on the final cycle of refinement was 2% of its estimated standard deviation. In the final difference Fourier synthesis, there were peaks of +0.3 and -0.3 e/Å$^3$ around the Cl atom and a peak of 0.4 e/Å$^3$ in the middle of the C(1)-C(9) bond. Final parameters are given in Tables V-VII and may be obtained as supplementary material.

**Acknowledgment.** We gratefully acknowledge support of this work by the College of Arts and Sciences of the Oklahoma State University in the form of salary (to K.D.B.) and the USPHS, National Cancer Institute, in the form of a grant (to D.v.d.H.; No. CA 17562).

**Registry No. 1a**, 77716-01-9; **1b'**, 77716-02-0; **1b''**, 77716-03-1; **1c'**, 77716-04-2; **1c''**, 77716-05-3; **1d**, 77716-06-4; **1e**, 77716-07-5; **1f** (isomer 1), 77716-08-6; **1f** (isomer 2), 77716-09-7; **1g**, 77743-50-1; **1h**, 77789-89-0; **2**, 18458-71-4; **3**, 18458-72-5; **4**, 29943-42-8; **5**, 62513-33-1; **6**, 77727-42-5; **7**, 77716-10-0; benzaldehyde, 100-52-7; 2-chlorobenzaldehyde, 89-98-5; paraformaldehyde, 30525-89-4; benzylamine, 100-46-9; bromobenzene, 108-86-1.

**Supplementary Material Available:** Table V (fractional coordinates of the unique atoms in **1e**), Table VI (hydrogen atom parameters), and Table VII (anisotropic thermal parameters) (3 pages). Ordering information is given on any current masthead page.

# Syntheses of Four Thiol-Substituted Crown Ethers

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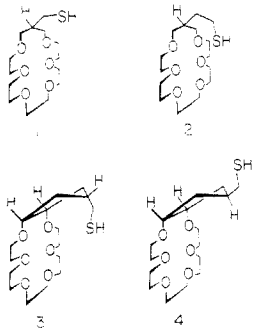
*Received February 4, 1981*

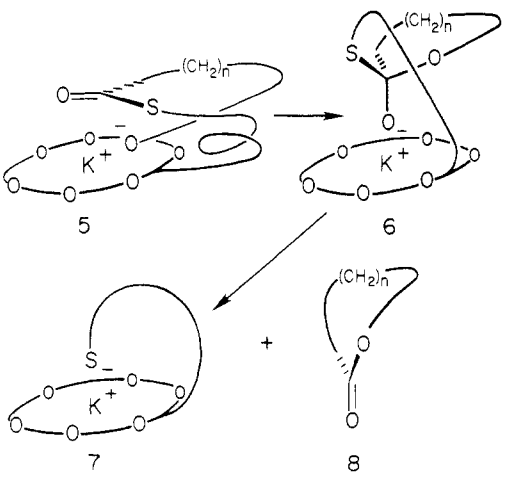
Approaches to thiol-substituted crown ethers of the 18-crown-6 and 19-crown-6 classes are described. Different modes of covalent attachment of the thiol to the crown ether provide variations in the spatial relationship of the thiol to the crown ether binding site.

Interactions of polyether ionophores with a broad range of cations have been extensively examined.[2] The nature of the host-guest[3] interaction is governed by the number, spacing, and identity of the donor atoms which make up the host binding site. Variations in substituents proximate to the binding sites have been used to alter binding specificity and/or chemical reactivity of the ionophores toward substrate ion pairs.[4] Herein we describe the synthesis of the crown ether series **1-4** in which the spatial relationship

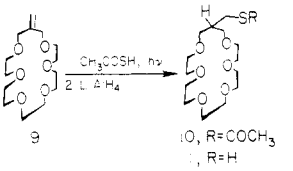


between the thiol and the binding site is varied through changes in the appendage between thiol and crown ether. The accompanying paper[5] describes the syntheses of potassium ω-alkoxy thioesters (e.g., **5**, Scheme I) from thiols **1-4** and discusses the effect of ionophore structure on the conversion of these reactive intermediates into macrocyclic lactones (macrolides) as depicted schematically in structures **5** → **6** → **7** + **8**.

Scheme I



Scheme II



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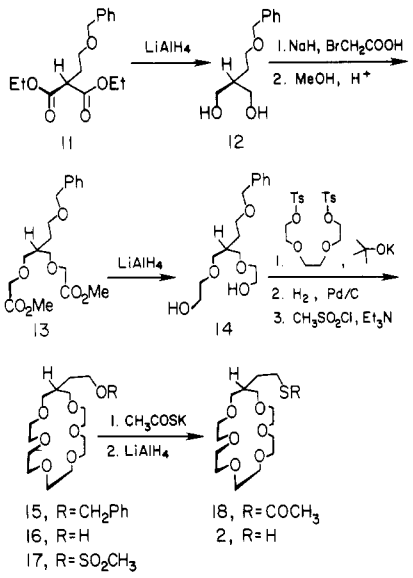
(2) For recent reviews see: (a) Stoddart, J. F. *Chem. Soc. Rev.* **1979**, *8*, 85; (b) Poonia, N. S.; Bajaj, A. V. *Chem. Rev.* **1979**, *79*, 389; (c) Izatt, R. M., Christensen, J. J., Eds. "Synthetic Multidentate Macrocyclic Compounds"; Academic Press: New York, 1978; (d) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8; (e) Fenton, D. E. *Chem. Soc. Rev.* **1977**, *6*, 325; (f) Gokel, G. W.; Durst, H. D. *Aldrichimica Acta* **1976**, *9*, 3; (g) *Synthesis* **1976**, 168; (h) Cram, D. J. *Tech. Chem. (N.Y.)* **1976**, *10*, 815; (i) Cram, D. J. *Pure Appl. Chem.* **1975**, *43*, 327.

(3) "Host-guest chemistry" is discussed by: Cram, D. J., Cram, J. M. *Science* **1974**, *183*, 803.

(4) For examples see: (a) Newcomb, M.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6405; (b) Shinkai, S.; Nakaji, T.; Nishida, Y.; Ogawa, T.; Manabe, O. *Ibid.* **1980**, *102*, 5860; (c) Chao, Y.; Weisman, G. R.; Sogah, G. D. Y.; Cram, D. J. *Ibid.* **1979**, *101*, 4948; (d) McKervey, M. A.; Mulholland, D. L. *J. Chem. Soc., Chem. Commun.* **1977**, 438; (e) Chang, C. K. *J. Am. Chem. Soc.* **1977**, *99*, 2819; (f) van Bergen, T. J., Kellogg, R. M. *Ibid.* **1977**, *99*, 3882; (g) ref 1a.

