methylsilyl ether), 114635-87-9; (±)-**26**, 111923-09-2; (±)-**28**, 111923-10-5; (±)-**29**, 114635-88-0; (±)-**30**, 111923-11-6; (±)-**31**, 111923-12-7; $HO(CH_2)_2NHCH_2Ph$, 104-63-2; $Br(CH_2)_2NHCH_2Ph \cdot HBr$, 33538-02-2; EtO_2CCH_2Br, 105-36-2.

Supplementary Material Available: Experimental details and spectral information for other new compounds not described in the present Experimental Section (3 pages). Ordering information is given on any current masthead page.

Synthesis of (Allyloxy)methyl-Substituted Diaza-18-crown-6 Compounds for Attachment to Silica Gel

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(Allyloxy)methyl-substituted *N,N'*-dibenzyldiaza-18-crown-6 was prepared by five different processes. A simple Okahara ring closure of an (allyloxy)methyl-substituted diazahexaethylene glycol proved to be the most convenient method. The corresponding *N,N'*-dihexyl- and *N,N'*-diethyldiaza-18-crown-6 compounds were also prepared. These (allyloxy)methyl-substituted crown compounds were covalently bonded to silica gel by first forming a diethoxymethylsilane containing the crown and coating this silane material onto silica gel and heating. The new silica gel–crown material separated Hg(II) ions from Cd(II) and Zn(II) when an aqueous solution of pH 2 containing equal concentrations of all three cation nitrates was passed over it.

Introduction

We are interested in the design of macrocyclic compounds for the selective complexation and separation of metal ions. An extensive compilation of equilibrium constant (K) data on cation–macrocycle complexation has been published.[1] In general, preferential complexation results when the relative sizes of the cation and ligand cavities are matched. This is particularly true with the crown ethers where 18-crown-6 forms a stronger complex with potassium than with any of the other alkali-metal ions while 21-crown-7 forms a stronger complex with cesium ions.[2] Often, the nature of the donor atoms in the macroring exert an even greater effect on complexation. This is particularly true with the nitrogen atom containing aza-crowns which are complexed much more strongly by the soft transition-metal ions than by the hard alkali-metal ions.[1]

Much of the recent work on the separation of metal ions using macrocyclic ligands has involved either the extraction of metal ions into organic solvents or the transport of metal ions through liquid membranes. We and others have studied macrocyclic systems that are selective in the extraction and/or transport of lithium,[3,4] copper(II),[5] potassium,[6] calcium,[7] and silver[8] ions to name only a few of the cations that have been studied.

One of the major problems with using organic solvents as the extraction/membrane solvent is that complexation of the macrocycle with metal ions is greatly changed in the organic solvent over that of water.[9] Often, the selectivity of a macrocycle for one cation over another observed in aqueous solution is reversed in the organic solvent.[10] The most extensive complexation data have been obtained in water or methanol–water mixtures.[1]

We have reported recently the synthesis of three silica gel bound crown compounds.[11] These new materials formed complexes with various metal ions with log K values which were within about 10% of the log K value for the association of the same cation with unbound crown in water. We now report the synthesis of the (allyloxy)-methyl-substituted diaza-18-crown-6 compounds needed to prepare the silica gel bound diaza-crowns. A preliminary study of the separation of certain heavy metal ions using this silica gel material is also presented.

Table I. Comparison of the Synthesis of Crown 1 in Number of Steps and Overall Yields

procedure	starting materials (no. of steps)	overall yield,[a] %
A (Scheme I)	**5** (2) + **6** (1) + (3)	12
B (Scheme I)	**13** (4) + diiodide (1) + (2)	6
C (Scheme I)	**15** (3) + **6** (1) + (1)	11
D (Scheme I)	**17** (4) + **6** (1) + (1)	14
E (Scheme II)	**21** (2) + (1)	34

[a] Yield is the product of all intermediate yields.

Results and Discussion

Our goal was to find a convenient and high yield, two- or three-step procedure to prepare the desired (allyl-

