The Synthesis of Chiral Dimethyl Substituted Macrocyclic Polyether-Diester Ligands (1)

Brian A. Jones, Jerald S. Bradshaw*and Reed M. Izatt

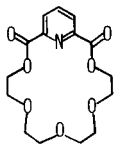
Department of Chemistry and Contribution No. 262 from the Institute for Thermochemical Studies, Brigham Young University, Provo, Utah 84602

Received August 11, 1981

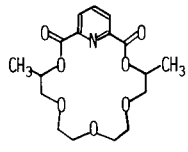
A new series of chiral macrocyclic polyether-diester ligands has been prepared from four chiral dimethyl substituted tetraethylene glycols (**15a,b,16,17**) and 2,6-pyridinedicarbonyl chloride (products **5a-7**), diglycolyl chloride (products **8-10**), thiadiglycolyl chloride (product **11**), 2,5-furandicarbonyl chloride (product **12**), 4-chloro-2,6-pyridinedicarbonyl chloride (product **13**), and 4-methoxy-2,6-pyridinedicarbonyl chloride (product **14**). The chiral dimethyl substituted tetraethylene glycols (**15a-17**) were prepared from ethyl (*S*)-lactate.

J. Heterocyclic Chem., **19**, 551 (1982).

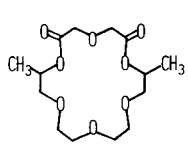
Since the discovery by Pederson (2,3) that macrocyclic polyethers form complexes with a wide variety of cations, the properties of these and related ligands have been intensively investigated. We have reported the synthesis and cation complexing properties of a large number of macrocyclic polyether-diester compounds (4-16). In general, while forming weaker complexes than their polyether counterparts, these diester macrocyclic ligands exhibit significant affinities for primary alkylammonium, alkali, and alkaline earth cations (9,10,12,13,16). For example, compound 1 complexed with Na^+, K^+, Rb^+, Ag^+, and Ba^{2+} ions in methanol with log K values of 4.3 to 4.9 (10). These ligands, like the macrocyclic polyethers, demonstrate a selectivity among the various cations. Compound **1** also complexed strongly with primary alkylammonium salts in methylene chloride-d_2 as shown by significant chemical shift changes in the ^1H nmr spectra (12).



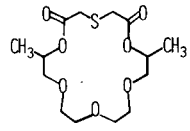
1



2



3



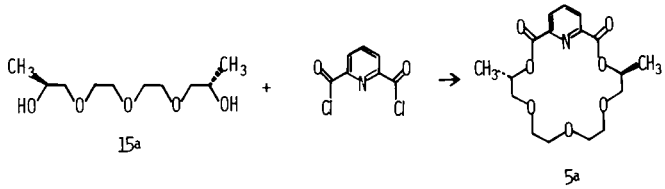
4

Studies of macrocyclic ligands with modified complexing abilities towards metal and organic cations led to the synthesis of compounds **2-4** (4). These ligands were mixtures of the *trans*- or enantiomeric pairs, the *cis*- or *meso*-isomer, and traces of ligands containing a positional isomer (where one of the methyl substituents is attached to the neighboring carbon atom) (4). The isomeric mixture content could be seen clearly in the ^1H nmr spectrum of the 1:1 complex of compound **2** with benzylammonium perchlorate in methylene chloride-d_2. The doublet peak for the methyl substituents in the macrocycle at δ 1.47 changed to two doublets at δ 1.44 (55%) and 1.53 (45%). The spectrum of the complex at $-50°$ showed the upper field doublet further split into two doublets of equal intensity. It was felt that the δ 1.44 doublet at $-50°$ was due to the *trans*-isomer because the dissociation energy of the complex would be the same with the ammonium salt on either face of the complex giving rise to peaks of equal intensity at low temperatures (4). The *cis*- and *trans*-isomers could not be separated.

We now report the synthesis of all three possible stereoisomers (*S,S; R,R* and *meso*) of the dimethyl substituted macrocyclic polyether-diester compounds that we could not otherwise separate. Ethyl (*S*)-lactate was used as the source of chirality for the dimethyl tetraethylene glycols that were used in the preparation of these macrocyclic compounds. Compounds **5-7** (see Figure 1) were prepared from 2,6-pyridinedicarbonyl chloride and the appropriate glycol. Similarly prepared were compounds **8-10** from diglycolyl chloride, compound **11** from thiadiglycolyl chloride, compound **12** from 2,5-furandicarbonyl chloride, compound **13** from 4-chloro-2,6-pyridinedicarbonyl chloride, and compound **14** from 4-methoxy-2,6-pyridinedicarbonyl chloride.

Results and Discussion.

Macrocyclic compounds **5-14** (Figure I) were prepared from the appropriate diacid chlorides and dimethyl substituted oligoethylene glycols as we have done previously (4-8,12,13,15). The synthesis of compound **5a** is shown below. Each reactant was dripped simultaneously into a large volume of warm rapidly stirred benzene. Yields varied from 17 to 76% (see Table I).



