Reductions of Activated Carbonyl Compounds with Chiral Bridged 1,4-Dihydropyridines. An Investigation of Scope and Structural Effects[1]

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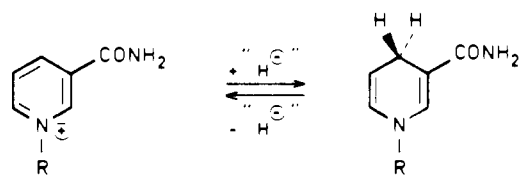
Abstract: A series of chiral bridged macrocyclic 1,4-dihydropyridines has been prepared, and the potential of these compounds for enantioselective reductions has been examined. A typical synthesis begins with pyridine-3-5-dicarboxylic acid (**9**, W = OH), which is coupled with (*S*)-valine to produce ultimately the bis-coupled product **10** (X = OH). This is converted to the bis(cesium carboxylate) and is allowed to react in dimethylformamide (DMF) solution at 10^{-2} to 5×10^{-3} M concentration with 1,5-dibromo-3-oxapentane. The macrocycle **11a** (R = $CH(CH_3)_2$) is obtained in 48% yield. Subsequent methylation with $CH_3I/Mg(ClO_4)_2 \cdot 1.5H_2O$ leads to the pyridinium perchlorate, which is reduced to 1,4-dihydropyridine with $Na_2S_2O_4$. In this manner, 28 different chiral bridged macrocyclic 1,4-dihydropyridines (**7**) have been synthesized by starting from valine, alanine, phenylglycine, phenylalanine, and proline. Various bridges of different compositions, lengths, and shapes have been incorporated. All these bridged compounds in a nonprotic solvent like CH_3CN in the presence of a stoichiometric amount of $Mg(ClO_4)_2 \cdot 1.5H_2O$ reduce activated carbonyl compounds to the corresponding alcohols; the corresponding pyridinium salt is formed. The most studied example is the reduction of ethyl phenylglyoxylate to ethyl mandelate. If the amino acids have the *S* configuration, the ethyl mandelate produced will have the *S* configuration. The enantiomeric excesses vary between 36% and 90% and decrease with increasing bridge length of the macrocycle from a maximum for a bridge with a length of five atoms (either pentamethylene or 3-oxapentyl). An explanation for these results is offered. It is assumed that the reactive species is a complex of bridged 1,4-dihydropyridine, Mg^{2+}, and carbonyl component. Although Mg^{2+} does not bind strongly to the macrocycles (log K_s 2–3 depending on the compound), this cation apparently has the ability to organize the macrocycles, even when they can assume several conformations of widely differing shape, into a common geometry which leads to reduction. The cation has the ability in fact to redistribute the conformational populations. These conclusions are supported by ^{13}C NMR studies of complexation as well as circular dichroism (CD) studies, which are reported separately.

Some of the organic cofactors involved in enzyme-catalyzed making and breaking of chemical bonds are primed with sufficient inherent chemical reactivity to carry out, independent of the accompanying protein, reactions related to or identical with those mediated by the cofactor–protein combination. Such examples of inherent reactivity are found in, for example, compounds structurally similar—or identical with—alkylcobalamines,[5] $NAD(P)^+/NAD(P)H$,[6] pyridoxal phosphate,[7] thiamine,[8] flavins,[9] and tetrahydrofolic acid.[10] True, the rates of such protein-free reactions are on the whole lower. This detracts not from the chemical interest, however. This inherent reactivity is, in fact, a source of no little evolutionary intrigue.[11] Inherent reactivity is not common to all cofactors, however. A case in point is biotin in its biologically important carboxylated form, which is readily shown to be in truth only a prosthetic substrate rather than any source of "active" CO_2.[12]

It is a logical step to attempt synthetic manipulation about an inherently reactive cofactor to produce molecules of modest molecular weight capable of performing enzymelike catalytic transformations under nonbiological conditions on a series of structurally related substrates. We, following a precedent already well set by others, have tried to realize this philosophy in a primitive fashion with pyridinium salt/1,4-dihydropyridine systems that can carry out the same type of redox chemistry embodied in the $NAD(P)^+/NAD(P)H$ shuttle illustrated with nicotinamide derivatives **1** and **2** in eq 1. In fact only the "hydride"[13] donation



(1)

1 **2**

(right to left in eq 1) has been examined, primarily because of the availability of abundant abiological precedent.[14] Reactions in the opposite direction, that is, oxidations of organic substrates by pyridinium salts, are, on the other hand, poorly characterized.[15]

Neither 1,4-dihydronicotinamide itself nor any other structurally related 1,4-dihydropyridine is kinetically an especially potent

(1) Two preliminary communications have appeared. (a) de Vries, J. G.; Kellogg, R. M. *J. Am. Chem. Soc.* **1979**, *101*, 2759. (b) Jouin, P.; Troostwijk, C. B.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 2091.

(2) CNRS/NATO Fellow 1980/1981.

(3) Taken in part from: De Vries, J. G., Ph.D. Thesis, University of Groningen, Sept 1979.

(4) Taken in part from: Troostwijk, C. B., Ph.D. Thesis, University of Groningen, Sept 1980.

(5) See, for example: Fischli, A.; Daly, J. J. *Helv. Chim. Acta* **1980**, *63*, 1628 and references cited therein.

(6) For a leading reference, see: (a) Kellogg, R. M. *Top. Curr. Chem.* **1982**, *101*, 111. (b) Kill, R. J.; Widdowson, D. A. *Bioorg. Chem.* **1978**, *4*, 239–275. (c) Kellogg, R. M. *Angew. Chem.* **1984**, *96*, 769.

(7) (a) Dugas, H.; Penney, C. "Bioorganic Chemistry. A Chemical Approach to Enzyme Action"; Springer-Verlag: New York, 1981; pp 419–447. (b) Walsh, C. "Enzymatic Reaction Mechanisms"; W. H. Freeman and Co.: San Francisco, 1979; pp 777–827.

(8) (a) Reference 7a, pp 447–458. (b) Reference 7b, pp 682–702.

(9) (a) See, for example: Bruice, T. C. *Prog. Bioorg. Chem.* **1976**, *4*, 1–87. (b) Reference 7b, pp 358–431.

(10) Hiemstra, H. C.; Bieräugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1982**, *23*, 3301 and references cited therein.

(11) (a) Visser, C. M. *Origins Life*, **1982**, *12*, 165. (b) Visser, C. M. *Naturwissenschaften* **1980**, *67*, 549.

(12) (a) Visser, C. M.; Kellogg, R. M. *J. Mol. Evol.* **1978**, *11*, 171. (b) Visser, C. M.; Kellogg, R. M. *Bioorg. Chem.* **1977**, *6*, 79.

(13) The word "hydride" as used here denotes only the entity ultimately transferred, not the mechanism.

(14) For an introductory review, see ref 7a, pp 388–400.

(15) For example: (a) Shirra, A.; Suckling, F. *Tetrahedron Lett.* **1975**, 332. (b) Ohnishi, Y.; Kitami, M. *Tetrahedron Lett.* **1978**, 4035. (c) Dittmer, D. C.; Blidner, B. B. *J. Org. Chem.* **1978**, *38*, 2873. (d) Overman, L. E. *J. Org. Chem.* **1972**, *37*, 4214. (e) Ohnishi, Y.; Tamiroso, S. *Tetrahedron Lett.* **1977**, 1909. (f) For realization of this reduction processes for pyridines in a photochemical reaction, see: Van Bergen, T. J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1972**, *84*, 845.

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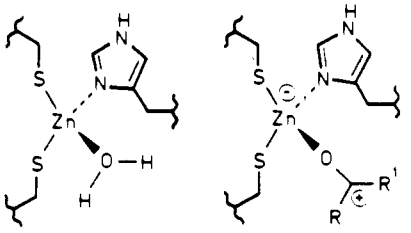
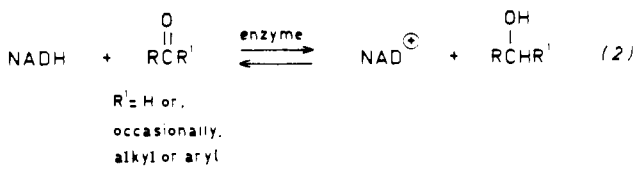
reducing agent. Certain quite electron-deficient compounds (for instance, some dyes or carbonyl compounds with very electron-withdrawing groups) will react spontaneously, but the examples are not numerous.[6b] Likewise, light-induced reductions are also known, examples being provided by certain sulfonium salts,[16,17] nitro compounds,[18] and alkyl halides.[19] These reactions have in general the characteristics of chain processes and are set off by electron transfer; large rate increases can be obtained in some cases by the use of dyes, especially $Ru^{II}(bipy)_3$, to harvest the light.[17,20] However, certainly in the realm of most carbonyl groups, such spontaneous reactions do not occur. There is a kinetic barrier to be overcome. Some type of activator is necessary to enhance the reactivity of the carbonyl group and/or the dihydropyridine. Certain metal ions can fill this role; if the metal ion is used repeatedly, i.e., with turnover, then it will fulfill a catalytic function.

The alcohol dehydrogenases provide the classical examples of metal ion activation (with catalysis) in the reduction of carbonyl groups (and the reverse reaction) by a 1,4-dihydropyridine. Horse liver, rat liver, human liver, and yeast and bacillar dehydrogenases all make use of a zinc ion, which seems in all cases to be held fast to the peptide chain by coordination to two cysteines and one histidine residue. The ligand shell of the tetracoordinate zinc ion is completed by a water molecule (see partial structure **3**).[21a-c]



3a **3b**

The exact role of amphoteric **3** is doubtlessly quite subtle. If, however, in the general reaction of eq 2 to the right the carbonyl



group displaces water in **3a**, then the zinc ion, although bonded to two negatively charged sulfide ligands, might act as an electrophile to polarize the carbonyl group as shown in extreme structure **3b**. This view is overly simplistic, but it has the virtue of a logical link with known in vitro chemistry of 1,4-dihydropyridines.