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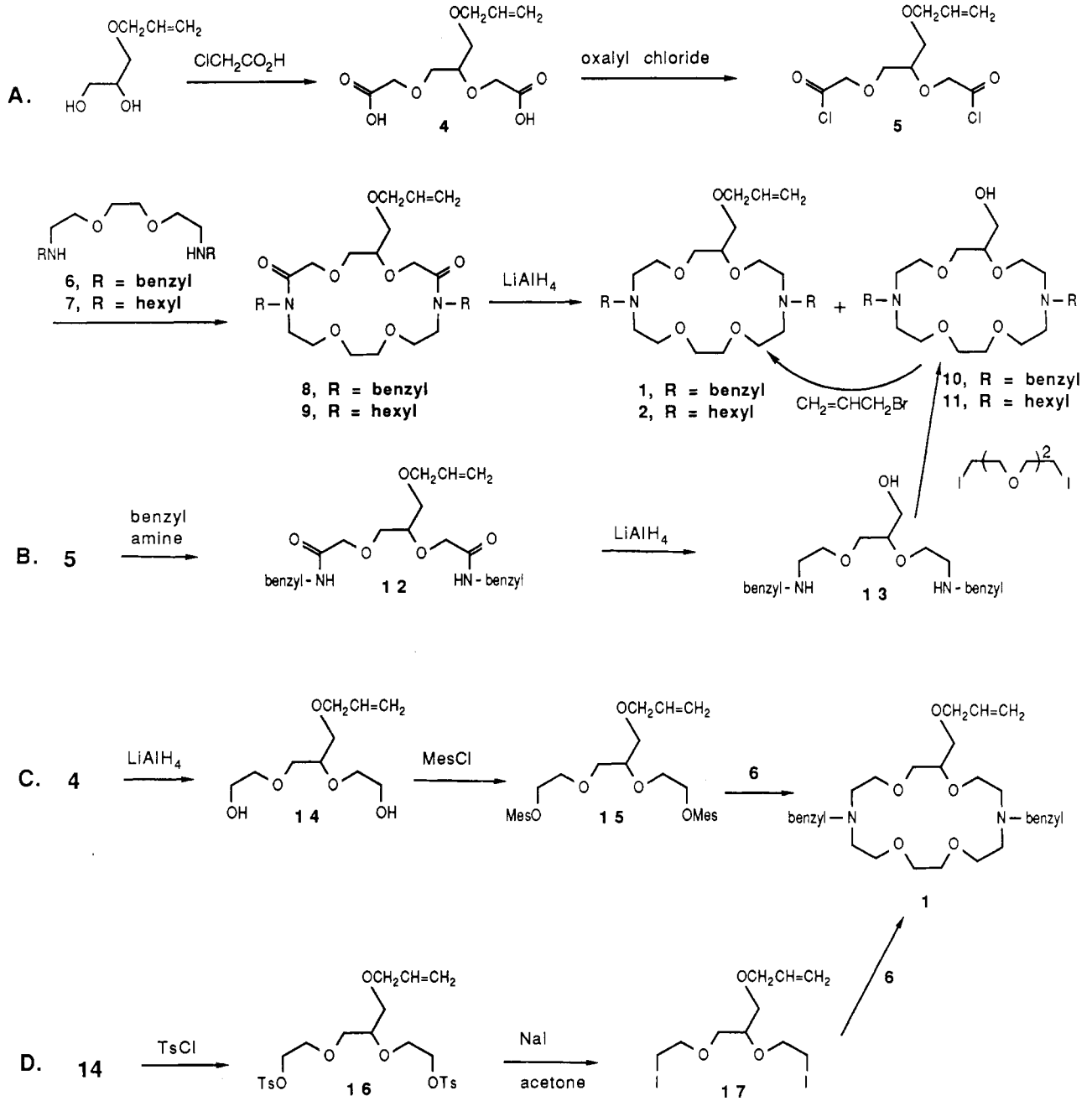
Scheme I. [(Allyloxy)methyl]-diaza-18-crown-6 Compounds from (Allyloxy)methyl-Substituted Triglycolic Acid



oxy)methyl-substituted diaza-18-crown-6 compounds. One requirement was to have some type of alkyl substituents on the two nitrogen atoms so that a later hydrosilyation reaction would be possible. A second requirement was to have a good overall yield of the final product. Having inexpensive starting materials was another important requirement. Functionalized crown compounds have served as important intermediates for the synthesis of the lariat crown ethers,[12] proton-ionizable crown ethers,[13] polymer supported crowns for use as catalysts,[14,15] and the silica gel bound crown ethers.[8,11] Only Bartsch and his co-workers have described the synthesis of functionalized diaza-18-crown-6 compounds.[16]

The first procedures we used were those used by others to prepare the diaza-crowns. In general, those procedures required too many steps. The six routes used by us to prepare the diaza-crowns are shown in Schemes I and II. The methods in Scheme I all used (allyloxy)methyl-substituted triglycolic acid as a starting material. This compound is not commercially available and its synthesis is not straight forward;[16] however, the reaction gave a 55% yield of the diacid. The two routes of Scheme II require *N,N'*-dialkyldiazaoligoethylene glycols which were prepared in high yields in a one-step synthesis.[23] More details concerning these synthetic methods are given below. Table I compares the number of steps and overall yields for these reactions.

