On the Synthesis of Monoamides of 18-Crown-6-tetracarboxylic Acid

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The synthesis of monoamides of (*R*,*R*,*R*,*R*)-18-crown-6-2,3,11,12-tetracarboxylic acid via reaction of primary and secondary amines with the crown ether bis-anhydride is explored. One equivalent of benzylamine gave a quantitative yield of a diamide, and the recovered crown ether suffered epimerization. The expected monoamide was prepared via initial partial hydrolysis of the bis-anhydride followed by benzylamine addition. The initial hydrolysis method fails for secondary amines, as nucleophilic attack is not competitive with epimerization. As a consequence, the stereochemical integrity of the starting material is lost and amide ester derivatives of this important framework crown ether are inaccessible by direct refunctionalization.

The focus of this paper is the tetraacid crown ether derived from *R*,*R*-(+)-tartaric acid (**1**) and its derivatives (Scheme 1). The first report described it as a "building block",[1] and virtually every report since has described the structure as providing a "framework" for appending additional functionality. There are well over 100 simple derivatives of this subunit known;[2] it appears at the core of our unimolecular channels[3] and as the vase of "bouquet" molecules.[4] There is a rich cation complexation chemistry of the parent tetraacid and derivatives in solution and in the solid state,[2,5] but it is the remarkable conformational control exerted by the tartaric acid-derived units which is the appealing structural feature of this framework element.[2,5,6] The preferred conformation of the carboxylate groups of **1** is *anti* with the carboxylates and derived groups in the *axial* positions of the macrocycle so appended groups confront one another across the face of the macrocycle and interact with bound primary ammonium guests.[2] Given the number of reports, there is little doubt of its reliability as a functional element for supramolecular systems.

Scheme 1 summarizes the body of the reaction chemistry.[2] Tetraacid **1** is smoothly converted to tetraacid chloride **2** with phosphorus chlorides in CH_2Cl_2 or $POCl_3$. Compound **2** reacts with primary amines in THF or other solvents to give the symmetrical tetraamides **3** which are usually isolated by chromatography in good to excellent yields. The diamide regioisomers *syn*-**5** and *anti*-**6** are readily prepared from bis-anhydride **4**. The diacid units of **1** are easily dehydrated with acetyl chloride, and both **5** and **6** are prone to the analogous reaction to produce the bis-imide **7**. Separation of mixtures of **5** and **6** can be achieved in some cases, and regioselective syntheses of *syn*-isomers have been reported in others.[2] The yields in syntheses of **5** and **6** are generally modest but are usually related to separation losses, and the reaction efficiency per anhydride group in **4** is generally high. Simple tetraesters **8** are quite rare, but complex esters have been prepared in modest yield by alkylation of the tetramethylammonium salts of **1** with iodides or mesylates. The conformational properties of **1** are directly exploited in the capping reactions of diamines with **2** or **4** to give "captands" **9** or **10**, respectively.[8]

The chemistry outlined in Scheme 1 has idiosyncrasies but is generally reliable. In our experience, the difficulties which do arise are solely due to the propensity of carboxylate crown ethers to bind to chromatographic supports. Thus we were confident that the synthetic plan outlined in Scheme 2 would have a good chance of success. As part of an ongoing plan to modify our ion channels to allow switching, the monoamide triacid **14** was designed to integrate a photoswitch. Elements of the design are discussed elsewhere.[9] We envisaged a capping reaction of bis-anhydride **4** with an amino alcohol (**11**) followed by selective hydrolysis of the ester **12** to give **13** which could then be further functionalized to **14** and thence to channel materials by esterification of the remaining carboxylates. Since imide formation is a known complication which prevents any further reaction to give amide esters,[7a] the amine **11** must be secondary. This plan failed, as did all other attempts to prepare monoamide triacids of secondary amines such as **13**. The nature of this failure is the basis of this report.

