to room temperature before filtering through Celite. The reaction mixture was then washed with 10% hydrogen chloride, water, and saturated sodium chloride and dried ($MgSO_4$). The reaction mixture was concentrated to an oil, **6** (20%) and **7** (80%), which was chromatographed on silica gel with hexane and ethyl acetate (5:1) to afford 1.02 g (81%) of **6** (32%), **7** (48%), and **10** (20%).

Bromination at the α-Position. To solution of 756 mg (3 mmol) of the 1,3-diketone (**6**, **7**, **10**) in 10 mL of acetic acid at room temperature was added 338 μL of bromine. The reaction mixture was allowed to stir for 15 min, then washed with water, saturated sodium bicarbonate, and saturated sodium chloride, and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford 1.2 g (98%) of a yellow solid: mp 210–212 °C dec (hexane–ethyl acetate); ^{13}C NMR ($CDCl_3$) 201.7, 153.9, 145.3, 140.7, 128.5, 127.9, 125.3, 122.4, 64.1, 45.2, 44.8, 31.9, 31.2, 27.6 ppm; ^1H NMR ($CDCl_3$) δ 2.43–2.48 (t, 2 H), 3.21–3.30 (m, 4 H), 3.56–3.64 (m, 2 H), 4.75–4.76 (m, 2 H), 6.78–6.81 (d, 1 H), 7.10–7.15 (t, 1 H), 7.20–7.26 (t, 1 H), 7.30–7.32 (s, 1 H); IR (KBr) 3009, 2946, 2931, 2848, 1695, 1639, 1404, 1292, 896 cm^{-1}; MS (70 eV), calcd for $C_{17}H_{14}O_2Br_2$ 409.9341, found 409.9346.

Bromination of the Double Bond. To a solution of 252 mg (1 mmol) of the 1,3-diketone (**6**, **7**, and **10**) in 10 mL of methylene chloride at −78 °C was added 56.4 μL (1.1 mmol) of bromine. The reaction was allowed to warm up to 0 °C, stirred for 30 min, then washed with saturated sodium bicarbonate, water, and saturated sodium chloride, and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield 400 mg (97%) of a diastereomeric mixture of 1,2-dibromides as a white solid. The crude solid was recrystallized from pentane and ether to afford 306 mg (74%): mp 160 °C dec; ^{13}C NMR ($CDCl_3$) 212.2, 212.0, 211.0, 209.5, 145.6, 145.2, 141.6, 140.5, 128.5, 127.0, 125.5, 125.2, 123.1, 122.4, 68.9, 67.5, 51.1, 50.0, 49.5, 48.4, 47.2, 45.3, 44.4, 35.6, 35.0, 32.3, 31.9, 28.8, 28.6, 28.4 ppm; ^1H NMR ($CDCl_3$) δ 2.2–2.8 (m, 12 H), 3.05–3.65 (m, 8 H), 4.38–4.50 (m, 2 H), 4.78–4.84 (br s, 2 H), 6.82–6.84 (d, 1 H), 6.89–6.92 (d, 2 H), 7.13–7.32 (m, 6 H); IR (KBr) 2931, 2854, 1763, 1727, 1693, 1478, 1458, 1440, 1281, 1248, 1216, 1176, 748 cm^{-1}; MS (70 eV), calcd for $C_{17}H_{16}O_2Br_2$ 411.9498, found 411.9499.