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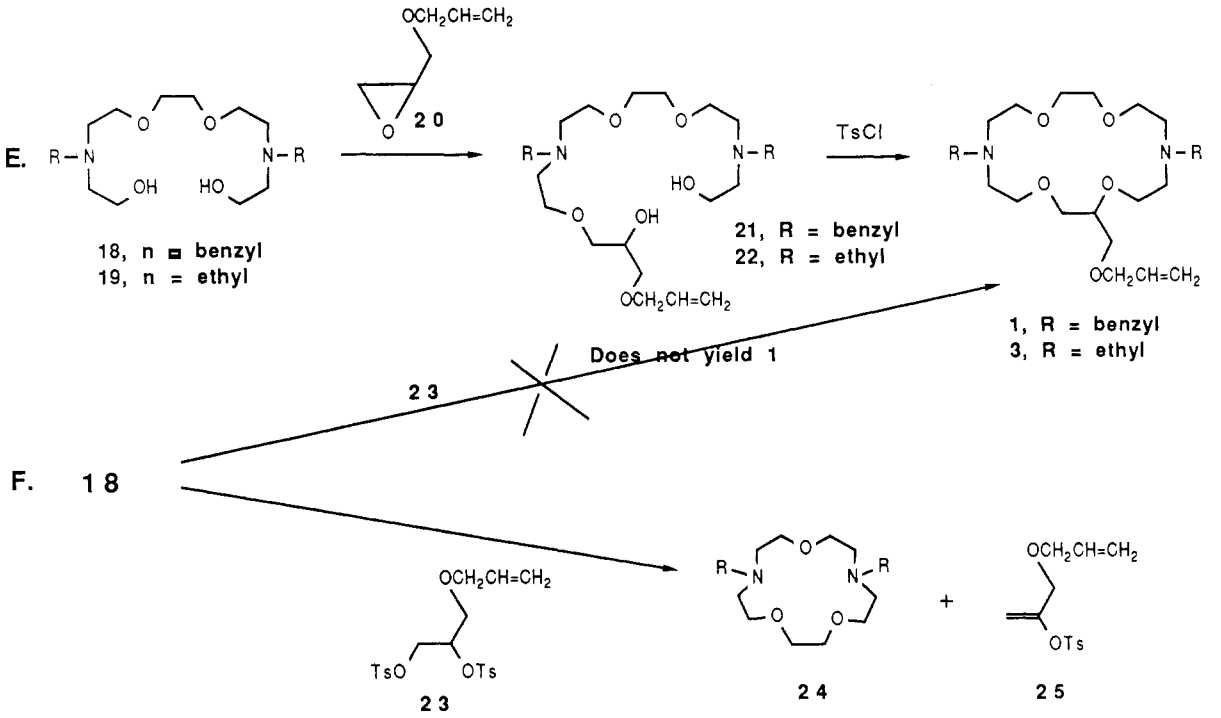
Scheme II. [(Allyloxy)methyl]-diaza-18-crown-6 Compounds from *N,N'*-Dialkyldiazaoligoethylene Glycol



The procedure used most often to prepare the diaza-crowns is through the cyclic diamide (**8**, **9** without the (allyloxy)methyl substituents and where R = H), as shown in Scheme I, procedure A. Stetter and Marx first used this procedure to prepare a number of macrocyclic aza compounds.[17] Procedure A was used extensively by Lehn to prepare the cryptands.[18] This procedure was used recently by Bartsch and his co-workers to prepare the N,N'-unsubstituted (hydroxymethyl)diaza-18-crown-6 (**10**, where R = H).[16] There are problems with this overall synthetic pathway. The diacid chloride **5** and diamine **6** or **7** need to be added simultaneously to a large amount of toluene to maintain high dilution. The reduction of cyclic diamide **8** or **9** by lithium aluminum hydride gave a mixture of the desired (allyloxy)methyl crowns (**1** or **2**) and the corresponding hydroxymethyl crowns (**10** or **11**). The ratio of **1** to **10** was 1:4 while the ratio of **2** to **11** was about 1:1. This ratio depended on the amount of lithium aluminum hydride used in the reaction. Only **10** and **11** were formed when an excess of lithium aluminum hydride was used. The crude mixture of **1** and **10** was treated with allyl bromide using potassium *tert*-butoxide as base to give a good yield of **1**. As shown in Table I, there are many steps in this sequence and the overall yield was only 12%.

Procedure B (Scheme I) is patterned after the synthesis of the parent unsubstituted diaza-18-crown-6 by Gokel and his co-workers[19] and Krakowiak and Kotelko.[20] The reduction of open-chain diamide **12** gave mainly hydroxymethyl diamine **13** although about 10% of the product appeared to be the corresponding (allyloxy)methyl analogue. Again, as discussed above, the ratio of **13** to its (allyloxy)methyl analogue depended on the amount of lithium aluminum hydride used in the reaction. Compound **13** could be converted to the corresponding (allyloxy)methyl compound but the yield was low because allyl bromide also reacted with the amine group at room temperature, using potassium *tert*-butoxide in *tert*-butyl alcohol, to give a mixture of at least five products. The ring-closure reaction of **13** with triethylene glycol diiodide gave only a 20% yield of **10**. This procedure has the problem of giving low yields in the ring-closure step and requires too many steps (see Table I).

In procedure C (Scheme I), the [(allyloxy)methyl]triglycolic acid was first reduced to give an 80% yield of diol **14**.[16] Dimesylate **15** was difficult to purify because it decomposed on silica gel. The ring-closure reaction of **15** with diamine **6** gave a 30% yield of **1**. The separation of **1** from the starting materials and other products required alumina chromatography which is a serious deficiency.

Procedure D (Scheme I) uses diiodide **17** which was prepared in a four-step synthesis. The final reaction of ditosylate **16** to form the diiodide was patterned after a similar reaction by Hegedus and Thompson.[21] It is important to note that diol **14** must be added to tosyl chloride to form ditosylate **16**. A hexaethylene glycol ditosylate dimer was produced when tosyl chloride was added to the diol as we have reported previously in connection with the synthesis of octyl-substituted diol ditosylates.[22] Procedure D requires many steps and the overall yield is low (Table I).