(5) Rastetter, W. H.; Phillion, D. P. *J. Org. Chem.*, following paper in this issue.

Scheme III




## Synthetic Approaches

**Mercaptomethyl Crown Ether 1.** Crown ether **9** (Scheme II), assembled from pentaethylene glycol and 3-chloro-2-(chloromethyl)-1-propene as described by Tomoi et al.,[6] serves as precursor for thiol-substituted crown ether **1**. Photochemical addition of thioacetic acid to **9** yields thioester **10**; reductive cleavage of **10** with $LiAlH_4$ yields thiol **1** (overall 82% from **9**).

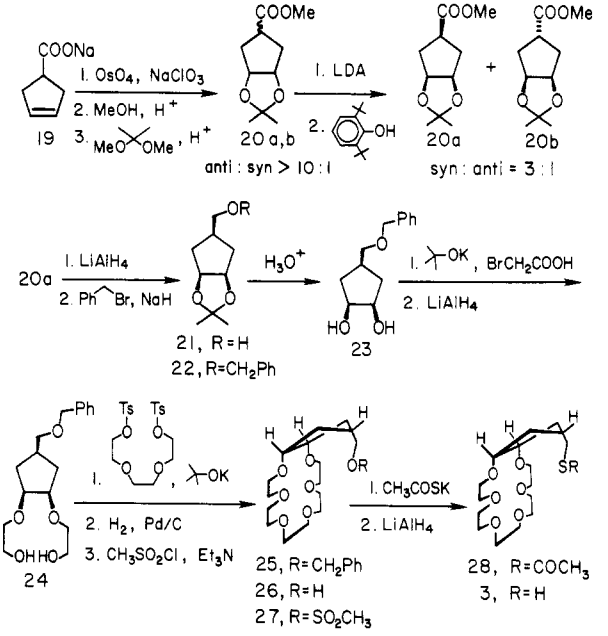
**Mercaptoethyl Crown Ether 2.** The functionalized segment of crown ether **2** is derived from malonic diester **11** (Scheme III). Reduction (**11** → **12**, 84%), homologation (**12** → **13** → **14**, overall 48%), and coupling with triethylene glycol ditosylate (57%) produces protected crown ether **15**. Hydrogenolysis and mesylation (**15** → **16** → **17**, overall 96%), displacement with potassium thioacetate, and reductive cleavage (**17** → **18** → **2**, overall 60%) afford the mercaptoethyl crown ether **2**.

The homologation sequence of Scheme III is preferable to direct coupling of diol **12** with pentaethylene glycol ditosylate. The latter route leads mainly to elimination of the tosylate rather than coupling.

**Convergent (3) and Divergent (4) Cyclopentano Crown Ethers.** The thiol appendages of epimeric crown ethers **3** and **4** converge and diverge, respectively, from the host binding site. Each crown ether is assembled from the corresponding epimer of acetonide methyl ester **20a,b**[7] (Scheme IV). The anti isomer **20b** is formed in preference to **20a** in a ratio greater than 10:1 by the sequence depicted in Scheme IV. The mixture can be converted into essentially pure **20b** upon treatment with methoxide.[7] In contrast, kinetic protonation of the lithium enolate derived from the mixture **20a,b** by hindered 2,6-di-*tert*-butylphenol gives predominantly (3:1) the syn isomer **20a**. Other proton sources (see Experimental Section) give lower syn/anti ratios in the kinetic protonation of the enolate.

Convergent cyclopentano crown ether **3** is assembled from protected syn diol ester **20a** as shown in Scheme IV. Reduction of **20a** (92%) produces differentially protected triol **21**. Conversion of **21** into **3** follows closely the protocol used to assemble crown ether **2** (Scheme III). Namely, **21** is benzylated (**21** → **22**, 89%) and deprotected (**22** → **23**, 100%). Homologation (**23** → **24**, 78%) and coupling with triethylene glycol ditosylate (65%) afford the cyclopentano crown **25**. The thiol is introduced via the sequence **25** → **26** → **27** → **28** → **3** (overall 58%).

Scheme IV




Protected anti diol ester **20b** (Scheme IV) displays the stereochemistry required for divergent cyclopentano crown ether **4**. Reduction to a differentially protected triol (see syn isomer **21**) and further elaboration as shown for the convergent series in Scheme IV gives crown ether **4**.

## Discussion

We have described[5,8] the use of thiol-substituted crown ethers as templates to facilitate ring closure of macrolides. As shown in general form in Scheme I, the generation of an $\omega$-alkoxy thioester (**5**) leads to an *S*- to *O*-acyl transfer, via **6**, affording crown thiolate salt **7** and macrolide **8**. The crown ether–potassium complex in **5** serves as an ionic template drawing the alkoxide oxygen into the proximity of the bound cation. The length and structure of the appendage connecting the ionophore to the thioester (coiled linkage in **5**) dictate the placement of the thioester relative to the reactive alkoxide and govern the facility of the ring closure step **5** → **6**. The appendage in the ideal crown template serves to anchor the mutually reactive alkoxide and thioester in close proximity and then allows the new alkoxide in **6** to form in intimate contact with the bound potassium cation. The influence of thiol/binding site geometry on functional group interactions in macrolide intermediates **5** and **6** is described in detail in the accompanying paper.[5]

## Experimental Section

**General Methods.** The following abbreviations are used: THF, tetrahydrofuran; LDA, lithium diisopropylamide; DMF, *N,N*-dimethylformamide; DMAP, 4-(dimethylamino)pyridine; DCC, *N,N'*-dicyclohexylcarbodiimide; DCU, *N,N'*-dicyclohexylurea.

$^1H$ NMR spectra (60 MHz) were obtained on a Varian T-60 or Hitachi Perkin-Elmer R-24B spectrometer; high-resolution $^1H$ NMR spectra (250 MHz) were obtained on a Bruker WM-250 superconducting spectrometer. Chemical shifts are reported downfield from $(CH_3)_4Si$ on the $\delta$ scale. Infrared spectra were

(6) Tomoi, M.; Abe, O.; Ikeda, M.; Kihara, K.; Kakiuchi, H. *Tetrahedron Lett.* **1978**, 3031.

(7) The assignment of stereochemistry for **20a** and **20b** is presented by: David, S.; Lepine, M.-C.; Lubineau, A. *Bull Soc. Chim. Fr.*, **1972**, 3580.