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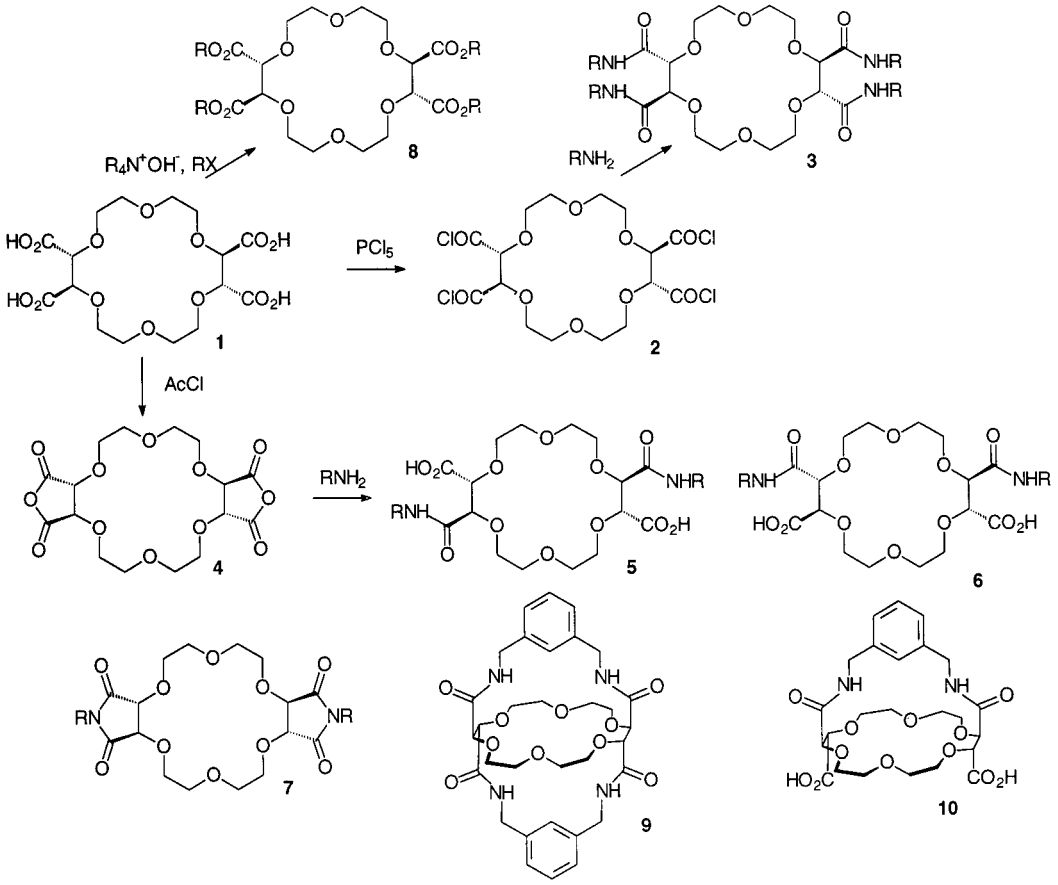
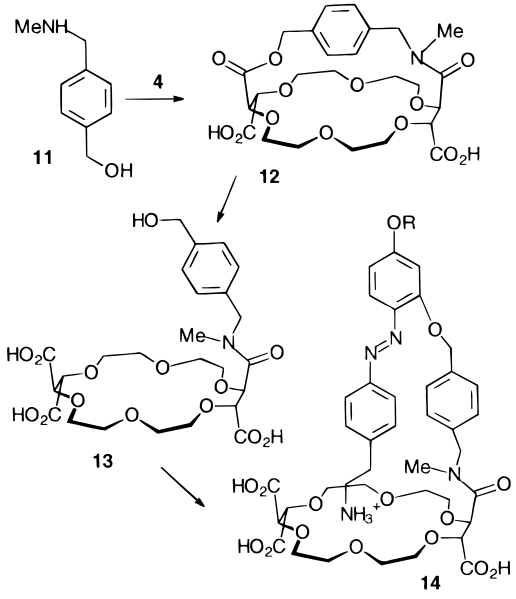
S0022-3263(97)00707-X CCC: $14.00