Formation of Dibenzo 1,3-Diketone 9. To a mixture of 132 mg (5.5 mmol) of sodium hydride in 20 mL of dry THF was added 1.03 g (2.5 mmol) of the dibromide **8**. The reaction mixture was then refluxed for 75 min and quenched with water. The reaction mixture was extracted with methylene chloride, and the combined organic layers were washed with water and saturated sodium chloride and dried ($MgSO_4$). The methylene chloride was removed by rotary evaporator to yield a solid, which was recrystallized from hexane and ethyl acetate to afford 433 mg (71%): mp 131–132 °C; ^{13}C NMR ($CDCl_3$) 201.3, 145.6, 142.6, 141.8, 135.8, 128.3, 126.8, 125.2, 123.8, 122.7, 66.9, 32.6, 32.1 ppm; ^1H NMR ($CDCl_3$) 2.53–2.58 (t, 2 H), 3.28–3.33 (t, 2 H), 6.60–6.62 (d, 1 H), 7.01–7.06 (t, 1 H), 7.19–7.24 (t, 1 H), 7.31–7.34 (d, 1 H), 7.87–7.91 (m, 2 H), 8.04–8.10 (m, 2 H); IR (KBr) 3062, 2923, 2850, 1743, 1701, 1594, 1480, 1452, 1332, 1292, 1253, 858, 789, 757 cm^{-1}; MS (70eV), calcd for $C_{17}H_{12}O_2$ 248.0837, found 248.0843.

Bromination of Alkene 6. To a solution of 126 mg (0.5 mmol) of the 1,3-diketone **6** in 3 mL of methylene chloride at −78 °C was added 28.2 μL (0.5 mmol) of bromine. The reaction was allowed to stir at this temperature for 20 min and was allowed to warm up to −40 °C and then poured into water. The methylene chloride layer was then extracted and washed with brine and dried ($MgSO_4$) to afford 204 mg (99%) of **11**. The orange solid was recrystallized from ether and pentane to afford 157 mg (77%) of the 1,2-dibromide: mp 108–108.5 °C; ^{13}C NMR ($CDCl_3$) 212.2, 213.4, 146.2, 139.8, 128.6, 127.3, 124.9, 124.0, 68.0, 49.9, 49.1, 44.5, 43.9, 39.7, 31.5, 28.1, 27.3 ppm; ^1H NMR ($CDCl_3$) δ 2.2–2.5 (m, 3 H), 2.6–2.8 (m, 3 H), 3.1–3.3 (m, 3 H), 3.4–3.5 (m, 1 H), 4.4–4.6 (m, 2 H), 6.98–7.00 (d, 1 H), 7.18–7.33 (m, 3 H); IR (KBr) 2900, 2851, 1723, 1422, 1280, 1182, 1151, 989, 741 cm^{-1}.

Acknowledgment. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

Registry No. 1, 80455-68-1; **2**, 18014-24-9; **3**, 100020-34-6; **4**, 100020-35-7; **6**, 100020-36-8; **6** (dibromide), 100101-38-0; **6** (diene), 100020-39-1; **7**, 100101-36-8; **8**, 100020-37-9; **9**, 95033-81-1; **10**, 100101-37-9; **11**, 100020-38-0; *cis*-diethyl cyclohexene-4,5-dicarboxylate, 4841-85-4; 1-indanone, 83-33-0; mercuric trifluoroacetate, 13257-51-7; mercuric chloride, 7487-94-7.

Synthesis of a Dithia-18-crown-6-tetracarboxylic Acid

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Received September 16, 1985

The synthesis, complexation properties and applications of macrocyclic polyethers of the crown ether and cryptand types continues to be a vigorous and growing area of chemistry.[1] It is widely recognized that variation in the nature of the donor sites (substitution of O by N or S, for example) leads to modified conformations of the ligands[2] and to control of complexation behavior.[3] Our interest in such heteroatom-substituted crown ethers is directed toward derivatives which would be capable of transporting group IIB (12)[19] and heavy metal cations across artificial membranes as an extension of our ongoing studies on group IA (1) and IIA (2) cations.[4-6] In addition, it is generally found that incorporation of tartrate-derived fragments into the 18-crown-6 framework results in a well-defined macrocycle conformation in which the carboxyl substituents are held pseudoaxially to the macrocycle plane.[7-10] Heteroatom substitution at the 7- and 16-positions would provide an additional NMR probe for the conformations of the ethylenedioxy fragments. Introduction of sulfur is also expected to provoke conformational changes due to the small C–S–C angle and the tendency for S binding sites to diverge from the macrocycle cavity.[2] From all these perspectives it was of interest to examine the synthesis of diheteroatom-substituted crown ethers incorporating tartrate-derived units. We report here the synthesis of the parent compound with sulfur donor sites namely **11** (Scheme I).

