Synthesis of Chiral Dibenzo-1,8-diaza-14-crown-4, Dibenzo-1,9-diaza-16-crown-4, and Dibenzo-1,10-diaza-18-crown-4 Ethers by Aromatic Nucleophilic Substitution. Application to the Preparation of Bicyclic Chiral Crown–LiI Complexes

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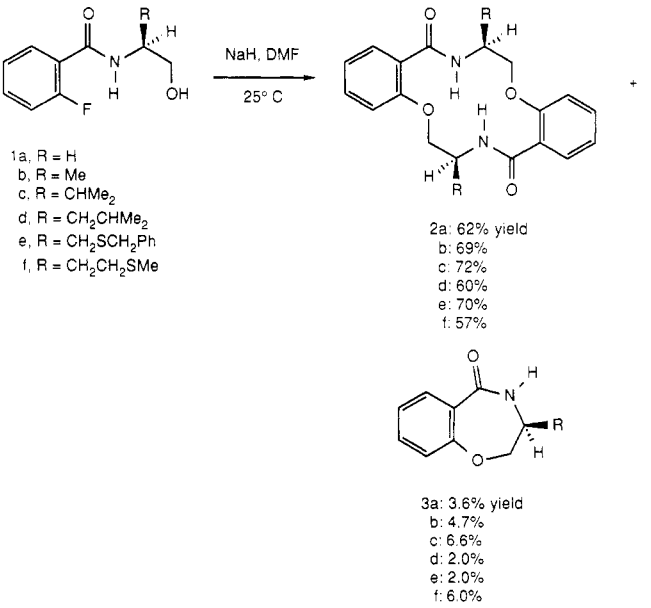
New methods for the preparation of dibenzo-1,8-diaza-14-crown-4, dibenzo-1,9-diaza-16-crown-4, and dibenzo-1,10-diaza-18-crown-4 ethers **2**, **4**, **5**, **14**, **15**, and **16** are described. Bimolecular cyclization of ortho-substituted benzamides (derived from 1,2-, 1,3-, and 1,4-amino alcohols), by a nucleophilic aromatic substitution process, requires the presence of a fluorine atom on the aromatic ring and the use of secondary benzamides. Tertiary benzamides result in unimolecular cyclization to a benzoxazepinone, e.g., **6** → **7** and **8** → **9**. Acyclic diamido alcohol **10** is obtained from reaction of an equimolar mixture of **1a** and **6a**. Macrocycle **13** could not be obtained from benzamide **12**, but **12** in combination with **1a** did provide the mixed macrocycle **14**. A template effect involving the sodium cation and the fluoride substituent is suggested to be operative in the bimolecular cyclization process. Two bicyclic crown–LiI complexes were prepared by (1) reduction of diamides **2a** and **2b** to secondary diamines **17a** and **17c**, (2) *N,N*-bridging with a triethylene glycol residue to give **18a** and **18b**, and (3) complexation with LiI to give **18c** and **18d**. Molecular structures for **2c**, **17a**, and **18d** were determined by X-ray analysis.

Interest in the mechanisms that enable molecular recognition[1] has stimulated an intense search for new strategies[2] directed at the construction of macrocyclic systems containing multiple coordination sites. We report a remarkably simple and efficient method for the synthesis of dibenzo-1,8-diaza-14-crown-4, dibenzo-1,9-diaza-16-crown-4, and dibenzo-1,10-diaza-18-crown-4 ethers. Macrocycles are generated in one step[3] via bimolecular cyclization of *o*-fluorobenzamides, which are derived from 1,2-, 1,3-, and 1,4-aminoalcohols by acylation with commercially available *o*-fluorobenzoyl chloride. Because chiral amino alcohols are readily available in enantiomercially pure form, the process is adaptable to the preparation of a wide variety of highly functionalized chiral crown systems.[4a] The utility of this new method for macrocycle synthesis is demonstrated by the preparation and characterization of two bicyclic crown–LiI complexes, one of which is chiral and available in enantiomerically pure form.

Results and Discussion

Macrocycle Synthesis. The process leading to the 14-crown-4 ring system consists of stirring a mixture of the *N*-(2-hydroxyethyl)-2-fluorobenzamide **1a–f** (~0.1 M) and sodium hydride in dimethylformamide (distilled from calcium hydride) at room temperature for 18 h (Scheme I). Dimethylformamide is removed by distillation at reduced pressure. The residue is dissolved in water and methylene chloride; extractive workup and flash chromatography on silica gel provides crystalline macrocycle **2a–f**, benzoazepinone **3a–f**, and unreacted starting material.[5] The indicated yields are for isolated products and are not corrected for unreacted starting materials.

Scheme I



We have examined the importance of the cation in the formation of the parent macrocycle, **2a**. With THF as solvent, **1a** provided **2a** in ~80% yield with NaH. Little if any macrocycle or benzoxazepinone was produced when

(1) For a recent review, see: Rebek, J. *Science (Washington, D.C.)* **1987**, *235*, 1478.

(2) (a) Gokel, G. W.; Korzeniowski, S. H. *Macrocyclic Polyether Synthesis*; Springer Verlag: New York, 1982. (b) Gokel, G. W.; Dishong, D. M.; Schultz, R. A.; Gatto, V. J. *Synthesis* **1982**, 997.

(3) A novel one-step synthesis of 4,13-diaza-18-crown-6 ethers by cyclization of four reacting components has been reported: Gatto, V. J.; Gokel, G. W. *J. Am. Chem. Soc.* **1984**, *106*, 8240.

(4) (a) For the use of D-ephedrine in chiral azamacrocycle construction, see: Wudl, F.; Gaeta, F. *J. Chem. Soc., Chem. Commun.* **1972**, 107. (b) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.

(5) For examples of the preparation and utilization of other dibenzo-14-crown-4 ethers, see ref 2 and (a) Olsher, U. *J. Am. Chem. Soc.* **1982**, *104*, 4006. (b) Johnston, D. L.; Horrocks, W. Dew., Jr. *Inorg. Chem.* **1971**, *10*, 687. (c) Kluiber, R. W.; Sasso, G. *Inorg. Chim. Acta* **1971**, *10*, 687. (d) Bradshaw, J. S.; Stott, P. E. *Tetrahedron* **1980**, *36*, 461. (e) Martin, J. W. L.; Wainwright, K. P.; Weerasuria, K. D. V.; Wild, S. B. *Inorg. Chim. Acta* **1985**, *99*, L5.

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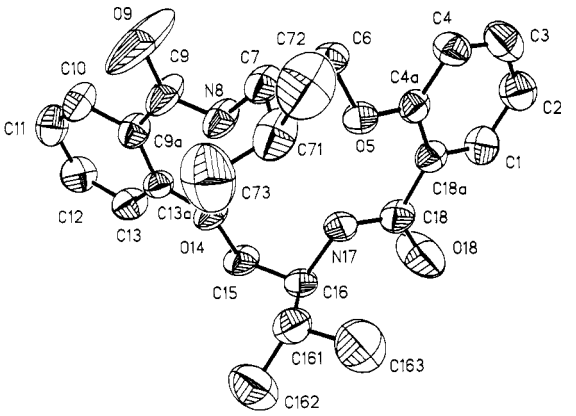


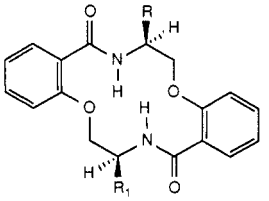
Figure 1. Molecular structure of **2c**.

increasing quantities of up to 3 equiv of *n*-BuLi or KH were used as bases.

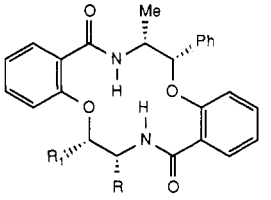
An important feature of this macrocycle synthesis is that high dilution techniques[6] can be avoided. In fact, low concentrations of starting benzamide result in a shift of the reaction toward benzoxazepinone formation. At an initial concentration of 0.008 M, **1a** is converted to benzoxazepinone **3a** (32%) and crown ether **2a** (22%).

Molecular compositions of **2a–f** and **3a–f** were determined by chemical ionization mass spectroscopy, from which intense M + 1 peaks were recorded, and combustion analyses. An X-ray structure determination was performed with **2c**; the molecular structure is shown in Figure 1. It is noteworthy that the solid-state conformation of **2c** has both carbonyl groups outside and both N–H groups inside the macrocyclic cavity. Furthermore, both isopropyl substituents are in an axial environment. Another intersting feature is the butterfly-like conformation of the macrocyclic ring not obvious in Figure 1 but apparent in another projection of **2c** (supplementary material). While **2c** has been found to undergo complexation with alkali metal cations by using the picric acid extraction method,[4b] we have not as yet determined binding constants and cation selectivity for macrocycles **2a–f**.

Macrocycles also have been prepared by bimolecular cyclization of pairs of amido alcohols **1a–f**. Treatment of an equimolar mixture of **1a** and **1f** by the previously described procedure gave **4b** (45% isolated yield), **2a** (10%), **2f** (5%), and unreacted starting materials. Similar isolated product ratios were obtained for reactions producing **4a** and **4c**. The relatively hindered amino alcohol (+)-norephedrine gave crown ether **5a** and the mixed crown ether **5b**.



4a, R = $CHMe_2$; R_1 = H: 40%
b, R = CH_2CH_2SMe; R_1 = H: 45%
c, R = $CHMe_2$; R_1 = Me: 41%

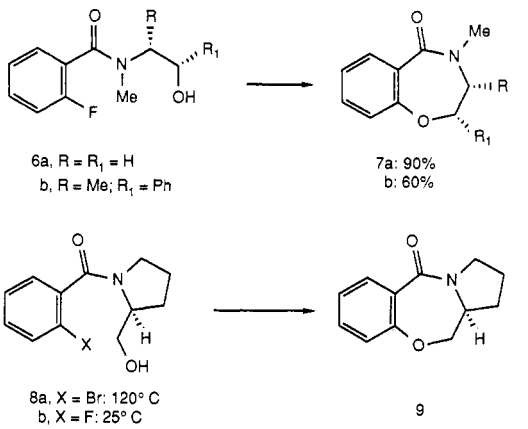


5a, R = Me; R_1 = Ph: 62%
b, R = R_1 H: 45%

From data gathered thus far, two requirements for the bimolecular cyclization process are clear (Scheme II). First, *only secondary amides provide macrocycles.* Tertiary amides result in unimolecular cyclization to give benzoxazepinones, e.g., **6a** → **7a** (25 °C, <18 h) and **6b** → **7b** (120 °C, ~4 h). Second, *macrocycle formation requires the presence of a fluorine atom on the aromatic ring of the benzamide.*[7,8] The bromine atom analogue of **1c** (F = Br) did not give either **2c** or benzoxazepinone **3c** under comparable or forcing (DMF, NaH, 120 °C) reaction conditions. However, with the tertiary 2-bromobenzamide **8a**, prepared from L-prolinol, cyclization occurred at 120 °C to give benzoxazepinone **9** in 70% isolated yield; with the fluorine atom analogue **8b**, cyclization occurred at 25 °C to give **9** in 88% yield.