Scheme 1



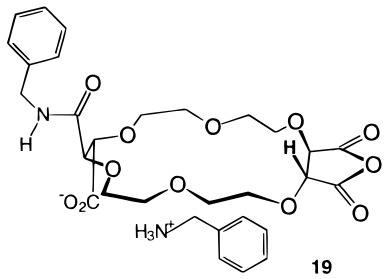
Scheme 2



Results and Discussion

The intramolecular capping reactions to give **9** or **10** proceed in high yield without recourse to high dilution conditions.[8] Initial attempts to achieve the capping reaction in Scheme 2 under similar conditions gave a complex mixture, and subsequent attempts used high dilution. In a typical procedure, equimolar solutions of bis-anhydride **4** (freshly prepared from **1**) and amine **11** were added simultaneously via syringe pumps to vigorously stirred dry THF containing excess Et_3N over 24−48 h (final concentration $< 5 \times 10^{-4}$ M). Removal of solvent gave a crude product with an encouraging NMR spectrum, but fractionation always revealed products of greater than expected NMR complexity. Hydrolysis to crude **13** resulted in only minor simplification of the NMR spectra. The most complete fractionation of crude **13** was achieved using countercurrent chromatography ($CHCl_3$:H_2O) followed by analysis of fractions by analytical gel permeation chromatography. This indicated that crude **13** contained several products in roughly comparable amounts. All products were apparently amides of crown ether poly-carboxylic acids, and many appeared to be isomers of **13**.

This disappointing set of results prompted us to examine a direct approach to **13** via addition of 1 equiv of the amine to the bis-anhydride followed by acidic workup (Scheme 3). Using the Thp-protected secondary amine **15a** required to give **13**, this route apparently produced a mixture of diamides *anti*-**17a** and *syn*-**18a** and **1**, the hydrolysis product of unreacted **4**. The expected monoamide **16a** was not found in significant amount. The first-formed intermediate crown ether anhydride must suffer attack by another molecule of **15a** much faster than does **4** itself. This result is quite general; 1 equiv of benzylamine (**15b**) reacts with **4** to yield exclusively the *anti*-diamide **17b** in quantitative conversion of the amine (assigned as *anti* on the basis of methine chemical shifts[2]). The presumed intermediate carboxylate anhydride requires a counterion as sketched below (**19**). We had supposed that excess Et_3N would ensure that Et_3NH^+ would play this role. The result suggests that this has not happened and that an intracomplex attack on the lower face of the remaining anhydride occurs readily to give the observed product.



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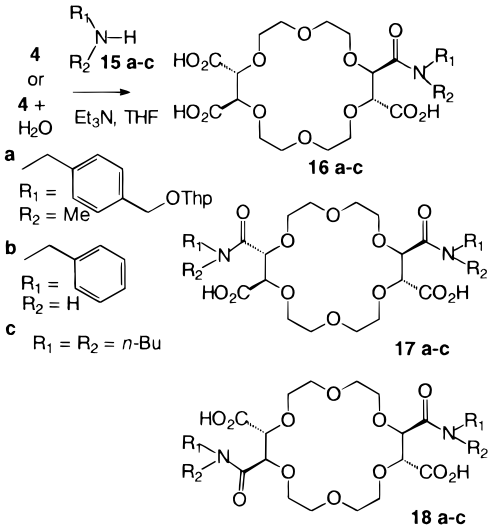
Quite apart from unexpected products, the most troubling aspect of the reaction of **4** with **15b** was that recovered crown ether **1** had *lost its chiral integrity during the reaction*. Pure **1** shows a strong methine singlet near 4.6 ppm in the ^{1}H NMR (CD_3OD); recovered **1** showed a complex pattern of singlets and doublets between 4.7 and 4.2 ppm. Similar complexity was observed in the ^{13}C NMR of recovered **1**. Pure **1** in CH_3OH has an optical rotation of $[\alpha]^{20}_D = +59.4$; recovered **1** from this experiment had an optical rotation of $[\alpha]^{20}_D = +7.3$. The same result was observed with the secondary amine, di-*N*-butylamine (**15c**): recovered **1** had $[\alpha]^{20}_D = +14.4$. In addition diamide **17c** showed additional complexity of the methine signals in both the ^{1}H and ^{13}C NMR spectra indicating that epimerization had occurred.