The first syntheses of sulfur-containing macrocycles currently recognized as crown ether derivatives substantially predate the syntheses of the "parent" oxa crown ethers and several different strategies have been reported.[12,13] In principle an efficient one-pot method like the

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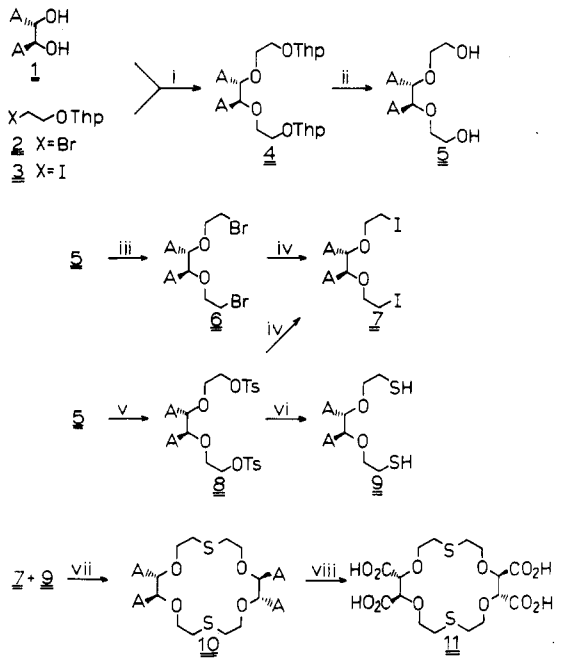
0022-3263/86/1951-0752$01.50/0

Scheme I[a]



[a] (i) TlOEt/DMF; (ii) H_3O^+; (iii) PBr_3; (iv) NaI/acetone; (v) TsCl/Et_3N; (vi) (1) H_2NCSNH_2, (2) $NaOH/H_2O$/room temperature; (vii) Cs_2CO_3/DMF; (viii) stoichiometric 10% HCl, 80 °C, 16 h.

one producing the oxa parent of **11** directly from the dithallium salt of tetramethyltartaramide and diethyleneglycol diiodide **8** would be highly desirable. However, this is unlikely to be successful for **11** due to the ready tendency of mustard derivatives to eliminate. The method chosen must be compatible with the chiral centers hence strong bases in excess must be avoided. From many points of view, the method of Kellogg using solid Cs_2CO_3 in DMF[14] appeared to be the method of choice for the macrocyclization; a yield of 90% is reported for 1,10-dithia-18-crown-6.[14] At the outset however, it was not known if this base system was capable of chiral center epimerization. Nor was the success of the macrocyclization assured since cyclization of tosylamides with the same base system is apparently intolerant of additional heteroatoms in the chains.[15]

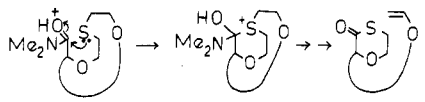
Results and Discussion

The synthetic route outlined in the scheme is based on the macrocyclization of the diiodide **7** and the dithiol **9**. Protected haloethanols **2** or **3** were allowed to react with the dithallium salt of **1** under a variety of conditions of concentration, time, and temperature. Yields of **4** from the iodide **3** were never better than 50%; elimination accounted for the bulk of the byproducts. The bromide **2** gave better conversions and conditions were optimized to produce **4** sufficiently pure for the subsequent step. Acidic hydrolysis of the tetrahydropyranyl ethers gave the diol **5** in 67% yield from **1** (via **2**). We initially envisaged using the dibromide for the final coupling, and reaction of **5** with PBr_3 produced **6** as expected. However **6** is water soluble and extensive extraction and chromatography degrades the yield to only 43%. The solid ditosylate **8** is more readily handled and is the intermediate of choice. The diiodide **7** was prepared from either **6** or **8** by halide exchange (NaI/acetone) in essentially quantitative yield from either precursor. The dithiol was prepared via the bis(isothiouronium) salt from **8** and excess thiourea. Decomposition of the disalt in aqueous sodium hydroxide at room temperature followed by extraction and chromatography gave **9**.