Despite careful spectroscopic and chromatographic examination of all product mixtures encountered in these studies, no evidence for acyclic reaction intermediates could be obtained (~2–5% limit of detection). This surprising feature of the reaction along with the cation and leaving group requirements are suggestive of a template

Scheme II



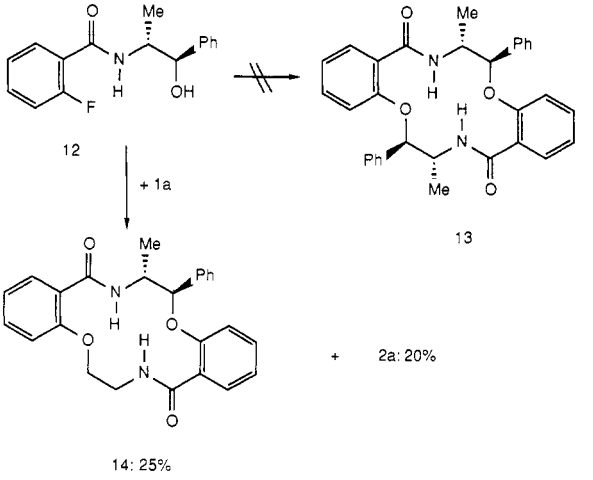
6a, R = R_1 = H
b, R = Me; R_1 = Ph

7a: 90%
b: 60%

8a, X = Br: 120° C
b, X = F: 25° C

9

Scheme III



12

+ 1a

13

+ 2a: 20%

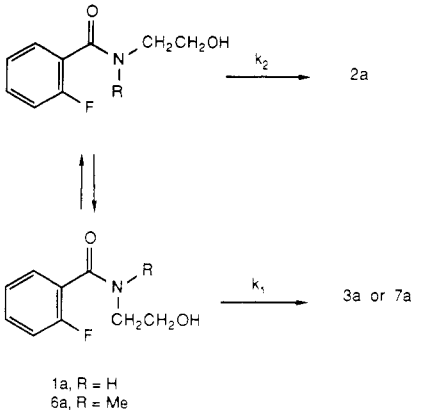
14: 25%

(6) (a) Cope, A. G.; Fenton, S. W. *J. Am. Chem. Soc.* **1951**, *73*, 1668. (b) Ziegler, K. In *Houben-Weyl, Methoden der Organischen Chemie*, Vol. IV/2, 4th ed.; Muller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1955; p 729.

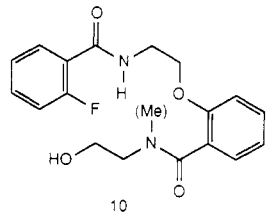
(7) For examples of the substitution of an activated fluorine atom on an aromatic ring, see: (a) Bader, H.; Hansen, A. R.; McCarthy, F. J. *J. Org. Chem.* **1966**, *31*, 2319. (b) Coffen, D. L.; Katonak, D. A.; Wong, F. *J. Am. Chem. Soc.* **1974**, *96*, 3966. (c) Coffen, D. L.; Wong, F. *J. Org. Chem.* **1974**, *39*, 1765. (d) Semmelhack, M. F.; Hall, H. T. *J. Am. Chem. Soc.* **1974**, *96*, 7091. (e) Moran, D.; Patel, M. N.; Tahir, N. A.; Wakefield, J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2310. (f) Walser, A.; Flynn, T.; Fryer, R. I. *J. Heterocycl. Chem.* **1975**, *12*, 737. (g) Meyers, A. I.; Williams, B. E. *Tetrahedron Lett.* **1978**, 223. (h) Reuman, M. Ph.D. Thesis, Colorado State University, 1982. (i) Effland, R. C.; Davis, L. *J. Heterocycl. Chem.* **1985**, *22*, 1071. This paper describes the preparation of the pyrrolo[2,1-*c*][1,4]benzoxazepine ring system by an intramolecular nucleophilic substituion of an aryl fluoride.

(8) An excellent discussion of aromatic nucleophilic substitution, with reference to the superb leaving character of the fluoride substituent (the element effect) in S_NAr-type reactions is found in March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; Chapter 13.

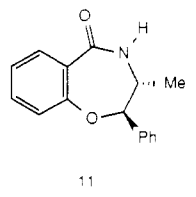
Scheme IV



effect.[9,10] In accord with this hypothesis, reaction of an equimolar mixture of **1a** and **6a** with NaH in DMF at 25 °C gave, in addition to the previously observed products **2a** and **7a**, the acyclic diamido alcohol **10** in ~25% yield. This substance, **10**, could not be cyclized to the 14-crown-4 ring system. We view the *N*-methyl substituent in **10** as a blocking group which disrupts the template that would promote carbon–oxygen bond formation. It is noteworthy, however, that the *N*-methyl substituent does not block the initial carbon–oxygen bond formation resulting in the formation of **10**. Further experiments designed to examine the validity of the template hypothesis are in progress.



10



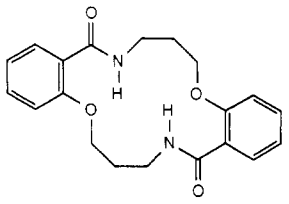
11

An interesting sensitivity of macrocycle formation to configuration of the starting benzamide was uncovered with the (−)-norpseudoephedrine derivative **12** (Scheme III). In contrast to the (+)-norephedrine derivative **6b** (NMe = NH) that gave macrocycle **5a**, **12** failed to give **13** under comparable experimental conditions. No reaction occurred between room temperature and 60 °C, and decomposition to a dark substance occurred at 120 °C. Cyclization to observable quantities of benzoxazepinone **11** also did not occur under any of these reaction conditions. However, bimolecular cyclization of an equimolar mixture of **12** and **1a** at room temperature provided the mixed-macrocycle **14** and the unsubstituted-macrocycle **2a**, along with recovered starting materials.

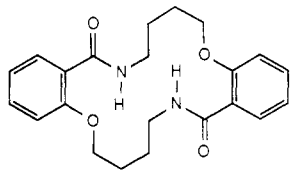
The source of the failure to generate **13** must reside in conformational constraints in the "template" producing macrocycles (kinetic effects) rather than product stability. Gauche interactions in **5a** resulting from the syn arrangement of methyl and phenyl substituents are relieved in **13** where these groups are anti oriented and able to assume relatively uncluttered axial conformations.

The successful formation of the mixed-macrocycle **14** presumably involves displacement of the fluoride group on **12** by the relatively unhindered alkoxide salt derived from **1a** as the first bond-forming step. This process is analogous to bond formation between **1a** and **6a** that produced **10**. While **10** did not undergo cyclization, the intermediate produced from **1a** and **12** gave **14** quite efficiently.

The bimolecular cyclization process, when extended to the 2-fluorobenzamides derived from 3-aminopropanol and 4-aminobutanol, provided an example of the exceedingly rare[11] dibenzo-1,9-diaza-16-crown-4 ether ring system, **15**, and a previously unreported dibenzo-1,10-diaza-18-crown-4 ether, **16**. As with the 14-crown-4 series, minor quantities of the corresponding products of unimolecular cyclization also were isolated from these reactions.



15: 45%



16: 38%

Mechanistic Considerations. The partial double-bond character of the amide C(O)–N bond results in the existence of configurational isomers. Nuclear magnetic resonance techniques have been used to establish the presence of these isomers and provide information about rotational barriers between isomers.[12] The free energies of activation ($\Delta G^{\ddagger}$) for the interconversions of isomers have been measured for a variety of amides. Dimethylformamide has been studied in greatest detail, and determinations of $\Delta G^{\ddagger}$ range from 20 to 22 kcal/mol.[12] Competitive delocalization with the phenyl group in *N,N*-dimethylbenzamide results in a lowering of the barrier height to ~15 kcal/mol, but ortho substituents force the aryl group out of the plane of the carbonyl group and raise the barrier, e.g., 19 kcal/mol for *N,N*-dimethyl-*o*-methoxybenzamide.[13a]

NMR techniques have been used to determine the distribution of syn and anti isomers of amides **1a** and **6a** (Scheme IV). As expected,[12] the ^{1}H NMR spectrum of **1a** ($CDCl_3$) is consistent with the presence of only a single rotational isomer, which must have the anti configuration (H anti to the carbonyl oxygen atom).[13b] The complexity of the spectrum for **1a** in $(CD_3)_2SO$ did not change down to −60 °C. The ^{1}H NMR spectrum of **6a** clearly shows the presence of two rotational isomers with a distribution of 65:35. The major isomer of **6a** displays -CH_2- resonances very near to those of **1a**, while the -CH_2- resonances for the minor isomer appear at 0.4 to 0.5 ppm higher field. These data are consistent with the assignment of anti geometry to the predominant isomer of **6a**.

A study of the effect of temperature on the ^{1}H NMR spectrum of **1a** in $(CD_3)_2SO$ showed peak coalescence between 100 and 105 °C for the two signals assigned to the *N*-methyl groups of the syn and anti isomers. The free energy of activation for isomer interconversion ($\Delta G^{\ddagger} \simeq 19$ kcal/mol) calculated from the NMR data[14] is in agreement with literature values for related ortho-substituted aryl amides.[13a]

(9) (a) Busch, D. H. *Rec. Chem. Progr.* **1964**, *25*, 107. (b) Eschenmoser, A. *Pure Appl. Chem.* **1969**, *20*, 1.

(10) Template effects have been proposed for certain macrocycle syntheses: (a) Kruizinga, W. H.f Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1979**, 286. (b) Reinhoudt, D. N.; de Jong, F.; Tomassen, H. P. M. *Tetrahedron Lett.* **1979**, 2067. (c) Newkome, G. R.; Kawato, T.; Benton, W. H. *J. Org. Chem.* **1980**, *45*, 626, and references cited therein. (d) Shanzer, A. *Bull. Soc. Chim. Belg.* **1983**, *92*, 411.