The most convenient method to prepare the diaza-18-crown-6 compounds is shown in procedure E (Scheme II). The starting diamines **18** or **19** were readily prepared[23] and epoxide **20** can be purchased. Purification of dibenzyl-substituted diaza diol **21** was difficult because of its high boiling point; however, it was purified by column chromatography. Compound **22**, on the other hand, was readily distilled. The Okahara ring-closure reaction using tosyl chloride gave excellent yields of **1** and **3** and they were easily purified. This procedure is a straightforward

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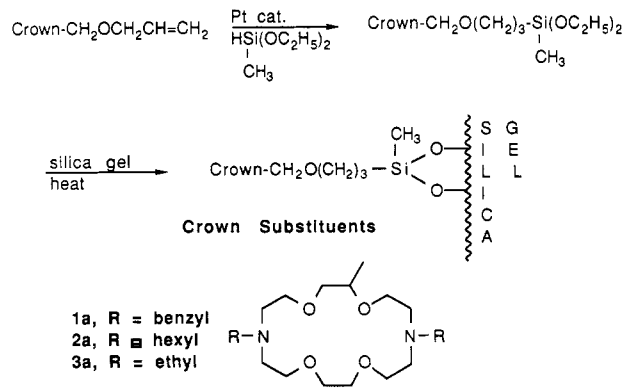
Scheme III. Preparation of Silica Gel Bound Crown Compounds



three-step synthesis of these valuable diaza-crown compounds with reasonably good overall yields of 34% for **1** (see Table I) and 35% for **3**.

Our initial attempt to prepare **1** is shown in procedure F (Scheme II). Diamine **18** was easy to prepare,[23] but treatment of **18** with ditosylate **23** using potassium *tert*-butoxide as the base, gave only *N,N'*-dibenzyldiaza-15-crown-5 (**24**) not crown **1**. This unusual reaction of **18** to form **24** also resulted when sodium hydride in THF or DMF was used. As reported,[23] ethylene glycol ditosylate and tosyl chloride can also be used in the Okahara ring-closure reaction of **18** to give crown **24**. A small amount of alkene **25** was also isolated when **18** and **23** were reacted. The unusual ring closure of **18** when reacted with **23** is probably caused by a cross tosylation of **18** by **23** followed by closure of the monotosylate.

The three diaza-18-crown-6 compounds (**1–3**) were attached to silica gel according to Scheme III.[11] The hydrosilylation reaction gave nearly a quantitative yield of the diethoxymethylsilane containing the diaza-crown compounds. A similar reaction with triethoxysilane gave the corresponding triethoxysilane containing the crown compound. The crown di- or triethoxysilane material was coated onto 60–200-mesh silica gel and the coated gel was heated to effect the linkage reaction. This procedure was nearly quantitative with the yield being 90% or greater. The number of crown sites on the silica gel was further verified by loading the sites to 100% capacity with Ag^+. The Ag^+ was then recovered and analyzed by using a sodium acetate–acetic acid buffer as eluent and atomic absorption spectroscopy for analysis.

Since the log K value for the association of metal ions with these silica gel bound crown compounds is nearly the same as that for the association of the same metal ions with the unbound crowns,[11] one should be able to predict and obtain specific separations of cations. For example, the log K values for the association of unbound diaza-18-crown-6 with Hg^{2+}, Cd^{2+}, and Zn^{2+} ions in aqueous solution are 17.85, 5.25, and 3.19, respectively.[1] Since Hg^{2+} has a much greater affinity for the diaza-crown, this ion should be selectively removed by a diaza-18-crown-6 column from solutions also containing Cd^{2+} and Zn^{2+}.

This separation was performed experimentally by using a solution of the three cation nitrates at 1×10^{-4} M at a pH of 2. At this pH value, binding with plain silica gel by these cations is small while only Hg^{2+} has a high enough log K (17.85) for significant binding with the macrocycle in competition with protons ($\log K_1 = 8.9$, $\log K_2 = 7.5$).[11] The metal ions were eluted from the column by using aqueous EDTA or thiosulfate solutions. The overall molar ratios of Hg^{2+} to Cd^{2+} and Zn^{2+} in the crown–column eluents were 11 and 9, respectively. These ratios were 20 or higher after the first 10% of eluent was collected. The ratio of Hg^{2+} to both Cd^{2+} and Zn^{2+} was 2 using plain silica gel. The amounts of Cd^{2+} and Zn^{2+} recovered from the diaza-crown–silica gel material were due to both their affinity for silica gel and to the loading solution which remained on the column (dead volume). Thus, it appears that the actual selectivity of the macrocycle for Hg^{2+} was much more than that observed. In addition, the eluents contained Hg^{2+} in a concentrated form. These results show that cation separations, recoveries, and concentrations, as in the case of Hg^{2+} versus Cd^{2+} and Zn^{2+}, can be predicted and performed from interaction data.

Experimental Section

IR spectra were obtained on a Beckman Acculab 2 spectrophotometer. The proton NMR spectra were obtained in a JEOL FX-90Q spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Atomic absorption spectroscopy was performed on a Perkin-Elmer Model 603 spectrometer. Starting materials were purchased from commercial sources where possible. Starting diacid **4** (Scheme I), diacid chloride **5**, diol **14**, and dimesylate **15** were prepared as reported by Bartsch and co-workers.[16] Diamines **6** and **7** (Scheme I) and diaza diols **18** and **19** were prepared as reported.[23] The purity of all new starting materials was determined by NMR spectroscopy to be 90% or better.