Table I. Synthesis of **11f** ($R = CH(CH_3)_2$) from **10** (X = OH) and 1,5-Dibromopentane in the Presence of M_2CO_3 in DMF[a]

m	yield (**11f**) %	m	yield (**11f**) %
Li	21[b,d]	Rb	70[c,d]
Na	41[c,d]	Cs	80[c,d]
K	64[c,d]		

[a] 6×10^{-3} M at 60 °C for 96 h in all cases. [b] Does not go into solution, remains gum. [c] Goes into solution during the course of reaction. [d] Isolated yield pure product after recrystallization from $CHCl_3$.

This link is illustrated with magnesium perchlorate, which is the most successful of the many metal ions tested for activation of carbonyl compounds toward reduction under abiological conditions by 1,4-dihydronicotinamide derivatives and similar 1,4-dihydropyridines.[22a-d] Although zinc ions are in some cases equally effective,[22d] a broader range of reactivity is found for magnesium. Opinions differ with regard to the specific role of these magnesium ions. There need not be, however, a mechanistic analogy with the enzymatic reactions, which occur in water, and these magnesium-promoted processes, which virtually unanimously take place in an aprotic solvent. For that matter, the mechanism by which 1,4-dihydronicotinamide and related compounds reduce a variety of "hydride" acceptors has received exhaustive (and exhausting) discussion. The main bone of contention is direct hydride transfer as opposed to a multistep process.[23] Another important, and complex, point is the orientation of 1,4-dihydropyridine and the carbonyl component relative to each other during the reduction process. Prelog,[24a] in pioneering investigations of the stereochemistry of ketone reductions using alcohol dehydrogenase, assumed in the "diamond lattice" model[25] that the carbonyl group, for reasons of diminishment of nonbonded interactions and maximum orbital overlap, lies over the dihydropyridine ring (**4**).

A very similar model has been suggested by Ohno et al.[26] to

(16) For some original observations of light-induced reductions of dihydropyridines, see: (a) Berson, J. A.; Brown, E. *J. Am. Chem. Soc.* **1955**, *77*, 450. (b) Kurz, J. L.; Hutton, R.; Westheimer, F. H. *J. Am. Chem. Soc.* **1961**, *83*, 584. (c) Frisnell, W. R.; Mackenzie, C. G. *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *45*, 1568. (d) Krasnovskii, A. A.; Brin, G. P; Drozdova, N. N., *Dokl. Akad. Nauk. SSSR* **1963**, *150*, 1157; *Chem. Abstr.* **1963**, *59*, 8994e. (e) Kill, R. J.; Widdowson, D. A. *J. Chem. Soc., Chem. Commun.* **1976**, 755.

(17) (a) Van Bergen, T. J.; Hedstrand, D.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1979**, *44*, 4953. (b) Hedstrand, D. M.; Kruizinga, W. H.; Kellogg, R. M. *Tetrahedron Lett.* **1978**, 1255.

(18) Ono, N.; Tamura, R.; Kaji, A. *J. Am. Chem. Soc.* **1980**, *102*, 2851.

(19) (a) Fukuzumi, S.; Hironaka, K.; Tanaka, T. *J. Am. Chem. Soc.* **1983**, *105*, 4722. (b) Benzylic sulfonates can also be reduced: Nakumura, K.; Yasui, S.; Ohno, A.; Oka, S. *Tetrahedron Lett.* **1983**, 2001.

(20) Originally observed by us[17] and later described independently for other systems by: (a) Pac, C.; Ihama, M.; Miyauchi, Y.; Sakurai, H. *J. Am. Chem. Soc.* **1981**, *103*, 6495. (b) Pac, C.; Miyauchi, Y.; Ishitani, O.; Ihama, M.; Yasuda, M.; Sakurai, H. *J. Org. Chem.* **1984**, *49*, 26.

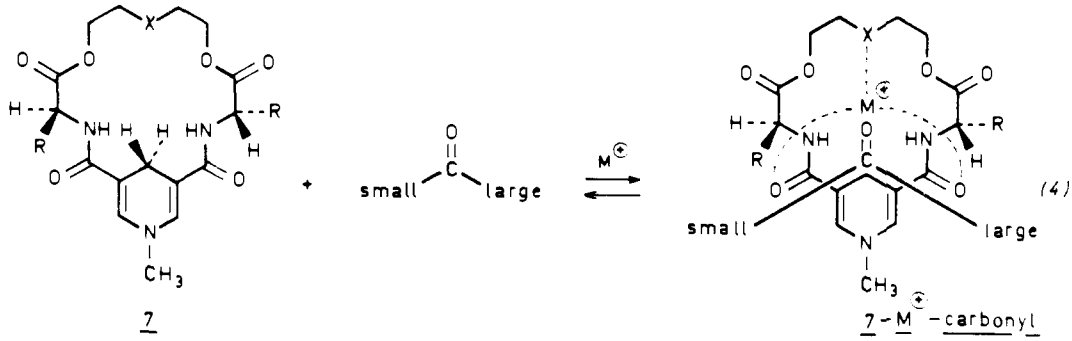
(21) Some pertinent references on the mechanism of enzyme action are: (a) Eklund, H.; Nordström, B.; Zeppezauer, F.; Söderland, G.; Ohlsson, J.; Boine, T.; Brändén, C. J. *FEBS Lett.* **1974**, *44*, 200. (b) Eklund, H.; Nordström, B.; Zeppezauer, E.; Söderland, G.; Ohlsson, J.; Boiwe, T.; Söderberg, B. O.; Tapia, O.; Brändén, C. I.; Akeson, A. *J. Mol. Biol.* **1976**, *102*, 27. (c) Eklund, H.; Brändén, C. I.; Jörnvall, H. *J. Mol. Biol.* **1976**, *102*, 61. (d) Adams, M. J.; Buchner, M.; Chandrasekhar, K.; Ford, G. C.; Hackett, M. L.; Liljas, A.; Rossmann, M. G.; El Smiley, J.; Allison, W. S.; Everse, J.; Kaplan, N. O.; Taylor, S. S. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, 1968. (e) Hill, E.; Tsemoglon, D.; Webb, L.; Banaszak, L. J. *J. Mol. Biol.* **1972**, *72*, 577. (f) Lazdunskij, M. *Prog. Bioorg. Chem.* **1974**, *3*, 112.

(22) See, for example: (a) Ohnishi, Y.; Numakunai, M.; Ohno, A. *Tetrahedron Lett.* **1975**, 3813. (b) Ohno, A.; Ikeguchi, M.; Kimura, T.; Oka, S. *J. Chem. Soc., Chem. Commun.* **1978**, 328. (c) Ohnishi, Y.; Kagami, M.; Ohno, A. *J. Am. Chem. Soc.* **1975**, *97*, 4766. (d) Gase, R. A.; Pandit, U. K. *J. Am. Chem. Soc.* **1979**, *101*, 7059.

(23) There has been mechanistic controversy between the groups of Ohno[23d] and Bruice,[23c] both of whom have examined the reduction of trifluoroacetophenone derivatives, which are sufficiently reactive to react spontaneously with 1,4-dihydronicotinamide derivatives. See, for pertinent discussions of mechanism: (a) Ohno, A.; Shio, T.; Yamamoto, H.; Oka, S. *J. Am. Chem. Soc.* **1981**, *103*, 2045. (b) Shinkai, S.; Ide, T.; Hamada, H.; Manabe, O.; Kunitake, T. *J. Chem. Soc., Chem. Commun.* **1977**, 848. (c) Powell, M. M.; Bruice, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 5834. (d) Ohno, A.; Kobayashi, H.; Nakamura, K.; Oka, S. *Tetrahedron Lett.* **1983**, *24*, 1263. A sampling of the types of mechanistic discussions is to be found in: (e) Chipman, D. M.; Yaniv, R.; Van Eikeren, P. *J. Am. Chem. Soc.* **1980**, *102*, 3244. (f) Van Eikeren, P.; Kenney, P.; Tokmakian, R. *J. Am. Chem. Soc.* **1979**, *101*, 7402. (g) Shinkai, S.; Tsuno, T.; Manabe, O. *Chem. Lett.* **1981**, 1203. (h) Ohno, A.; Yasui, S.; Nakamura, K.; Oka, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 290. (i) Ohno, A.; Yasui, S.; Yamamoto, H.; Oka, S., Ohnishi, Y. *Bull Chem. Soc. Jpn.* **1978**, *51*, 294. (j) Martens, F. M.; Verhoeven, J. W.; Gase, R. A.; Pandit, U. K.; De Boer, T. J. *Tetrahedron* **1978**, *34*, 443. (k) Blankenhorn, G. In "Pyridine–Nucleotide-Dependent Dehydrogenases"; Sund, H., Ed.; Walter de Gruyter: West Berlin, 1977; pp 185–205. (l) Van Laar, A.; Van Ramesdonk, H. J.; Verhoeven, J. W. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 157. (m) Van Lier, P. M.; Donkersloot, M. C. A.; Koster, A. S.; Van Hooff, H. J. G.; Buck, H. M., *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 119. (n) Donkersloot, M. C. A.; Buck, H. M. *J. Am. Chem. Soc.* **1981**, *103*, 6554. (o) For an extensive discussion of arguments for a single step reduction of acridinium ions, see: Powell, M. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 7139. (p) Also: Ohno, A.; Yamamoto, H.; Oka, S. *J. Am. Chem. Soc.* **1981**, *103*, 2041. (q) Also: Ohno. A.; Kobayashi, H.; Oka, S.; Goto, T. *Tetrahedron Lett.* **1983**, 5123.