Macrocyclization proceeded as described by Buter and Kellogg.[14] An equimolar solution of **7** and **9** in DMF was added dropwise to Cs_2CO_3 in DMF at 50 °C. Evaporation of solvent gave crude **10**, which appeared from the ^1H NMR spectrum to be predominantly the desired product. However, final purification was hampered by the affinity of **10** for solvent. A similar problem was reported for other macrocyclic sulfides prepared by Buter and Kellogg.[14] In the case of **10**, the yield of purified product was only 18%. The structure was characterized by ^1H and ^{13}C NMR, elemental analysis, and a strong parent ion and characteristic fragmentations in the mass spectrum of **10**.

Acidic hydrolysis of the amides of **10** using hot 25% HCl as previously utilized[5,8,16] gave a complex mixture of products. The ^1H and ^{13}C NMR spectra of this mixture clearly suggested that macrocycle cleavage had occurred. Indeed a minor amount of tartaric acid was detected in the sample by ion chromatography, indicating virtually total destruction of the macrocycle. More cautious hydrolysis using stoichiometric 10% HCl at 80 °C for 18 h gave a solution with a ^1H NMR spectrum consistent with that expected for **11**, but evaporation under high vacuum gave a sample containing acyclic impurities together with dimethylammonium hydrochloride and **11**. Ultimately a sequence of ion-exchange steps involving a strong acid cation-exchange resin (to remove $(CH_3)_2NH_2^+$) and the silver salt of **11** (to remove Cl^-) was utilized to isolate **11**. The purification turns on the solubility of the silver salt of **11** at pH 5; all acyclic impurities form fortuitously insoluble silver salts.

The purified macrocycle **11** is somewhat prone to decomposition in concentrated acidic solutions but an aqueous solution at pH 3 can be kept for several days without noticable degradation. It is likely that the decomposition which occurs with amide hydrolysis involves attack of S on the carboxyl carbon to produce an S-alkylated thioxane derivative (eq 1).



(1)

Elimination would produce a thiolactone/vinyl ether which would rapidly degrade in acidic solution. Cleavage products bearing secondary hydroxyl groups on the tartrate derived fragments are readily identified by ^{13}C NMR; double decomposition at the same end of the macrocycle would produce the tartaric acid detected.

The macrocycle **11** does in fact complex metal cations as expected. The purification exploits the silver complex salt, and we have determined a variety of stability constants for complexation of metals by potentiometric titration.[7] For **11** as the tetraanion we find log K values of 5.7 ± 0.2 for Ag^+, 3.3 ± 0.2 for K^+, and 3.9 ± 0.2 for Cd^{2+} (water, I = 0.05 with $(CH_3)_4NCl$, 25 °C). For comparison the tetraanion of the parent all oxygen crown under the same conditions gives 3.0 ± 0.5 for Ag^+, 5.0 ± 0.1 for K^+, and 8.4 ± 0.4 for Cd^{2+}. The literature values for the unsubstituted 1,10-dithia-18-crown-6 are 4.34 for Ag^+ in water and 1.1 for K^+ in methanol.[17] Clearly the electrostatic