Since a base is required for the amide-forming reactions, we reasoned that we could avoid the problem of the extra anhydride by first reacting **4** with 1 equiv of water. The product diacid anhydride would then react with the amine nucleophile. This expectation was confirmed with the primary amine **15b**. The product mixture consisted of a 50% (statistical) yield of **16b**, a 1:1 mixture of **17b** and **18b**, and some recovered **1** which was stereochemically intact ($[\alpha]^{20}_D = +59.7$). The monoamide **16b** was easily recovered from the mixture by a solvent extraction sequence. The same reaction and separation process with **15c** was not as satisfactory as the monoamide **16c** coextracted with the *syn*- and *anti*-diamides **17c** and **18c**. The NMR spectra of these mixtures showed minor impurities which would indicate a low level of epimerization, and the recovered tetraacid **1** was only 91% optically pure ($[\alpha]^{20}_D = +54.6$). Nonetheless we proceeded with the required secondary amine **15a** in the hope that the epimerization would be minimal. The expected **16a** was a component of the product mixture, but it was clear from the ^{1}H and ^{13}C NMR spectra that epimerization had occurred to a larger extent than in the reaction with **15c**. Moreover, the recovered tetraacid **1** was only 82% optically pure ($[\alpha]^{20}_D = +49.0$), and its ^{1}H NMR spectrum showed considerable complexity.

All results indicate that the crown ether anhydride can be isomerized by the bases present. Abstraction of the α-proton of the anhydride could result in an anion, or in a ketene, and either intermediate would lead to loss of stereochemical integrity. The synthetic outcomes observed therefore depend on the relative efficiencies of the amines as bases or nucleophiles. Amine basicity in non-hydrogen-bonding solvents such as dichloromethane follows the inductive order $NH_3 < 1° < 2° < 3°$ [10] and the reverse order in polar hydrogen-bonding solvents such as water. In nonpolar hydrogen-bond acceptor solvents such as diethyl ether, the stabilization of the conjugate

Scheme 3



acid is sufficient to make Et_3N a slightly weaker base than *n*-butylamine.[11] The difference is not large, so it is likely that the bases in the THF system (**15a**−**c**, Et_3N) are of similar basicity. Amine nucleophilicity usually follows amine basicity.[12] More significant for our system is the reported marked dependence of steric effects on the rates of ester amminolysis (in diethyl ether[13] or acetonitrile[14]). Thus we expect the primary benzylamine (**15b**) to react significantly faster as a nucleophile with anhydrides than the secondary amines **15a**,**c**. It happens that secondary amines present an unfavorable combination of characteristics (sufficient basicity and sufficient steric bulk) to frustrate the simple preparation of amides of the type our design requires.

Epimerization at the α-carbon is an inherent difficulty in the use of the 18-crown-6-tetracarboxylic acid as a framework element. In hindsight it might have been predictable from the well-known racemization reactions of peptides,[15] but we know of no directly relevant prior reports of epimerization of tartaric acid diether anhydrides.[16] In previous work on tetraester derivatives epimerization was noted as a peripheral problem that was successfully overcome by a change of reaction type.[3,7a] In this instance the problem runs deeper and is unlikely to be resolved simply.[17]

From the available information it appears that **1** as a framework element will reliably support **only** the following types of transformations: (i) symmetrical tetraesters by carboxylate alkylation, (ii) symmetrical tetraamides via the acid chloride **2** and primary amines, and (iii) *syn*- or *anti*-diamide diacids via the bis-anhydride **4** and primary amines. Apart from derivatives reported

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(17) Control experiments involving only **4** and Et_3N, DMAP, or 2,2,6,6-tetramethylpiperidine in THF showed detectable levels of epimerization (hydrolysis, isolation of **1**, $[\alpha]_D$) after 2 h at rt. Preliminary work on alternative coupling reactions (carbodiimides, active esters) has indicated that complex product mixtures are not restricted to the reactions reported here; Cross, G. Ph.D. Thesis, University of Victoria, British Columbia, Canada, 1994.

here, only two other exceptions to the rules above are known: a symmetrical tetraamide from *N*,*N*-dioctylamine[18] and a pair of *syn*- and *anti*-diamide diacids also from *N*,*N*-dioctylamine.[19] Designs of future supramolecular targets based on **1** as a framework element should humor its limitations.