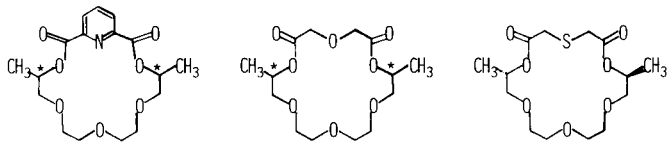
15a

5a

Table 1

Physical Properties of Chiral and Achiral Macrocyclic Compounds

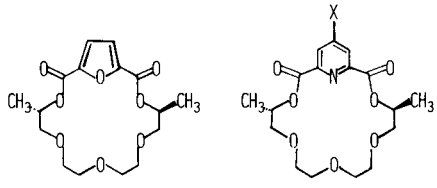
Compound	$[\alpha]_D^{25}$ (c = 1.00, chloroform)	MP(BP)	Yield
2	0	81-83°	19%
5a	−13.9°	91-92	27
5b	−13.7°	94	48.5
6	+13.2	92-92	24
7	−0.07	102-103	38
3	0	(170°/1mm)	32
8	+46.5	(170°/1mm)	22
8 (hydrate)	---	57-68	---
9	−46.1	oil	17
9 (hydrate)	---	63-66	---
10	---	oil	24
4	0	(180°/1mm)	43
11	+57.8	58	23
12	−27.3	80	23.5
13	−3.98	oil	76
14	−6.90	98-99	17



5a,b - S,S
6 - R,R
7 - MESO

8 - S,S
9 - R,R
10 - MESO

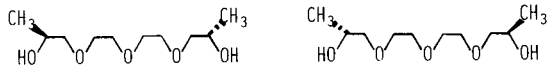
11 - S,S



12 - S,S

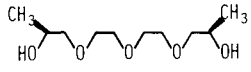
13 X=Cl - S,S
14 X=OCH$_3$ - S,S

FIGURE I



15a,b - S,S

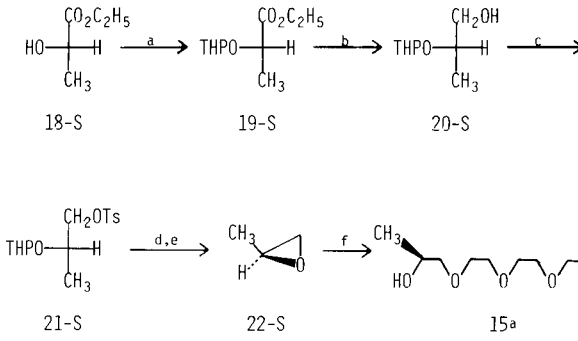
16 - R,R



17 - MESO

FIGURE II

Glycol **15** (Figure II), having the (*S,S*) configuration, has been previously prepared (17,18). We first prepared glycol **15a** from (*S*)-2-methyloxirane (**22-S**) obtained by the procedure of Ghirardelli (19) as shown in Scheme I. A small amount of positional isomeric material (where one methyl substituent is on the second carbon atom) was produced by this method as has been shown previously when unsymmetrical epoxides were used in glycol synthesis (4). Attack at the more hindered C-2 position of the epoxide by the alkoxide resulted in production of 5 to 10% of the positional isomer. This impurity was not detected by spectroscopic means until the glycol had been incorporated into the macrocyclic ligand. The small doublet at δ 1.10 and the multiplet at δ 4.50 in the ^{1}H nmr spectrum of compound **5a** are due to this positional isomer. We decided to prepare glycol **15** without any positional isomeric impurities. We therefore used the procedure shown in Scheme II, which was also used by Ghirardelli (17) and Cooper and Walborsky (18), to prepare **15b**.

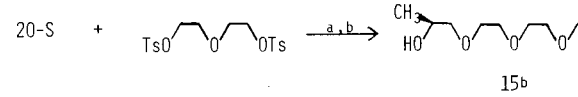


18-S 19-S 20-S

21-S 22-S 15a

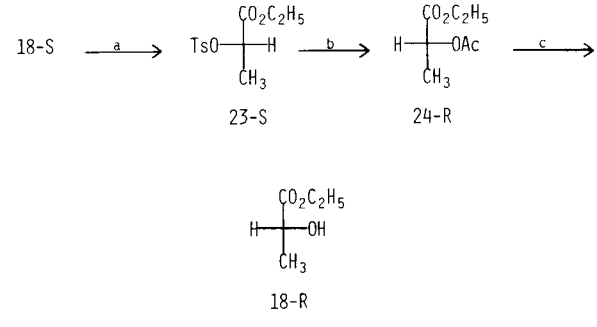
(a) 2,3-Dihydropyran, H^+; (b) $LiAlH_4$; (c) TsCl, pyridine; (d) MeOH, H^+; (e) KOH; (f) Na, diethylene glycol.

SCHEME I



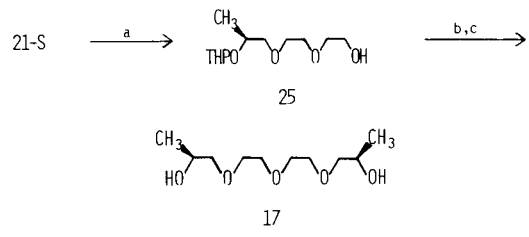
(a) NaH; (b) MeOH, H^+.

SCHEME II



(a) TsCl, pyridine; (b) KOAc, DMSO; (c) EtOH, H^+.

SCHEME III



(a) NaH, diethylene glycol(excess); (b) 21-R, NaH; (c) MeOH, H^+.