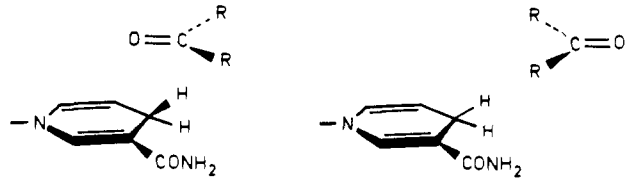
(24) (a) Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119. (b) Also: Bentley, R. "Molecular Asymmetry in Biology"; Academic Press: New York, 1970; Vol. III, p 36.

(25) For a discussion with examples of this analysis developed by Prelog,[24a] see: Jones, J. B.; Beck, J. F. In *Tech. Chem.* (N. Y. **1976**, *10*, 107–401.



7 7-M⊕-carbonyl

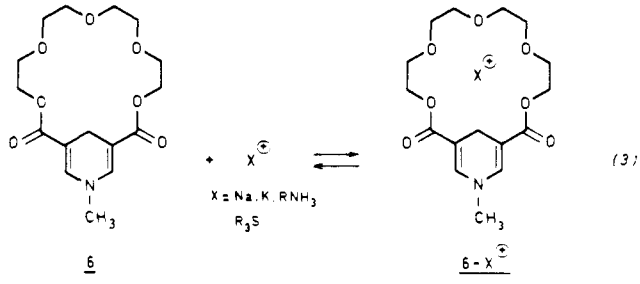
explain the sense of chiral induction in the nonenzymatic reduction of ethyl phenylglyoxylate to ethyl mandelate by a chiral 1,4-dihydronicotinamide. On the other hand, in pig lactate de-



4 5

hydrogenase and lobster 3-phosphoglyceraldehyde dehydrogenase (imidazole rather than zinc activates the hydroxyl/carbonyl group) as well as horse alcohol dehydrogenase, the geometrical arrangement of carbonyl (or alcohol if one considers the other side of the equilibrium) appears to be closer to the antiparallel arrangement of **5**.[27] (The interested reader should, however, consult ref 27 for a fuller discussion of possible catalytic mechanisms consistent with known active-site structures of dehydrogenases.)

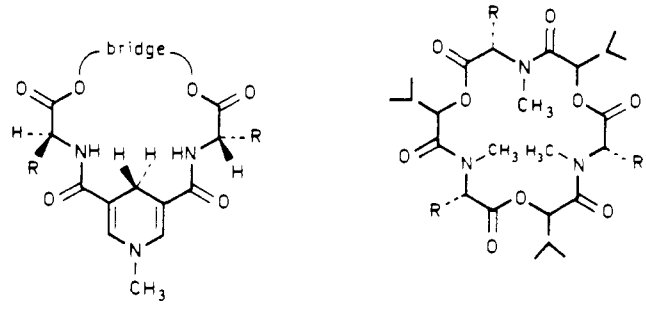
We have attempted to blend some of the foregoing considerations with our own experience and synthetic techniques. We have designed compounds wherein a suitable 1,4-dihydropyridine is incorporated in a macrocyclic ring. Our hope was to use the macrocyclic ring as a "crown ether" segment, which would hold a metal ion in a fixed and predictable position relative to the 1,4-dihydropyridine. The observation summarized in eq 3 lies behind this hope.[28] Compound **6**, for example, has a reasonable



6 6-X⊕

affinity for cations like Na^+, K^+, and RNH_3^+[29] as well as an unanticipated capacity for the reduction of some sulfonium salts.[17] A crystal structure determination on a Na^+ derivative of **6** with a molecule of acetone incorporated revealed—in the crystal structure—an unfavorable geometry for reduction.[29]

Further efforts at model building with an eye also toward the design of a chiral system led us to the general concept enbodied in structure **7**. With a properly chosen bridge, there is an ar-



7 8

chitectural resemblance to the peptide antibiotic enniatin (**8**). This material, in contrast to a crown ether, coordinates metal ions through its three amide oxygens, which move out-of-plane to form three points of a tetrahedron, on which the metal ion can rest. In a number of cases, two ligands surround the cation.[30] In **7** as illustrated, only two amino acids are incorporated (*S* enantiomers illustrated); if the bridge is symmetrical, the molecule has C_2 symmetry and the hydrogens at the 4-position of the 1,4-dihydropyridine are chemically equivalent. If the two amides of **7** rotate partially out-of-plane (at the price of some loss of conjugation), then when a third binding site is provided in the bridge, the possibility for complexation (and subsequent enantioselective reaction) shown in eq 4 is opened. The geometry leading to the transition state for reduction is essentially that of **5**. The chiral barriers formed by the amino acids provide the basis for enantiodifferentiation.

We have had to modify somewhat this primitive idea although we find it a surprisingly good approximation as well as justification of the foregoing eclectic considerations.

Results

A. Synthesis. The desired chiral bridged 1,4-dihydropyridines **7** were obtained by the general route shown in Scheme I. Each step illustrated involved special features, which are discussed in sequence.

The preparation of **10** from **9** and the respective amino acids had to be carried out on a multigram scale with different amino acids and, of course, without racemization. Several different approaches were developed, starting from pyridine-3,5-dicarboxylic acid (**9**, W = OH). To obtain 1,4-dihydropyridines with reactivity characteristics close to that of nicotinamide, it is a virtual necessity that at least one electron-withdrawing group be located vinylo-

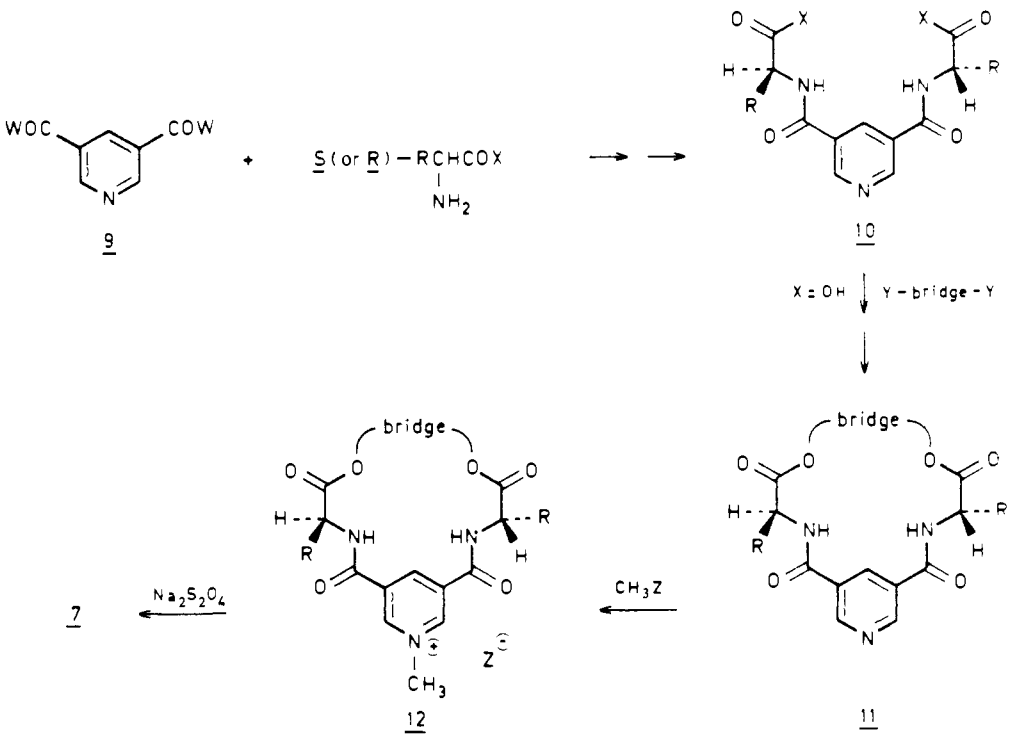
(26) (a) Ohno, A.; Kimura, T.; Yamamoto, H.; Kim, S. G.; Oka, S.; Ohnishi, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1535. (b) Ohno, A.; Ikeguchi, M.; Kimura, T.; Oka, S. *J. Am. Chem. Soc.* **1979**, *101*, 7036. (c) Van der Kerk, S. H.; Van Gerresheim, W.; Verhoeven, J. W. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 143. On the basis of kinetic isotope effects and ab initio calculations a linear transition state has been proposed with *no* rotational barrier for rotation of the carbon relative to the 1,4-dihydropyridine. (d) See also: Ohno, A.; Lee, J. H.; Yasuma, T.; Oka, S. *Tetrahedron Lett.* **1984**, 1995. (e) Awano, H.; Hirabasyashi, T.; Tagaki, W., *Tetrahedron Lett.* **1984**, 2005. (f) Van Ramesdonk, H. J.; Verhoeven, J. W.; Pandit, U. K.; De Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1978**, 97, 195. (g) Van Ramesdonk, H. J.; Verhoeven, J. W.; De Boer, T. J. *Bioorg. Chem.* **1977**, *6*, 403.

(27) Grau, U. M. In "The Pyridine Nucleotide Coenzymes"; Everse, J., Anderson, B., You, K.-S., Eds.: Academic Press: New York, 1982; pp 135–187.

(28) Van Bergen, T. J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1977**, *99*, 3882.

(29) Van der Veen, R. H.; Kellogg, R. M.; Vos, A.; Van Bergen, T. J. *J. Chem. Soc., Chem. Commun.* **1978**, 923.