Experimental Section

Proton NMR spectra were recorded at 250 or 360 MHz in $CDCl_3$, CD_3OD, or acetone-d_6. Carbon NMR spectra were recorded at 62.89 or 90.57 MHz in $CDCl_3$, CD_3OD, or acetone-d_6. High-resolution EI mass spectra were recorded using perfluorokerosene as standard. High-resolution LSIMS were recorded with either glycerol or *m*-nitrobenzyl alcohol (NMBA) as matrix and Cs/Na iodides as standard. Optical rotation measurements were recorded using a low-volume (1.5 mL) cell with a 10 cm path length and spectral grade methanol as solvent. Dichloromethane was distilled before use. THF was dried by refluxing over, then distilling from, K metal under a dry N_2 atmosphere and was freshly dried for each procedure. Solutions in organic solvents were dried using anhydrous $MgSO_4$. Compounds **1** and **4** were prepared as previously[2] and were identical with previous samples.

4-[(*N*-Methylamino)methyl]benzyl Alcohol (11). Compound **11** has been reported, but no preparation or characterization was provided.[20] Our sample was prepared from methyl 4-bromobenzoate, via the *N*-Me amide,[21] transmetalation with BuLi followed by carbonation to the benzoic acid,[22] conversion to the methyl ester, and reduction with excess $LiAlH_4$ in THF to give **11** as a colorless oil: ^{1}H NMR (CD_3OD) δ 2.33 (s, 3H), 3.65 (s, 2H), 4.58 (s, 2H), 4.88 (br s, 2H), 7.27−7.34 (m, 4H); ^{13}C NMR (CD_3OD) δ 35.4, 56.0, 64.8, 128.0, 129.4, 139.1, 141.4; HRMS (EI) calcd for $C_9H_{13}NO$ *m*/*z* 151.09979, found *m*/*z* 151.10015 (49).

4-[(*N*-Methylamino)methyl]-*O*-(2-tetrahydropyranyl)benzyl Alcohol (15a). Compound **15a** has been reported,[20] but no preparation or characterization was provided. To a solution of **11** as its HCl salt (520 mg, 2.78 mmol) in DMF (10 mL) were added dihydropyran (2 mL, 22 mmol) and conc HCl (1 drop), and the resulting solution was stirred at rt overnight. The solution was evaporated to give a light brown solid. This material was dissolved in CH_3OH (5 mL), added to a suspension of basic anion exchange resin in CH_3OH (100 mL), and stirred overnight. The mixture was filtered and the filtrate evaporated to give **15a** as a colorless oil (400 mg, 61%): ^{1}H NMR ($CDCl_3$) δ 1.4−1.9 (m, 6H), 2.34 (s, 3H), 3.46 (m, 1H), 3.65 (s, 2H), 3.83 (m, 1H), 4.40 (d, J = 12 Hz, 1H), 4.63 (m, 1H), 4.68 (d, J = 12 Hz, 1H), 7.24 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.2, 25.3, 30.4, 35.6, 55.5, 61.9, 68.4, 97.5, 127.8, 128.1, 139.0, 140.6; HRMS (+LSIMS, NMBA) calcd for $C_{14}H_{22}NO_2$ *m*/*z* 236.1652, found *m*/*z* 236.1683 (100).

