (82%) of **4** as a colorless oil; IR (neat, cm^{-1}) 3220, 2880, 1740, 1460, 1375, 1245, 1080; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (br s, 1 H), 4.20-3.75 (series of m, 6 H), 3.45 (t, J = 6.6 Hz, 2 H), 3.42-3.25 (m, 2 H), 2.58-2.51 (m, 1 H), 2.20-1.65 (series of m, 12 H), 1.55-1.40 (m, 2 H), 1.20 (br envelope, 11 H), 0.84 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.8, 95.9, 90.5, 89.0, 71.0, 70.7, 69.7, 69.6, 67.2, 36.7, 33.9, 32.5, 31.7, 30.2, 29.7, 29.3, 29.2, 26.8, 26.6, 26.1, 24.1, 22.5, 14.0; MS *m/z* (M^+) calcd 413.2902, obsd 413.2934.

Anal. Calcd for $C_{23}H_{40}O_6$: C, 66.94; H, 9.77. Found: C, 66.97; H, 9.68.

(5R,6R*,11R*,17S*)-17-Hydroxy-1,7,12-trioxatrispiro[4.0.4.0.4.3]octadecan-16-one (28).* A cold

(-78 °C), magnetically stirred solution of **27** (1.16 g, 4.36 mmol) in dry THF (75 mL) was treated with potassium hexamethyldisilazide (17.3 mL of 0.5 M in toluene, 8.65 mmol) followed by chlorotrimethylsilane (1.19 g, 11.0 mmol) 3 h later. Adoption of the predescribed workup after another 3 h afforded the silyl enol ether which was oxidized with *m*-chloroperbenzoic acid (1.96 g of 90%, 10.26 mmol) in several portions. The usual processing and subsequent chromatography (silica gel, elution with 50-95% ethyl acetate in petroleum ether) furnished 910 mg (73%) of **28** as a white solid, mp 82 °C; IR (neat, cm^{-1}) 3440, 1730, 1450, 1380, 1300, 1250, 1000; ^1H NMR (300 MHz, $CDCl_3$) δ 4.23 (dd, J = 8.5, 11.3 Hz, 1 H), 4.11-3.68 (s, 6 H), 3.16 (br s, 1 H), 2.19-1.73 (series of m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.0, 94.5, 92.1, 85.1, 70.5, 69.5, 68.0, 67.1, 40.9, 33.3, 32.9, 27.3, 26.8, 26.3, 25.3; MS *m/z* (M^+) calcd 282.1461, obsd 282.1475.

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found: C, 63.71; H, 8.02.

Methyl (2R,2'R*,2"R*)-Octahydro-2"-(2-hydroxyethyl)-[2,2':2'(3'H),2"-terfuran]-2(3H)-carboxylate (30).* To a stirred solution of **28** (910 mg, 3.23 mmol) in methanol (25 mL) was added lead tetraacetate (1.73 g, 3.90 mmol). After 45 min of stirring, the usual workup followed to afford 840 mg (83%) of aldehyde **29** as a clear oil; IR (neat, cm^{-1}) 1715, 1450, 1300, 1265, 1230, 1190, 1065; ^1H NMR (300 MHz, $CDCl_3$) δ 9.65 (t, J = 2.9 Hz, 1 H), 3.99-3.80 (m, 6 H), 3.73-3.57 (m, 2 H), 3.65 (s, 3 H), 3.10 (dd, J = 3.4, 15.0 Hz, 1 H), 2.35-2.25 (m, 1 H), 2.20-1.56 (series of m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.2, 174.8, 93.4, 91.3, 91.1, 70.6, 69.8, 67.7, 52.2, 50.9, 34.4, 33.2, 31.2, 27.0, 25.7, 24.4; MS *m/z* (M^++1) calcd 313.1651, obsd 313.1557.

Reduction of this material with sodium borohydride (700 mg, 18.5 mmol) in methanol (20 mL) at 0 °C and chromatography on silica gel (elution with ethyl acetate) gave rise to 740 mg (88%) of **30** as a colorless oil; IR (neat, cm^{-1}) 3460, 1730, 1450, 1265, 1230, 1200, 1065, 1020; ^1H NMR (300 MHz, $CDCl_3$) δ 4.00-3.55 (m, 8 H), 3.64 (s, 3 H), 3.40 (br s, 1 H), 2.46-2.37 (m, 1 H), 2.32-2.08 (m, 3 H), 1.99-1.55 (m, 9 H), 1.50-1.40 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.6, 94.0, 91.9, 91.5, 70.7, 69.1, 67.9, 60.0, 52.1, 39.2, 34.0, 33.9, 31.3, 26.6, 26.0, 24.4; MS *m/z* (M^+-CH_3OH) calcd 282.1461, obsd 282.1465.