(30) For a review, see: Hilgenfeld, R.; Saenger, W. *Top. Curr. Chem.* **1982**, *101*, 3. The enniatins and related compounds will also form 2:1 complexes or complexes of even more complex stoichiometry.



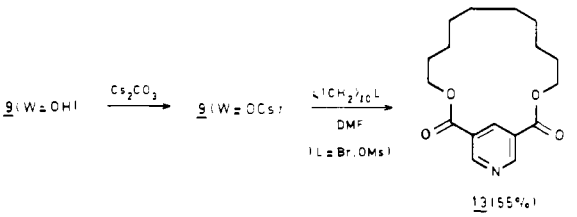
gously to the pyridine nitrogen; 3,5-dicarboxylic acid derivatives, in addition to meeting the architectural aspects of our intentions, have the added virtue of the absence of the rather nucleophilic enaminic C-5 of nicotinamide.[31] The 2,6-dimethylated derivative obtained from Hantzsch condensation of acetoacetate ester, ammonia, and formaldehyde was a particularly attractive alternative to **9** for we had already developed methods of incorporating this ring system into crown ethers. However, difficulties experienced in alkylating the pyridine nitrogen of these rather hindered systems as well as other problems[32] discouraged us from continuing with these pyridine derivatives. For these reasons, the choice fell on much less sterically hindered **9** (W = OH) despite the knowledge that methyl groups at the 2,6-position would have given about an additional 100-mV reduction potential relative to the unsubstituted system.[33] The redox potential available from **7**, ultimately to be derived from **9**, was expected, however, to be very close to, or greater than, that of 1,4-dihydronicotinamide itself.[33]

After some exploratory, and unsatisfactory, work with azide and mixed anhydride (X = N_3 and $O_2COC_2H_5$, respectively) derivatives of **9**, the choice fell on **9**, W = Cl. This acid chloride is obtained by reaction of **9**, W = OH, in $SOCl_2$ as solvent with a small amount of added dimethylformamide (DMF). The material is quite sensitive both to hydrolysis and polymerization.

In the first approach examined to reach **10**, **9** (W = Cl) was coupled with the amino acid (X = $OCH_2COC_6H_5$). Either Z ($C_6H_5CH_2OCO$–) or Boc ($(CH_3)_3COCO$–) is suitable for protection of the amino group prior to esterification. The protecting group was removed thereafter with HBr/CH_3CO_2H. R from the amino acid was isopropyl, benzyl, or methyl (valine, phenylalanine, and alanine, respectively). Proline and phenylglycine are discussed separately. Coupling with **9** (W = Cl) occurred smoothly in benzene in the presence of a slight excess of triethylamine to give **10** (X = $OCH_2COC_6H_5$). The choice of the phenacyl ester was made on the consideration that deblocking normally is carried out with KSC_6H_5; phenacyl phenyl sulfide and the insoluble potassium carboxylate of the amino acid are the products.[34] In the present application, deblocking was carried out with $CsSC_6H_5$, and the *cesium* salts **10** (X = OCs) were obtained. The reasoning behind the use of cesium will be presented in the paragraphs on ring closure.

In initial attempts, the obvious method of direct Schotten–Baumann coupling of **9** (W = Cl) and the amino acids was stymied by the sensitivity of the acid chloride. We found subsequently that this direct coupling could be carried out on a large scale and in good yield when a two-phase system consisting of 50% aqueous NaOH with dissolved amino acid and CH_2Cl_2 with dissolved **9** (X = Cl) was allowed to react with vigorous stirring at 5–10 °C (the temperature should go no higher). Coupling product **10** (X = OH) precipitates on careful acidification with formic acid. Details of all procedures and yields are given in the Experimental Section.

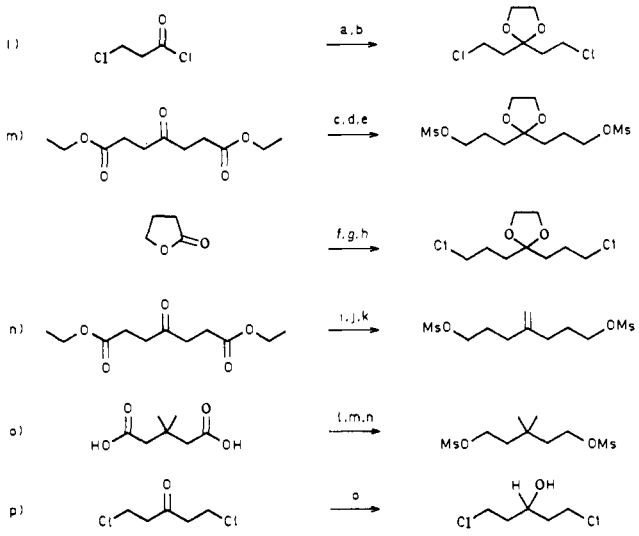
We developed separately a method for carrying out the critical ring closure step wherein **10** is bridged to produce **11**. A pertinent example is shown in eq 5. In this case the diacid is neutralized



with an equivalent amount of Cs_2CO_3, and the dicesium salt in a concentration of 6×10^{-3} M in dimethylformamide (DMF) was allowed to react at 40–50 °C with 1,10-decamethylene dibromide or dimesylate. This general method, derived from an extrapolation of observations of Wang et al.,[35] has been successfully applied by us to the synthesis of macrolides,[36] macrocyclic sulfides,[37] and other macrocycles.[38] A hypothesis for the effect of cesium ions has

(31) Van Bergen, T. J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1976**, *98*, 1962.
(32) Kellogg, R. M.; Van Bergen, T. J.; Van Doren, H.; Hedstrand, D.; Kooi, J.; Kruizinga, W. H.; Troostwijk, C. B. *J. Org. Chem.* **1980**, *45*, 2854.
(33) Piepers, O.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1982**, 403.
(34) (a) Sheehan, J. C.; Daves, G. D., Jr. *J. Org. Chem.* **1964**, *29*, 2006. (b) Stelakatos, G. C.; Paganou, A.; Zervas, L. *J. Chem. Soc. C* **1966**, 1191.
(35) Wang, S.-S.; Gisin, B. F.; Winter, D. P.; Makofske, R.; Kulesha, J. D.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 1286.
(36) Kruizinga, W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 5183.
(37) Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4481.

Scheme II

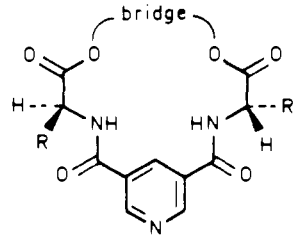


[a] $H_2C{=}CH_2/AlCl_3$. [b] $HO(CH_2)_2OH$/*p*-TsOH. [c] $HO(CH_2)_2OH$/PPTS.[74] [d] $LiAlH_4/(C_2H_5)_2O$. [e] $CH_3SO_2Cl/(C_2H_5)_3N$. [f] $NaOCH_3$. [g] HCl/H_2O. [h] $HO(CH_2)_2OH$/PPTS.[74] [i] $(C_6H_5)_3PCH_2/(C_2H_5)_2O$. [j] $LiAlH_4/(C_2H_5)_2O$. [k] $CH_3SO_2Cl/(C_2H_5)_3N$. [l] C_2H_5OH/HCl. [m] $LiAlH_4/(C_2H_5)_2O$. [n] $CH_3SO_2Cl/(C_2H_5)_3N$. [o] $NaBH_4/CH_3OH$.

been advanced.[36,39] The subject has been reviewed recently.[40]

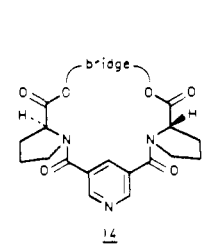
Cyclization with the products **10** (X = OH) was carried out by using this general approach. Concentrations of the dicesium salts in dry, distilled DMF were in the 5–10 mM range. The desired bridge component was used as dibromide, dimesylate, or dichloride. The latter compounds reacted somewhat more sluggishly (reaction temperature of about 90 °C instead of the usual 40–55 °C) although no pronounced differences in yields were obtained.

By this approach, the compounds **11** shown, derived from (*S*)-valine, (*S*)-alanine, (*S*)-phenylalanine, and (*R*)-phenylglycine (see, however, following paragraphs), were synthesized. Yields are those of pure product obtained in the cyclization step. (*R*)-Valine (D series) was used to prepare some enantiomers of **11** as illustrated. Those examples derived from unnatural enantiomers of the amino acids will be referred to by specific inclusion of the configurational prefix before the compound number. The (*S*)-proline series **14a–d** was prepared by first protecting the proline nitrogen, followed by conversion to the phenacyl ester, followed by deblocking and coupling with **9** (W = Cl). The cesium carboxylate was prepared by deblocking with $CsSC_6H_5$, and this



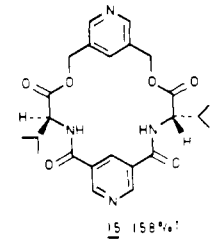
11a–p (yield %)

bridge	R: $(CH_3)_2$-CH	CH_3	C_6H_5-CH_2	C_6H_5
(a) $-(CH_2)_2O(CH_2)_2-$	48	22	42	60
(b) $-CH_2(CH_2OCH)_2CH_2$	52		52	
(c) $-CH_2(CH_2OCH_2)_3CH_2-$	65			
(d) $-(CH_2)_3-$	53			
(e) $-(CH_2)_4-$	70			
(f) $-(CH_2)_5$	80		33	44
(g) $-(CH_2)_6$	65			
(h) $-(CH_2)_8-$	60			
(i) $-(CH_2)_{10}-$	60			
(j) $-(CH_2)_{12}-$	60			
(k) $-m\text{-}CH_2C_6H_4CH_2$	50			
(l) $-(CH_2)_2C[O(CH_2)_2O](CH_2)_2-$	50			
(m) $-(CH_2)_3C[O(CH_2)_2O](CH_2)_3-$	35			
(n) $-(CH_2)_2CH_2C(CH_2)CH_2(CH_2)_2$	40			
(o) $-(CH_2)_2C(CH_3)_2(CH_2)_2-$	65		44	
(p) $-(CH_2)_2CHOH(CH_2)_2-$	57			