SCHEME IV

Glycol **16**, having the (*R,R*) configuration, was prepared using the same reactions as given in Scheme II except intermediates with the (*R*) configuration were used. We inverted ethyl (*S*)-lactate to the (*R*) configuration as shown in Scheme III. Inversion about the chiral center was >99% as evidenced by comparison of the specific rotation of the (*R*)-acetoxy compound **24**-*R* (Scheme III) with that of the (*S*) isomer prepared by the reaction of ethyl (*S*)-lactate with acetyl chloride. Glycol **16** was impure because it exhibited a specific rotation opposite in sign but only 75% of its mirror image, glycol **15b**. This was not considered serious as two derivatives, ligands **6** and **9**, were prepared which had opposite rotations as compared to their mirror images.

Glycol **17**, with the *meso* configuration was prepared as shown in Scheme IV. The glycol had a small specific rotation (about 2% of that for **15b**) indicating the presence of a small amount of optically active contaminant.

Satisfactory elemental analysis for glycols **15a-17** could not be obtained probably because of their affinity for water. Good analyses were obtained on all the macrocyclic compounds obtained from these glycols.

The structures proposed for the macrocyclic compounds are consistent with data obtained from ir and ^1H and ^{13}C nmr spectra, combustion analysis, molecular weight determinations, physical properties, and polarized light rotation measurements.

The macrocyclic ligands containing aromatic subcyclic units exhibited a different sign in the rotation of polarized light over that of the parent glycol, whereas the ligands without aromatic units retained the same sign (Table I). The presence of a substituent in the 4-position in the pyridine series gave macrocycles with considerably lower specific rotations than those bearing a hydrogen atom in this position.

The chiral macrocyclic compounds, as expected, have different physical properties than their racemic analogues (4). Yields, melting points and specific rotationns for some of these compounds are summarized in Table I.

The ^1H nmr spectrum of the complex of compound **7** with benzylammonium perchlorate in methylene chloride-d_2 showed the doublet for the methyl group at δ 1.50. This doublet separated into two doublets of unequal intensity at $-50°$. Complexes of compounds **5b** and **6** under identical conditions showed a doublet at δ 1.43 at ambient temperatures separating into two doublets of equal intensity at $-50°$. These data are in agreement with original interpretations of the results from ^1H nmr studies of the complexes of compound **2** (4).

Low temperature ^1H nmr studies are in progress on the complexes of these chiral macrocyclic ligands with chiral primary ammonium salts. Preliminary results indicate a small difference in complex stability between the enantiomers of the ammonium salts by some of these chiral ligands. The results of the ^1H nmr study will be reported when finished.

EXPERIMENTAL

Ir spectra were obtained on a Beckman Acculab 2 spectrophotometer. The proton and Carbon-13 nmr (^1H and ^{13}C nmr) spectra were obtained on a JEOL FX-90Q spectrometer. Elemental analysis were performed by MHW Laboratories, Phoenix, Arizona. Molecular weights were obtained by osmometry on a Hitachi Perkin-Elmer model 115 molecular weight apparatus. Rotations were determined on a Perkin Elmer 141 Polarimeter. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

Starting Materials.

The following diacid chlorides were prepared as described previously. Diglycolyl and thiodiglycolyl chloride (7), 2,5-furandicarbonyl chloride (13,20), 4-chloro-2,6-pyridinedicarbonyl chloride and 4-methoxy-2,6-pyridinedicarbonyl chloride (12). 2,6-Pyridinedicarbonyl chloride was used as received from Aldrich Chemical Co.

(2*S*,12*S*)-4,7,10-Trioxatridecane-2,12-diol (**15a** and **15b**) (see Schemes I and II).

a) (Scheme I) (*S*)-2-Methyloxirane (**22**-*S*) was first prepared from ethyl (*S*)-lactate (**18**-*S*) (Aldrich) by the procedure of Ghirardelli (19). Diethylene glycol (35.66 g, 0.336 mole) was placed in a three necked flask fitted with a stirrer, dropping funnel and a dry ice-acetone condenser. After a catalytic amount of sodium (1 g) was added and dissolved and the stirred mixture heated to 80°, (*S*)-2-methyloxirane (**22**-*S*) (39.0 g, 0.67 mole) was added over a one hour period. The reaction mixture was stirred at 80° for two days and then distilled to give **15a** as a colorless oil, 20 g (27%), bp 135/1 mm; $[\alpha]_D^{25} = +42.4°$ (c 1.00, chloroform); ir: 3430 (broad), 1110 (broad) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.10 (d, 6H, J = 6.3 Hz), 3.41 (m, 4H), 3.66 (s, 8H), 3.92 (m, 2H), 4.17 (s, 2H); ^{13}C nmr (^1H decoupled) (deuteriochloroform): δ 18.6, 66.0, 70.3, 70.4, 77.2.

b) (Scheme II) The procedure of Cooper and Walborsky (18) was followed to give compound **15b** as a colorless oil, bp 135°/1 mm; $[\alpha]_D^{25} = +43.6°$ (c 1.00, chloroform); ir: 3430 (broad), 1110 (broad) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.10 (d, 6H, J = 6.3 Hz), 3.41 (m, 4H), 3.66 (s, 8H), 3.92 (m, 2H), 4.17 (s, 2H); ^{13}C nmr (^1H decoupled) (deuteriochloroform): δ 18.6, 66.0, 70.3, 70.4, 77.2.

Anal. Calcd. for $C_{10}H_{22}O_5$: mol. wt. 222.3. Found: mol. wt. 224.7.

Ethyl (*S*)-2-(4-Toluenesulfonoxy)propanoate (**23**-*S*, Scheme III).