(8) (a) Rastetter, W. H.; Phillion, D. P. *Tetrahedron Lett.* **1979**, 1469; (b) *J. Org. Chem.* **1980**, *45*, 1535.

obtained on a Perkin-Elmer 567 or 283B grafting infrared spectrophotometer. High-resolution mass spectra were recorded on a Mattauch-Herzog (Du Pont Instruments) mass spectrometer.

Melting points are uncorrected and were obtained in open capillaries with a Mel-Temp or a Thomas-Hoover melting point apparatus. Analytical liquid chromatography (LC) was performed with a Waters Associates Model ALC/GPC 204 system. Analytical vapor-phase chromatography (GLC) was performed with a Varian Series 3700 chromatograph (flame-ionization detector).

Thin-layer chromatography (TLC) plates were plastic- or glass-backed E. Merck 0.2-mm silica gel F-254 and plastic-backed E. Merck 0.2-mm neutral aluminum oxide 60 F-254 (Type E). Ultraviolet light, 7.5% ethanolic phosphomolybdic acid, or an iodine tank was used in TLC visualization. Column chromatography employed E. Merck silica gel 60 (70–230 mesh) or Ventron basic, neutral, or acidic aluminum oxide (60 mesh). Flash chromatography was performed according to Still et al.[9] by using E. Merck silica gel 60 (230–400 mesh) or Mallinckrodt silicic acid (100 mesh). All preparative-scale silica gel flash chromatographic separations were performed in a 50-mm column filled to a height of ca. 6 in. with adsorbent; compound loadings of ca. 3.0 g per separation were used. Preparative scale silicic acid flash chromatographic separations were performed in a 20 mm column filled to a height of ca. 4 in. with adsorbent; compound loadings of ca. 3.0 g per separation were used.

THF was dried by distillation from sodium–benzophenone ketyl. Benzene, $CH_2Cl_2$, and DMF reagent solvents were statically dried over activated 4-Å sieves. Dry reagent Mallinckrodt $Et_2O$ was used directly. A nitrogen atmosphere was used in reactions employing dry solvents; an air atmosphere was used in reactions employing aqueous media.

**Mercaptomethyl Crown Ether 1.** A stirred solution of olefin crown ether **9**[6] (9.00 g, 31.0 mmol) in thioacetic acid (25 mL, 350 mmol) was photolyzed at ambient temperature overnight with a Hanovia medium-pressure Hg lamp (quartz apparatus). The mixture was concentrated in vacuo, a second portion of thioacetic acid added (25 mL, 350 mmol), and the photolysis repeated under the same conditions. Removal of excess thioacetic acid in vacuo afforded crude thioacetate **10** as a yellow oil. GLC analysis (4.2% SE-30) revealed 100% conversion of **9** into **10**: $^1$H NMR (60 MHz, $CDCl_3$) 1.23 (1 H, m), 2.29 (3 H, s), 2.94 (2 H, d, $J$ = 7 Hz), 3.50 (4 H, d, $J$ = 6 Hz), 3.60 (20 H, m). The photoadduct was used in the next step without purification.

Crude thioacetate **10** (31.0 mmol) in THF (32 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (2.7 g, 71 mmol) in THF (30 mL). The resulting mixture was stirred overnight and carefully acidified (10% aqueous HCl). Extractive workup ($H_2O/CH_2Cl_2$) and high-vacuum distillation afforded mercaptomethyl crown ether **1** (8.27 g, 82% from olefin **9**) as a colorless oil. An analytically pure sample was prepared by silicic acid flash chromatography (sequentially eluted with 1:1 $Et_2O$–pentane, EtOAc, and THF) then Kugelrohr distillation [200–220 °C ($10^{-5}$ mmHg)]: $^1$H NMR (250 MHz, $CDCl_3$) 1.32 (1 H, t, $J$ = 8.5 Hz), 1.99 (1 H, septet, $J$ = 5.9 Hz), 2.61 (2 H, dd, $J$ = 6.6, 8.5 Hz), 3.51–3.68 (24 H, m); IR (neat, NaCl) 2860, 2550, 1466, 1447, 1350, 1290, 1247, 1110 (br), 1035, 987, 939, 850, 740 cm$^{-1}$; exact mass calcd for $C_{14}H_{27}O_6$ ($M^+$ – SH) $m/e$ 291.180 77, found 291.177 56. Anal. Calcd for $C_{14}H_{28}O_6S$: C, 51.83, H, 8.70; O, 29.59; S, 9.88. Found: C, 51.81; H, 8.74; O, 29.73; S, 9.64.

**Diethyl [2-(Benzyloxy)ethyl]malonate (11).** To a stirred suspension of NaH (2.9 g, 120 mmol) in THF (30 mL) cooled with an ice–water bath was added dropwise diethyl malonate (31.7 g, 200 mmol). To the resulting enolate solution was added 2-(benzyloxy)ethyl bromide (22.25 g, 103 mmol), and the mixture was refluxed for 5 h. Extractive workup ($H_2O/CHCl_3$), chromatography (90 g silica gel, $Et_2O$), and distillation in vacuo afforded 26.32 g (87%) of colorless oily diester **11**: $^1$H NMR (60 MHz, $CDCl_3$) 1.23 (6 H, t, $J$ = 7 Hz), 2.20 (2 H, q, $J$ = 7 Hz), 3.50 (2 H, t, $J$ = 7 Hz), 3.57 (1 H, t, $J$ = 7 Hz), 4.13 (4 H, q, $J$ = 7 Hz), 4.43 (2 H, s), 7.27 (5 H, s); exact mass calcd for $C_9H_{15}O_5$ ($M^+$ – $C_7H_7$) $m/e$ 203.091 95, found 203.092 88.

**Diol 12.** A solution of diester **11** (26.32 g, 89.4 mmol) in $Et_2O$ (130 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (6.80 g, 179.2 mmol) in $Et_2O$ (50 mL) cooled with an ice–water bath. The reaction mixture was warmed to ambient temperature, stirred overnight, and then quenched carefully by the addition of excess $Na_2SO_4 \cdot 10H_2O$. After the mixture was stirred several hours, the resulting thick white suspension was filtered, and the salts were washed thoroughly with hot THF. The combined filtrates were concentrated under reduced pressure and then distilled in vacuo, affording 15.86 g (84%) of pure, oily diol **12**: $^1$H NMR (60 MHz, $CCl_4$) 1.53 (3 H, m), 3.43 (6 H, m), 4.00 (2 H, t, $J$ = 5 Hz, $D_2O$ exchangeable), 4.37 (2 H, s), 7.17 (5 H, s); exact mass calcd for $C_{12}H_{16}O_2$ ($M^+$ – $H_2O$) $m/e$ 192.115 03, found 192.117 90.