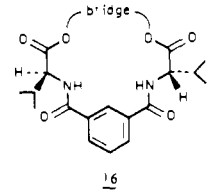


14

bridge	yield (%)
a) $-(CH_2)_2O(CH_2)_2-$	42
b) $-CH_2(CH_2OCH_2)_2CH_2-$	45
c) $-(CH_2)_5-$	52
d) $-(CH_2)_{12}$	35

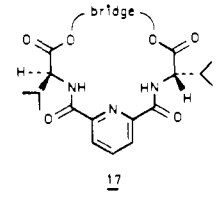


15 158%



16

bridge	yield (%)
a) $-(CH_2)_2O(CH_2)_2-$	33
b) $-CH_2(CH_2OCH_2)_2CH_2-$	42
c) $-(CH_2)_5-$	36
d) $-(CH_2)_6-$	35
e) $-(CH_2)_{12}-$	47



17

bridge	yield (%)
a) $-(CH_2)_2O(CH_2)_2-$	49
b) $-CH_2(CH_2OCH_2)_2CH_2-$	53
c) $-(CH_2)_5-$	65
d) $-(CH_2)_6-$	10 (oil)
e) $-(CH_2)_{12}-$	45

(38) For example: Van Keulen, B. J.; Kellogg, R. M.; Piepers, O. *J. Chem. Soc., Chem. Commun.* **1979**, 285. (b) Vriesema, B. K.; Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 110.

(39) This cesium salt approach to macrocycles has also been used recently with success by others. See, for instance: (a) Barbier, M. *J. Chem. Soc., Chem. Commun.* **1982**, 668. (b) Potts, K. T.; Cipullo, M. J. *J. Org. Chem.* **1982**, *47*, 3038. (c) Hosseini, M. W.; Lehn, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 3524. (d) Vögtle, F.; Klieser, B. *Synthesis* **1982**, 294. (e) Dietrich-Buchecker, C. O.; Sauvage, J. P.; Kintzinger, J. P. *Tetrahedron Lett.* **1983**, 5095. (f) Diderich, F., private communication. Recently (Galli, C.; Mandolini, L. *J. Chem. Soc., Chem. Commun.* **1982**, 251) commented, however, that "...the behavior of this system appears to display no special features". The crux of their criticism lies in a comparison with the effective molarity values ($k_{intra}k_{inter}^{-1}$) for the ring closures of ω-halocarboxylates (Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591). For the formation of 15-membered lactones and larger, these values hold fairly constant at about 5×10^{-2} M. This means that for such lactones if the reaction is carried out in a batch process at a concentration equal to the effective molarity concentration, the yield of lactone should be in theory at least 50%. Since the procedures described here are also batch processes, the concentrations used are usually in the range of 10^{-2} M, and the macrocycles range in general from 16-membered (**11d**, R = $CH(CH_3)_2$) to 25-membered (**11j**, R = $(CH_3)_2CH$) the above criticism should apply to the present work also (Mandolini and Galli commented only on ref 36). Two carboxylate–carbon bonds form during the generation of **11**. This likely occurs sequentially although this has not been proved formally. In a sequential scheme, the effective molarity for the (second) ring-closure step should be no higher than 10^{-2} M. From the Mandolini/Galli analysis, a reasonably constant yield of 50% or higher independent of cation is expected. This is, as shown in Table I as well as ref 36 and 37, clearly not the case. The yields of the ring closures are very cation dependent. We believe, as described elsewhere,[36] that ion-pairing effects are responsible for these observations. The synthetic utility of the cesium salts is obvious. The criticisms of Mandolini and Galli are based on misleading extrapolations of kinetic data and should, in our opinion, be treated with circumspection. Set for further discussion: Stellou, K.; Poupart, M. A. *J. Am. Chem. Soc.* **1983**, *105*, 7130.

(40) Klieser, B.; Rossa, L.; Vögtle, F. *Kontakte (Darmstadt)* **1984**, *1*, 3.

Table II. Reduction of Activated Ketones **22** by 1,4-Dihydropyridines **7**

entry	compd	amino acid	bridge	chem yield,[a] %	ee,[b] %	major enantiomer	substrate R^1	substrate R_2
1	**7a**	L-valine	$-(CH_2)_2O(CH_2)_2-$	80	86	*S*	C_6H_5	$CO_2C_2H_5$
2	**7b**	L-valine	$-(CH_2)_2O(CH_2)_2O(CH_2)_2-$	c	43	*S*	C_6H_5	$CO_2C_2H_5$
3	**7c**	L-valine	$-(CH_2)(CH_2OCH_2)_3(CH_2)-$	60	54	*S*	C_6H_5	$CO_2C_2H_5$
4	**7e**	L-valine	$-(CH_2)_4-$	75	55–70[d]	*S*	C_6H_5	$CO_2C_2H_5$
5	**7f**	L-valine	$-(CH_2)_5-$	70	90	*S*	C_6H_5	$CO_2C_2H_5$
6	**7g**	L-valine	$-(CH_2)_6-$	75	88	*S*	C_6H_5	$CO_2C_2H_5$
7	**7h**	L-valine	$-(CH_2)_8-$	80	83	*S*	C_6H_5	$CO_2C_2H_5$
8	**7i**	L-valine	$-(CH_2)_{10}-$	75	53	*S*	C_6H_5	$CO_2C_2H_5$
9	**7j**	L-valine	$-(CH_2)_{12}-$	60	42	*S*	C_6H_5	$CO_2C_2H_5$
10	**7k**	L-valine	m-$CH_2C_6H_4CH_2-$	75	86	*S*	C_6H_5	$CO_2C_2H_5$
11	**7l**	L-valine	$-(CH_2)_2C(OCH_2)_2(CH_2)_2-$	50	65	*S*	C_6H_5	$CO_2C_2H_5$
12	**7m**	L-valine	$-(CH_2)_3CO(CH_2)_3-$	64	38	*S*	C_6H_5	$CO_2C_2H_5$
13	**7n**	L-valine	$-(CH_2)_3CCH_2(CH_2)_3-$	60	45	*S*	C_6H_5	$CO_2C_2H_5$
14	**7o**	L-valine	$-(CH_2)_2C(CH_3)_2(CH_2)_2-$	80	25	*S*	C_6H_5	$CO_2C_2H_5$
15	**7p**	L-valine	$-(CH_2)_2CHOH(CH_2)_2-$	50	64	*S*	C_6H_5	$CO_2C_2H_5$
16	**7a**	L-phenylalanine	$-(CH_2)_2O(CH_2)_2-$	60	87	*S*	C_6H_5	$CO_2C_2H_5$
17	**7a**	L-phenylalanine	$-(CH_2)_2O(CH_2)_2-$	30	84	*S*	C_6H_5	$CONHC_2H_5$
18	**7a**	L-phenylalanine	$-(CH_2)_2O(CH_2)_2-$	55	60	*S*	m-$C_6H_4OC_6H_5$	CO_2CH_3
19	**7a**	L-phenylalanine	$-(CH_2)_2O(CH_2)_2-$	58	20	*S*	m-$C_6H_4OC_6H_5$	$CONH_2$
20	**7f**	L-phenylalanine	$-(CH_2)_5-$	70	80	S	C_6H_5	$CO_2C_2H_5$
21	**7o**	L-phenylalanine	$-(CH_2)_2C(CH_3)_2(CH_2)_2-$	60	55	S	C_6H_5	$CO_2C_2H_5$
22	**7a**	L-alanine	$-(CH_2)_2O(CH_2)_2-$	62	65	S	C_6H_5	$CO_2C_2H_5$
23	**19a**	L-proline	$-(CH_2)_2O(CH_2)_2-$	50	none		C_6H_5	$CO_2C_2H_5$
24	**7g**	D-valine	$-(CH_2)_6-$	70	85	R	C_6H_5	$CO_2C_2H_5$
25	**20a**	L-valine	$-OCH_3$	60	10	R	C_6H_5	$CO_2C_2H_5$
26	**20b**	L-valine	$-(CH_2)_2OCH_3$	70	18	R	C_6H_5	$CO_2C_2H_5$

[a] The degree of conversion of the substrate was measured by following the appearance of the phenyl protons (sharp singlet) of ethyl mandelate by ^1H NMR spectroscopy; experiments were performed at least in duplicate. [b] Calculated on the basis of $[\alpha]^{24}_D$ −104° (EtOH)[89] for the pure enantiomer (*R*), and cross-checked by ^{19}F NMR evaluation of the (3*R*,3*R*,3*R*)-3,3,3-(trifluoromethyl)-2-methoxy-2-phenylpropionate ester (Mosher's reagent: ref 42). [c] The chemical yield was not calculated owing to decomposition of the 1,4-dihydropyridine. [d] The 1,4-dihydropyridine **7e** is in this case very unstable probably owing to ring strain and is contaminated by 1,2-dihydro isomer; this leads to inconsistent results.

Table III. Reduction of **22** ($R^1 = C_6H_5$, $R^2 = CO_2C_2H_5$) with Nonbridged Chiral Dihydropyridines[a]

dihydropyridines	yield % **23** ($R^1 = C_6H_5$, $R^2 = CO_2C_2H_5$)	ee	major enantiomer
20a	60	10	*R*
20b	70	18	*R*
21	58	5	*R*

[a] Conditions analogous to those described in Table II.