Ethyl (*S*)-lactate (**18**-*S*) (118 g, 1.0 mole) was dissolved in 300 ml of pyridine and cooled to 0° in an ice bath. 4-Toluenesulfonyl chloride (190.6 g, 1.0 mole) was then added at a rate so that the temperature of the solution did not exceed 10° (about 1 hour). The resulting mixture was stirred for 2 hours and then placed in the refrigerator overnight. The pyridine hydrochloride which formed was removed by filtration and washed three times with 50 ml portions of benzene. The solvents were removed under vacuum, 100 ml of toluene was added and the solution

was distilled under vacuum to remove the residual pyridine. The resulting pink oil was continuously extracted with pentane for 16 hours. Compound **23**-*S* crystallized from the pentane as white needles (237 g, 87%), mp 25°; $[\alpha]_D^{25} = -37.3$ (c 1.5 in chloroform).

Ethyl-(*R*)-2-acetoxypropanoate (**24**-*R*, Scheme III).

Ethyl (*S*)-2-(4-toluenesulfonoxy)propanoate (**23**-*S*) (200 g, 0.734 mole) was dissolved in 300 ml of dimethyl sulfoxide. Anhydrous potassium acetate (216 g, 2.20 mole) was added and the mixture stirred overnight. The resulting suspension was extracted five times with 400 ml portions of ether. The combined ether extracts were washed twice with 200 ml of water, dried over anhydrous magnesium sulfate, and the solvents were removed under vacuum. The resulting yellow syrup was distilled to give **24**-*R* as a colorless oil, 100 g (85%), bp 88°/32 mm; $[a]_D^{25} = +48.5°$ (c 1.00 chloroform), ir: 1745 cm^{-1}; ^1H nmr δ 1.27 (t, 3H, J = 7.0 Hz), 1.49 (d, 3H, J = 7.5 Hz), 2.11 (s, 3H), 4.20 (q, 2H, J = 7.5 Hz), 5.05 (q, 1H, J = 7.5 Hz); ^{13}C nmr (acetone-d_6) (^1H off-resonance decoupled): (*S*) 14.2 q, 17.0 q, 20.4 q, 61.4 t, 69.1 d, 170.2 s, 170.9 s.

Ethyl (*S*)-2-Acetoxypropanoate (**24**-*S*) (Prepared to Verify the Inversion Step Above).

Ethyl (*S*)-lactate (**18**-*S*) (11.8 g, 0.10 mole) was dissolved in 100 ml of benzene and acetyl chloride (23 g, 0.29 mole) was added. The solution was refluxed for two hours, the solvents removed under vacuum, and the product distilled to give **24**-*S* as a colorless oil, 7.0 g (44%), bp 88°/32 mm; $[a]_D^{25} = -49.0°$ (c 1.00, chloroform). The ir and ^1H nmr spectra were identical with those of compound **24**-*R* above.

Ethyl (*R*)-Lactate (**18**-*R*, Scheme III).

Ethyl (*R*)-2-acetoxypropanoate (**24**-*R*) (79.3 g, 0.50 mole) was dissolved in 800 ml of absolute ethanol and 4-toluenesulfonic acid (0.5 g) was added. The solution was slowly distilled over 3 days to a volume of 200 ml. Sodium carbonate (2 g) was added and the mixture was filtered. The filtrate was distilled to give 72 g of a colorless oil. Gas chromatographic analysis showed the product to consist of two fractions in the ratio of four to twenty-one. The major fraction had a ^1H nmr spectrum identical to that of ethyl (*S*)-lactate (**18**-*S*) while the minor fraction corresponded to starting **24**-*R*. Since the two components were inseparable by distillation, they were used together in the following step.

Ethyl (*R*)-2-(Tetrahydro-2'-pyranoxy)propanoate (**19**-*R*).

The impure ethyl (*R*)-lactate (**18**-*R*) (60.5 g, 0.51 mole) was added to 2,3-dihydropyran (72.8 g, 0.87 mole) acidified with 10 drops of 12 *N* hydrochloric acid in a 500 ml flask. A water bath was used to keep the temperature moderate and the solution was stirred overnight. Sodium carbonate (8 g) was added and the stirring was continued for an additional hour. The mixture was then filtered, concentrated under vacuum, and distilled to give a clear oil (69 g). Analysis of ^1H nmr showed that the product was contaminated with **24**-*R*. This product was used without further purification in the following step.

(*R*)-2-(Tetrahydro-2-pyranoxy)-1-propanol (**20**-*R*).

A solution of the impure ethyl (*R*)-2-(tetrahydro-2-pyranoxy)propanoate (**19**-*R*) (69 g) in 100 ml of dry ether was slowly added to a solution of lithium aluminum hydride (11 g, 0.29 mole) in 300 ml of ether at 0°. After the addition was completed, the ice bath was removed and the solution was refluxed for 48 hours. To the cooled solution was added successively: 11 ml of water, 8.5 ml of 20% sodium hydroxide solution, and 18 ml of water. A white granular precipitate formed which was filtered and washed three times with ether. The filtrate and ether washings were combined and concentrated under vacuum and distilled to give 50 g of a colorless oil, bp 77°/1.0 mm. Gas chromatographic analysis showed the product to be contaminated with propylene glycol (from the reduction of compound **24**-*R*). This was removed by counter current extraction of the product using ether and water as solvents. (Compound **20**-*R* with the large non-polar tetrahydropyran blocking group remained in the ether phase). The combined ether extracts were dried (magnesium sulfate) and concentration under vacuum gave a clear oil, 42 g (52% from compound **24**-*R*); ir and ^1H nmr were identical with those of compound **20**-*S* (Scheme I) (19).