**Homologated Diol 14.** A solution of bromoacetic acid (287.3 g, 2.07 mol) in THF (500 mL) was added dropwise to a stirred mixture of diol **12** (167.4 g, 0.796 mol) and NaH (98 g, 4.08 mol) in THF (2.55 L) cooled with an ice–water bath. The resulting thick, white suspension was refluxed for 8 h, cooled to ambient temperature, and concentrated under reduced pressure. The residual oily solid was diluted with $CH_3OH$ (4.5 L), carefully acidified with $H_2SO_4$ (90 mL, 1.69 mol), and refluxed overnight. Removal of the solvent, extractive workup ($H_2O/Et_2O$), filtration through alumina (900 g, EtOAc), and distillation in vacuo ($10^{-5}$ mmHg) afforded oily diester **13**: $^1$H NMR (60 MHz, $CDCl_3$) 1.69 (2 H, q, $J$ = 7 Hz), 2.09 (1 H, m), 3.49 (6 H, m), 3.63 (6 H, s), 3.96 (4 H, s), 4.40 (2 H, s), 7.16 (5 H, s); exact mass calcd for $C_{18}H_{28}O_7$ ($M^+$) $m/e$ 354.167 85, found 354.168 59.

The distillate (diester **13**) was added to THF (200 mL) and the resulting solution added dropwise to an excess of $LiAlH_4$ (60.4 g, 1.6 mol) in THF (1.0 L) cooled with an ice–water bath. The mixture was stirred overnight at ambient temperature and then quenched carefully by the addition of $Na_2SO_4 \cdot 10H_2O$. After the mixture was stirred several hours, the resulting thick, white suspension was filtered, and the collected salts were washed thoroughly with hot THF. The combined filtrates were concentrated under reduced pressure and then chromatographed (1000 g, silica gel, EtOAc and then THF), affording 113.5 g (48% from **12**) of pure, oily diol **14**: $^1$H NMR (60 MHz, $CDCl_3$) 1.63 (2 H, q, $J$ = 7 Hz), 2.05 (1 H, m), 3.05 (2 H, br s), 3.52 (14 H, m), 4.48 (2 H, s), 7.30 (5 H, s); exact mass calcd for $C_{16}H_{26}O_5$ ($M^+$) $m/e$ 298.178 02, found 298.178 75.

**(Benzyloxy)ethyl Crown Ether 15.** A solution of triethylene glycol ditosylate (30.8 g, 67.2 mmol) in THF (300 mL) was added rapidly to a stirred solution of *t*-BuOK (15.7 g, 139.9 mmol) and diol **14** (20.0 g, 67.0 mmol) in THF (1.04 L). The mixture then was heated to 35 °C and stirred for 3 days. After cooling to ambient temperature, the mixture was filtered, and the collected salts were washed with THF. The combined filtrates were concentrated, affording a thick, dark oil which was extracted with hot hexanes to remove the soluble crown ether from insoluble polymer. Concentration of the hexane extracts and chromatography (basic alumina, 40:1 by weight vs. crude **15**, hexane to EtOAc gradient) gave 15.8 g (57%) of oily crown ether **15**: $^1$H NMR (60 MHz, $CDCl_3$) 1.63 (2 H, q, $J$ = 7 Hz), 2.00 (1 H, m), 3.52 (26 H, m), 4.45 (2 H, s), 7.25 (5 H, s); IR (neat, NaCl) 3085, 3060, 3030, 2860, 1451, 1351, 1295, 1248, 1206, 1115 (br), 740, 700 cm$^{-1}$.

**Mercaptoethyl Crown Ether 2.** A solution of benzyl ether **15** (14.5 g, 35.2 mmol) in $CH_3OH$ (200 mL) was hydrogenated (Parr apparatus) over 10% Pd/C (0.995 g) until hydrogen uptake ceased. The resulting mixture was filtered and then concentrated under reduced pressure, giving crown ether alcohol **16** (11.8 g) in quantitative yield: $^1$H NMR (60 MHz, $CDCl_3$) 1.63 (2 H, q, $J$ = 6 Hz), 2.03 (1 H, m), 3.27 (1 H, br s), 3.60 (26 H, m); IR (neat, NaCl) 3450 (br), 2870, 1450, 1353, 1300, 1250, 1115 (br) cm$^{-1}$.

A solution of $CH_3SO_2Cl$ (3.3 mL, 42.6 mmol) in $CH_2Cl_2$ (80 mL) was added dropwise to a stirred solution of alcohol **16** (11.8 g, 35.2 mmol) and $Et_3N$ (8.0 mL, 57.4 mmol) in $CH_2Cl_2$ (120 mL) cooled to –10 °C. After the addition the mixture was stirred 20 min, diluted with cold $CH_2Cl_2$, and washed sequentially with cold 5% HCl(aq), cold saturated $NaHCO_3$(aq), and cold $H_2O$. Drying ($MgSO_4$) and removal of solvent afforded oily mesylate **17**: 14.7 g (96%); $^1$H NMR (60 MHz, $CDCl_3$) 1.86 (3 H, m), 2.97 (3 H, s), 3.54 (24 H, m), 4.30 (2 H, t, $J$ = 7 Hz).

A mixture of mesylate **17** (14.7 g, 36.7 mmol) and potassium thioacetate (6.30 g, 55.2 mmol) in acetone (160 mL) was refluxed overnight. The mixture then was cooled, filtered, and concentrated under reduced pressure. The resulting oil was partitioned between

(9) Still, W. C.; Kahn, M., Mitra, A. *J. Org. Chem.* 1978, *43*, 2923.

$H_2O$ and $CHCl_3$, and the organic phase was dried ($MgSO_4$) and concentrated to afford oily thioacetate **18**. TLC (neutral alumina, EtOAc) indicated complete conversion of mesylate **17** into thioester **18**: $^1H$ NMR (60 MHz, $CDCl_3$) 1.74 (3 H, m), 2.26 (3 H, s), 2.91 (2 H, t, $J$ = 7 Hz), 3.52 (24 H, m); IR (neat, NaCl) 2870, 1690, 1450, 1352, 1298, 1250, 1175, 1120 (br), 939 $cm^{-1}$.