Methyl (2R,2'R*,2"R*)-Octahydro-2"-[2-(octyloxy)ethyl]-[2,2':2'(3'H),2"-terfuran]-2(3H)-carboxylate (31).* Heating a mixture of **30** (740 mg, 2.36 mmol), *n*-octyl iodide (11.1 g, 46.2 mmol) and silver oxide (6.3 g, 27.2 mmol) at 90 °C for 24 h afforded 760 mg (76%) of **31**; colorless oil (neat, cm^{-1}) 1745, 1730, 1460, 1285, 1235, 1195, 1175, 1110, 1070, 1025; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05-3.25 (series of m, 10 H), 3.66 (s, 3 H), 2.35-1.45 (series of m, 16 H), 1.25 (br envelope, 10 H), 0.84 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.6, 94.0, 91.8, 90.4, 70.8, 70.7, 69.0, 68.5, 67.9, 51.9, 37.7, 34.0, 32.6, 31.74, 31.71, 29.8, 29.4, 29.2, 26.7, 26.2, 24.4, 22.6, 14.0; MS *m/z* (M^+) calcd 426.2981, obsd 426.2977.

Anal. Calcd for $C_{24}H_{42}O_6$: C, 67.57; H, 9.93. Found: C, 67.36; H, 9.94.

(2R,2'R*,2"R*)-Octahydro-2"-[2-(octyloxy)ethyl][2,2':2'(3'H),2"-terfuran]-2(3H)-carboxylic Acid (5).* Hydrolysis of **31** (680 mg, 1.60 mmol) with potassium *tert*-butoxide (1.62 g, 14.5 mmol) in ether (20 mL) and water (0.1 mL) as described earlier gave rise to oily **5** (540 mg, 82%); IR (neat, cm^{-1}) 2870, 1760, 1110, 1060, 735; ^1H NMR (300 MHz, $CDCl_3$) δ 4.21 (ddd, J = 6.1, 7.8, 7.8 Hz, 1 H), 4.04-3.97 (m, 1 H), 3.86-3.68 (m, 4 H), 3.44 (dd, J = 6.8, 6.8 Hz, 1 H), 3.39-3.27 (m, 2 H), 2.76-2.69 (m, 1 H), 2.17-1.67 (series of m, 14 H), 1.55-1.46 (m, 2 H), 1.40-1.18 (series of m, 10 H), 0.85 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm

172.4, 97.5, 90.6, 89.0, 71.2, 69.9, 67.5, 66.9, 37.3, 31.9, 31.8, 30.4, 29.7, 29.4, 29.2, 27.0, 26.7, 26.6, 26.2, 22.6, 14.0; MS *m/z* (M^+) calcd 412.2825, obsd 412.2836.

Anal. Calcd for $C_{23}H_{40}O_6$: C, 66.96; H, 9.78. Found: C, 66.81; H, 9.69.

Methyl (2R,2'R*,2"S*)-2"-(Formylmethyl)octahydro[2,2':2'(3'H),2"-terfuran]-2(3H)-carboxylate (33).* Oxidation of **32** (100% α) (170 mg, 0.60 mmol) with lead tetraacetate (970 mg, 2.19 mmol) in methanol (20 mL) at 0 °C for 2 h delivered 140 mg (74%) of **33** as a colorless oil; IR (neat, cm^{-1}) 1730, 1450, 1275, 1240, 1200, 1080, 1025; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (d, J = 1.1 Hz, 1 H), 4.00-3.60 (m, 6 H), 3.47 (s, 3 H), 2.88 (d, J = 2.3 Hz, 1 H), 2.40-1.65 (series of m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.3, 174.7, 93.1, 91.6, 89.8, 69.9, 69.4, 68.6, 52.2, 51.1, 33.9, 33.3, 31.9, 26.8, 26.3, 24.8; MS *m/z* (M^+) calcd 312.1571, obsd 312.1561.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 61.52; H, 7.75. Found: C, 61.85; H, 7.76.

Comparable oxidation of the β-isomer afforded **33** in 97% yield.