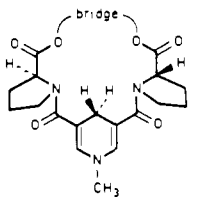
was allowed to react in DMF solution with the desired bridge component as dimesylate.

For purposes of comparison, macrocycles **15–17** were also prepared. The synthesis of **15**, **16** and **17** followed the general route described above. The syntheses of the bridge components (Scheme II) are described in the Experimental Section. (*S*)-Valine is the easiest amino acid to handle, and for this reason, most of the work on structural variation in the bridge was carried out in this series. The other amino acids led to in general products with less amenable polarities and solubility properties.

The cesium salt approach to these macrocycles has stood us in good stead. For the case of **11f** (R = $CH(CH_3)_2$), the effect of change of cation in DMF as the solvent on the yield of the ring closure was examined. A clear trend (Table I) of increasing yield of the macrocycle with increasing size of the cation is found and is entirely in accord with observations previously made.[36,39]

Alkylation (mostly methylation) of the bridged compounds **11** and **14** was examined under a variety of conditions. The most effective method developed was methylation with methyl iodide in CH_3CN in the presence of (or sometimes added subsequently) $Mg(ClO_4)_2 \cdot 1.5H_2O$.[41] The precipitation of MgI_2 helps drive the reaction to completion. Yields of **12** and the salts **18** from proline derivatives **14** were essentially quantitative as judged by the ^1H NMR spectra taken of the salts after purification (usually) by flash chromatography. No attempts were made to obtain analytical samples at this stage.

Reductions to the desired 1,4-dihydropyridines **7a–c**, **7f–p** (R = $CH(CH_3)_2$), and **19a–d** occurred virtually quantitatively with $Na_2S_2O_4$ in pH 7 buffered solution. The light-yellow products



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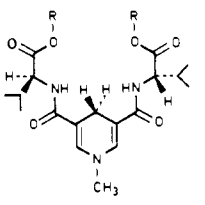

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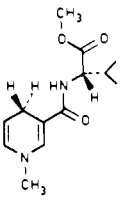


21

bridge

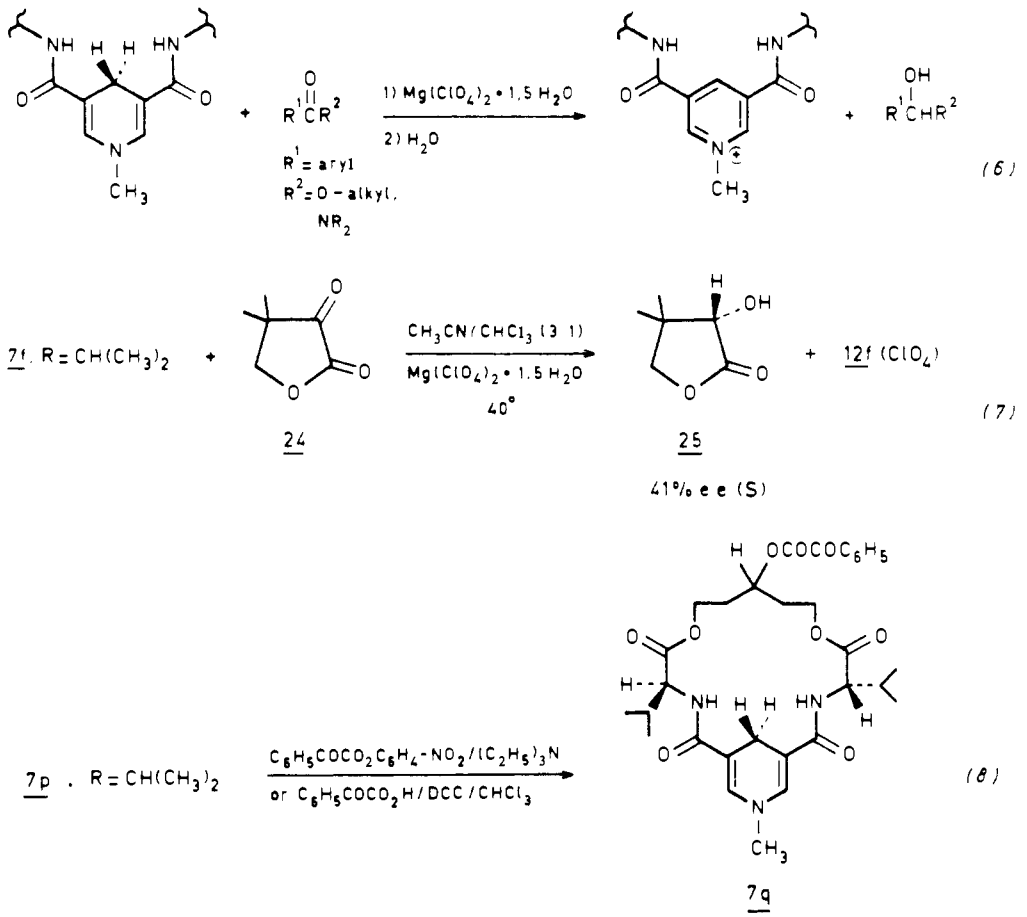
a) $-(CH_2)_2O(CH_2)_2-$
b) $-CH_2(CH_2OCH_2)_2CH_2-$
c) $-(CH_2)_5-$
d) $-(CH_2)_{12}-$

a) R = CH_3
b) R = $(CH_2)_2OCH_3$

were usually purified by flash chromatography. Exclusively, 1,4-reduction took place within the detection limits of the NMR apparatus. Owing to air sensitivity of many of these compounds, they were used directly without further characterization. This alkylation–reduction sequence failed for **11d** and **e** (R = $CH(CH_3)_2$), which were apparently too strained. The structure of **7m** (R = $CH(CH_3)_2$) is a derivative of the bridge component used (ketone instead of acetal). The acetal persistently hydrolyzed during workup in this case. Compound **15** was not alkylated. By straightforward routes, the nonbridged compounds **20a** and **21** were also prepared for comparison purposes.

All products from natural amino acids are believed to be optically pure. There is good precedent for lack of racemization in the various amino acid manipulations. In principle, although it seems unlikely in view of the low basicity of the reaction medium, epimerization might conceivably occur during, for example, ring

(41) In practice $Mg(ClO_4)$ cannot be dried beyond this point. See, for example: Gase, R. A.; Pandit, U. K. *J. Am. Chem. Soc.* **1979**, *101*, 7059 and references contained therein. The material we used contained usually 1.5–2.0 equiv of H_2O.



closure of **10** to **11**. Such epimerization at one center would create a meso diastereomer. For **7a** ($R = CH_2C_6H_5$), chosen as a representative example of an end product of the general synthetic route, the compound was digested totally in HCl, and the freed amino acid was assayed with L-amino acid oxidase; 99.8% of the theoretical amount of L-(*S*)-phenylalanine was accounted for by the enzyme assay.

B. Reductions. The various 1,4-dihydropyridines prepared were allowed to react with activated carbonyl compounds **22**. The general reaction scheme is shown in eq 6. The results of the various reductions are collected in Table II. A standard procedure was to allow a solution of the 1,4-dihydropyridine (0.2 M) and α-ketocarboxylic acid derivative (slight excess) to react at ambient temperature with a stoichiometric amount of $Mg(ClO_4)_2 \cdot 1.5H_2O$ dissolved in $CH_3CN/CHCl_3$ (3:1). Although the reaction times vary considerably (no rate studies have been done because, among other reasons, the reaction mixtures often become heterogeneous), a reaction time of 96 h was usually maintained to allow the reaction to go to completion (the disappearance of the green fluorescence of dihydropyridine signals the end of the reaction). Reactions were done under N_2 or Ar to prevent air oxidation of the 1,4-dihydropyridine. Water was added to the reaction mixture, and the desired alcohols were isolated by preparative thin-layer chromatography (TLC) followed by kugelrohr distillation. No crystallizations were carried out. The scale was usually 1 mmol of 1,4-dihydropyridine for each experiment.

The optical rotations of the pure alcohols were measured and were used to calculate optical yields. These optical yields were cross-checked with enantiomeric excesses determined for some cases by esterification with (2*R*)-3,3,3-(trifluoromethyl)-2-methoxy-2-phenylpropionyl chloride[42] followed by ^{19}F NMR; the peaks were well separated. Use was made also of literature data in which optical rotations have been correlated with enantiomeric excesses. For this reason, data are given here as enantiomeric excesses. The pertinent quantitative data are given in the Experimental Section.

In addition to the experiments listed in Table II, various other investigations of the effect of structure on the asymmetric induction were carried out. The nonbridged dihydropyridines **20a** and **b** and **21** reacted cleanly with ethyl phenylglyoxylate **22** ($R^1 = C_6H_5$, $R^2 = CO_2C_2H_5$) under conditions described above. These results are given in Table III.

Some investigations of the effect of variation of structure in the carbonyl compound were carried out. As seen from those results given in Table IV wherein **7a** ($R = CH(CH_3)_2$) is used as the reducing agent, this structural dependence is indeed quite great. Not listed in Table IV are the results of attempted reduction of a number of other carbonyl substrates. Derivatives of **22** (R^1 = alkyl) are reduced sluggishly (ethyl pyruvate, for instance), but difficulties in isolation, sluggishness of reaction, and the apparent formation of side products discouraged us from further exploration of these compounds. Simple ketones like cyclohexanones or aldehydes (either aromatic or aliphatic) are barely reduced by the dihydropyridines described here.