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Table I. ^1H and ^{13}C NMR Data (δ) for Compounds Prepared[a,b]

compd		$(CH_3)_2N$	C=O	CHO	$CH_2CH_2CH_2$	R	
4	^1H	2.9, 3.15		4.8	3.3–4.1 (m)	OCHO	$CH_2CH_2CH_2$
						4.6	1.6 (m)
	^{13}C	35.1, 26.6	168.8	75.9	68.1 (4 lines)	98.2	18.7, 24.8, 25.0
5	^1H	2.9, 3.10		4.8	3.7 (br s)	OH 4.1	
	^{13}C	35.8, 37.2	169.3	76.4	70.9, 61.6		
6	^1H	2.9, 3.15		4.8	3.7, 3.4		
					(A_2B_2, J = 7 Hz)		
	^{13}C	35.6, 37.2	168.6	76.3	69.0, 30.4		
7	^1H	2.9, 3.15		4.8	3.8, 3.2		
					(A_2B_2, J = 7 Hz)		
	^{13}C	35.6, 37.1	168.4	76.2	67.1, 2.9		
8	^1H	2.9, 3.10		4.8	3.75, 4.1	Ar	CH_3
					(A_2B_2, J = 7 Hz)	7.2, 7.9	2.40
						(AB, J = 8 Hz)	
	^{13}C	35.6, 37.1	168.4	76.4	69.0, 66.9	127.8, 129.8	21.8
9[c]	^1H	2.90, 3.20		4.82	3.70, 2.80		
					(A_2B_2, J = 7.1 Hz)		
	^{13}C	35.6, 36.9	169.0	76.5	67.5, 23.1		
10	^1H	2.90, 3.20		4.81	3.90, 2.81		
					(A_2B_2, J = 7.1 Hz)		
	^{13}C	35.5, 37.2	169.0	75.9	69.2, 31.8		
11[d]	^1H			4.35	3.81, 2.91		
	^{13}C		172.3	79.0	70.8, 29.2		

[a] In $CDCl_3$ vs. Me_4Si unless noted otherwise. [b] Satisfactory elemental analyses (±0.4% C, H, N, S, Br) were obtained for all compounds except 4 and 7, which were used without purification. [c] D_2O solvent. [d] D_2O, pD ≠ 3.1, solvent.

effect and the heteroatom effect can act in concert (Ag^+) but the selectivity of complexation (Ag^+/K^+) is degraded by the addition of charged groups. It is also clear that the ability of **11** to complex by using primarily the charged groups is poor when the hole size and/or donor sites are not optimal (Cd^{2+}). The ligand **11** thus exhibits an interesting balance of effects that should lead to novel selectivity sequences. The details of the complexation chemistry of **11** will be published separately.

Experimental Section

General Details. Melting points were taken on a Koefler hot stage microscope (uncorrected). Proton NMR spectra were recorded with a Perkin-Elmer R32 (90 MHz, CW) or Bruker WM 250 (250 MHz, FT) spectrometer in $CDCl_3$ solvent with Me_4Si as internal standard or in D_2O with external Me_4Si in $CDCl_3$ as reference. Carbon NMR spectra were recorded at 93.8 MHz (WM 250) in $CDCl_3$ with the central solvent line as standard (77.0 ppm relative to Me_4Si) or in D_2O with a frequency reference for this solvent previously calibrated against external Me_4Si in $CDCl_3$. The mass spectra were recorded with a Finnegan 3300 GC-MS instrument with methane chemical ionization. Elemental analyses were performed by Canadian Microanalytical Services, Vancouver, BC.

2-(2-Bromoethoxy)tetrahydropyran (2) and 2-(2-Iodoethoxy)tetrahydropyran (3). Bromoethanol (50 g, 0.40 mol) and dihydropyran (50 g, 0.59 mol) were mixed, and 2 drops of concentrated HCl was added. An exothermic reaction ensued. The mixture was stirred without heating for 1 h, solid $NaHCO_3$ (10 g) was added, the slurry was stirred a further 30 min, and the solids were removed by filtration. Distillation at reduced pressure gave a forerun of unreacted dihydropyran followed by **2**: bp 82 °C (0.5 mmHg); 72.5 g (86% yield); ^1H NMR ($CDCl_3$) δ 1.6 (6 H, br s), 3.3–4.1 (6 H, br m), 4.6 (1 H, br s).