(2*R*,12*R*)-4,7,10-Trioxatridecane-2,12-diol (**16**).

The procedure of Cooper and Walborsky (18), used to prepare the (2*S*,12*S*)-isomer (**15b**), was followed using (*R*)-2-(tetrahydro-2'-propanoxy)-1-propanol (**20**-*R*) (39.0 g, 0.243 mole) and diethylene glycol ditosylate (50 g, 0.24 mole) to give 16 g (50%) of **16**, bp 135°/1.0 mm; $[\alpha]_D^{25} = -32.9°$ (c 1.00, chloroform); ir, ^1H and ^{13}C nmr specra were identical with those of the (2*S*,12*S*) isomer (**15b**).

(*S*)-2-(Tetrahydro-2'-pyranoxy)-4,7-dioxa-9-nonanol (**25**, Scheme IV).

(*S*)-1-(4'-Toluenesulfonoxy)-2-(tetrahydro-2'-pyranoxy)propane (**21**-*S*) (118 g, 0.375 mole) was added over a 2 hour period to a solution containing diethylene glycol (240 g, 2.25 moles), dimethyl sulfoxide (500 ml), and sodium (20 g, 0.83 mole). The mixture was stirred overnight at 50°, poured into 200 ml of water, and extracted continuously with hot hexane for 12 hours. The hexane was removed under vacuum and the product distilled to give **25** as a pale yellow oil, 85 g (68%), bp 135°/0.8 mm; ir: 3460 (broad), 1120 (broad) cm^{-1}; ^1H nmr (deuteriochloroform): (δ): 1.1 (m, 3H), 1.5 (m, 6H), 3.7 (m, 14H), 4.7 (m, 1H). This compound was used without further purification.

(*R*)-1-(4'-Toluenesulfonoxy)-2-(tetrahydro-2'-pyranoxy)propane (**21**-*R*, Scheme IV).

(*R*)-2-(Tetrahydro-2'-pyranoxy)-1-propanol (**20**-*R*) (35 g, 0.218 mole) was added to 150 ml of pyridine and the resulting solution was cooled to 0° in an ice bath. 4-Toluenesulfonyl chloride (43 g, 0.23 mole) was then added over a one hour period. The mixture was then held at 0-5° for 3 additional hours and stored in the refrigerator overnight. Ether (100 ml) was added and the pyridine hydrochloride which had formed was removed by filtration. The solids were washed 3 times with 100 ml portions of ether, the filtrate and ether washings were combined and concentrated under reduced pressure. Toluene (100 ml) was added and the solvents again removed under vacuum to remove the last traces of pyridine. The product was dissolved in 1 liter of ether; washed twice with 100 ml portions of aqueous 1 *M* sodium carbonate, washed with brine to reduce the water content, and then dried over anhydrous calcium sulfate. The solvents were removed under reduced pressure with the last traces removed by heating to 80° under high vacuum to give a very thick yellow syrup, 57.7 g (84%); ir and ^1H nmr were identical to those of compound **21**-*S* (Scheme I) (19).

(*Meso*)-4,7,10-Trioxatridecane-2,12-diol (**17**, Scheme IV).

Sodium hydride (6.6 g, 0.28 mole) (free of oil) was suspended in 200 ml of dry dimethyl sulfoxide. (*S*)-2-(Tetrahydro-2'-pyranoxy)-4,7-dioxa-9-nonanol (**25**) (43.5 g, 0.18 mole) was added over a one hour period. The mixture was stirred for two additional hours until the evolution of gas stopped. (*R*)-1-(4'-Toluenesulfonoxy)-2-(tetrahydro-2'-pyranoxy)propane (**21**-*R*) (57.7 g, 0.18 mole) was then added and the mixture stirred overnight. Glycol **17** was isolated in the same manner as glycol **15b** (Scheme II) to give 6.6 g (16%) of a colorless oil, bp 135°/1 mm; $[\alpha]_D^{25} = +0.75°$ (c neat). The ir and ^1H nmr spectra were identical to those for compound **15b**.

General Procedure for the Synthesis of Macrocyclic Compounds.

The glycol and acid chloride each dissolved in 250 ml of benzene were added simultaneously to 1 liter of rapidly stirred benzene at 50°. After evolution of gaseous hydrogen chloride ceased, the solvent was removed under reduced pressure. The product was isolated by a hot hexane extraction (7,8). Specific details are given for each compound.

(4*S*,14*S*)-4,14-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]-heneicosa-1(21),17,19-triene-2,16-dione (**5a**).

2,6-Pyridinedicarbonyl chloride (4.69 g, 0.023 mole) and glycol **15a** (5.11 g, 0.023 mole) were used. The crude product was crystallized from hexane and the gummy crystals were recrystallized from ethanol to give a

white crystalline solid, 2.2 g (27%), mp 91-92°; $[\alpha]_D^{25} = -13.9°$ (c 1.00, chloroform); ir: 1720 cm^{-1} ^1H nmr (acetone-d_6) (δ) 1.36 (d, 6H, J = 6.3 Hz, $OCHCH_3$), 3.43-3.93 (m, 12H, $OCHCH_2$, OCH_2), 5.04-5.39 (m, 2H, COOCH), 8.1-8.4 (m, 3H) (also a small doublet at 1.10 and a multiplet at 4.5 due to the presence of about 5% of the positional isomer was detected); ^{13}C nmr (^1H decoupled) (acetone-d_6): δ 16.1, 71.2, 72.2, 73.4, 73.6, 128.0, 139.1, 149.8, 165.7.