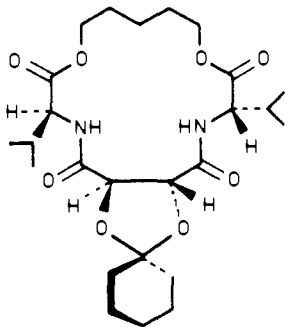
The reduction of ketopantolactone **24** to pantolactone **25** was briefly investigated (eq 7). Enantioselective syntheses of **25** by microbiological[43] and chemical means [44] have been described. Chiral 1,4-dihydropyridine derivatives have also been used to give **25** in enantiomeric excesses ranging from 38% to 51%.[45a-c] With **7f** ($R = CH(CH_3)_2$) (**7k**, $R = CH(CH_3)_2$, was also used in initial experiments), reduction barely proceeded at room temperature. However, at 40 °C over a period of several days, reduction did

(42) Dale, J. A.; Duff, D. L.; Mosher, H. S. *J. Org. Chem.* **1968**, *33*, 3245.

(43) Wilkin, D. R.; Dyar, R. E. *Arch. Biochem. Biophys.* **1978**, *189*, 251.

(44) (a) Purko, M.; Nelson, W. O.; Wood, W. A. *J. Biol. Chem.* **1954**, *207*, 51. (b) Brown, G. M.; Reynolds, J. J. *Annu. Rev. Biochem.* **1963**, *32*, 419. (c) Ojima, I.; Kogure, T.; Terasaki, T. *J. Org. Chem.* **1978**, *43*, 3444.

(45) (a) Ohno, A.; Ikeguchi, M.; Kimura, T.; Oka, S. *J. Am. Chem. Soc.* **1979**, *101*, 7036. (b) Seki, M.; Baba, N.; Oda, J.; Inouye, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4613. (c) Inouye, Y. In "Asymmetric Reactions and Processes in Chemistry"; Eliel, E. L., Otsuka, S., Eds.; American Chemical Society: Washington, DC, 1981; ACS Symp. Ser. No. 185, pp 268–271.



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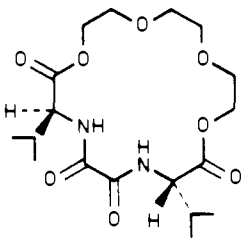

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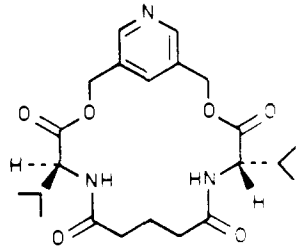

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Table IV. Reductions of **22** Derivatives with **7a** (R = $CH(CH_3)_2$) in the Presence of $Mg(ClO_4)_2 \cdot 1.5 H_2O$[a]

R^1	R^2	% conv. to alcohol **23**	ee, %	major enantiomer
C_6H_5	CO_2CH_3	85	80	*S*
C_6H_5	$CO_2(CH_2)_2OCH_3$	61	50	*S*
C_6H_5	$CO_2CH(CH_3)_2$	67	54	*S*
C_6H_5	$CO_2C(CH_3)_3$	0	*b*	*b*
C_6H_5	$COCF_3$	58	68	*S*
C_6H_5	$CONH_2$	69	64	*S*
C_6H_5	$CONHC_2H_5$	37	78	*S*
$4\text{-}C_2H_5C_6H_4$	$CO_2CH(CH_3)_2$	55	48	*S*
$3\text{-}C_6H_5OC_6H_4$	CO_2CH_3	58	20	*S*
$3\text{-}C_6H_5OC_6H_4$	$CONH_2$	55	60	*S*

[a] Conditions similar to those described in Table II. [b] Not applicable.

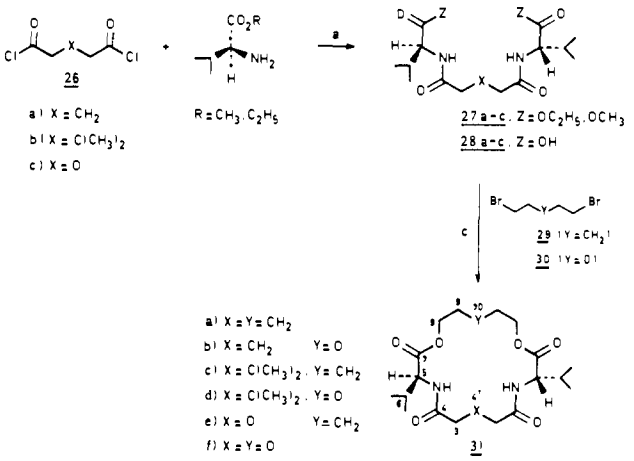
occur smoothly to give **25** in about 90% yield as estimated by ^1H NMR. Workup problems greatly hindered the isolation of **25**, which is very soluble in water. The enantiomeric excess is moderate.

An attempt was made to carry out an intramolecular reduction by means of the approach shown in eq 8. Compound **7q** (R = $CH(CH_3)_2$) was prepared as shown from **7p** (R = $CH(CH_3)_2$). From molecular models (CPK), the fit of the phenylglyoxylate segment over the dihydropyridine looked quite good. Unfortunately **7q**, (R = $CH(CH_3)_2$) could not be characterized well owing to insolubility. In the presence of $Mg(ClO_4)_2 \cdot 1.5H_2O$, the compound did go into solution in CH_3CN and produced a pyridinium salt, as established from ^1H NMR spectra. However, despite repeated efforts, an identifiable mandelic acid derivative could not be characterized, likely owing to the difficulties in removing this unit from the pyridinium salt formed.

The results with the proline-derived compounds **19a–d** are unexpected. The ethyl mandelate obtained on reduction of ethyl phenyloxylate had no or only barely measurable rotation. The reactions were very sluggish, and the conversions, measured by ^1H NMR, were only in the 30–50% range even after 120 h. The 1,4-dihydropyridine was totally consumed, however. This behavior—both slowness of reaction and trivial transfer of chirality—was observed only in this series of compounds.

C. Complexation Studies. Knowledge of the architecture of the complexes formed between these bridged 1,4-dihydropyridines and Mg^{2+} ions is fundamental to the understanding of the stereochemical course of the reductions. The amide carbonyl group is an obvious ligating site[46] although the 1,4-dihydronicotinamide system is itself sufficiently electron-rich to ligate cationic species like $Mg(ClO_4)_2$[26a] or Zn^{2+} salts.[47] The role of such complexes, together with metal ion–substrate complexes, and 1,4-dihydronicotinamide–metal ion–substrate ternary complexes in reductions

Scheme III



[a] $(C_2H_5)_2O/(C_2H_5)_3N/0$ °C. [b] To **29a–c**, 0.1 N $NaOH/H_2O/C_2H_5OH$/room temperature/16 h. [c] Cs_2CO_3/DMF(6×10^{-3} M)/70–80 °C/72 h.

is not simple.[26,41,47] This is scarcely surprising when one considers that the metal salts in strongly dielectric[48] aprotic solvents like CH_3CN are only partially dissociated and therefore consist of several electrophiles that differ in the number and kinds of ligands as well as the number of solvent molecules about the metal.[47]

We expected ^{13}C NMR spectroscopy to provide structural information. The 1,4-dihydronicotinamide system is known to give readily measurable shifts in the ^{13}C NMR spectra, and, of course, this NMR technique has received extensive attention for studying crown ether and cryptate–metal ion interactions.[49] For the cases at hand, the amide carbonyl carbons should shift downfield on complexation;[50] other carbon atoms are likely to be affected, but the direction of the shift is more difficult to predict.[47,50]

Some additional comparison compounds had first to be prepared. The syntheses of **31a–f** as shown in Scheme III follow the general approach already described. Some compounds derived from phenylalanine analogous to **27** and **28** but with open chains have been described previously.[50] The hydrolyses of **27a–c** were virtually quantitative with 0.1 N NaOH in C_2H_5OH/H_2O (1:1). Essentially the same procedure as shown in Scheme III was used to synthesize **32** (from (*R,R*)-tartaric acid), **33** (from oxalic acid), and **34** (from pyridine-3,5-dicarboxylic acid followed by reduction with $LiAlH_4$ and conversion to the hydrobromide with HBr). Synthetic details and physical properties of all these compounds

(46) Welti, M.; Pretsch, E.; Clementi, E.; Simon, W. *Helv. Chim. Acta* **1982**, *65*, 1996 and previous papers from the Simon group.

(47) (a) Hughes, M.; Price, R. H. *J. Inorg. Nucl. Chem.* **1978**, *40*, 703. (b) Hughes, M.; Price, R. H.; Wyeth, P. *J. Nucl. Chem.* **1978**, *40*, 713. (c) Hughes, M.; Prince, R. H. *J. Inorg. Nucl. Chem.* **1978**, *40*, 719.

(48) (a) Walden, P. *Z. Phys. Chem.* **1906**, *54*, 182. (b) Walden, P.; Birr, E. J. *Z. Phys. Chem.* **1929**, *144*, 269.

(49) For example: Stoddart, J. F. *Chem. Soc. Rev.* **1979**, *8*, 85 and references contained therein.

(50) (a) Lodi, T.; Marchelli, R.; Dossena, A.; Dradi, E.; Casnati, G. *Tetrahedron* **1982**, *38*, 2055. (b) Marchelli, R.; Dradi, E.; Dossena, A.; Casnati, G.; *Tetrahedron* **1982**, *38*, 2061 and references contained therein.