5-[(Allyloxy)methyl]-1,10-dibenzyl-2,9-dioxo-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (8) (Procedure A). Diacid chloride **5** (1.7 g, 5.95 mmol) in 50 mL of toluene and 1.95 g (5.95 mmol) of diamine **6** were added simultaneously under nitrogen to 200 mL of toluene containing 1.5 g of triethylamine at 0–3 °C during a 10-h period. The mixture was stirred at room temperature for 48 h. The resulting solid was filtered off and the solid was washed with toluene. The combined toluene solutions were evaporated under vacuum and the residue was chromatographed on alumina (toluene/ethanol 20/1) to give 1.29 g (40%) of **8** as an oil: IR (neat) 1640, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (m, 19 H), 4.60 (m, 8 H), 5.20 (m, 2 H), 5.80 (m, 1 H), 7.25 (m, 10 H); MS, m/e 540. This material was used in the next step without further purification.

5-[(Allyloxy)methyl]-1,10-dihexyl-2,9-dioxo-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (9) (Procedure A). Compound **9** was prepared as above for **8** to give a 42% yield of an oil: IR (neat) 1640, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 6 H, J = 7.0 Hz), 1.25 (m, 16 H), 3.60 (m, 27 H), 5.30 (m, 2 H), 5.80 (m, 1 H). This material was used in the next step without further purification.

5-[(Allyloxy)methyl]-1,10-dibenzyl-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (1) and Its 5-Hydroxymethyl Analogue 10. A solution of compound **8** (2.1 g, 3.9 mmol) in 50 mL of THF was slowly added to a stirring solution of 5 g (0.13 mol) of lithium aluminum hydride in 100 mL of THF at 0 °C. The mixture was stirred under reflux for 36 h. After cooling, 5 mL of water, 5 mL of 15% aqueous sodium hydroxide, and then 10 mL of water were added successively to the mixture at 0 °C. The solid material was filtered and the residue was washed with hot THF. The filtrate and THF washings were concentrated under reduced pressure. The residue was chromatographed on alumina using 20/1 toluene/ethanol as eluant to give 0.30 g (15%) of **1** and 1.1 g (60%) of **10** as viscous oils. The spectral properties for **1** are as follows: ^1H NMR ($CDCl_3$) δ 2.80 (t, 8 H, J = 7.2 Hz), 3.60 (m, 21 H), 4.00 (d, 2 H, J = 6.5 Hz), 5.20 (m, 2 H), 5.80 (m, 1 H), 7.34 (s, 10 H); MS, m/e 512. Anal. Calcd for $C_{30}H_{44}O_5N_2$: C, 70.28; H, 8.65. Found: C, 70.12; H, 8.71. The spectral properties for **10** are as follows: ^1H NMR ($CDCl_3$) δ 2.80 (m, 8 H), 3.60 (m, 22 H), 7.30 (m, 10 H).

Conversion of 10 into 1 (Procedure A). A mixture of 1 g (21 mmol) of **10**, 0.72 g (6 mmol) of allyl bromide, 0.3 g (2.6 mmol) of potassium *tert*-butoxide, and 50 mL of *tert*-butyl alcohol was stirred at 68 °C for 2 h. The mixture was filtered, the solvent and excess allyl bromide were evaporated, and the residue was passed through a short alumina column (toluene/ethanol 20/1) to give 1.03 g (90%) of **1** which had the same spectral properties as reported above.

5-[(Allyloxy)methyl]-1,10-dihexyl-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (2) and Its 5-Hydroxymethyl Analogue 11 (Procedure A). Compound **9** (2.05 g, 3.9 mmol) was reduced by lithium aluminum hydride as above for the preparation of **1** and **10**. The product was purified as above to give 0.68 g (35%) of **2** and 0.9 g (50%) of **11**. The spectral properties for **2** are as follows: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6 H, J = 5.4 Hz), 1.27 (m, 16 H), 2.40 (m, 4 H), 2.75 (t, 8 H, J = 6 Hz), 3.62 (m, 17 H), 4.00 (m, 2 H), 5.20 (m, 2 H), 5.82 (m, 1 H); MS, m/e 500. Anal. Calcd for $C_{28}H_{56}O_5N_2$: C, 67.72; H, 11.27. Found: C, 67.72; H, 11.43. The spectral properties for **11** are as follows: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6 H, J = 5.0 Hz), 1.30 (m, 16 H), 2.45 (m, 4 H), 2.75 (m, 8 H), 3.60 (m, 18 H); MS, m/e 460.

***N,N'*-Dibenzyl-4-[(allyloxy)methyl]-3,6-dioxaoctanedicarboxamide (12) (Procedure B).** A solution of 10.5 g (0.01 mol) of benzylamine and 10.1 g (0.01 mol) of triethylamine in 60 mL of benzene was slowly added to a stirring solution of 14.25 g (0.05 mol) of **5** in 100 mL of benzene at 5–8 °C. The mixture was allowed to warm to room temperature and stirred for 5 h. The mixture was concentrated under reduced pressure and the residue was dissolved in 200 mL of chloroform. The chloroform solution was washed with 20 mL of water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (toluene/ethanol 20/1) to give 12.46 g (70%) of **12** as an oil: IR (neat) 3320, 1650, 1520, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.65 (m, 7 H), 3.90 (s, 2 H), 4.05 (s, 2 H), 4.40 (dd, 4 H, J = 2 Hz), 5.15 (m, 2 H), 5.63 (m, 1 H), 7.2 (s, 10 H). This material was used in the next step without further purification.