Methyl (2R,2'R*,2"S*)-Octahydro-2"-(2-hydroxyethyl)-[2,2':2'(3'H), 2"-terfuran]-2(3H)-carboxylate (34).* Reduction of **33** (240 mg, 0.77 mmol) in methanol (20 mL) with sodium borohydride (210 mg, 5.6 mmol) as before gave **34** as a colorless oil (180 mg, 75%); IR (neat, cm^{-1}) 3460, 1730, 1070, 1020; ^1H NMR (300 MHz, $CDCl_3$) δ 4.00-3.76 (m, 6 H), 3.69 (s, 3 H), 3.64-3.56 (m, 2 H), 2.96 (s, 1 H), 2.72-2.62 (m, 1 H), 2.36-2.31 (m, 2 H), 2.25-1.65 (series of m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 175.1, 94.1, 92.8, 91.6, 70.1, 69.1, 69.0, 59.8, 52.3, 38.5, 34.2, 32.6, 31.6, 28.3; MS *m/z* (M^+) calcd 314.1729, obsd 314.1711.

Methyl (2R,2'R*,2"S*)-Octahydro-2"-[2-(octyloxy)ethyl]-[2,2':2'(3'H),2"-terfuran]-2(3H)-carboxylate (35).* A mixture of **34** (180 mg, 0.57 mmol) and silver oxide (2.64 g, 11.4 mmol) in *n*-octyl iodide (4.0 g, 17.0 mmol) was heated at 90 °C for 24 h and worked up as above to give 170 mg (72%) of **35** as a colorless oil; IR (neat, cm^{-1}) 3460, 1740, 1465, 1270, 1240, 1200, 1180, 1080; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94-3.29 (series of m, 13 H), 2.46-1.15 (series of m, 26 H), 0.86-0.80 (m, 3 H), ^{13}C NMR (75 MHz, $CDCl_3$) ppm 175.1, 94.3, 91.6, 89.8, 70.9, 70.1, 68.9, 68.7, 67.3, 52.2, 37.1, 32.0, 31.7, 31.4, 29.4, 29.3, 29.2, 27.8, 27.3, 26.2, 25.7, 25.1, 22.6, 14.0; MS *m/z* (M^+) calcd 426.2981, obsd 426.2951.

Anal. Calcd for $C_{24}H_{42}O_6$: C, 67.57; H, 9.93. Found: C, 67.73; H, 10.06.

(2R,2'R*,2"S*)-Octahydro-2"-[2-(octyloxy)ethyl][2,2':2'(3'H),2"-terfuran]-2(3H)-carboxylic Acid (6).* Treatment of **35** (170 mg, 0.41 mmol) with potassium *tert*-butoxide (460 mg, 4.11 mmol) in ether (15 mL) and water (0.15 mL) as described earlier afforded 100 mg (61%) of **6** as a colorless oil; IR (neat, cm^{-1}) 3220, 2890, 1775, 1470, 1380, 1070, 920; ^1H NMR (300 MHz, $CDCl_3$) δ 4.06-3.97 (m, 2 H) 3.84-3.69 (m, 4 H), 3.50-3.38 (m, 2 H), 3.37-3.32 (m, 2 H), 2.59-2.52 (m, 1 H), 2.23-1.76 (series of m, 13 H), 1.58-1.48 (m, 2 H), 1.42-1.22 (m, 11 H), 0.86 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.0, 91.0, 90.9, 88.7, 71.2, 70.8, 69.3, 67.9, 67.2, 37.6, 32.3, 32.0, 31.8, 30.5, 29.8, 29.4, 29.2, 27.1, 26.7, 26.4, 26.2, 22.6, 14.0; MS *m/z* (M^+) calcd 412.2825, obsd 412.2823.

Anal. Calcd for $C_{23}H_{40}O_6$: C, 66.96; H, 9.78. Found: C, 66.80; H, 9.90.

Determination of Association Constants K_a. All ultraviolet (UV) measurements were made on a Hewlett Packard 8452A diiode array spectrophotometer at 24-26 °C and 380 nm. All glassware was base-