Anal. Calcd. for $C_{17}H_{23}NO_7$: C, 57.78; H, 6.56; mol. wt. 353.4. Found: C, 57.87; H, 6.46; mol. wt. 350.2.

(4*S*,14*S*)-4,14-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (**5b**).

2,6-Pyridinedicarbonyl chloride (13.77 g, 0.067 mole) and glycol **15b** (15.00 g, 0.067 mole) were used. The crude product was crystallized twice from ethanol to give white crystals, 11.57 g (48.5%), mp 94°; $[\alpha]_D^{25} = -13.7°$ (c 1.00, chloroform); ir: 1720 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.44 (d, 6H, J = 6.4 Hz, $OCHCH_3$), 3.60-4.08 (m, 12H, $OCHCH_2$, OCH_2), 5.12-5.46 (m, 2H, COOCH), 6.9-7.4 (m, 3H); ^{13}C nmr (^1H decoupled) (acetone-d_6): δ 16.1, 71.2, 72.3, 73.4, 73.7, 128.0, 139.1, 149.9, 165.7.

Anal. Calcd. for $C_{17}H_{23}NO_7$: C, 57.78; H, 6.56; mol. wt. 353.4. Found: C, 57.87; H, 6.46; mol. wt. 350.9.

(4*R*,14*R*)-4,14-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (**6**).

2,6-Pyridinedicarbonyl chloride (5.51 g, 0.027 mole) and glycol **16** (6.00 g, 0.027 mole) were used. The crude product was crystallized twice from ethanol to give white crystals, 2.25 g (24%), mp 91-92°, $[\alpha]_D^{25} = +13.2°$ (c 1.00, chloroform); ir: 1720 cm^{-1}; ^1H nmr (acetone-d_6): δ 1.38 (d, 6H, J = 6.4 Hz, $OCHCH_3$), 3.5-3.9 (m, 12H, $OCHCH_2$, OCH_2CH_2), 5.1-5.4 (m, 2H, COOCH), 7.15-7.33 (m, 3H); ^{13}C nmr (acetone-d_6) (^1H decoupled): δ 16.1, 71.2, 72.2, 73.4, 73.7, 128.1, 139.2, 149.8, 165.7.

Anal. Calcd. for $C_{17}H_{23}NO_7$: C, 57.78; H, 6.56; mol. wt. 353.4. Found: C, 58.03; H, 6.59; mol. wt. 359.0.

(*Meso*)-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (**7**).

2,6-Pyridinedicarbonyl chloride (1.66 g, 0.0081 mole) and glycol **17** (1.81 g, 0.0081 mole) were used. The crude product was crystallized twice from ethanol to give white crystals, 1.09 g (38%), mp 102-103°, $[\alpha]_D^{25} = -0.07°$ (c 0.75, chloroform); ir: 1720 cm^{-1}; ^1H nmr (acetone-d_6): δ 1.35 (d, 6H, J = 6.5 Hz, $OCHCH_3$), 3.55-3.81 (m, 12H, $OCHCH_2$, OCH_2), 5.10-5.42 (m, 2H, COOCH), 7.08-7.38 (m, 3H); ^{13}C nmr (^1H decoupled) (acetone-d_6); δ 16.3, 70.8, 71.7, 73.4, 73.6, 128.5, 139.2, 149.5, 165.6.

Anal. Calcd. for $C_{17}H_{23}NO_7$: C, 57.78; H, 6.56; mol. wt. 353.4. Found: C, 57.53; H, 6.72; mol. wt. 353.7.

(8*S*,18*S*)-8,18-Dimethyl-1,4,7,10,13,16-hexaoxacyclooctadecane-2,6-dione (**8**).

Diglycolyl chloride (10.2 g, 0.06 mole) and glycol **15b** (13.00 g, 0.06 mole) were used. The crude product was crystallized twice from wet hexane to give white crystals, 6.1 g, mp 57-68°; ^1H nmr analysis showed the presence of one equivalent of water in the macrocycle. The crystals were placed in a vacuum dessicator over phosphorus pentoxide and heated at 80° for 24 hours. A small portion was distilled to give a thick, colorless, hygroscopic syrup, 4.2 g total yield (22%), bp 170°/1.0 mm, $[\alpha]_D^{25} = +46.5°$ (c 1.00, chloroform); ir: 1745 cm^{-1}; ^1H nmr (acetone-d_6): δ 1.17 (d, 6H, J = 6.3 Hz, $OCHCH_3$), 3.24-3.66 (m, 12H, $OCHCH_2$, OCH_2), 4.20 (s, 2H, $COCH_2$), 4.97-5.36 (m, 2H, COOCH); ^{13}C nmr (^1H decoupled) (acetone-d_6): δ 16.1, 67.1, 70.1, 70.6, 71.3, 73.6, 169.8.

Anal. Calcd. for $C_{14}H_{28}O_8$: C, 52.50; H, 7.55; mol. wt. 320.5. Found: C, 52.46; H, 7.70; mol. wt. 315.1.

(8*R*,18*R*)-8,18-Dimethyl-1,4,7,10,13,16-hexaoxacycloocetadecane-2,6-dione (**9**).