(11) Only one prior example, 11,12,23,24-tetrahydro-10*H*,22*H*-tetrabenzo[*b*,*g*,*j*,*o*][1,9,5,13]dioxadiazacyclohexadecine-10,22-dione, could be located: Lieb, F.; Eiter, K. *Liebigs Ann. Chem.* **1976**, 203.

(12) Stewart, W. E.; Siddall, T. H., III *Chem. Rev.* **1970**, *70*, 517.

(13) (a) Fryer, C. W.; Conti, F.; Franconi, C. *Ric. Sci. Rend. Sez. A* **1965**, *35*, 788. (b) Staab, H. A.; Lauer, D. *Chem. Ber.* **1968**, *101*, 864.

(14) Allerhand, A.; Gutowsky, H. S.; Jonas, J.; Meinzer, R. A. *J. Am. Chem. Soc.* **1966**, *88*, 3185.

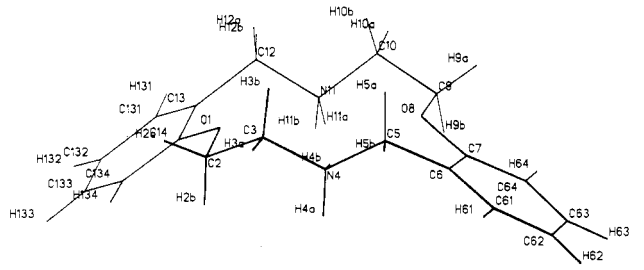


Figure 2. Molecular structure of **17a**.

A rationale for the difference in reactivity of **1a** (and by implication, **1b–f**) and **6a**, that is intended to be used as a guide in future studies, is now presented. Cyclization of **1a** or **6a** to benzoxazepinone **3a** or **7a** must occur from the alkoxide salt of the syn isomer, while bimolecular cyclization of **1a** might occur from the anti isomer. On the basis of ^{1}H NMR spectral data, the anti/syn distribution for **1a** must be >99:1 in favor of the anti isomer. Bimolecular cyclization is the dominant reaction pathway at high concentrations of **1a**, but at low concentrations of **1a**, cyclization to benzoxazepinone **3a** becomes competitive. The anti/syn distribution for **6a** is 65:35 and perhaps the relatively abundant syn isomer steers the reaction toward cyclization to benzoxazepinone **7a**, even at high concentrations of **6a**.

Application to the Preparation of Bicyclic Crown–LiI Complexes. There continues to be a high level of interest in the preparation and characterization of complexes of alkali metal and related cation salts with crown ethers.[15] Our recent involvement in this area originates from a desire to design and construct chiral ion-binding macrocycles that may be used to promote stereocontrolled carbon–carbon bond formation. As a first step, we would like to develop strategies that will complement the enantioselective Birch reduction–alkylation of benzoic acid derivatives.[16] The current state-of-the-art requires covalently attached chiral auxiliaries that influence the sense and degree of asymmetric induction in the alkylation step. We imagine that the next level of sophistication toward enantioselectivity will incorporate achiral alkali metal enolates in complexation with chiral stereodirectors. It should be possible to design complexing agents that bind selectively to (1) the alkali metal cation, (2) the enolate anion, or (3) both components, each at different locations on the macrocycle. Toward this goal, we now report the preparation of two complexes with LiI, **18c** and **18d**, both derived from macrocycles described in the first part of this paper.

Reduction of diamide **2a** to diamine **17a** was performed in 82–84% yields with lithium aluminum hydride or the borane–dimethyl sulfide complex in the presence of boron trifluoride etherate. With the more sterically hindered macrocycles **2b** and **2c**, only the borane–dimethyl sulfide method provided acceptable yields (70–75%) of diamines **17c** and **17d**. An X-ray structure determination was performed with **17a** and, as shown in the molecular structure (Figure 2), the conformation of the macrocyclic ring is similar to that observed with **2c**. The projection

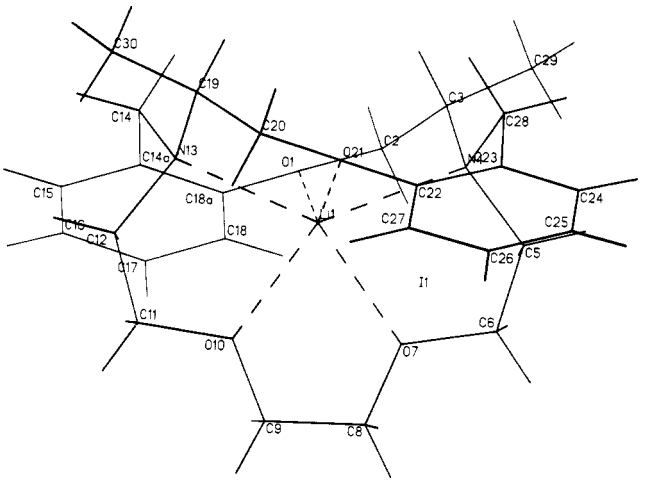
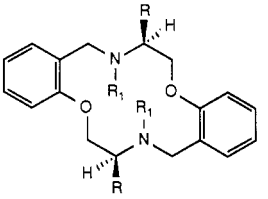
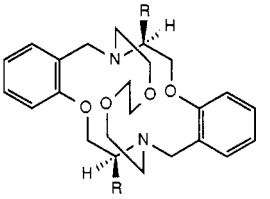


Figure 3. Molecular structure of **18d**. Li–donor distances (Å): O(1) 2.016, N(4) 2.362, O(7) 2.198, O(10) 2.165, N13) 2.344, O(21) 2.021. Li–I distance: 6.504; Li–H(18) nearest molecular neighbor, 3.093.

in Figure 2 shows the butterfly-like conformation already mentioned for **2c**.

For purposes of additional characterization, **17a** was converted to the *N,N*-diacetyl derivative **17b**, and **17d** was converted to the *N,N*-dimethyl derivative **17e**. These compounds gave satisfactory combustion analyses, but we have not as yet completed conformational and binding studies of these macrocycles.





17a, R = R_1 = H
b, R = H; R_1 = COMe
c, R = Me; R_1 = H
d, R = $CHMe_2$; R_1 = H
e, R = $CHMe_2$; R_1 = Me

18a, R = H
b, R = Me
c = 18a[LiI]
d = 18b[LiI]

Treatment of **17a** with 1,2-bis(2-iodoethoxy)ethane in acetonitrile in the presence of sodium iodide and excess sodium carbonate gave bicyclic diamine **18a**.[17,18] Complexation of **18a** with LiI gave **18c** as a colorless crystalline material. This substance gave an acceptable analysis for each element present in the complex. In a related fashion, **17c** was converted to the bicyclic diamine **18b**, from which the lithium iodide complex **18d** was generated. Elemental characterization and an X-ray structure determination established the structure of this substance as that shown in Figure 3.

It was interesting to find that complex **18d** has the methyl substituents oriented syn to the bridging triethylene glycol residue. In contrast to the isopropyl groups observed in the molecular structure of diamide **2c**, the methyl substituents in **18d** are in equatorial rather than axial environments. We would like to determine the source of this stereoselectivity; however, at present we note that this discovery represents a potentially useful technique for changing the orientation of substituents at the chiral

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centers of the 14-crown-4 macrocycles.

Experimental Section

^{1}H NMR (200 MHz) spectra were recorded on a Varian XL-200 NMR spectrometer ($CDCl_3$ solvent, tetramethylsilane internal standard). Infrared spectra were recorded on either a Perkin-Elmer 198 or a Perkin Elmer-137 infrared spectrometer (polystyrene standard). Mass spectra were recorded on a Hewlett-Packard HP 5987A GC–mass spectrometer. Elemental analyses were determined by Spang Microanalytical Laboratories, Eagle Harbor, MI. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Melting point ranges were determined on a Thomas Hoover melting point apparatus using open capillary tubes. Solvents were distilled under a nitrogen atmosphere as follows: dimethylformamide (DMF) from CaH_2; tetrahydrofuran (THF) from sodium/benzophenone; methylene chloride from P_2O_5.

Preparation of 2-Fluoro-*N*-(2-hydroxyethyl)benzamide (1a). General Method of Preparation. A mixture of monoethanolamine (848 mg, 13.8 mmol) in methylene chloride (15 mL) and aqueous (10%) sodium hydroxide (5 mL) was cooled (0 °C) in an ice bath. To this vigorously stirred solution was added a solution of 2-fluorobenzoyl chloride (2.0 g, 13 mmol) in methylene chloride (20 mL) over 15 min. The reaction mixture was then allowed to warm to room temperature and stirring was continued for an additional hour. Water (20 mL) was added and the organic layer separated. The aqueous layer was washed with methylene chloride (10 mL) and the combined organic extracts were washed with brine (50 mL) and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave a pale yellow oil which was chromatographed on silica gel (1:1 hexane/ethyl acetate) to afford **1a** as a colorless oil (2.33 g, 100%): ^{1}H NMR ($CDCl_3$) δ 3.37 (br s, 1 H), 3.60 (q, J = 4 Hz, 2 H), 3.76 (q, J = 4 Hz, 2 H), 7.02–7.52 (m, 4 H), 8.0 (dt, J_d = 2, J_t = 8 Hz, 1 H); IR (film) 3300, 1650 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 184 (M^+ + 1, 100).

Anal. Calcd for $C_9H_{10}NO_2F$: C, 59.00; H, 5.50. Found: C, 58.96; H, 5.55.

(1′*S*)-2-Fluoro-*N*-[1-(hydroxymethyl)ethyl]benzamide (1b): isolated as colorless crystals (73%); mp 75–77 °C; $[\alpha]^{24}_D$ –53.8° (c 0.42, methylene chloride); ^{1}H NMR ($CDCl_3$) δ 1.30 (d, J = 7 Hz, 3 H), 4.38 (s, 2 H), 4.40 (m, 1 H), 5.94 (br s, 1 H), 6.96–7.22 (m, 2 H), 7.58 (m, 1 H), 8.05 (dt, J_d = 2 Hz, J_t = 8 Hz, 1 H), 8.17 (dt, J_d = 2, J_t = 8 Hz, 1 H); IR ($CHCl_3$) 3455, 1645, 1600 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 198 (M^+ + 1, 100).

(1′*S*)-2-Fluoro-*N*-[1-(hydroxymethyl)-2-methylpropyl]benzamide (1c): isolated as a pale yellow oil (97%); $[\alpha]^{27}_D$ –27.08° (c 0.49, methylene chloride); ^{1}H NMR ($CDCl_3$) δ 0.99 (dd, 6 H), 1.98 (m, 1 H), 3.76 (m, 2 H), 3.8 (br s, 1 H), 6.90 (br s, 1 H), 7.10–7.36 (m, 3 H), 7.48 (m, 1 H), 8.08 (d$_t$, J_d = 2, J_t = 8 Hz, 1 H); IR (film) 3440, 3200, 1635 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 226 (M^+ + 1, 100).