6-(Hydroxymethyl)-1,12-diphenyl-2,11-diaza-5,8-dioxadodecane (13) (Procedure B). Compound **12** (2.6 g, 7.2 mmol) was reduced by lithium aluminum hydride as above for the preparation of **1** and **10**. The crude product was chromatographed on silica gel (isopropyl alcohol) to give 1.24 g (60%) of **13** and some of the (allyloxy)methyl analogue of **13** (0.24 g, 10%). The spectral properties for **13** are as follows: IR (neat) 3300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3 H), 2.80 (m, 4 H), 3.60 (m, 9 H), 3.80 (s, 4 H), 7.25 (s, 10 H); MS, m/e 358. Anal. Calcd for $C_{21}H_{30}O_3N_2$: C, 70.36; H, 8.43. Found: C 70.20; H, 8.47. The spectral properties of the allyloxymethyl analogue of **13** were as follows: ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 2 H), 2.80 (m, 4 H), 3.60 (m, 9 H), 3.80 (s, 4 H), 4.00 (d, 2 H, J = 6 Hz), 5.20 (m, 2 H), 5.90 (m, 1 H), 7.25 (s, 10 H).

Preparation of 10 from 13 (Procedure B). A mixture of 1.07 g (3.0 mmol) of **13**, 1.3 g (3.5 mmol) of 1,8-diiodo-3,6-dioxaoctane, 0.3 g (2.0 mmol) of sodium iodide, 3 g of sodium carbonate, and 200 mL of acetonitrile was stirred under reflux for 25 h. The mixture was evaporated under reduced pressure and 200 mL of chloroform was added to the residue. The salts were filtered and the filtrate was concentrated under reduced pressure. The residue was chromatographed on alumina (toluene/ethanol 100/1) to give 0.3 g (20%) of **10** which exhibited the same spectral properties as reported above.

Preparation of 1 from 15 (Procedure C). *n*-Butyllithium (0.56 g, 8.8 mmol) dissolved in 100 mL of hexane was added dropwise to a stirring solution of 2.88 g (8.8 mmol) of **6** in 250 mL of THF. This mixture was stirred for 1 h at room temperature, whereupon 3.3 g (8.8 mmol) of **15** in 100 mL of THF was added, and the resulting mixture was stirred overnight at room temperature and then for 36 h under reflux. The solvents were removed under reduced pressure and 20 mL of water was added. The aqueous mixture was extracted three times with 50-mL portions of dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on alumina (toluene/ethanol 150/1) to give 1.35 g (30%) of **1**. The spectral properties of **1** were identical with those reported above.

4-[(Allyloxy)methyl]-3,6-dioxa-1,8-octanediol Ditosylate (16) (Procedure D). Compound **14** (9.0 g, 41 mmol) was added to 19.1 g (1 mol) of tosyl chloride in 150 mL of pyridine at −5 to −10 °C over a 2-h period. The mixture was then allowed to warm to room temperature and stirred over night at room temperature. The mixture was added to 200 mL of a 1:1 mixture of ice and concentrated hydrochloric acid. The acid solution was extracted three times with 250-mL portions of dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (dichloromethane) to give 13.0 g (60%) of **16**: ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 6 H), 3.80 (m, 15 H), 5.20 (m, 2 H), 5.90 (m, 1 H), 7.40 (d, 4 H, J = 7.5 Hz), 7.80 (d, 4 H, J = 7.5 Hz). Compound **16** was used in the next step without further purification.

4-[(Allyloxy)methyl]-1,8-diiodo-3,6-dioxaoctane (17) (Procedure D). A mixture of 9.9 g (18.7 mmol) of **16**, 16.85 g (112.4 mmol) of sodium iodide, 4.9 g (46 mmol) of sodium carbonate, and 250 mL of acetone was refluxed for 24 h. The acetone was evaporated and the residue was dissolved in 200 mL of ether. The ether solution was washed with two 100-mL portions of 5% aqueous sodium thiosulfate and then with two 100-mL portions of saturated brine. The ether solution was dried over anhydrous magnesium sulfate and then concentrated to give 6.6 g (80%) of **17** as an oil: ^{1}H NMR ($CDCl_3$) δ 3.20 (t, 4 H, J = 6 Hz), 3.70 (m, 7 H), 3.90 (t, 2 H, J = 8 Hz), 4.0 (m, 2 H), 5.20 (m, 2 H), 5.85 (m, 1 H); MS, m/e 440. This material was used in the next step of procedure D without further purification.

Preparation of 1 from 17 (Procedure D). A mixture of 0.48 g of **17** (1.1 mmol), 0.33 g (1 mmol) of **6**, 2 g of sodium carbonate, 0.1 g of sodium iodide, and 150 mL of acetonitrile was stirred under reflux for 25 h. The solvent was evaporated under reduced pressure and the residue was dissolved in 100 mL of chloroform. The salts were filtered and the filtrate was concentrated under reduced pressure. The crude product was chromatographed on alumina (toluene/ethanol 30/1) to give 0.45 g (80%) of **1** which had the same spectral properties as reported above.