Without further purification the entire batch of thioacetate **18** (ca. 35 mmol) in THF (45 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.80 g, 47.4 mmol) in THF (30 mL). Extractive workup (10% HCl(aq)/$CHCl_3$) and column chromatography (activity III neutral alumina, 40:1 by weight vs. crude **2**, $Et_2O$) afforded oily crown thiol **2** contaminated (TLC) by symmetrical crown disulfide (from oxidation of **2** during chromatography). The oil was directly reduced with $NaBH_4$ (759.2 mg, 20.1 mmol) in EtOH (100 mL) at 0 °C for 30 min. Extractive workup (5% HCl(aq)/$CHCl_3$), drying ($MgSO_4$), and removal of solvent yielded pure oily crown thiol **2** (7.79 g, 65% from benzyl ether **15**).

A purification scheme superior to alumina chromatography (vide supra) yields analytically pure crown thiol **2** and consists of silicic acid flash column chromatography (1:1 $Et_2O$–pentane, EtOAc, and THF) followed by Kugelrohr distillation [200–220 °C ($10^{-5}$ mmHg)]: $^1H$ NMR (250 MHz, $CDCl_3$) 1.34 (1 H, t, $J$ = 7.5 Hz), 1.64 (2 H, q, $J$ = 7.5 Hz), 1.98 (1 H, septet, $J$ = 7.5 Hz), 2.56 (2 H, q, $J$ = 7.5 Hz), 3.47 (4 H, m), 3.65 (20 H, m); IR (neat, NaCl) 2860, 2550, 1445, 1349, 1290, 1247, 1110 (br), 1038, 985, 939, 865 $cm^{-1}$; exact mass calcd for $C_{15}H_{30}O_6S$ ($M^+$) $m/e$ 338.176 31, found 338.172 56. Anal. Calcd for $C_{15}H_{30}O_6S$: C, 53.23; H, 8.93; O, 28.36; S, 9.47. Found: C, 53.39; H, 9.07; O, 28.33; S, 9.19.

**Acetonide Methyl Esters 20a,b.** Epimeric esters **20a,b** were made by a modification of the literature procedure.[7] A stirred solution of cyclopentene-4-carboxylic acid[10] (51.3 g, 458 mmol), $NaHCO_3$ (46.1 g, 549 mmol), $NaClO_3$ (58.5 g, 550 mmol), and $OsO_4$ (1.0 g, 3.9 mmol) in $H_2O$ (460 mL) was heated to 70 °C for 11 h. The resulting black solution was adjusted to pH 7 with concentrated $H_2SO_4$ and then evaporated under reduced pressure. The residue was stirred with $CH_3OH$ (1.4 L) and filtered. The filtrate was made slightly acidic with concentrated $H_2SO_4$ and refluxed overnight. After neutralization with excess $NaHCO_3$, filtration, and concentration under reduced pressure, 2,2-dimethoxypropane (500 g, 4.8 mol) was added to the residue. The mixture was acidified with concentrated $H_2SO_4$, refluxed 1 h, poured into $Et_2O$, and washed with $NaHCO_3$(satd, aq) and with $H_2O$. Drying ($MgSO_4$), removal of solvent and distillation (0.5 mmHg) afforded esters **20a,b** (47.1 g, 51% from cyclopentene-4-carboxylic acid). GLC (4.2% Carbowax) indicated an approximately 13:1 ratio of anti/syn isomers, **20b** and **20a**, respectively. The isomers were characterized individually after separation (vide infra).

**Ester (20a,b) Enolate Kinetic Protonation.** To a stirred solution of LDA (353 mmol) in THF (350 mL) at −78 °C was added dropwise a solution of epimers **20a,b** (47.1 g, 235 mmol) in THF (470 mL). Stirring was continued for 30 min at −78 °C and then the solution was transferred via cannula to a stirred solution of 2,6-di-*tert*-butylphenol (218.2 g, 1.058 mol) in THF (1.05 L) at −78 °C. The mixture was stirred 5 min, warmed to ambient temperature, and concentrated under reduced pressure. Extractive workup (10% HCl(aq)/$Et_2O$, $NaHCO_3$(satd, aq) wash) and removal of solvent gave a mixture of **20a,b** and the phenol. Suction filtration of the mixture through a plug of silica gel with hexanes eluted the phenol; esters **20a,b** were eluted together with $Et_2O$. Separation of **20a** and **20b** was achieved by flash chromatography (silica gel, 30% $Et_2O$ in pentane). The separated epimers were distilled at 1 mmHg. Data for **20a** (syn isomer): 25.0 g (53%); >99% pure by GLC (4.2% Carbowax) with no detectable anti isomer (**20b**) present; $^1H$ NMR (250 MHz, $CDCl_3$) 1.24 (3 H, s), 1.35 (3 H, s), 1.85 (2 H, m), 2.45 (2 H, dd, $J$ = 3.2, 14.0 Hz), 2.79 (1 H, tt, $J$ = 3.2, 8.1 Hz), 3.67 (3 H, s), 4.61 (2 H, half an AA′XX′ pattern); IR (neat, NaCl) 2980, 2925, 1730, 1430, 1367, 1343, 1315, 1300–1110 (br), 1085, 1045, 1010, 980, 938, 918, 878, 850, 813, 785, 760 $cm^{-1}$; exact mass calcd for $C_9H_{13}O_4$ ($M^+$ − $CH_3$) $m/e$ 185.081 38, found 185.078 39. Data for **20b** (anti epimer): 6.0 g (13%); >95% pure by GLC (4.2% Carbowax) with no detectable syn isomer (**20a**) present; $^1H$ NMR (250 MHz, $CDCl_3$) 1.24 (3 H, s), 1.39 (3 H, s), 1.68 (2 H, br t, $J$ = 12–14 Hz), 2.08 (2 H, ddd, $J$ = 1.1, 6.0, 14.0 Hz), 2.98 (1 H, tt, $J$ = 6.0, 12.0 Hz), 3.63 (3 H, s), 4.62 (2 H, half an AA′XX′ pattern); IR (neat, NaCl) 2950 (br), 1730, 1435, 1370, 1310, 1290–1140 (br), 1095, 1040, 980, 930, 895, 840, 830, 800, 760 $cm^{-1}$; exact mass calcd for $C_9H_{13}O_4$ ($M^+$ − $CH_3$) $m/e$ 185.081 38, found 185.080 67.

Other proton sources gave lower syn/anti ratios in the kinetic protonation of the lithium enolate from **20a,b**. For example, $CH_3COOH$ in THF at −78 °C, 4% $CH_3COOH$ on activity I acidic alumina in THF at −78 °C, and 4% $CH_3COOH$ on silica gel in THF at −78 °C gave a 1:1 **20a/20b** ratio. Hindered 2,6-di-*tert*-butylphenol in THF at ambient temperature (rather than at −78 °C, vide supra) gave 3:2 **20a/20b**.