Anal. Calcd for $C_{12}H_{16}NO_2F$: C, 63.98; H, 7.16. Found: C, 64.06; H, 7.21.

(1′*S*)-2-Fluoro-*N*-[1-(hydroxymethyl)-3-methylbutyl]benzamide (1d): isolated as colorless crystals (92%); mp 53–54 °C; $[\alpha]^{24}_D$ –39.7° (c 0.32, methylene chloride); ^{1}H NMR ($CDCl_3$) δ 0.92 (dd, J = 8 and 2 Hz, 6 H), 1.42 (m, 2 H), 1.72 (m, 1 H), 3.61–3.84 (dd, J = 10 and 16 Hz, 3 H), 4.32 (m, 1 H), 6.84 (br m, 1 H), 7.16 (dd, J = 8 and 12 Hz, 1 H), 7.30 (t, 1 H), 7.50 (m, 1 H), 8.10 (d$_t$, J_d = 2, J_t = 8 Hz, 1 H); IR ($CHCl_3$) 3445, 1640, 1600; chemical ionization mass spectrum, m/z (relative intensity) 240 (M^+ + 1, 100).

Anal. Calcd for $C_{13}H_{18}NO_2F$: C, 65.25; H, 7.58. Found: C, 65.12; H, 7.62.

(1′*R*)-2-Fluoro-*N*-[1-(hydroxymethyl)-2-(benzylthio)ethyl]benzamide (1e): isolated as pale yellow crystals (54%); mp 62–64 °C; ^{1}H NMR ($CDCl_3$) δ 2.77 (d, J = 7 Hz, 2 H), 2.98 (br s, 1 H), 3.97 (s, 2 H), 3.40 (2 dd, J = 6 Hz, 1 H), 4.34 (br m, 2 H), 7.10–7.59 (m, 9 H), 8.45 (dt, J_d = 2, J_t = 8 Hz, 1 H); IR ($CHCl_3$) 3395, 1635, 1600, 1538, 1220, 755 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 320 (M^+ + 1, 100).

(1′*S*)-2-Fluoro-*N*-[1-(hydroxymethyl)-3-(methylthio)propyl]benzamide (1f): isolated as colorless crystals (76%); mp 80.0–80.5 °C; $[\alpha]^{27}_D$ –23.9° (c 1.15, methylene chloride); ^{1}H NMR ($CDCl_3$) δ 1.93 (dt, J = 8 Hz, 2 H), 2.78 (s, 3 H), 2.58 (t, J = 8 Hz, 2 H), 3.49 (m, 1 H), 3.74 (m, 2 H), 4.30 (br s, 1 H), 7.08 (t, 1 H), 7.13 (dt, 2 H), 7.45 (m, 1 H), 8.00 (dt, J_d = 2, J_t = 8 Hz, 1 H); IR ($CHCl_3$) 3450, 2420, 1660, 1615, 1520, 1480, 1300, 1215, 1195 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 258 (M^+ + 1, 72).

Anal. Calcd for $C_{12}H_{16}NO_2SF$: C, 56.01; H, 6.27. Found: C, 56.12; H, 6.35.

6,7:13,14-Dibenzo-1,8,4,11-dioxadiazacyclotetradecane-5,12-dione (2a) and 6,7-Benzo-1-ox-4-azepin-5-one (3a). General Method of Preparation. A solution of **1a** (188 mg, 1.03 mmol) and sodium hydride (73 mg, 3.1 mmol) in DMF (10 mL) was stirred at room temperature for 24 h. Solvent was removed in vacuo, and water (50 mL) was added to the brown residue. The resulting suspension was washed with methylene chloride (2 × 25 mL), and the combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, and evaporated to afford a colorless semisolid. Flash chromatography (silica gel, 9:1 hexane/ethyl acetate) gave **3a** as a colorless oil (6.03 mg, 3.63%): ^{1}H NMR ($CDCl_3$) δ 1.22 (br s, 1 H), 4.06 (t, J = 9 Hz, 2 H), 4.38 (t, J = 9 Hz, 2 H), 6.90 (t, J = 8 Hz, 1 H), 7.02 (d, J = 8 Hz, 1 H), 7.38 (t, 1 H), 7.66 (d, J = 8 Hz, 1 H); IR (film) 3255, 2400, 1625, 1600, 1475, 1350, 1255, 1230, 1060, 935, 750 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 164 (M^+ + 1, 100).

Anal. Calcd for $C_9H_9NO_2$: C, 66.24; H, 5.56. Found: C, 66.27; H, 5.46.

2a was isolated as colorless crystals (102 mg, 62%). Analytically pure **2a** was obtained by recrystallization from hexane/ethyl acetate: mp 220–222 °C; ^{1}H NMR ($CDCl_3$) δ 4.04 (q, 4 H), 4.32 (t, 4 H), 7.00 (d, J = 8 Hz, 2 H), 7.10 (t, 2 H), 7.49 (dt, J = 2 and 8 Hz, 2 H), 8.16 (dd, J = 2 and 8 Hz, 2 H), 8.37 (br s, 2 H); IR ($CHCl_3$) 3430, 1655, 1600, 1529, 1295, 1225, 1040 cm^{-1}; electron impact mass spectrum, m/z (relative intensity) 326 (M^+, 100).

Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56. Found: C, 66.32; H, 5.55.

(3*S*,10*S*)-3,10-Dimethyl-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane-5,12-dione (2b): isolated as colorless crystals (69%); mp 209–210 °C; $[\alpha]^{25}_D$ –110.21° (c 0.48, methylene chloride); ^{1}H NMR ($CDCl_3$) δ 1.52 (d, J = 6 Hz, 6 H), 4.25 (m, 1 H), 4.72 (m, 2 H), 6.94 (d, J = 8 Hz, 2 H), 7.08 (dt, J = 8 Hz, 1 Hz, 2 H), 7.42 (dt, J = 8 Hz, 2 Hz, 2 H), 8.14 (dd, J = 8 Hz, 2 Hz, 2 H), 8.26 (br d, 2 H); IR ($CHCl_3$) 3420, 1650, 1600, 1518, 1480, 1225 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 355 (M^+ + 1, 100).

Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.77; H, 6.26. Found: C, 67.65; H, 6.31.

(3*S*)-3-Methyl-6,7-benzo-1-ox-4-azepin-5-one (3b): isolated as a colorless oil (4.66%); $[\alpha]^{27}_D$ –48.3° (c 1.00, methylene chloride); ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J = 6 Hz, 3 H), 1.62 (br s, 1 H), 3.93 (m, 1 H), 4.46 (m, 2 H), 6.85 (t, J = 7 Hz, 1 H), 7.02 (d, J = 8 Hz, 1 H), 7.35 (t, 2 Hz, 1 H), 7.62 (d, J = 8 Hz, 1 H); IR (film) 3385, 1640, 1600 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 178 (M^+ + 1, 100).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26. Found: C, 67.65; H, 6.31.

(3*S*,10*S*)-3,10-Diisopropyl-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane-5,12-dione (2c): isolated as colorless crystals (72%); mp 244–245 °C; $[\alpha]^{29}_D$ –224.75° (c 1.2, methylene chloride); ^{1}H NMR ($CDCl_3$) δ 1.1 (d, J = 6 Hz, 12 H), 2.08 (m, 2 H), 4.08 (dd, J = 8 Hz, J = 2 Hz, 2 H), 4.28 (td, J_t = 8 Hz, J_d = 2 Hz, 2 H), 4.64 (d, J = 8 Hz, 2 H), 7.0 (d, J = 6 Hz, 2 H), 7.1 (t, J = 6 Hz, 2 H), 7.46 (td, J_t = 8 Hz, J_d = 2 Hz, 2 H), 8.24 (dd, J = 8 Hz, J = 2 Hz, 2 H), 8.44 (d, J = 8 Hz, 2 H); IR ($CHCl_3$) 3400, 1638 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 410 (M^+ + 1, 100).

Anal. Calcd for $C_{24}H_{30}N_2O_4$: C, 70.21; H, 7.36. Found: C, 70.04; H, 7.43. Crystals of **2c** suitable for X-ray analysis were obtained from hexane and ethyl acetate by the isothermal distillation technique.

(3*S*)-3-Isopropyl-6,7-benzo-1-ox-4-azepin-5-one (3c): isolated as a colorless oil (6.64%); $[\alpha]^{26}_D$ –25.7° (c 0.82, methylene chloride; ^{1}H NMR ($CDCl_3$) δ 0.98 (2 d, J = 7 and 13 Hz, 6 H), 1.50 (br s, 1 H), 1.79 (m, 1 H), 4.13 (q, 2 H), 4.42 (t, 1 H), 6.89 (t, J = 8 Hz, 1 H), 7.02 (d, J = 8 Hz, 1 H), 7.58 (dt, J_d = 3, J_t

= 8 Hz, 1 H), 7.66 (dd, J = 3 and 8 Hz, 1 H); IR (film) 3400, 1640, 1625, 1485, 1360, 1310, 1255, 1235, 1065, 960, 755 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 206 (M^+ + 1, 100).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.21; H, 7.36. Found: C, 70.07; H, 7.34.

(3*S*,10*S*)-3,10-Diisobutyl-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane-5,12-dione (2d): isolated as colorless crystals (60%); mp 235–236 °C; $[\alpha]^{24}_D$ −139.3° (*c* 0.6, methylene chloride); ^1H NMR ($CDCl_3$) δ 1.04 (2 d, J = 7 Hz, 12 H), 1.68 (m, 2 H), 1.86 (m, 4 H), 4.28 (q(AB), J = 8 Hz, 2 H), 4.74 (m, 2 H), 7.05 (d, J = 8 Hz, 2 H), 7.17 (t, J = 8 Hz, 2 H), 7.50 (t, J = 8 Hz, 2 H), 8.27 (d, J = 8 Hz, 2 H), 8.44 (br d, J = 8 Hz, 2 H); IR ($CHCl_3$) 3418, 1640, 1600 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 439 (M^+ + 1, 100).

Anal. Calcd for $C_{26}H_{34}N_2O_4$: C, 71.20; H, 7.82. Found: C, 71.48; H, 7.42.