The corresponding iodide was prepared by halide exchange. The bromide **2** (44.8 g, 0.186 mol) was added to a solution of NaI (130 g, 0.93 mol) in acetone (450 mL) at reflux. The resultant slurry was stirred at reflux for 16 h, and the mixture was cooled, evaporated to a solid mass, and transferred to the top of a short column of neutral alumina. The column was washed with 1 L of CH_2Cl_2, and the eluent was evaporated to yield **3** (48.7 g, 91%): ^1H NMR ($CDCl_3$) δ 1.6 (6 H, br s), 3.1–4.1 (6 H, br m), 4.7 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 3.0 (CH_2I), 18.6, 24.8, 29.8 (Thp CH_2), 61.4 (Thp CH_2O), 67.5 (CH_2O), 97.8 (CH).

(2*R*,3*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-2,3-bis[2-(tetrahydropyranyloxy)ethoxy]succinamide (4). Thallous ethoxide (21 g, 84 mmol) was added dropwise via syringe to a solution of (2*R*,3*R*)-*N*,*N*,*N*′,*N*′-tetramethyl tartaramide (**1**)[17] (8.1 g, 40 mmol) in 900 mL of dry dimethylformamide (DMF). The resultant slurry was mechanically stirred under an inert atmosphere and warmed to 50 °C, where upon the bromide **2** (21.8 g, 104 mmol) was added in one portion. The mixture was heated at 65 °C for a further 14 h and cooled, the thallous bromide was removed by filtration, and the solvent was removed by evaporation at reduced pressure. The oily product was dissolved in CH_2Cl_2 and filtered through a pad of Celite, the eluent was evaporated, and the final traces of DMF were removed by evaporation at high vacuum. The crude sample of **4** (16.9 g, 92%, predominantly **4** by ^1H NMR) was used without further purification. Spectral data are given in Table I.

(2*R*,3*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-2,3-bis(2-hydroxyethyl)succinamide (5). The crude bis(tetrahydropyranyl) ether **4** (132 g, 33.5 mmol) was dissolved in 100 mL of a 1:1 (v/v) mixture of H_2O and methanol, 2 drops of concentrated HCl was added, and the mixture was stirred at reflux for 1 h, cooled, and evaporated. The oil was dissolved in water and extracted with 2 × 100 mL portions of ether, and the water layer was evaporated at high vacuum until a solid was obtained. Recrystallization from methanol/water gave **5** (7.1 g, 73%), mp 100–102 °C. Spectral data are given in Table I.

(2*R*,3*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-2,3-bis(2-bromoethoxy)succinamide (6). The diol **5** (10.1 g, 34 mmol) was dissolved in 75 mL of $CHCl_3$, and PBr_3 (8.2 g, 30 mmol) was added. The mixture was stirred at reflux for 2 h, cooled, and extracted with 2 × 100 mL portions of water. The aqueous extract was extracted with $CHCl_3$ on a continuous extractor for 16 h, and the combined organic phases were dried over Na_2SO_4 and evaporated. The crude dibromide was purified by chromatography on neutral alumina using toluene/$CHCl_3$ (1:1) as eluent to give **6** (6.1 g, 43%) as an oil. Spectral data are given in Table I.

(2*R*,3*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-2,3-bis(2-iodoethoxy)succinamide (7). The ditosylate **8** (4.0 g, 6.6 mmol) was added to a solution of NaI (6.0 g, 40 mmol) in 50 mL of dry acetone at reflux. The resultant slurry was stirred at reflux overnight, cooled,

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(18) Seebach, D.; Oei, H. A. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 634.

(19) In this paper the periodic group notation in parentheses is in accord with recent actions by IUPAC and ACS nomenclature committees. A and B notation is eliminated because of wide confusion. Groups IA and IIA become groups 1 and 2. The d-transition elements comprise groups 3 through 12, and the p-block elements comprise groups 13 through 18. (Note that the former Roman number designation is preserved in the last digit of the new numbering: e.g., III → 3 and 13.)

evaporated to a solid mass, and filtered through a short column of neutral alumina with 500 mL of CH_2Cl_2 as eluent. Evaporation gave the diiodide **7** (3.4 g, quantitative) which was used without further purification. Spectral data are given in Table I. Alternatively the dibromide **6** could be used in place of **8**.