**Acetonide Alcohol 21.** A solution of syn acetonide ester **20a** (25.0 g, 125 mmol) in THF (125 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (7.10 g, 187 mmol) in THF (125 mL) cooled by an ice–water bath. The mixture was stirred at ambient temperature overnight, quenched carefully with excess $Na_2SO_4 \cdot 10H_2O$, and filtered, and the collected salts were washed with THF. The filtrates were combined, evaporated, and distilled (96–97 °C, 0.55 mmHg) affording pure alcohol **21** (19.9 g, 92%) as a colorless oil: >99% pure by LC (refractive index detector, 100-Å μ-Porasil, EtOAc) with no detectable anti alcohol epimer (reduction product from **20b**, vide infra) present; $^1H$ NMR (250 MHz, $CDCl_3$) 1.27 (3 H, s), 1.46 (3 H, s), 1.75–1.93 (5 H, m), 2.22 (1 H, m), 3.67 (2 H, d, $J$ = 7.4 Hz), 4.63 (2 H, half an AA′XX′ pattern); IR (neat, NaCl) 3420 (br), 2985, 2920, 1450, 1428, 1370, 1260, 1220, 1200, 1170, 1145, 1112, 1075, 1050–1000 (br), 962, 912, 873, 810, 788, 718 $cm^{-1}$; exact mass calcd for $C_8H_{13}O_3$ ($M^+$ − $CH_3$) $m/e$ 157.086 47, found 157.084 66.

**Acetonide Benzyl Ether 22.** A solution of alcohol **21** (16.9 g, 98.1 mmol) in DMF (75 mL) was added to NaH (2.90 g, 120.8 mmol) in DMF (50 mL). When $H_2$ evolution slowed, a solution of benzyl bromide (15.2 mL, 127.8 mmol) in DMF (75 mL) was added dropwise to the alkoxide solution with ice–water cooling. The mixture was stirred 2 h at 0 °C then at ambient temperature overnight. Extractive workup ($H_2O/Et_2O$) and distillation in vacuo afforded colorless oily benzyl ether **22**: 23.0 g (89%); >95% pure by LC (refractive index and UV detectors, 100-Å μ-Porasil, 1:4 $Et_2O$–pentane); $^1H$ NMR (250 MHz, $CDCl_3$) 1.25 (3 H, s), 1.36 (3 H, s), 1.84 (4 H, m), 2.30 (1 H, m), 3.50 (2 H, d, $J$ = 7.7 Hz), 4.50 (2 H, s), 4.61 (2 H, half an AA′XX′ pattern), 7.22–7.33 (5 H, m); IR (neat, NaCl) 3080, 3060, 3025, 2985, 2920, 2850, 1600, 1582, 1495, 1450, 1380, 1368, 1263, 1220, 1200, 1170, 1130–1060 (br), 1045, 1025, 960, 935, 874, 834, 730, 690 $cm^{-1}$; exact mass calcd for $C_{16}H_{22}O_3$ ($M^+$) $m/e$ 262.156 89, found 262.154 85.

**Diol Benzyl Ether 23.** A heterogeneous mixture of acetonide **22** (23.0 g, 88.0 mmol) in THF–$H_2O$ (1:1, 320 mL) containing concentrated HCl (50 drops) was stirred for 4 days. Extractive workup ($NaHCO_3$(satd, aq)/$Et_2O$) and flash chromatography (silica gel, 1:4 pentane–EtOAc yielded crystalline diol **23**: 19.5 g (100%); mp 54.5–55.0 °C; $^1H$ NMR (250 MHz, $CDCl_3$) 1.54 (2 H, dt, $J$ = 5.5, 14.3 Hz), 2.06 (2 H, ddd, $J$ = 6.6, 9.9, 14.3 Hz), 2.27 (1 H, m), 2.98 (2 H, d, $J$ = 8.5 Hz), 3.40 (2 H, d, $J$ = 3.3 Hz), 3.89 (2 H, m), 4.55 (2 H, s), 7.32 (5 H, m); IR (neat, NaCl) 3390 (br), 3080, 3060, 3025, 2925, 2850, 1600, 1583, 1495, 1453, 1400, 1360, 1205, 1075 (br), 1026, 910, 853, 800, 732, 693 $cm^{-1}$; exact mass calcd for $C_{13}H_{18}O_3$ ($M^+$) $m/e$ 222.125 59, found 222.125 43.

**Homologated Diol 24.** A solution of bromoacetic acid (123.1 g, 885.7 mmol) in THF (300 mL) was added dropwise to a stirred solution of diol **23** (19.5 g, 87.7 mmol) and potassium *tert*-butoxide (177.7 g, 1.58 mol) in THF (700 mL) cooled by an ice–water bath. The thick white suspension was stirred at ambient temperature for 3 days. The mixture was poured into excess 10% HCl(aq) and the aqueous phase extracted thoroughly with $Et_2O$. The combined $Et_2O$ extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was dissolved in THF (250 mL) and added dropwise to a stirred suspension of $LiAlH_4$ (67.2 g, 1.77 mol) in THF (250 mL) cooled by an ice–water bath. After being stirred overnight at ambient temperature, the reaction mixture was quenched carefully by addition of EtOAc (200 mL) followed by 10% HCl(aq). Extractive workup (HCl(aq)/$Et_2O$, $NaHCO_3$(satd, aq) wash) and flash chromatography (silica gel, 5% $CH_3OH$–EtOAc) afforded oily diol **24**: 21.3 g (78%); $^1H$ NMR (250 MHz, $CDCl_3$) 1.58 (2 H, dt, $J$ = 6.6, 13.2 Hz), 1.97 (2 H, m),

(10) Murdock, K. C.; Angier, R. B. *J. Org. Chem.* **1962**, *27*, 2395.

2.18 (1 H, m), 3.36 (2 H, br s), 3.38 (2 H, d, $J$ = 7.0 Hz), 3.50 (2 H, m), 3.66 (6 H, m), 3.82 (2 H, half an AA'XX' pattern), 4.48 (2 H, s), 7.31 (5 H, m); IR (neat, NaCl) 3390, 3080, 3060, 3025, 2930, 2850, 1600, 1583, 1493, 1450, 1355, 1200, 1150, 1075 (br), 925, 890, 732, 691 $cm^{-1}$; exact mass calcd for $C_{17}H_{26}O_5$ ($M^+$) $m/e$ 310.1780, found 310.1760.