(3*S*)-3-Isobutyl-6,7-benzo-1-ox-4-azepin-5-one (3d): isolated as a colorless oil (2.0%); $[\alpha]^{30}_D$ −78.7° (*c* 0.46, methylene chloride); ^1H NMR ($CDCl_3$) δ 0.98 (2 d, J = 7 Hz, 6 H), 1.25 (br s, 1 H), 1.38 (m, 1 H), 1.62 (m, 1 H), 1.84 (m, 1 H), 3.98 (t, J = 7 Hz, 1 H), 4.45 (m, 2 H), 6.89 (t, J = 8 Hz, 1 H), 7.02 (d, J = 8 Hz, 1 H), 7.40 (dt, J_t = 8 Hz, J_d = 2 Hz, 1 H), 7.68 (dd, J = 2 and 8 Hz, 1 H); IR (film) 3255, 1640, 1615, 1580, 1255, 1065, 950 cm^{-1}; chemical ionization spectrum, m/z (relative intensity) 220 (M^+ + 1, 100).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82. Found: C, 71.30; H, 7.72.

(3*R*,10*R*)-3,10-Bis[(benzylthio)methyl]-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane-5,12-dione (2e): isolated as a pale yellow oil (70%); $[\alpha]^{27}_D$ +78.2° (*c* 1.02, methylene chloride); ^1H NMR ($CDCl_3$) δ 2.62–2.72 (dd, J = 13 and 8 Hz, 2 H), 2.80–2.89 (dd, J = 6 and 10 Hz, 2 H), 3.72 (s, 4 H), 4.14 (dd, J = 8 and 3 Hz, 1 H), 4.64 (d, J = 8 Hz, 2 H), 4.65 (br m, 1 H), 6.98 (d, J = 8 Hz, 2 H), 7.12–7.38 (m, 16 H), 7.48 (t, 2 H), 8.18 (dd, J = 2 and 8 Hz, 2 H); IR ($CHCl_3$) 3418, 1645, 1600, 1510, 1480, 1225 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 599 (M^+ + 1, 100).

Anal. Calcd for $C_{34}H_{34}N_2O_4S_2$: C, 68.19; H, 5.72. Found: C, 68.08; H, 5.71.

(3*R*)-3-[(Benzylthio)methyl]-6,7-benzo-1-ox-4-azepin-5-one (3e): isolated as a pale yellow oil (2.0%); $[\alpha]^{29}_D$ +10.1° (*c* 1.06, methylene chloride); ^1H NMR ($CDCl_3$) δ 2.59 (dd, J = 8 and 13 Hz, 1 H), 2.82 (dd, J = 8 and 13 Hz, 1 H), 3.78 (s, 2 H), 4.30 (m, 1 H), 4.85 (m, 2 H), 6.81 (t, 1 H), 7.05 (d, J = 8 Hz, 1 H), 7.36 (m, 5 H), 7.70 (d, J = 8 Hz, 1 H); IR (film) 3250, 1635, 1615, 1490, 1255, 1065, 760 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 300 (M^+ + 1, 100).

Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 68.19; H, 5.73. Found: C, 68.25; H, 5.65.

(3*S*,10*S*)-3,10-Bis[2-(methylthio)ethyl]-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane-5,12-dione (2f): isolated as colorless crystals (57%); mp 185–187 °C; $[\alpha]^{26}_D$ −107.4° (*c* 1.44, methylene chloride); ^1H NMR ($CDCl_3$) δ 2.08 (m, 4 H), 2.13 (s, 6 H), 2.69 (t, J = 7 Hz, 4 H), 4.23 (dd, J = 3 and 9 Hz, 2 H), 4.42 (d, J = 8 Hz, 2 H), 4.77 (m, 2 Hz), 6.99 (d, J = 8 Hz, 2 H), 7.14 (t, J = 9 Hz, 2 H), 7.48 (dt, J = 2 and 8 Hz, 2 H), 8.20 (dd, J = 2 and 8 Hz, 2 H), 8.29 (br d, J = 9 Hz, 2 H); IR ($CHCl_3$) 3420, 1650, 1600, 1520, 1480, 1225 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 475 (M^+ + 1, 100).

Anal. Calcd for $C_{24}H_{30}N_2O_4S_2$: C, 60.72; H, 6.37. Found: C, 60.76; H, 6.25.

(3*S*)-3-[2-(Methylthio)ethyl]-6,7-benzo-1-ox-4-azepin-5-one (3f): isolated as a pale yellow oil (6.0%); $[\alpha]^{26}_D$ −12.2° (*c* 1.0, methylene chloride); ^1H NMR ($CDCl_3$) δ 1.24 (s, 1 H), 1.92 (m, 2 H), 2.14 (s, 3 H), 2.66 (t, J = 8 Hz, 2 H), 4.03 (br s, 1 H), 4.49 (m, 2 H), 6.86 (t, J = 8 Hz, 1 H), 7.36 (d, J = 8 Hz, 1 H), 7.61 (t, J = 8 Hz, 1 H), 7.66 (d, J = 8 Hz, 1 H); IR (film) 3250, 1635, 1615, 1485, 1255, 1225, 1065, 955 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 238 (M^+ + 1, 100).

Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37. Found: C, 60.80; H, 6.40.

Preparation of Mixed Dimers. General Method of Preparation. A mixture of **1a** (245 mg, 1.33 mmol), **1c** (299 mg, 1.33 mmol), and sodium hydride (64 mg, 2.65 mmol) in DMF (15 mL) was stirred for 24 h at room temperature. The reaction mixture was subjected to flash chromatography (silica gel, 4:1, hexane/ethyl acetate) to afford **2a**, **4a**, and **2c**, respectively. Analytically pure samples were obtained by recrystallization from hexane/ethyl acetate.

(3*S*)-3-Isopropyl-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane-5,12-dione (4a): isolated as colorless crystals (40%); mp 199–200 °C; $[\alpha]^{28}_D$ −119.58° (*c* 0.48, ethanol); ^1H NMR ($CDCl_3$) δ 1.15 (2 d, J = 6 Hz, 6 H), 2.14 (m, 1 H), 3.62 (m, 1 H), 4.15–4.00 (m, 6 H), 7.02 (dd, J = 2 and 8 Hz, 2 H), 7.15 (m, 2 H), 7.46 (t, J = 8 Hz, 2 H), 8.17 (dd, J = 2 and 8 Hz, 2 H), 8.23 (dd, J = 2 and 8 Hz, 2 H), 8.36 (br s, 1 H), 8.45 (br d, 1 H); IR ($CHCl_3$) 3420, 1650, 1600 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 369 (M^+ + 1, 100).

Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.45; H, 6.56. Found: C, 68.08; H, 6.67.

(3*S*)-3-[2-(Methylthio)ethyl]-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane-5,12-dione (4b): isolated as colorless crystals (45%); mp 153–155 °C; $[\alpha]^{28}_D$ −78.17° (*c* 0.82, ethanol); ^1H NMR ($CDCl_3$) δ 2.09 (m, 2 H), 2.13 (s, 3 H), 2.69 (t, J = 8 Hz, 2 H), 3.68 (m, 1 H), 4.12–4.51 (m, 5 H), 4.75 (br d, J = 8 Hz, 1 H), 7.00 (dd, J = 2 and 8 Hz, 2 H), 7.14 (t, J = 8 Hz, 2 H), 7.49 (t, J = 8 Hz, 2 H), 8.18 (t, 2 H), 8.15 (br d, 2 H); IR ($CHCl_3$) 3420, 1655, 1600, 1530 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 401 (M^+ + 1, 100).

Anal. Calcd for $C_{21}H_{24}N_2O_4S$: C, 62.98; H, 6.04. Found: C, 63.01; H, 6.12.

(3*S*,10*S*)-3-Methyl-10-isopropyl-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane-5,12-dione (4c): isolated as colorless crystals (41%); mp 160–162 °C; $[\alpha]^{24}_D$ −161° (*c* 0.3, chloroform); ^1H NMR ($CDCl_3$) δ 1.11 (dd, J = 4 and 8 Hz, 6 H), 1.51 (d, J = 6 Hz, 3 H), 2.04 (m, 1 H), 4.08 (dd, J = 3 and 9 Hz, 2 H), 4.30 (m, 3 H), 4.62 (d, J = 9 Hz, 1 H), 4.73 (m, 1 H), 7.00 (dd, J = 3 and 8 Hz, 2 H), 7.11 (m, 2 H), 7.48 (m, 2 H), 8.12 (dd, J = 2 and 8 Hz, 2 H), 8.57 (br d, 1 H); IR ($CHCl_3$) 3420, 1645, 1600, 1525 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 383 (M^+ + 1, 100).

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.08; H, 6.85. Found: C, 69.10; H, 6.97.

[2*S*,3*R*,9*S*,10*R*]-2,9-Diphenyl-3,10-dimethyl-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane-5,12-dione (5a): isolated as crystalline needles (62%) following the procedure used for preparation of **4a**; mp 349–351 °C; $[\alpha]^{29}_D$ −145° (*c* 0.6, methylene chloride); ^1H NMR ($CDCl_3$) δ 1.32 (d, J = 7 Hz, 6 H), 4.72 (m, 2 H), 5.73 (d, J = 2 Hz, 2 H), 6.64 (d, J = 8 Hz, 2 H), 7.06 (t, 2 H), 7.21 (t, 2 H), 7.46 (m, 10 H), 8.20 (d, J = 8 Hz, 2 H), 8.70 (br d, 2 H); IR ($CHCl_3$) 3250, 1635, 1615 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 507 (M^+ + 1, 45), 344 (22), 254 (20), 231 (100).

(2*S*,3*R*)-2-Phenyl-3-methyl-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane-5,12-dione (5b): isolated as colorless crystals (45%) following the procedure used for preparation of **4a**; mp 151–153 °C; $[\alpha]^{25}_D$ −49.12° (*c* 0.34, ethanol); ^1H NMR ($CDCl_3$) δ 1.20 (d, J = 6 Hz, 3 H), 3.50–3.74 (m, 1 H), 4.22–4.44 (m, 2 H), 4.5 (m, 1 H), 5.57 (d, J = 2 Hz, 1 H), 6.59 (d, J = 8 Hz, 1 H), 6.98–7.20 (m, 4 H), 7.38 (m, 7 H), 8.17 (dd, J_d = 2 Hz, 2 H), 8.53 (br d, 2 H); IR ($CHCl_3$) 3420, 1655 1600, 1525 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 417 (M^+ + 1, 100).

Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 72.09; H, 5.81. Found: C, 71.63; H, 5.96.