(2*R*,3*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-2,3-bis[2-(tosyloxy)ethoxy]succinamide (8). The diol **5** (23 g, 78 mmol) was dissolved in a mixture of triethylamine (20 mL) and CH_2Cl_2 (20 mL) at 10 °C, and solid *p*-toluenesulfonyl chloride (30.5 g, 160 mmol) was added. The mixture was allowed to stand at ambient temperature for 24 h, diluted with a further 200 mL of CH_2Cl_2, extracted with 3 × 100 mL portions of cold 1 M HCl, dried over Na_2SO_4, and evaporated to a solid gum. The gum was triturated to a solid with a minimum of ether, and the solid was recrystallized from ether/petroleum ether to yield **8** (35.8 g, 78%), mp 105–107 °C. Spectral data are given in Table I.

(2*R*,3*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-2,3-bis(2-mercaptoethoxy)succinamide (9). The ditosylate **8** (12 g, 20 mmol) and thiourea (5 g, 70 mmol) were dissolved in 50 mL of absolute ethanol and stirred at reflux for 3 h. After removal of the solvent, the ^1H NMR spectrum of a small sample of the product showed the complete loss of the signal at δ 4.1 (CH_2OTs) and a new signal at δ 3.3 ($CH_2S^+=$). The crude isothiouronium salt was dissolved in 25 mL of 1M NaOH solution and stirred at ambient temperature for 48 h. The mixture was brought to pH 7 with HCl and extracted with $CHCl_3$ on a continuous extractor for 16 h, and the organic extract was dried with Na_2SO_4 and evaporated to a brown oil. This mixture was separated by chromatography on neutral alumina using a gradient of methanol (0.5–5% (v/v)) in $CHCl_3$. The dithiol **9** eluted at 4–5% CH_3OH (5.0 g, 78%). Spectral data are given in Table I.

(2*R*,3*R*,11*R*,12*R*)-*N*,*N*,*N*′,*N*′,*N*″,*N*″,*N*‴,*N*‴-Octamethyl-1,4,10,13-tetraoxa-7,16-dithiacyclooctadecane-2,3,11,12-tetracarboxamide (10). A solution of dithiol **9** (1.3 g, 4.0 mmol) and diiodide **8** (1.06 g, 4.0 mmol) in 100 mL of dry DMF was added dropwise over 6 h to a stirred suspension of anhydrous Cs_2CO_3 (1.43 g, 4.4 mmol) in 500 mL of dry DMF under inert atmosphere at 50 °C. The mixture was stirred a further 16 h at this temperature, the solvent was removed under vacuum, the solids were suspended in $CHCl_3$ and removed by filtration, and the solvent and residual DMF were removed by evaporation at high vacuum. The solid product was dissolved in water (100 mL) and extracted successively with 50 mL of toluene and 50 mL of ether to remove less polar impurities and then with 3 × 50 mL of CH_2Cl_2. The CH_2Cl_2 extract was purified by chromatography on silica using a gradient of methanol (0–5% (v/v)) in $CHCl_3$ as eluent to give **10**, which was recrystallized from ether/methanol (0.42 g, 18%): mp 164–169 °C; MS (CH_4, CI), *m/e* (relative intensity) 581 (40, M + 1), 536 (8, M + 1 − Me_2NH_2), 508 (19, (M + 1 − DMF) + 1) [typical fragments of tartaramide crown ethers].[5,8,15]