**Benzyl Ether Crown 25.** A solution of diol **24** (21.3 g, 68.6 mmol) and potassium *tert*-butoxide (7.70 g, 68.6 mmol) in THF (750 mL) was maintained at 35 °C. To this mixture was added dropwise a solution of potassium *tert*-butoxide (7.70 g, 68.6 mmol) in THF (375 mL) at half the rate of addition of a second solution of triethylene glycol ditosylate (31.5 g, 68.7 mmol) in THF (375 mL). The resulting mixture was stirred 2 days and then suction filtered through a plug of activity III neutral alumina (THF). Chromatography (activity III neutral alumina, 40:1 by weight vs. crude **25**, EtOAc) yielded crown either **25**: 19.0 g (65%); $^1H$ NMR (250 MHz, $CDCl_3$) 1.58 (2 H, dt, $J$ = 6.2, 13.2 Hz), 1.94 (2 H, ddd, $J$ = 6.3, 8.8, 13.2 Hz), 2.20 (1 H, m), 3.39 (2 H, d, $J$ = 7.4 Hz), 3.68 (20 H, m), 3.82 (2 H, half an AA'XX' pattern), 4.49 (2 H, s), 7.32 (5 H, m); IR (neat, NaCl) 3080, 3060, 3025, 2920, 2860, 1448, 1345, 1288, 1243, 1196, 1105 (br), 1022, 982, 937, 730, 690, 672 $cm^{-1}$; exact mass calcd for $C_{23}H_{36}O_7$ ($M^+$) $m/e$ 424.246 10, found 424.246 56.

**Alcohol Crown Ether 26.** Hydrogenolysis of benzyl ether crown **25** (19.0 g, 44.8 mmol) by the procedure given for hydrogenolysis **15** → **16** (vide supra) gave **26** as an oil: (15.0 g (100%); $^1H$ NMR (250 MHz, $CDCl_3$) 1.68 (2 H, m), 1.93 (2 H, m), 2.21 (1 H, m), 2.44 (1 H, br s), 3.54, (2 H, t, $J$ = 4.8 Hz), 3.66 (20 H, m), 3.82 (2 H, half an AA'XX' pattern); IR (neat, NaCl) 3310 (br), 2980, 1448, 1350, 1292, 1247, 1105 (br), 940, 868, 838, 743 $cm^{-1}$; exact mass calcd for $C_{16}H_{30}O_7$ ($M^+$) $m/e$ 334.199 15, found 334.201 73.

**Convergent Cyclopentano Crown Ether Thiol 3.** The alcohol to thiol conversion **26** → **3** was accomplished via mesylate **27** and thioacetate **28** by the procedure reported for the analogous conversion alcohol **16** → mesylate **17** → thioacetate **18** → thiol **2** (vide supra). Data for mesylate **27**: white solid; $^1H$ NMR (60 MHz, $CDCl_3$) 1.55–2.38 (5 H, m), 2.97 (3 H, s), 3.66 (22 H, m), 4.13 (2 H, d, $J$ = 7 Hz). Data for oily thioacetate **28**: $^1H$ NMR (60 MHz, $CDCl_3$) 1.55–2.38 (5 H, m), 2.30 (3 H, s), 2.98 (2 H, d, $J$ = 6 Hz), 3.64 (22 H, m); IR (neat, NaCl) 2910, 1686, 1548, 1468, 1452, 1351, 1248, 1105 (br), 952, 832, 745, 652, 621 $cm^{-1}$. Data for thiol **3**: purified by column chromatography (activity III neutral alumina, 100:1 by weight vs. crude **3**, 1:1 $Et_2O$–EtOAc); yield 318 mg of oily thiol (58% from alcohol **26**); $^1H$ NMR (250 MHz, $CDCl_3$) 1.31 (1 H, t, $J$ = 8.1 Hz), 1.56 (2 H, m), 2.00 (3 H, m), 2.57 (2 H, t, $J$ = 7.4 Hz), 3.66 (20 H, m), 3.79 (2 H, half an AA'XX' pattern); IR (neat, NaCl) 2860, 2550, 1446, 1347, 1290, 1245, 1110 (br), 983, 936, 867, 840, 705 $cm^{-1}$. An analytical sample was prepared by silicic acid flash chromatography followed by Kugelrohr distillation. Anal. Calcd for $C_{16}H_{30}O_6S$: C, 54.83; H, 8.63; O, 27.39; S, 9.15. Found: C, 54.87; H, 8.68; O, 27.47; S, 8.93.

**Divergent Cyclopentano Crown Ether Thiol 4.** The route from anti acetonide ester **20b** to crown thiol **4** is exactly analogous to the route reported in detail for the conversion **20a** → **3** (vide supra). Data for the intermediates in the divergent series are given below. For identification the number of the *corresponding intermediate from the convergent series* from Scheme IV is given following the data heading for each compound.

**Data for anti acetonide alcohol (syn isomer, 21)**: bp 96–100 °C (0.85 mmHg); reduction yield 4.9 g (95%) of colorless oil; >95% pure by LC (refractive index detector, 100-Å $\mu$-Porasil, EtOAc) with no detectable syn isomer **21** present; $^1H$ NMR (250 MHz, $CDCl_3$) 1.18–1.33 (2 H, m), 1.27 (3 H, s), 1.42 (1 H, br s), 1.42 (3 H, s), 1.93 (2 H, ddd, $J$ = 1.1, 5.9, 12.9 Hz), 2.40 (1 H, ttt, $J$ = 6.0, 6.0, 12.0 Hz), 3.61 (2 H, d, $J$ = 5.9 Hz), 4.64 (2 H, half an AA'XX' pattern); IR (neat, NaCl) 3410 (br), 2920, 1440, 1425, 1370, 1300, 1260, 1205, 1170, 1130, 1100, 1080, 1037, 1019, 982, 953, 937, 912, 890, 880, 835, 826, 790, 720 $cm^{-1}$; exact mass calcd for $C_8H_{13}O_3$ ($M^+ - CH_3$) $m/e$ 157.086 47, found 157.085 29.

**Data for anti acetonide benzyl ether (syn isomer, 22)**: benzylation yield 5.7 g (76%) of oil; >99% pure by GLC (4.2% Carbowax); $^1H$ NMR (250 MHz, $CDCl_3$) 1.27 (3 H, s), 1.27 (2 H, m), 1.42 (3 H, s), 1.94 (2 H, dd, $J$ = 5.9, 14.0 Hz), 2.49 (1 H, ttt, $J$ = 6.0, 6.0, 12.0 Hz), 3.42 (2 H, d, $J$ = 6.3 Hz), 4.49 (2 H, s), 4.62 (2 H, half an AA'XX' pattern), 7.31 (5 H, m); IR (neat, NaCl) 3085, 3060, 3030, 2980, 2930, 2850, 1600, 1585, 1497, 1452, 1378, 1369, 1304, 1262, 1205, 1171, 1105 (br), 1039, 990, 959, 932, 886, 829, 732, 692 $cm^{-1}$; exact mass calcd for $C_{15}H_{19}O_3$ ($M^+ - CH_3$) $m/e$ 247.133 42, found 247.135 20.