washed and rinsed sequentially with acetone and distilled, demineralized water (twice) prior to drying. All volume transfers were done by difference using Hamilton gas tight syringes. Spectral grade solvents and distilled, demineralized water were used throughout. Host solutions that were 0.02-0.075 M in $CDCl_3$ were prepared in 200 mL volumetric flasks. Picrate salts were oven-dried at 85 °C for at least 48 h prior to use. Aqueous solutions were prepared in 25.00 mL volumetric flasks that were 0.0150 M in Li^+, Na^+, and K^+ picrate. Into each of several 12-mL centrifuge tubes was transferred 0.50 mL of the appropriate picrate solution, and to another was added 1.0 mL of H_2O. To each of the tubes including the one containing H_2O was added 0.20 mL of the host solution. The tubes were covered immediately by glass stoppers and briefly centrifuged to force the organic phase completely to the bottom of each tube. The two layers in each tube were mixed thoroughly with a Vortex Genie for 1 min. The tubes were then placed in the centrifuge for 10 min at high speed. Aliquots varying from 50-100 μL of the organic phase (depending on its color intensity) were carefully removed from each tube and transferred to 5-mL volumetric flasks which were filled to the mark with CH_3CN. For each aliquot size, a blank was also made by measuring the desired volume from the $CDCl_3$ layer of the H_2O blank, placing it in a 5-mL volumetric flask, and diluting to the mark with CH_3CN. The UV absorption of each 5 mL solution was measured against the appropriate blank solution at 380 nm. The same cell with the same orientation in the spectrophotometer was used for each solution. Ten measurements were made for each sample and averaged. The average of these values for the several solutions was used as the absorbance (a).

The association constants K_a were calculated using the equation:

$$K_a = R / \{(1-R)K_d\{[G_i]_{aq}-R[H_i]_{org}(V_{org}/V_{aq})\}^2\}$$

where R is the molar ratio of picrate to host; K_d is the distribution constant of the picrate salts between the two layers in the absence of host; $[G_i]_{aq}$ is the initial concentration of the guest (picrate salt) in H_2O; $[H_i]_{org}$ is the initial host concentration in $CDCl_3$; V_{org} is the volume of $CDCl_3$, V_{aq} is the volume of H_2O.

The R value was obtained using the Boer's Law relationship a = ebc, where a is the absorbance, e is the extinction coefficient, b is the path length of the cell, and c is the concentration of the measured species. [The values of the extinction coefficient (e) used for each salt were those determined by Cram et al. (reference *a* of Table I) and are as follows (at 380 nm in CH_3CN): e (lithium picrate) = 16,900; e (sodium picrate) = 16,900; e (potassium picrate) = 16,900]. The total millimoles of picrate in the measured aliquot was equal to the product of c (= abe) and the volume of the measured solution which was 5 mL. The millimoles of host was the product of the host concentration and the aliquot volume. The guest to host molar ratio, R, which was the same in the measured aliquot as in the original $CDCl_3$ layer, was given by the millimoles of picrate salt divided by the millimoles of host.

The K_d values used in the calculation of each K_a were those measured by Cram and coworkers and are as follows: 1.42×10^{-3} for lithium picrate; 1.74×10^{-3} for sodium picrate; and 2.55×10^{-3} for potassium picrate.

Phospholipid Bilayer Transport Studies. Large unilamellar vesicles were prepared from egg-yolk phosphatidylcholine by a modification of the dialytic detergent removal technique introduced by Reynolds and coworkers[15] and described in our previous papers.[7-12] A typical preparation would have a total of ca 50-60 μmol of lipid in 3 cm^3 of aqueous lithium chloride solution (100 mM). Three 12 h dialyses (> 2 liters each) at 40 °C produced large detergent-free unilamellar vesicles (LUV). The vesicle suspension was split into three

measured portions of about 1 cm^3 each and to each portion was added an equal volume of a solution containing sodium tripolyphosphate (10 mM), sodium chloride (50 mM), and choline chloride (20 mM). A small amount (1-2 μL) of a solution of dysprosium chloride (1 M) was then added to generate a chemical shift difference of ca 4.5 ppm between the 'in' and 'out' ^{23}Na signals.

^{23}Na NMR spectra were recorded on a Bruker MSL500 spectrometer in St. Andrews operating in high resolution mode using 10 mM o.d. tubes. In all cases, the spectrometer was field-frequency locked on the ^{2}H signal from $^{2}H_2O$ in the inner compartment of a coaxial tube. All spectra were obtained at ambient laboratory temperature (293 K). Passive exchange of the Li^+ inside the vesicles (initially 100% of the alkali metal ions in) with the Na^+ outside the vesicles (initially 50% of the alkali metal ions out) was followed by measuring the intensity of the 'in' signal for ca 20 min, at which point an aliquot of ionophore in methanol solution (a few μL) was added rapidly and the rate of passive plus mediated exchange was measured. The amount of ionophore added was sufficient to generate an ionophore/PC ratio of between 1/1000 and 1/200. The infinity value for the 'in' signal was found either by allowing the system itself to reach equilibrium or by adding a small amount of an efficient naturally occurring ionophore such as salinomycin. The difference between the two rates gave the mediated rate of exchange.

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