1-[(Allyloxy)methyl]-6,15-dibenzyl-3,9,12-trioxaheptadecane-1,17-diol (21) (Procedure E). Allyl glycidyl ether (**20**) (3.93 g, 34.4 mmol) was slowly dripped into a stirring mixture of 0.4 g (6.9 mmol) of pulverized potassium hydroxide and 43.0 g (0.1 mol) of **18** at 80 °C over a 1-h period. The mixture was cooled and neutralized with about 4 mL of 5% aqueous sulfuric acid. The water was removed by adding benzene and removing the benzene–water azeotrope. The resulting oil was chromatographed on alumina (toluene/ethanol 200/1) to give 11.85 g (65%) of **21**: IR (neat) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.75 (m, 8 H), 3.20 (m, 2 H), 3.55 (m, 17 H), 3.75 (s, 4 H), 4.00 (m, 2 H), 5.25 (m, 2 H), 5.90 (m, 1 H), 7.32 (s, 10 H); MS, m/e 530. This material was used in the next step without further purification.

1-[(Allyloxy)methyl]-6,15-diethyl-3,9,12-trioxaheptadecane-1,17-diol (22) (Procedure E). Compound **22** was prepared as above for **21** from **19** except after the water was removed, the crude product was distilled to give **22** (70%): bp 200–203 °C/0.07 mmHg; IR (neat) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 6 H, J = 5.4 Hz), 2.80 (m, 12 H), 3.70 (m, 21 H), 5.35 (m, 2 H), 6.00 (m, 1 H); MS, m/e 406. This material was used in the next step to prepare **3** without further purification.

Preparation of 1 from 21 (Procedure E). Solutions of 5.3 g (10 mmol) of **21** in 50 mL of dioxane and 2.2 g (11 mmol) of tosyl chloride in 50 mL of dioxane were simultaneously added to 2.0 g (50 mmol) of sodium hydroxide dissolved in 100 mL of dioxane at 80 °C over a 3-h period. The resulting mixture was refluxed for 24 h. The mixture was cooled, filtered, and evaporated under reduced pressure. The residue was chromatographed as above to give 3.17 g (62%) of **1**.

5-[(Allyloxy)methyl]-1,10-diethyl-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (3) (Procedure E). Compound **3** was prepared as above for **1** by using 4.06 g (10 mmol) of **22** and 2.2 g (11 mmol) of tosyl chloride. The crude product was chromatographed on alumina (toluene/ethanol 150/1) to give 2.45 g (63%) of **3** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 6 H, J = 7.2 Hz), 2.70 (m, 12 H), 3.60 (m, 17 H), 4.00 (m, 2 H), 5.30 (m, 2 H), 5.85 (m, 1 H); MS, m/e 389. Anal. Calcd for $C_{20}H_{40}O_5N_2$: C, 61.83; H, 10.38. Found: C, 61.88; H, 10.30.

Attempted Preparation of 1 from 18 and 23 (Procedure F). A solution of 4.4 g (10 mmol) of **23** (prepared as **16** above from 3-(allyloxy)-1,2-ethanediol) in 100 mL of dioxane was added to a stirring mixture of 0.82 g (20 mmol) of potassium metal dissolved in 300 mL of *tert*-butyl alcohol and 4.16 g (10 mmol) of **18** at 60 °C over a 5-h period. The mixture was refluxed for 24 h, filtered, and evaporated under reduced pressure. The residue was chromatographed on alumina (toluene/ethanol 100/1) to give 2.71 g (65%) of 1,7-dibenzyl-4,10,13-trioxa-1,7-diazacyclopentadecane (**24**) as an oil. The physical properties of **24** were the same

as reported.[19,23] 4-Oxa-1,6-heptadien-2-ol tosylate (**25**) (1.12 g, 42%, based on alkene **23** starting material) was also isolated: ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3 H), 3.85 (m, 4 H), 5.20 (m, 4 H), 5.80 (m, 1 H), 7.35 (d, 2 H, J = 10.6 Hz), 7.80 (d, 2 H, J = 10.8 Hz).

Determination of Macrorcycle Sites and Separation of Mercury(II) from Zinc(II) and Cadmium(II). The silica gel bound crown compound **1a** (Scheme III) was prepared as reported from **1**.[11] Columns containing macrocycle-bonded silica gel and plain silica gel were prepared by using 2.3 g of the particular silica material supported in 19-mm-diameter glass columns by tampon (cellulose) material. For the macrocycle site determination, solutions at pH 8 with 0.167 M $Mg(NO_3)_2$ and various concentrations of Ag^+ both greater and less than 10 ppm were used to load the column until the pH and concentration of Ag^+ coming out of the column equaled that for the original solution. The Ag^+ on the columns was eluted by using a solution of 0.1 M sodium acetate and 1 M acetic acid. The amount of Ag^+ bound to the column was constant when Ag^+ loading concentrations of 10 ppm or greater were used indicating the column was being loaded to capacity. For the Hg^{2+} separation, the column was preconditioned to pH 2 by using 500 mL of 0.01 M nitric acid. A 100-mL solution (in 25-mL aliquots) of 1×10^{-4} M Hz^{2+}, Cd^{2+}, and Zn^{2+} nitrates and 0.01 M HNO_3 was passed through the column. A total of 50 mL of either 0.03 M EDTA (pH 10.5) or 0.1 M $Na_2S_2O_3$ in 10-mL aliquots was then passed through the column. The pH values were adjusted by using sodium hydroxide. The amounts of Ag^+ or Hg^{2+}, Cd^{2+}, and Zn^{2+} in each solution were determined by atomic absorption spectroscopy. The concentrated Mg^{2+} or acid was present in the solutions subjected to the columns to minimize (in the case of Hg^{2+}, Zn^{2+}, and Cd^{2+}) or negate (Ag^+) the interaction of plain silica gel with the heavy metal ions. Commercially available reagent-grade chemicals and distilled, deionized water were used in all experiments. These experiments were performed in triplicate with standard deviation of less than 10%.