(2*R*,3*R*,11*R*,12*R*)-1,4,10,13-Tetraoxa-7,16-dithiacyclooctadecane-2,3,11,12-tetracarboxylic Acid (11). The tetraamide **10** (130 mg, 0.22 mmol) was dissolved in 2 mL of D_2O, 200 μL of concentrated HCl was added, and the mixture was heated at 80 °C for 18 h. ^1H NMR showed complete loss of methyl amide resonances. The mixture was diluted with 5 mL of H_2O and passed down a short column of Dowex 50 H (H^+ form, 200 mesh, 10 g of resin) and eluted with H_2O until the eluent was neutral. The combined acidic eluent was concentrated to 2 mL at a temperature below 35 °C by using high vacuum. Silver oxide was freshly precipitated from $AgNO_3$ (600 mg) and tetramethylammonium hydroxide pentahydrate (800 mg) in 5 mL of H_2O. The Ag_2O was washed until neutral and suspended in 5 mL of H_2O, and the concentrated eluent (above) was added. The solid slurry was agitated periodically for 30 min, the solids were settled by centrifugation, and the supernatant was filtered through a 0.45-μm filter to remove traces of suspended solid. This solution (ca 6 mL) was again passed through a Dowex column as above, and the combined acidic fractions were concentrated to approximately 1 mL as previously. This sample was free of Cl^- (no precipitate with Ag^+) and free of Ag^+ (no precipitate with Cl^-). Evaporation at high vacuum gave the tetraacid **11** as a pale yellow brittle foam (75 mg, 71%). The elemental analysis indicated this product to be the monohydrate. This was confirmed by titration: equivalent weight calculated for **11**, 113 g/equiv; for **11**·H_2O, 122.5 g/equiv; found, 121.7 g/equiv. The parent hexaoxa tetraacid forms a similar hydrate,[8] but it is not known if this is a specific complex of H_2O.

Acknowledgment. This ongoing research was supported by the National Sciences and Engineering Research Council of Canada.

Registry No. **1**, 26549-65-5; **2**, 17739-45-6; **3**, 96388-83-9; **4**, 100190-94-1; **5**, 100190-95-2; **6**, 100190-96-3; **7**, 100190-97-4; **8**, 100190-98-5; **9**, 100190-99-6; **10**, 100191-00-2; **11**, 100191-01-3; 2-bromoethanol, 540-51-2; thiourea, 62-56-6.

Transient Protection. 2. One-Flask Synthesis of 6-*O*-[(4-Nitrophenyl)ethyl]-2′-deoxyguanosine Nucleosides

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Received December 14, 1984

Transient protection of both the 3′- and 5′-hydroxyl groups of **1a** or of the 3′-hydroxyl group of **1b**, followed by Mitsunobu alkylation with 2-(4-nitrophenyl)ethanol gave the O^6-protected nucleosides **4a** or **4b** in good yield in a one-flask procedure. Similar reactions with 3-hydroxypropionitrile or 2-(phenylsulfonyl)ethanol, however, were unsuccessful. Reaction of **1b** without 3′-hydroxyl protection led to formation of a stable $N^3 \rightarrow 3'$ cyclonucleoside, **7a**.

Results and Discussion

The degradation of guanine nucleosides during oligonucleotide synthesis is a well known phenomenon.[1] The findings by Reese[2,3] and by Hata[4,5] that guanine residues are subject to both O^6 sulfonylation with condensing reagents and to O^6 phosphorylation with activated nucleotides implicated the O^6 position as the source of this degradation. We then devised a sulfonylation/displacement route for specific O^6 alkylation of deoxyguanosine and showed that O^6 protection with any of several β-substituted ethyl derivatives completely eliminated reaction of the base with condensing agents.[6] Moreover, we reported use of three of these protecting groups, the (nitrophenyl)ethyl, cyanoethyl, and (phenylthio)ethyl groups, in the syntheses of several short oligonucleotides.[7-9]

We simplified our sulfonylation/displacement route by replacing the 5′- and 3′-*tert*-butyldimethylsilyl protecting groups originally used with a 5′-dimethoxytrityl and a 3′-levulinyl group.[9] We also attempted to use transient protection instead of the levulinyl group, but this route never gave satisfactory results. Recently, Pfleiderer has reported an alternative route for introduction of the (nitrophenyl)ethyl group via a Mitsunobu reaction.[10,11] For

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