Diglycolyl chloride (3.08 g, 0.018 mole) and glycol **16** (4.00 g, 0.018 mole) were used. The crude product was crystallized twice from wet hexane to give crystals of mp 63-66°. The crystals were dried at 80°/0.5 mm over phosphorus pentoxide for 24 hours to give a colorless hygroscopic syrup; 1.0 g (17%), $[\alpha]_D^{25} = -46.1°$ (c 1.00, chloroform); ir: 1750 cm^{-1}; ^1H nmr (acetone-d_6): δ 1.18 (d, 6H, J = 6.8 Hz, $OCHCH_3$), 3.29-3.68 (m, 12H, $OCHCH_2$, OCH_2), 4.20 (s, 2H, $COCH_2$), 4.24 (s, 2H, $COCH_2$), 5.00-5.38 (m, 2H, COOCH); ^{13}C nmr (^1H decoupled) (acetone-d_6): δ 16.4, 67.6; 70.4; 71.0; 71.7; 73.9; 170.0.

Anal. Calcd. for $C_{14}H_{24}O_8$: C, 52.50; H, 7.55; mol. wt. 320.5. Found: C, 52.33; H, 7.42; mol. wt. 323.0.

Meso-8,18-Dimethyl-1,4,7,10,13,16-hexaoxcyclooctadecane-2,6-dione (**10**).

Diglycolyl chloride (1.46 g, 0.0086 mole) and glycol **17** (1.9 g, 0.0086 mole) were used. The crude product was extracted with pentane in a liquid-liquid extractor. The pentane was removed under reduced pressure to give a light yellow oil, 0.67 g (24%); ir: 1745 cm^{-1}; ^1H nmr (acetone-d_6): δ 1.20 (d, 6H, J = 6.4 Hz, $OCHCH_3$), 3.29-3.68 (m, 12H, $OCHCH_2$, OCH_2), 4.27 (s, 4H, $COCH_2$), 4.98-5.33 (m, 2H, COOCH); ^{13}C nmr (^1H decoupled) (acetone-d_6): δ 16.4, 67.9, 70.5, 70.9, 71.6, 73.8, 170.4.

Anal. Calcd. for $C_{14}H_{24}O_8$: C, 52.50; H, 7.55; mol. wt. 320.5. Found: C, 52.50; H, 7.46; mol. wt. 310.2.

(8*S*,18*S*)-8,18-Dimethyl-1,7,10,13,16-pentaoxa-4-thiacyclooctadecane-2,6-dione (**11**).

Thiadiglycolyl chloride (5.89 g, 0.0315 mole) and glycol **15a** (7.00 g, 0.0315 mole) were used. The crude product was crystallized twice from hexane to give flakes, 2.4 g (23%), mp 58°; $[\alpha]_D^{25} = +57.8$ (c 1.00, chloroform); ir: 1725 cm^{-1}; ^1H nmr (acetone-d_6): δ 1.20 (d, 6H, J = 6.8 Hz, $OCHCH_3$), 3.27-3.72 (m, 16H, $OCHCH_2$, OCH_2, $COCH_2$), 4.92-5.26 (m, 2H, COOCH); ^{13}C nmr (^1H decoupled) (acetone-d_6): δ 16.4, 34.0, 71.1, 71.8, 73.8, 169.7.

Anal. Calcd. for $C_{14}H_{24}O_7S$: C, 49.99; H, 7.19; mol. wt. 336.4. Found: C, 49.97; H, 7.42; mol. wt. 335.7.

(4*S*,14*S*)-4,14-Dimethyl-3,6,9,12,15,20-hexaoxabicyclo[15.2.1]eicosa-1(19),17-dione-2,6-dione (**12**).

2,5-Furandicarbonyl chloride (6.0 g, 0.027 mole) and glycol **15b** (5.21 g, 0.027 mole) were used. The crude product was crystallized twice from 80% ethanol and then from hexane to give white flakes, 2.17 g (23.5%), mp 80°; $[\alpha]_D^{25} = -27.29°$ (c 1.00, chloroform); ir: 1710 cm^{-1}; ^1H nmr (acetone-d_6): δ 1.38 (d, 6H, J = 6.1 Hz, $OCHCH_3$), 3.52-4.00 (m, 12H, $OCHCH_2$, OCH_2), 4.96-5.28 (m, 2H, COOCH), 7.35 (s, 2H, aromatic H); ^{13}C nmr (^1H decoupled) (acetone-d_6): δ 16.1, 71.0, 71.8, 73.3, 73.5, 119.2, 147.5, 158.1.

Anal. Calcd. for $C_{16}H_{22}O_8$: C, 56.13; H, 6.48; mol. wt. 342.4. Found: C, 56.13; H, 6.40; mol. wt. 342.1.

(4*S*,14*S*)-19-Chloro-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo-[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (**13**).

4-Chloro-2,6-pyridinedicarbonyl chloride (10.4 g, 0.044 mole) and glycol **15b** (9.85 g, 0.044 mole) were used. The crude product was extracted twice with pentane in a continuous extractor. The solvent was removed under vacuum to give a very thick, pale yellow syrup (12.9 g, 76%) which could not be distilled or crystallized $[\alpha]_D^{25} = -3.98°$ (c 1.00, chloroform); ir: 1715 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.44 (d, 6H, J = 6.8 Hz, $OCHCH_3$), 3.60-4.10 (m, 12H, $OCHCH_2$, OCH_2), 5.13-5.46 (m, 2H, COOCH), 8.27 (s, 2H); ^{13}C nmr (^1H decoupled) (deuteriochloroform): δ 15.8, 70.6, 71.8, 73.1, 73.4, 127.7, 146.1, 150.2, 163.9.