**Data for anti diol benzyl ether (syn isomer, 23)**: acetonide hydrolysis yield 4.2 g (87%) of crystalline diol; mp 56–57 °C; $^1H$ NMR (250 MHz, $CDCl_3$) 1.65 (2 H, m), 1.85 (2 H, m), 2.26 (2 H, br s), 2.58 (1 H, m), 3.30 (2 H, d, $J$ = 6.3 Hz), 4.10 (2 H, br m), 4.48 2 H, s), 7.31 (5 H, m); IR (neat, NaCl) 3395 (br), 3085, 3060, 3010, 2930, 2855, 1493, 1470, 1450, 1436, 1405, 1362, 1212, 1070, 1022, 905, 750, 691, 660 $cm^{-1}$; exact mass calcd for $C_{13}H_{18}O_3$ ($M^+$) $m/e$ 222.125 59, found 222.126 16.

**Data for anti homologated diol (syn isomer, 24)**: homologation yield 1.70 g (61%) of oily diol; $^1H$ NMR (250 MHz, $CDCl_3$) 1.57 (2 H, dt, $J$ = 5.1, 12.1 Hz), 1.95 (2 H, m), 2.50 (1 H, m), 3.31 (2 H, d, $J$ = 6.3 Hz), 3.50 (2 H, m), 3.68 (8 H, m), 3.89 (2 H, half an AA'XX' pattern), 4.48 (2 H, s), 7.30 (5 H, m); IR (neat, NaCl) 3380 (br), 3080, 3050, 3020, 2920, 2860, 1600, 1580, 1492, 1448, 1352, 1200, 1075 (br), 897, 805, 728, 690 $cm^{-1}$; exact mass calcd for $C_{10}H_{19}O_5$ ($M^+ - C_7H_7$) $m/e$ 219.123 25, found 219.121 89.

**Data for divergent benzyl ether crown (convergent isomer, 25)**: yield 1.18 g (51%) of oily crown ether; $^1H$ NMR (250 MHz, $CDCl_3$) 1.51 (2 H, dt, $J$ = 5.1, 12.1 Hz), 1.96 (2 H, m), 2.50 (1 H, m), 3.30 (2 H, d, $J$ = 6.6 Hz), 3.66 (20 H, m), 3.86 (2 H, half an AA'XX' pattern), 4.47 (2 H, s), 7.30 (5 H, m); IR (neat, NaCl) 3080, 3060, 3020, 2880, 1602, 1583, 1493, 1449, 1350, 1290, 1245, 1198, 1110 (br), 1022, 982, 940, 865, 848, 732, 691 $cm^{-1}$; exact mass calcd for $C_{23}H_{36}O_7$ ($M^+$) $m/e$ 424.246 10, found 424.245 57.

**Data for divergent alcohol crown ether (convergent isomer, 26)**: hydrogenolysis yield 0.93 g (100%) of oily alcohol; $^1H$ NMR (250 MHz, $CDCl_3$) 1.50 (2 H, dt, $J$ = 7.0, 13.6 Hz), 1.95 (2 H, m), 2.28 (1 H, br s), 2.40 (1 H, m), 3.46 (2 H, d, $J$ = 6.6 Hz), 3.64 (20 H, m), 3.86 (2 H, half of AA'XX' pattern); IR (neat, NaCl) 3330 (br), 2890 (br), 1450, 1348, 1290, 1243, 1105 (br), 1029, 948, 830 $cm^{-1}$; exact mass calcd for $C_{16}H_{30}O_7$ ($M^+$) $m/e$ 334.199 15, found 334.197 93.

**Data for divergent cyclopentano crown ether thiol 4**: yield 0.675 g (69% from alcohol crown ether) of oily thiol after Kugelrohr distillation at 200–220 °C ($10^{-5}$ mmHg); $^1H$ NMR (250 MHz, $CDCl_3$) 1.24 (1 H, t, $J$ = 7.7 Hz), 1.44 (2 H, dt, $J$ = 6.6, 13.6 Hz), 2.02 (2 H, m), 2.47 (1 H, m), 2.49 (2 H, t, $J$ = 7.0 Hz), 3.66 (20 H, m), 3.89 (2 H, half of an AA'XX' pattern); IR (neat, NaCl) 2860, 2550, 1445, 1346, 1289, 1242, 1118 (br), 980, 938, 863, 837 $cm^{-1}$; exact mass calcd for $C_{16}H_{30}O_6S$ ($M^+$) $m/e$ 350.176 31, found 350.177 24. Anal. Calcd for $C_{16}H_{30}O_6S$: C, 54.83; H, 8.63; O, 27.39; S, 9.15. Found: C, 54.63; H, 8.83; O, 27.20; S, 8.99.

**Registry No.** **1**, 77661-77-9; **2**, 72037-30-0; **3**, 77661-78-0; **4**, 77714-59-1; **9**, 69496-19-1; **10**, 77661-79-1; **11**, 41478-45-9; **12**, 77661-80-4; **13**, 77661-81-5; **14**, 77661-82-6; **15**, 77661-83-7; **16**, 77661-84-8; **17**, 77661-85-9; **18**, 77661-86-0; **19**, 77661-87-1; **20a**, 77714-60-4; **20b**, 39798-12-4; **21** (isomer 1), 77661-88-2; **21** (isomer 2), 77714-61-5; **22** (isomer 1), 77661-89-3; **22** (isomer 2), 77714-62-6; **23** (isomer 1), 77661-90-6; **23** (isomer 2), 77714-63-7; **24** (isomer 1), 77661-91-7; **24** (isomer 2), 77714-64-8; **25** (isomer 1), 77661-92-8; **25** (isomer 2), 77714-65-9; **26** (isomer 1), 77661-93-9; **26** (isomer 2), 77714-66-0; **27**, 77661-94-0; **28**, 77661-95-1; diethyl malonate, 105-53-3; 2-(benzyloxy)ethyl bromide, 1462-37-9; triethylene glycol ditosylate, 19249-03-7; 2,2-dimethoxypropane, 77-76-9.