***N*-Methyl-*N*-(2-hydroxyethyl)-2-fluorobenzamide (6a).** 2-Fluorobenzoyl chloride (5.00 g, 31.6 mmol) in methylene chloride was added to a stirred solution of *N*-methylaminoethanol (2.80 mL, 34.8 mmol) in a 1:1 mixture of methylene chloride (30 mL) and 10% NaOH (30 mL) at 0 °C. After the addition of the acid chloride was complete, the reaction mixture was warmed to room temperature and stirred for 4 h. The two layers were separated and the aqueous layer was extracted with chloroform (3 × 30 mL). The organic layers were combined and dried over anhydrous magnesium sulfate. Solvent was removed to give **6a** as a clear oil (5.01 g, 96%): ^1H NMR ($CDCl_3$, mixture of rotational isomers) δ 2.88–3.10 (br s with overlapping singlet at 3.10, 4 H), 3.65 (t,

J = 4 Hz, 2 H), 3.86 (t, J = 4 Hz, 2 H), 7.16 (m, 2 H), 7.4 (m, 2 H); IR (film) 3380, 1608 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 198 (M^+ + 1, 100).

Anal. Calcd for $C_{10}H_{12}NO_2F$: C, 60.90; H, 6.13. Found: C, 60.45; H, 6.27.

(1′*R*,2′*S*)-*N*-Methyl-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-2-fluorobenzamide (6b). 2-Fluorobenzoyl chloride (5.00 g, 31.5 mmol) in dry methylene chloride (15 mL) was added to a stirred solution of D-ephedrine (5.7 g, 34.6 mmol) and triethylamine (10 mL, 73 mmol) in methylene chloride (35 mL) at 0 °C. After the addition of the acid chloride was complete, the reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was washed with 5% HCl (50 mL), saturated sodium bicarbonate solution (50 mL), and brine (50 mL). The organic layer was dried over anhydrous magnesium sulate and the solvent was removed to give a colorless foam. Crystallization with ether afforded **6b** (6.2 g, 68%) as colorless crystals: mp 128–130 °C; ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 1.20 (d, J = 8 Hz, 3 H), 2.66 (s, 3 H), 4.92 (d, J = 2 Hz, 1 H), 4.60 (m, 1 H), 5.0 (t, J = 2 Hz, 1 H), 7.06 (m, 3 H), 7.40 (m, 6 H); IR ($CHCl_3$) 3800, 1620 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 288 (M^+ + 1, 100).

Anal. Calcd for $C_{17}H_{18}NO_2F$: C, 71.06; H, 6.30. Found: C, 70.62; H, 6.43.

4-Methyl-6,7-benzo-1-ox-4-azepin-5-one (7a). A solution of **6a** (1.97 g, 10 mmol) and sodium hydride (240 mg, 10 mmol) in DMF (50 mL) was stirred at room temperature for 18 h. Solvent was removed in vacuo and water (20 mL) was added to the residue. The mixture was washed with chloroform (3 × 50 mL) and the combined organic layers were dried over anhydrous magnesium sulfate. Removal of solvent and flash column chromatography (silica gel, 4:1 ethyl acetate/hexane) gave **7a** (962 mg, 54%): ^{1}H NMR ($CDCl_3$) δ 3.2 (s, 3 H), 3.50 (t, J = 3 Hz, 2 H), 4.38 (t, J = 3 Hz, 2 H), 7.0 (d, J = 6 Hz, 1 H), 7.14 (t, J = 6 Hz, 1 H), 7.40 (t, J = 4 Hz, 1 H), 7.81 (d, J = 6 Hz, 1 H), IR ($CHCl_3$) 1638 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 178 (M^+ + 1, 100).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.77; H, 6.25. Found: C, 67.75; H, 6.09.

(2*S*,3*R*)-3,4-Dimethyl-2-phenyl-6,7-benzo-1-ox-4-azepin-5-one (7b). A solution of **6b** (2.87 g, 10.0 mmol) and sodium hydride (240 mg, 10.0 mmol) in DMF (50 mL) was stirred at 120 °C for 4 h. Reaction workup as described for **7a** and crystallization from ethyl acetate/hexane gave **7b** (2.1 g, 78%): mp 155 °C; ^{1}H NMR ($CDCl_3$) δ 1.13 (d, J = 6 Hz, 3 H), 2.91 (s, 3 H) 4.03 (m, 1 H), 5.18 (br s, 1 H), 7.11 (m, 3 H), 7.43 (m, 5 H), 8.00 (d, J = 4 Hz, 1 H); IR ($CHCl_3$) 1625 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 268 (M^+ + 1, 100).

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41. Found: C, 76.36; H, 6.45.

(2′*S*)-*N*-(2-Bromobenzoyl)-2-(hydroxymethyl)pyrrolidine (8a). 2-Bromobenzoyl chloride (500 mg, 2.30 mmol) in methylene chloride (5.00 mL) was added to a stirred solution of L-prolinol (250 mg, 2.5 mmol) and triethylamine (0.6 mL, 4.8 mmol) in methylene chloride (12 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. Reaction workup as described for **8b** and flash chromatography (silica gel, 4:1 ethyl acetate/chloroform) gave **8a** (450 mg, 69%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.08 (m, 4 H), 3.32 (br s, 2 H), 3.88 (t, J = 4 Hz, 2 H), 4.44 (q, J = 3 Hz, 1 H), 4.97 (br s, 1 H), 7.40 (m, 3 H), 7.68 (d, J = 6 Hz, 1 H); IR (film) 3390, 1612 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 285 (M^+ + 1, 100).

Anal. Calcd for $C_{12}H_{14}NO_2Br$: C, 50.72; H, 4.96. Found: C, 50.59; H, 4.89.

(2′*S*)-*N*-(2-Fluorobenzoyl)-2-(hydroxymethyl)pyrrolidine (8b). 2-Fluorobenzoyl chloride (1.58 g, 10.0 mmol) in dry methylene chloride (15 mL) was added to a stirred solution of L-prolinol (1.1 g, 11 mmol) and triethylamine (2.00 mL, 14.0 mmol) in methylene chloride (35 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 4 h. A solution of 5% HCl (50 mL) was added and the mixture was washed with chloroform (3 × 50 mL). The organic layers were combined, washed with saturated sodium bicarbonate solution (50 mL) and brine (50 mL), and dried over anhydrous magnesium sulfate, and solvent was evaporated to give a pale yellow oil. Flash column chromatography (silica gel, 4:1 ethyl acetate/chloroform) gave **8b** as colorless crystals (1.7 g, 76%): mp 64–66 °C; ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 3 H), 2.20 (m, 1 H), 3.44 (t, J = 4 Hz, 2 H), 3.82 (m, 2 H), 4.42 (m, 1 H), 7.22 (m, 2 H), 4.80 (t, J = 2 Hz, 1 H), 7.50 (m, 2 H); IR ($CHCl_3$) 3380, 1625 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 224 (M^+ + 1, 100).

Anal. Calcd for $C_{12}H_{14}NO_2F$: C, 64.56; H, 6.32. Found: C, 64.46; H, 6.35.

(2a*S*)-2*H*-[2,1-*c*]Pyrrolidino-1,4-benzoxazepin-5-one (9). Method A. A solution of **8a** (200 mg, 0.7 mmol) and sodium hydride (50 mg, 2.1 mmol) was stirred in DMF (5 mL) at 120 °C for 2 h. Reaction workup as described for **7a**, except that chromatography was unnecessary, and crystallization from ethyl acetate/hexane gave **9** (100 mg, 70%).

Method B. A solution of **8b** (350 mg, 1.5 mmol) and sodium hydride (108 mg, 4.5 mmol) were stirred in DMF (20 mL) at room temperature for 18 h. Reaction workup as described for **7a**, except that chromatography was unnecessary, and crystallization from ether/pentane afforded **9** (246 mg, 88%): mp 135–136 °C; ^{1}H NMR ($CDCl_3$) δ 1.66 (m, 1 H), 1.86 (m, 2 H), 2.16 (m, 1 H) 3.78 (t, J = 6 Hz, 2 H), 3.86 (m, 1 H), 4.08 (t, J = 8 Hz, 1 H), 4.38 (dd, J = 8 Hz, J = 1 Hz, 1 H), 7.0 (d, J = 6 Hz, 1 H), 7.3 (t, J = 6 Hz, 1 H), 7.4 (t, J = 6 Hz, 11 H), 8.60 (dd, J = 6 Hz, J = 1 Hz, 1 H); IR ($CHCl_3$) 1620 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 204 (M^+ + 1, 100).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.44. Found: C, 71.09; H, 6.46.

***o*-[2-[(*o*-Fluorobenzoyl)amino]ethoxy]-*N*-methyl-*N*-(2-hydroxyethyl)benzamide (10).** A mixture of **1a** (368 mg, 2.01 mmol), **6a** (396 mg, 2.01 mmol), and sodium hydride (169 mg, 7.04 mmol) in DMF was stirred at room temperature for 24 h. Solvent was removed by distillation and water (20 mL) was added to the residue. The mixture was washed with methylene chloride (2 × 25 mL), and the combined organic layers were dried over anhydrous sodium sulfate and evaporated to give a yellow oil. Flash chromatography (silica gel, 4:1 hexane/ethyl acetate) afforded **10** (150 mg, 20%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 3 H), 3.62 (br t, 3 H), 3.74 (d, J = 4 Hz, 2 H), 4.08 (t, 2 H), 4.33 (t, 2 H), 6.98–7.59 (m, 7 H), 8.30 (d, J = 2 and 8 Hz, 1 H), 8.52 (br s, 1 H); IR (film) 3380, 1640, 1610, 1600; chemical ionization mass spectrum, m/z (relative intensity) 361 (M^+ + 1, 15), 180 (100).

(1′*R*,2′*R*)-2-Fluoro-*N*-(2-hydroxy-1-methyl-2-phenylethyl)benzamide (12): prepared in 99% yield following the general method for preparation of **1a**; colorless crystals mp 87–90 °C; ^{1}H NMR ($CDCl_3$) δ 1.10 (d, J = 8 Hz, 3 H), 3.30 (d, J = 4 Hz, 1 H), 4.42 (m, 1 H) 4.73 (t, J = 4 Hz, 1 H), 6.94 (br t, 1 H), 7.08–7.60 (m, 8 H), 8.04 (dt, J_d = 2, J_t = 8 Hz, 1 H); IR ($CHCl_3$) 3450, 1650, 1610, 1515 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 274 (M^+ + 1, 100).