Typical High-Dilution Capping Reaction Procedure: Attempted Preparation of 12 and 13. A solution of triethylamine (23 mL, 16.8 g, 166 mmol) in dry THF (900 mL) was stirred at maximum speed at room temperature under an atmosphere of dry N_2. To this were added simultaneously, via dual syringe pumps, a solution of **11** (1.66 mmol) in dry THF (60 mL) and a solution of dianhydride **4** in dry THF (60 mL) at 1 mL/h over 2−3 days. After a further day, the reaction mixture was evaporated, and the product was passed through a strong acid cation exchange resin, eluting with 90% CH_3OH/water. The product was hydrolyzed by refluxing for 2 h in $(CH_3)_4N^+OH^-$ in CH_3OH (2 M, 25 mL), and the ammonium salt was removed with another strong acid cation exchange column, eluting with water. In no instance were simple product mixtures produced.

Attempted Preparation of 16a. To a stirred solution of dianhydride **4** (605 mg, 1.5 mmol) in dry THF (100 mL) was added dropwise a solution of **15a** (300 mg, 1.28 mmol) and triethylamine (1.0 g, 10 mmol) in dry THF (50 mL), and the resulting solution was stirred overnight. The reaction mixture was evaporated, and the residue was partitioned between dilute aqueous acid and $CHCl_3$. The ^{1}H NMR spectrum of the organic extract indicated predominantly diamides from integration of the aromatic and crown ether signals. The aqueous extract was continuously extracted with $CHCl_3$ overnight. The continuous organic extract was analyzed by HPLC using a gel permeation column (Alltech; 500 Å, 5 mm column, 25 cm × 1 cm i.d., elution with CH_3OH at ∼30 atm, UV detection at 254 nm), and two large peaks were seen along with many smaller ones. Samples of the two major fractions were isolated by pooling the products from repeated injections onto this column. One fraction contained very little material and was composed of several compounds according to the ^{13}C NMR spectrum. The other fraction was identified as impure diamides (**17a** and **18a**): ^{1}H NMR (acetone-d_6) showed the relative integrated areas for the crown ether OCH_2 peaks (16H) and the aromatic *H* peaks (4H per ring) to be 2:1, so there must be two aromatic rings per crown ether: ^{13}C NMR (acetone-d_6) δ 33.4, 35.0, 51.1, 53.0, 64.3, 70.5−71.4 (7 peaks), 78.9, 79.1, 81.6, 81.7, 127.5, 127.6, 127.8, 128.5, 136.5, 136.8, 142.3, 142.6, 169.5, 170.6.

***N*,*N*′-Dibenzyl-2,12-dicarbamoyl-(2*R*,3*R*,11*R*,12*R*)-1,4,7,10,13,16-hexaoxacyclooctadecane-3,11-dicarboxylic Acid (17b).** To a stirred solution of dianhydride **4** (500 mg, 1.23 mmol) in dry THF (50 mL) was added dropwise a solution of benzylamine (132 mg, 1.23 mmol) and triethylamine (1 mL, 7 mmol) in dry THF (25 mL), and the resulting solution was stirred overnight. Water (25 mL) was then added, and this solution was stirred for 0.5 h. The reaction mixture was evaporated and then partitioned between dilute aqueous acid and $CHCl_3$. The organic layer was dried and evaporated to give *anti*-diamide **17b** (400 mg, 100%) as a colorless glass: ^{1}H NMR ($CDCl_3$) δ 3.2−3.8 (m, 16H), 4.19 (s, 2H), 4.35 (s, 2H), 4.37 (m, 2H), 4.48 (m, 2H), 7.10−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 43.1, 69.2, 70.2, 70.3, 70.8, 79.9, 80.1, 127.3, 127.8, 128.5, 138.8, 170.3, 171.3; HRMS (−LSIMS, NMBA) calcd for $C_{30}H_{37}N_2O_{12}$ *m*/*z* 617.2347, found *m*/*z* 617.2336 (100).

The aqueous extract was reduced to a small volume and passed through a strong acid cation exchange resin eluting with water. The eluate was evaporated to a colorless glass which was identified as epimerized tetraacid **48** (290 mg, 0.66 mmol, 100%): ^{1}H NMR (CD_3OD) δ 3.1−3.9 (m, 16H), 4.2−4.6 (m, 4H); ^{13}C NMR (CD_3OD) δ 71.0−76.0 (several peaks), 80.8−81.8 (several peaks), 171−173 (several peaks); −LSIMS (NMBA) *m*/*e* 439 ($M - 1^-$); $[\alpha]^{20}_D$ = +7.3 (*c* 1.0, CH_3OH).