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Registry No. **1**, 114719-03-8; **1a**, 114719-04-9; **2**, 114719-05-0; **2a**, 114719-06-1; **3**, 114719-07-2; **3a**, 114719-08-3; **5**, 107106-37-6; **6**, 66582-26-1; **7**, 105399-99-3; **8**, 114719-09-4; **9**, 114719-10-7; **10**, 114719-11-8; **11**, 114719-12-9; **12**, 114719-13-0; **13**, 114719-14-1; **14**, 107106-38-7; **15**, 107106-39-8; **16**, 114719-15-2; **17**, 114719-16-3; **18**, 113585-52-7; **19**, 113585-54-9; **20**, 106-92-3; **21**, 114719-17-4; **22**, 114719-18-5; **23**, 114719-19-6; **24**, 94195-16-1; **25**, 114719-20-9; Hg^{2+}, 14302-87-5; $H(CH_3)Si(OC_2H_5)_2$, 2031-62-1; triethoxysilane, 998-30-1; 5-[[3-(triethoxysilyl)propoxy]methyl]-1,10-dibenzyl-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane, 114719-21-0; 5-[[3-(triethoxysilyl)propoxy]methyl]-1,10-dihexyl-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane, 114719-22-1; 5-[[3-(triethoxysilyl)propoxy]methyl]-1,10-diethyl-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane, 114719-23-2; allyl bromide, 106-95-6.

Chorismate Mutase Inhibitors: Synthesis and Evaluation of Some Potential Transition-State Analogues

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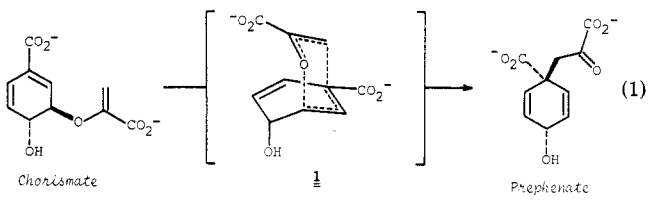
A number of bicyclic diacids have been synthesized as potential transition state analogue inhibitors of chorismate mutase, including the oxa- and carbabicyclic diacids **5**, **8**, **9**, and **13**. An unsuccessful attempt was made to generate the oxabicyclic nitronate **10**, which proved to be very labile toward hydrolysis; instead, the oximinolactone **11** and carbabicyclic nitronate **12** were prepared as potentially more accurate mimics of the postulated transition state **1**. The oxabicyclic diacids were prepared from the Diels–Alder adduct of butadiene and dimethyl itaconate, via selenocyclization of cyanohydrin **17**, elimination of the selenoxide and epoxidation of the olefin **18**, isomerization of epoxide **19** to the allylic alcohol **20**, hydrolysis of the nitrile, and stereochemical manipulation of the bridge carboxyl group. The carbabicyclic compounds were similarly accessible by electrophilic cyclization of β-keto ester **37**, affording ketone **43** via the cyclopropane **40** and selenide **41**. Methylenation of **43** and formation and selective rearrangement of the diepoxide **49** were key steps in further elaboration to the diester **36**. A shorter route to diene **48** was also developed, involving the one-pot bismethylenation of lactone **45** with an excess of $Cp_2Ti(Cl)CH_2AlMe_2$. The oximinolactone **11** and nitronate **12** were prepared by nitrosation or nitration of the protected diesters **30** and **53**, respectively, followed by hydrolysis and decarboxylation. The endo isomer of oxabicyclic diacid **5** proved to be the most potent inhibitor known for a chorismate mutase, with a K_i value of 0.12 μM against the chorismate mutase–prephenate dehydrogenase from *Escherichia coli*. The related isomeric and carbabicyclic analogues **8**, **9**, and **13** are less tightly bound (13 μM < I_{50} < 100 μM), and the oximinolactone **11** and nitronate **12** are poor inhibitors (I_{50} > 4 mM).

Introduction

Organic synthesis in a bioorganic setting often has the added challenge of design of the target molecule in addition to its actual construction. This point is underscored in the development of inhibitors of the chorismate mutases, enzymes that catalyze the rearrangement of chorismic acid to prephenic acid (eq 1). In this paper, we describe the three phases of such a project, namely, the design, synthesis, and evaluation of several bicyclic molecules designed to mimic the presumed transition state **1**.



(1)

Transition-State Analogues

A number of fundamental strategies have been developed for the design of enzyme inhibitors based on considerations of the catalytic reaction mechanism.[1,2] A particularly effective approach is to devise a molecule that

(1) "Suicide inhibition": Walsh, C. *Tetrahedron* **1982**, *38*, 871–909. Abeles, R. H. *Pure Appl. Chem.* **1980**, *53*, 149–160.

(2) Transition-state analogues: Wolfenden, R. *Annu. Rev. Biophys. Bioeng.* **1976**, *5*, 271–306. Stark, G. R.; Bartlett, P. A. *Pharmacol. Ther.* **1984**, *23*, 45–78.

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