(2*R*,3*R*)-2-Phenyl-3-methyl-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane-5,12-dione (14): prepared in 25% yield (colorless oil) following the general method for preparation of compound **4a**; ^{1}H NMR ($CDCl_3$) δ 1.57 (d, J = 6 Hz, 3 H), 3.65–3.86 (m, 1 H), 4.36–4.53 (cp, 2 H) 4.70 (m, 1 H), 5.56 (d, 1 H), 6.76 (d, J = 8 Hz, 1 H), 7.00 (m, 4 H), 7.18–7.36 (m, 7 H), 7.40 (dt, J = 8 and 2 Hz, 2 H), 8.20 (dd, J = 2 and 8 Hz, 1 H), 8.53 (br d, 1 H); IR (film) 3420, 1655, 1600 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 417 (M^+ + 1, 100).

7,8:15,16-Dibenzo-1,9,5,13-dioxadiazacyclohexadecane-6,14-dione (15): prepared in 45% yield (colorless crystals) following the general method for preparation of **2a**; mp 197–199 °C; ^{1}H NMR ($CDCl_3$) δ 2.28 (m, 4 H), 3.72 (q, 4 H), 4.42 (t, 4 H), 7.02 (d, J = 8 Hz, 2 H), 7.05 (d, J = 8 Hz, 2 H), 7.44 (t, 2 H), 8.21 (dd, J = 2 and 8 Hz, 2 H), 8.33 (br s, 2 H); IR ($CHCl_3$) 3400, 1645, 1600 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 355 (M^+ + 1, 100).

Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26. Found: C, 67.71; H, 6.23.

8,9:17,18-Dibenzo-1,10,6,15-dioxadiazacycloctadecane-7,16-dione (16): prepared in 38% yield (colorless crystals) following the general method for preparation of **2a**; mp 210–212 °C; ^{1}H NMR ($CDCl_3$) δ 1.80–2.05 (m, 8 H), 3.70 (t, 4 H), 4.22 (t, 4 H), 7.00 (d, J = 8 Hz, 2 H), 7.12 (dt, J = 2 and 8 Hz, 2 H), 7.44 (dt, J = 2 and 8 Hz, 2 H), 8.02 (br s, 2 H), 8.25 (d, J = 8 Hz, 2 H); IR ($CHCl_3$) 3400, 1640, 1600 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 383 (M^+ + 1, 28), 342 (100),

266 (68), 252 (65), 142 (66), 116 (42).

6,7:13,14-Dibenzo-1,8,4,11-dioxadiazacyclotetradecane (17a). General Method for the Reduction of Macrocyclic Diamides. To a solution of **2a** (590 mg, 1.81 mmol) in THF (25 mL) was added boron trifluoride etherate (642 mg, 4.53 mmol, freshly distilled from calcium hydride). The mixture was brought to reflux and borane–dimethyl sulfide complex (0.40 mL, 10 M) was added. After 10 min the dimethyl sulfide was removed by distillation. The remainder of the reaction mixture was refluxed for 5 h. Solvent was removed and hydrochloric acid (10 mL, 6 N) was added to the oily residue. After 4 h at reflux, the mixture was washed with methylene chloride (2 × 100 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave a brown oil; flash chromatography (silica gel, 1:9 hexane/ethyl acetate) afforded **17a** (437 mg, 82%) as colorless crystals: mp 158–160 °C; ^{1}H NMR ($CDCl_3$) δ 2.69 (br s, 2 H), 3.10 (t, 4 H), 3.85 (s, 4 H), 4.17 (t, 4 H), 6.89 (q, 4 H), 7.25 (m, 4 H); IR ($CHCl_3$) 3325, 1600, 1450, 1230, 1115, 1035 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 299 (M^+ + 1, 100). Crystals suitable for X-ray analysis were obtained from a mixture of hexane–ethyl acetate–chloroform (1:1:1) by the slow evaporation technique.

Lithium Aluminum Hydride Reduction of 6,7:13,14-Dibenzo-1,8,4,11-dioxadiazacyclotetradecane (17a). To an ice-cold solution of lithium aluminum hydride (930 mg, 24.5 mmol) in THF (25 mL) maintained under an atmosphere of nitrogen was added **2a** (800 mg, 2.45 mmol). The mixture was gradually warmed to room temperature and then refluxed for 48 h. Saturated sodium sulfate solution (1 mL) was added and the mixture was refluxed for 15 min and then suction filtered. Evaporation of the solvent in vacuo gave a colorless solid and recrystallization from hexane/ethyl acetate gave **17a** (617 mg, 84%), identical with the material prepared by the reduction of **2a** with the borane–dimethyl sulfide complex.

4,11-Diacetyl-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane (17b). The dihydrochloride salt of **17a** (148 mg, 0.40 mmol) was dissolved in a mixture (2:1) of methanol–methylene chloride (50 mL). Ammonia was bubbled through the mixture for 0.5 h. The mixture was filtered and the solvent evaporated in vacuo to give **17a** which was dissolved in dry methylene chloride (5 mL). To this mixture was added freshly distilled acetic anhydride (98 mg, 0.96 mmol) and pyridine (1 mL). The mixture was stirred under a nitrogen atmosphere for 12 h. Removal of the solvents in vacuo gave a dark brown oil. Hydrochloric acid (20 mL, 6 N) was added and the mixture was washed with methylene chloride (2 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous sodium sulfate. Removal of the solvent afforded **17b** as an oil; flash chromatography (silica gel, 1:1 hexane/ethyl acetate) gave **17b** as colorless crystals (114 mg, 70%): mp 218–220 °C; ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ 2.14, 2.19, 2.36, 2.38 (4 s, 6 H), 3.68 (m, 4 H), 4.23 (m, 4 H), 4.89, 4.91, 5.10 (3 s, 4 H), 6.85 (q, 2 H), 7.12 (q, 2 H), 7.30 (m, 3 H), 7.50 (m, 1 H); IR ($CHCl_3$) 1635, 1600, 1445, 1225, 1125, 1025 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 383 (M^+ + 1, 100).

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.08; H, 6.85. Found: C, 68.78; H, 6.92.

(3*S*,10*S*)-3,10-Dimethyl-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane (17c) was prepared from **2b** (720 mg, 2.03 mmol), boron trifluoride etherate (722 mg, 5.08 mmol), and borane–dimethyl sulfide complex (0.51 mL, 10 M) following the general procedure used to prepare **17a**. Flash chromatography (silica gel, 1:9 hexane/ethyl acetate) gave **17c** (500 mg, 75%) as a pale yellow solid: mp sublimes above 250 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 6 Hz, 6 H), 3.25 (m, 2 H), 3.83 (m, 4 H), 4.25 (m, 4 H), 6.93 (m, 4 H), 7.30 (m, 4 H); IR ($CHCl_3$) 3390, 1600, 1445, 1235 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 327 (M^+ + 1, 100). An acceptable analysis could not be obtained.

(3*S*,10*S*)-3,10-Diisopropyl-6,7:13,14-dibenzo-1,8,4,11-dioxadiazacyclotetradecane (17d) was prepared from **2c** (1.48 g, 3.61 mmol), boron trifluoride etherate (1,28 g, 9.04 mmol), and borane–dimethyl sulfide complex (0.91 mL, 10 M) following the procedure used to prepare **17a**. Flash chromatography (silica gel, 1:9 hexane/ethyl acetate) afforded **17d** (967 mg, 70%); as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.02 (dd, J = 4 and 8 Hz, 12 H), 2.12 (m, 2 H), 2.79 (br s, 2 H), 2.89 (m, 2 H), 3.70 (d, 13 Hz, 2 H), 3.85 (m, 4 H), 4.06 (dd, J = 3 and 9 Hz, 2 H), 6.90 (m, 4 H), 7.23 (m, 4 H); IR (film) 3350, 1600 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 383 (M^+ + 1, 100). An acceptable analysis was obtained via derivative **17e**.

[7(*S*)-(7*R,16*R**)]-7,8,16,17-Tetrahydro-6,15-dimethyl-5*H*,14*H*-7,16-bis(1-methylethyl)dibenzo[*f*,*m*][9,18]dioxa-6,15-diazacyclotetradecine (17e).** A mixture of **17d** (113 mg, 0.30 mmol), sodium hydride (18 mg, 0.74 mmol), and iodomethane (84 mg, 0.59 mmol) was stirred at room temperature for 24 h. Water (20 mL) was added to the resulting yellow solution and the mixture was washed with methylene chloride (2 × 50 mL). The combined organic layers were washed with hydrochloric acid (10 mL, 6N), saturated sodium bicarbonate (20 mL), and brine (20 mL) and dried over anhydrous sodium sulfate. Removal of the solvent afforded **17e** as a yellow semisolid; flash chromatography (silica gel, 4:1 hexane/ethyl acetate) gave **17e** (48 mg, 40%) as colorless crystals: mp 133–134 °C; $[\alpha]^{27}_D$ −59.67° (*c* 0.3, methylene chloride); ^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 7 Hz, 6 H), 1.06 (d, J = 6 Hz, 6 H), 1.82 (m, 2 H), 2.30 (s, 6 H), 2.63 (m, 2 H), 4.18 (m, 4 H), 4.16 (s, 4 H), 6.92 (d, J = 8 Hz, 2 H), 7.02 (t, 2 H), 7.26 (t, 2 H), 7.58 (d, 2 H); IR ($CHCl_3$) 2960, 1600, 1450, 1235 cm^{-1}; chemical ionization mass spectrum, m/z (relative intensity) 411 (M^+ + 1, 100).

Anal. Calcd for $C_{26}H_{38}N_2O_2$: C, 76.05; H, 9.32. Found: C, 75.99; H, 9.32.

2,3,5,6,8,9,11,12-Octahydro-14*H*-13,4-(ethanoxy[1,2]-benzenomethano)-4*H*-1,7,10,4,13-benzotrioxadiazacyclohexadecine (18a) and the LiI Complex (18b). A solution containing diamine **17a** as its dihydrochloride salt (1.67 mg, 0.45 mmol) in acetonitrile, 1,2-bis(2-iodoethoxy)ethane[17] (195 mg, 0.52 mmol), sodium carbonate (528 mg, 4.97 mmol), and sodium iodide (68 mg, 0.45 mmol) was refluxed for 24 h. Filtration of the insoluble materials followed by evaporation of solvent gave a dark brown oil which was dissolved in hydrochloric acid (6 N, 10 mL). The unreacted starting materials were extracted into methylene chloride (2 × 50 mL). The aqueous acidic layer was made basic with solid potassium carbonate. The mixture was washed with methylene chloride (2 × 50 mL). The combined organic layers were washed with water (25 mL) and brine (50 mL) and dried over anhydrous sodium sulfate. Evaporation of solvent gave a colorless oil. Chromatography (neutral alumina, 9.5:0.5 ethyl acetate/hexane) gave **18a** as a brown gummy liquid 142 mg (79%). This material was suitable for complexation with LiI: ^{1}H NMR ($CDCl_3$) δ 2.88–3.00 (br m, 2 H), 3.12 (br d, J = 8 Hz, 2 H), 3.20–3.90 (br m, 12 H), 4.10 (m, 3 H), 4.12 (br s, 1 H), 4.42 (m, 4 H), 6.95 (q, 3 H), 7.40 (q, 5 H); chemical ionization mass spectrum, m/z (relative intensity) 413 (M^+ + 1, 100), 117 (68).