***N*-Benzyl-2-carbamoyl-(2*R*,3*R*,11*R*,12*R*)-1,4,7,10,13,16-hexaoxacyclooctadecane-3,11,12-tricarboxylic Acid (16b).** To a stirred solution of dianhydride **4** (200 mg, 0.5 mmol) in dry THF (1 mL) was added water (9 mL, 9 mg, 0.5 mmol), and the resulting solution was stirred at room temperature for 2 days. To this was added a solution of benzylamine (59 mg, 0.55 mmol) and triethylamine (220 mg, 2.2 mmol) in a few milliliters of dry THF. A precipitate formed initially but soon dissolved. The solution was stirred for 2 h and then evaporated to a white foam. This was dissolved in a small volume of water and passed through a small column of strong acid cation exchange resin, eluting with water. The product from this column was partitioned between water and $CHCl_3$. The organic extract contained a ∼2:1 mixture of *anti*-diamide **17b** and *syn*-diamide **18b** (30 mg total, 0.05 mmol, 10%): ^{1}H NMR ($CDCl_3$) δ 3.2−3.8 (m, 16H), 4.2−4.6 (m, 8H), 7.1−7.3 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 42.9, 43.2, 68.6−71.0 (7 peaks), 79.8, 79.9, 80.5, 81.7, 127.3, 127.8, 128.0, 128.3, 128.4, 128.5, 138.3, 138.8, 169.8, 170.2, 171.6, 171.9.

The aqueous extract was continuously extracted with $CHCl_3$ overnight. The continuous extract was dried and evaporated to give monoamide **16b** as a white foam (150 mg, 0.28 mmol, 56%): ^{1}H NMR (acetone-d_6) δ 3.40−3.85 (m, 16H), 4.35 (d, J = 3 Hz, 1H), 4.38 (d, J = 3 Hz, 1H), 4.47 (d, J = 3 Hz), 4.49 (d, J = 3 Hz, 1H), 4.50 (m, 1H), 4.64 (m, 1H), 7.20−7.50 (m, 5H); ^{13}C NMR (acetone-d_6) δ 43.3, 69.9−71.6 (7 peaks), 80.8, 80.9, 81.0, 81.4, 127.5, 128.8, 128.9, 140.5, 170.8, 171.2, 171.3, 171.6;

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HRMS (−LSIMS, MNBA) calcd for $C_{23}H_{30}NO_{13}$ *m*/*z* 528.1717, found *m*/*z* 528.1725.

The remaining aqueous extract contained predominantly tetraacid **1**: ^{1}H NMR (acetone-d_6) δ 3.35−3.90 (m, 16H), 4.40 (s, 4H); ^{13}C NMR (acetone-d_6) δ 70.2, 70.7, 80.6, 171.5; −LSIMS (NMBA) *m*/*z* 439 (M − 1, 100).

Attempted Preparation of 16a. Using the procedure as described above, bis-anhydride **4** (360 mg, 0.89 mmol), water (16 mL, 16 mg, 0.90 mmol), amine **15a** (250 mg, 1.06 mmol), and triethylamine (450 mL, 327 mg, 3.2 mmol) gave an initial organic extract whose ^{1}H NMR spectrum integrated roughly as the monoamide **16a** but the methine region of the spectrum was complex. Similarly the ^{13}C NMR spectrum had far too many peaks, most noticeably in the carbonyl and methine regions. The continuous extract similarly gave overly complex spectra, and no unambiguous assignments were made. The aqueous extract contained partially epimerized tetraacid **1**: $[\alpha]^{20}_D = +49.0$ (*c* 1.1, CH_3OH).

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Supporting Information Available: ^{13}C NMR spectra of **11**, **15a**, **16b**, and **17b** and ^{1}H NMR spectra of **16b** and a sample of epimerized **1** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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