Anal. Calcd. for $C_{17}H_{22}ClNO_7$: C, 52.65; H, 5.72; mol. wt. 387.8. Found: C, 52.45; H, 5.75; mol. wt. 420.1.

(4*S*,14*S*)-4,14-Dimethyl-19-methoxy-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (**14**).

4-Methoxy-2,6-pyridinedicarbonyl chloride (7.37 g, 0.0315 mole) and glycol **15b** (7.00 g, 0.0315 mole) were used. The crude product was crystallized twice from ethanol to give white crystals, 2.1 g (17.3%), mp 98-99°; $[\alpha]_D^{25} = -6.90°$ (c 1.00, chloroform); ir: 1720 cm^{-1}; ^1H nmr (acetone-d_6): δ 1.36 (d, 6H, J = 6.8 Hz, $OCHCH_3$), 3.52-3.92 (m, 12H, $OCHCH_2$, OCH_2), 4.05 (s, 3H, OCH_3), 5.04-5.36 (m, 2H, COOCH), 7.66 (s, 2H); ^{13}C nmr (^1H decoupled) (acetone-d_6): δ 16.1, 56.7, 71.1, 72.1, 73.4,

73.6, 113.8, 151.4, 165.6, 168.0.

Anal. Calcd. for $C_{18}H_{25}NO_6$: C, 56.39; H, 6.57; mol. wt. 383.4. Found: C, 56.23; H, 6.55; mol. wt. 380.3.

Acknowledgement.

Financial support of this work by the National Science Foundation (CHE-800059) is gratefully acknowledged. B. A. Jones was the recipient of a research grant from the Associated Students of Brigham Young University. We also wish to thank Dr. S. T. Jolley for many helpful discussions.

REFERENCES AND NOTES

(1) Presented at the Eighth International Congress of Heterocyclic Chemistry, Graz, Austria, August 23-28, 1981.

(2) C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 7017 (1967).

(3) C. J. Pedersen, "Synthetic Multidentate Macrocyclic Compounds", in "Synthetic Macrocyclic Compounds", R. M. Izatt and J. J. Christensen, eds., Academic Press, New York, N.Y., 1978, pp 1-53.

(4) J. S. Bradshaw and S. T. Jolley, *J. Heterocyclic Chem.*, **16**, 1157 (1979).

(5) J. S. Bradshaw, C. T. Bishop, S. F. Nielson, R. E. Asay, D. R. K. Masihdas, E. D. Flandors, D. D. Hansen, R. M. Izatt and J. J. Christensen, *J. Chem. Soc., Perkin Trans, I,* 2505 (1976).

(6) M. D. Thompson, J. S. Bradshaw, S. F. Nielsen, C. T. Bishop, F. T. Cox, P. E. Fore, G. E. Maas, R. M. Izatt and J. J. Christensen, *Tetrahedron,* **33**, 3317 (1977).

(7) G. E. Maas, J. S. Bradshaw, R. M. Izatt and J. J. Christensen, *J. Org. Chem.*, **42**, 3937 (1977).

(8) J. S. Bradshaw, R. E. Asay, G. E. Maas, R. M. Izatt and J. J. Christensen, *J. Heterocyclic Chem.*, **15**, 825 (1978).

(9) R. M. Izatt, J. D. Lamb, C. E. Maas, R. E. Asay, J. S. Bradshaw and J. J. Christensen, *J. Am. Chem. Soc.*, **99**, 2365 (1977).

(10) R. M. Izatt, J. D. Lamb, R. E. Asay, G. E. Maas, J. S. Bradshaw, J. J. Christensen and S. S. Moore, *ibid.*, **99**, 6134 (1977).

(11) J. S. Bradshaw, G. E. Maas, R. M. Izatt and J. J. Christensen, *Chem. Rev.*, **79**, 37 (1979).

(12) J. S. Bradshaw, G. E. Maas, J. D. Lamb, R. M. Izatt and J. J. Christensen, *J. Am. Chem. Soc.*, **102**, 467 (1980).

(13) J. S. Bradsahw, S. L. Baxter, J. D. Lamb, R. M. Izatt and J. J. Christensen, *ibid.*, **103**, 1821 (1981).

(14) J. S. Bradshaw, R. E. Asay, S. L. Baxter, P. E. Fore, S. T. Jolley, J. D. Lamb, G. E. Maas, M. D. Thompson, R. M. Izatt and J. J. Christensen, *Ind. Eng. Chem. Prod. Res. Dev.*, **19**, 86 (1980).

(15) J. S. Bradshaw, S. T. Jolley and B. A. Jones, *J. Heterocyclic Chem.*, **17**, 1317 (1980).

(16) J. D. Lamb, R. M. Izatt, C. S. Swain, J. S. Bradshaw and J. J. Christensen, *J. Am. Chem. Soc.*, **102**, 479 (1980).

(17) R. G. Ghirardelli, personal communication (1979).

(18) K. D. Cooper and H. M. Walborsky, *J. Org. Chem.*, **46**, 2110 (1981).

(19) R. G. Ghirardelli, *J. Am. Chem. Soc.*, **95**, 4987 (1973).

(20) P. Iten, A. Hofmann and C. Engster, *Helv. Chim. Acta,* **61**, 430 (1978).