18a was dissolved in 1,2-dichloroethane (2 mL) and excess anhydrous lithium iodide was added. The mixture was stirred at room temperature for 1.5 h and filtered, and the filtrate was concentrated in vacuo to give a yellow oil. Crystallization from methylene chloride and tetrahydrofuran afforded **18c** as colorless crystals (100 mg, 53%): mp 250 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.05–2.16 (m, 2 H), 2.22 (d, J = 2 Hz, 1 H), 2.76 (dt, J = 2 Hz, 1 H), 3.02–3.60 (m, 14 H), 3.90–4.00 (dd, J = 2 and 10 Hz, 2 H), 4.32 (d, J = 10 Hz, 2 H), 4.71 (t, 2 H), 7.80 (t, 2 H), 7.20 (d, J = 8 Hz, 2 H), 7.33 (d, J = 8 Hz, 2 H), 7.40 (t, 2 H).

Anal. Calcd for $C_{24}H_{32}N_2O_4LiI$: C, 52.76; H, 5.90; N, 5.13; I, 23.22; Li, 1.27. Found: C, 52.70; H, 5.92; N, 5.19; I, 23.05; Li, 1.21.

2,3,5,6,8,9,11,12-Octahydro-3,19-dimethyl-14*H*-13,4-(ethanoxy[1,2]benzenomethano)-4*H*-1,7,10,4,13-benzotrioxadiazacyclohexadecine (18b) and the LiI Complex (18d). 18b and **18d** were prepared by the procedure described for **18a** and **18c**. Column chromatography (neutral alumina, 9:1 ethyl acetate/hexane) gave **18b** as a light brown oil (72 mg, 27%): ^{1}H NMR ($CDCl_3$) δ 1.07 (d, J = 8 Hz, 6 H), 2.30–2.59 (m, 4 H), 2.90 (dt, J = 2 and 8 Hz, 3 H), 3.20 (br m, 2 H), 2.25 (s, 4 H), 3.48–3.64 (m, 6 H), 4.61–4.22 (m, 3 H), 6.86 (t, 4 H), 7.14–7.32 (dt, 4 H). **18d** was isolated as colorless needles; mp 250 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.12 (dd, J = 2 and 8 Hz, 6 H), 2.00–2.20 (m, 2 H), 2.36–2.46 (dd, J = 2 and 12 Hz, 2 H), 2.52–2.61 (d, J = 12 Hz, 1 H), 2.97 (d, J = 8 Hz, 2 H), 3.16–3.32 (m, 4 H), 3.38 (d, J = 8 Hz, 2 H), 3.42–3.60 (m, 1 H), 3.64–3.94 (m, 6 H), 4.20 (d, 1 H),

4.48–4.60 (t, 1 H), 7.00–7.52 (m, 8 H); chemical ionization mass spectrum of LiI complex **18d**, m/z (relative intensity) 441 ($M^+ + 1 - 24$), 306 (42), 266 (80), 257 (85), 266 (100), 201 (63), 173 (47), 142 (92).

Anal. Calcd for $C_{26}H_{36}N_2O_4LiI$: C, 54.36; H, 6.31; N, 4.85; Li, 1.20; I, 22.19. Found: C, 53.96; H, 6.20; N, 4.85; Li, 1.16; I, 22.54. Crystals suitable for X-ray analysis were obtained from methylene chloride and THF by the isothermal distillation technique.

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Registry No. **1a**, 111904-31-5; **1b**, 111904-32-6; **1c**, 111904-33-7; **1d**, 111904-34-8; **1e**, 111904-35-9; **1f**, 111904-36-0; **2a**, 111904-37-1; **2b**, 111904-38-2; **2c**, 111904-39-3; **2d**, 111904-40-6; **2e**, 111904-41-7; **2f**, 111904-42-8; **3a**, 703-51-5; **3b**, 111904-43-9; **3c**, 111904-44-0; **3d**, 111904-45-1; **3e**, 111904-46-2; **3f**, 111904-47-3; **4a**, 111904-48-4; **4b**, 111904-49-5; **4c**, 111904-50-8; **5a**, 111904-51-9; **5b**, 111904-52-0; **6a**, 111904-53-1; **6b**, 111957-22-3; **7a**, 708-05-4; **7b**, 111904-54-2; **8a**, 111904-55-3; **8b**, 111904-56-4; **9**, 94225-47-5; **10**, 111904-57-5; **12**, 111904-58-6; **14**, 111957-23-4; **15**, 111904-59-7; **16**, 111904-60-0; **17a**, 96740-35-1; **17a**·2HCl, 111904-63-3; **17b**, 111904-64-4; **17c**, 111904-65-5; **17d**, 111904-66-6; **17e**, 111904-67-7; **18a**, 111904-68-8; **18b**, 111904-69-9; **18c**, 111904-70-2; **18d**, 111933-51-8; $H_2NCH(Me)CH_2OH$, 78-91-1; $H_2N(CH_2)_2OH$, 141-43-5; 2-FC_6H_4COCl, 393-52-2; (±)-$H_2NCH(CHMe_2)CH_2OH$, 16369-05-4; (±)-$H_2NCH(CH_2CHMe_2)CH_2OH$, 16369-17-8; (±)-$H_2NCH(CH_2SCH_2Ph)CH_2OH$, 65309-78-6; (±)-$MeS(CH_2)_2CH(NH_2)CH_2OH$, 16720-80-2; $MeNH(CH_2)_2OH$, 109-83-1; 2-BrC_6H_4COCl, 7154-66-7; (1*R*,2*R*)-$H_2NCH(Me)CH(Ph)OH$, 37577-07-4; $H_2N(CH_2)_3OH$, 156-87-6; $H_2N(CH_2)_4OH$, 13325-10-5; L-prolinol, 23356-96-9; D-ephedrine, 299-42-3; 1,2-bis(2-iodoethoxy)ethane, 36839-55-1.

Supplementary Material Available: Additional projections, tables of crystal structure data, atomic coordinates, bond lengths, bond angles, anisotropic parameters, and hydrogen atom coordinates for **2c**, **17a**, and **18d** (23 pages). Ordering information is given on any current masthead page.

Enantioselective Total Synthesis of (+)-Perhydro-219A from an Anthranilic Acid Derivative

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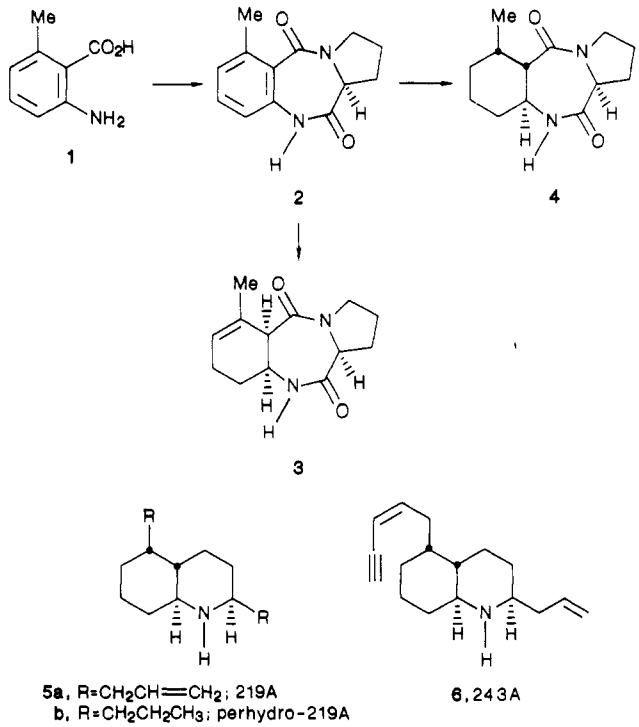
The first total synthesis of a *trans*-decahydroquinoline alkaloid derivative, (+)-perhydro-219A, is described. Key steps of the synthesis include the directed metalation–ethylation of 6-methylpyrrolobenzodiazepine-5,11-dione **2** to give the C(6)-*n*-propyl derivative **7**, the stereoselective Birch reduction of **7** to give the perhydrobenzodiazepinedione **8**, and the stereoselective hydrogenation of the $\Delta^{1,2}$ imine **15** to give (+)-perhydro-219A (**5b**). An enantioselective synthesis of *cis*-decahydroquinoline **18** also is described.

Pyrrolobenzodiazepine-5,11-dione **2**, readily available from 6-methylanthranilic acid (**1**) and the chiral auxiliary L-proline, undergoes Birch reduction with potassium (4.4 equiv) to give the cis-fused tetrahydrobenzene derivative **3**. Removal of the auxiliary from **3** and analogues provides chiral cyclohexanes for use in organic synthesis. A detailed study of the Birch reduction and reductive alkylation of several anthranilic derivatives, together with an enantioselective total synthesis of (+)-pumiliotoxin C from **3**, has been reported.[1] Also described are optimized conditions for the complimentary reduction of **2** to the trans-fused hexahydrobenzene derivative **4** (91% isolated yield).

We were particularly interested in the development of a reliable conversion of **2** into **4**, because of a recent report by Daly and co-workers[2] of a new class of *trans*-decahydroquinoline alkaloids obtained from skin extracts of poison frogs of Colombia. Two alkaloids, 219A (**5a**) and 243A (**6**), have been isolated as major constituents from one population of *Dendrobates histrionicus* and shown to be 2,5-disubstituted *trans*-decahydroquinolines by NMR spectral analysis and an X-ray diffraction study of the hydrochloride salt of 219A. Catalytic hydrogenation of the hydrobromide salt of 219A provided perhydro-219A (**5b**).



These and other *trans*-decahydroquinoline alkaloids may possess interesting pharmacological properties as has

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(2) Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986**, *42*, 3453.

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