Table V. Influence of $Mg(ClO_4)_2 \cdot 1.5H_2O$ on ^{13}C NMR Chemical Shifts of Various (Bridged) 1,4-Dihydropyridines and Related Model Compounds[b,c]

	shift[d] rel to uncomplexed compd,[e] carbon atom										
compd	1	2	3	4	4′	5	6	7	8	9	10
11a[a]	0.63	2.45	−1.09	+1.20	−0.73	+0.52	−0.04	−0.75	0.52	−0.20	
11g[a]	0.40	3.30	−1.47	1.40	−0.81	+1.27	−0.70	0.40	1.00	−0.19	−0.42
20b[a]	0.15	3.50	−1.75	1.48	−0.94	+0.66	−1.89	0.15	1.52	−0.40	0.99[f]
6	0.39	2.53	−0.70	1.68	−0.57	*g*	*g*	*g*	*g*	*g*	*g*
27a			−1.04	2.90	0.36	0.66	0.0	−1.23	0.42	0.0	
27b			−1.37	2.63	0.71	0.78	−0.43	−1.28	0.59	0.0	−0.19
27c			−1.74	1.24		1.13	0.0	−0.30	0.55	0.0	
35[a]	0.51	3.45	1.78	0.36	−1.23	1.21	−0.40				
31a[b]			−0.13	3.55	0.16	0.80	−0.29	−1.93	0.51	0.22	−0.17
31b[b]			0.73	4.39	0.13	0.80	−0.58	−1.85	0.39	0.0	0.0
31e[b]			−0.56	2.27	0.77	0.75	−0.26	−1.20	0.16	0.0	−0.21
31f[b]			−0.44	2.83	0.66	0.76	−0.39	−1.48	0.35	0.0	0.0

[a] For numbering code for table, see drawings in text. Only those carbon atoms are listed that give measurable shifts. [b] for numbering code (**31a,b,e,f**), see numbering in Scheme V. [c] Both components 0.2 M in $CDCl_3/CD_3CN$ (1:1) at 25 °C. [d] Relative to TMS internal standard. A positive value indicates a downfield shift relative to shift in absence of $Mg(ClO_4)_2$. [e] Assignment made from analysis of coupled spectra. The carbonyl carbons are always separated 3–4 ppm in the noncomplexed compounds. From models it is clear that the amide carbonyl consistently appears at 167 ± 0.5 ppm and the ester carbonyl at 171–172 ppm. [f] Refers to OCH_3 chemical shift difference. [g] Bridge signals not assigned unambiguously. Only very small shifts observed.

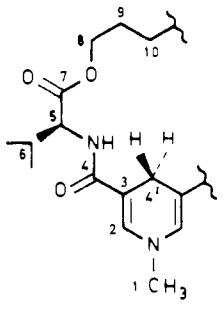
Table VI. Association Constants for Various (Bridged) 1,4-Dihydropyridines and Related Model Compounds[a]

compound	cation	solvent	log K_{ass}
18-crown-6	K^+	CH_3OH	6.3 ± 0.1 (lit.[50] 6.01)
18-crown-6	K^+	CH_3CN	6.0 ± 0.1 (lit.[6a])
7f	Mg^{2+}[b]	CH_3CN	2.8 ± 0.1[c]
20a	Mg^{2+}	CH_3CN	2.5 ± 0.1[c]
11f	Mg^{2+}	CH_3CN	1.9 ± 0.2
34	Mg^{2+}	CH_3CN	2.5 ± 0.1
31b	Mg^{2+}	CH_3CN	3.1 ± 0.1
31b	K^+	CH_3CN	*d*
31b	Li^+	CH_3CN	1.9 ± 0.2
16c	Li^+	CH_3CN	2.7 ± 0.1
17c	Li^+	CH_3CN	2.6 ± 0.1
16c	K^+	CH_3CN	*d*

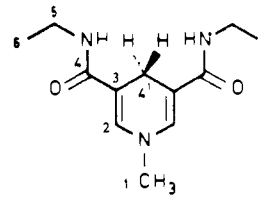
[a] Measured at room temperature by conductiometric methods. Data treatment following methods described in ref 49 on the assumption (but see text) that 1:1 complexes are formed. [b] $Mg(ClO_4)_2 \cdot 1.5H_2O$ used. [c] A small amount of *p*-cresol is added as oxidation inhibitor. [d] Too small to measure.

are given in the Experimental Section.[51]

Pertinent ^{13}C NMR shift data are collected in Table V. Compounds have been chosen, which differ significantly in structural aspects. The nonbridged example **35** is also included as a comparison compound for the 2-methoxyethyl derivative **20b**.



^{13}C numbering code



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A trend that emerges is that M^{2+} induces appreciable shifts through the 1,4-dihydropyridine ring completely in accord with the observations of Hughes and Prince,[47] and at the carbonyl carbons, especially those of the amide, which are shifted downfield. The ester carbonyl carbons, on the other hand, shift either upfield (**11a**) or downfield (**11g**). A downfield shift is also observed for the crown ether 1,4-dihydropyridine **6**.

In the series **31a,b,e,f**, the magnitudes of the shifts for the carbonyl carbons increase, and a clear trend of downfield shifts for the amide and upfield shifts for the ester carbonyl carbons is observed. Shifts for other carbon atoms follow roughly the same lines as those observed for the bridged 1,4-dihydropyridine derivatives. The increased magnitudes of the chemical shifts are consistent with stronger complexation. This picture is, however,

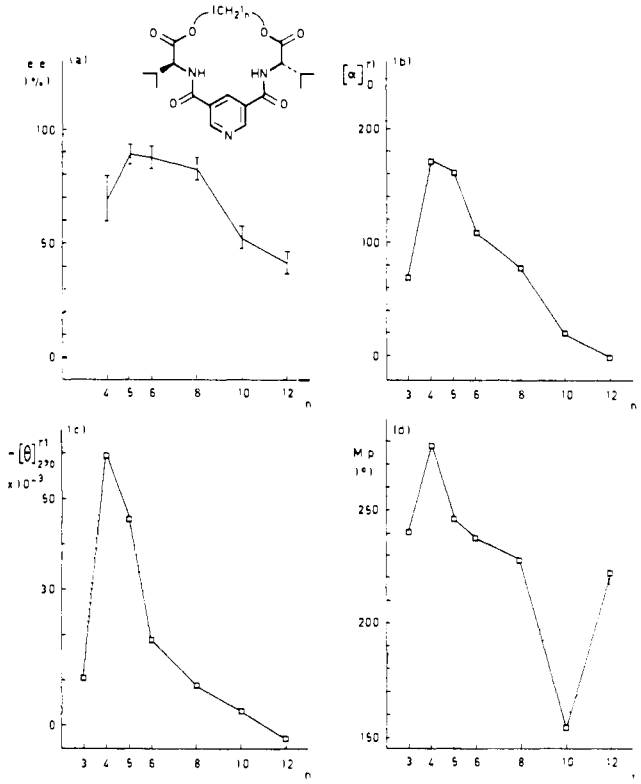
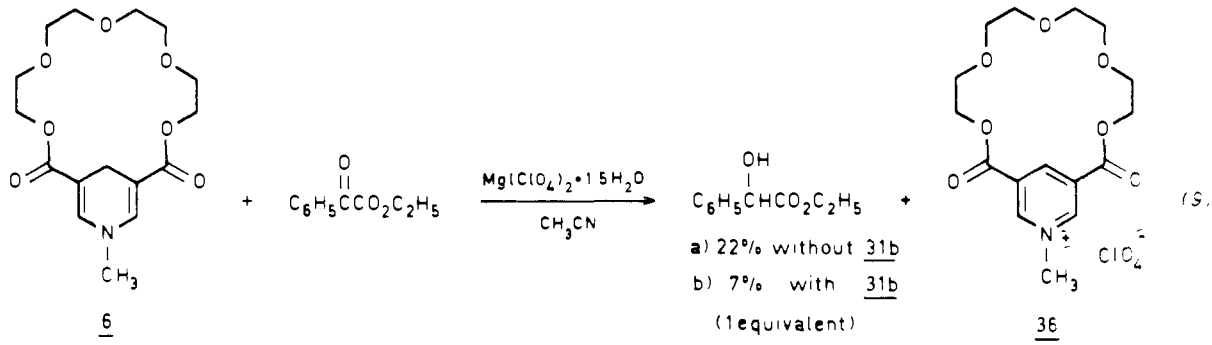


Figure 1. (a) Upper left gives the enantiomeric excesses for reductions of ethyl phenylglyoxylate by **7f–j** (R = $CH(CH_3)_2$) as a function of bridge length. Note that compounds **11f–j** are illustrated rather than the 1,4-dihydropyridines **7**. (b) Upper right gives the $[\alpha]^n_D$ values for **11f–g** (illustrated in drawing) again as a function of the same bridges. (c) Lower left is a presentation of the molar ellipticities for **11f–g**. (de) Lower right is a plot of melting points for **11f** and **g**.

(51) For other examples of chiral macrocycles that contain amino acids, see, for example: Wudl, F.; Gaete, F. *J. Chem. Soc., Chem. Commun.* **1972**, 107. Zinić, M.; Bosnić-Kašnar, B.; Kolbah, D. *Tetrahedron Lett.* **1980**, 1365. (c) Katagi, T.; Kuriyama, H. *Heterocycles* **1982**, *19*, 1681. (d) Chadwick, I. A.; Sutherland, I. O.; Newton, R. F. *J. Chem. Soc., Chem. Commun.* **1981**, 992. (e) Review of associated literature: Jolley, S. T.; Bradshaw, J. S.; Izatt, R. M. *J. Heterocycl. Chem.* **1982**, *19*, 3. (f) For ureas as ligands see, for example: Cram, D. J.; Katz, H. E. *J. Am. Chem. Soc.* **1983**, *105*, 135.



6 36

likely not complete. A ^{13}C NMR titration curve (not illustrated) for **31b** of the magnitude of the amide carbonyl carbon shift as a function of $Mg(ClO_4)_2 \cdot 1.5\ H_2O$ concentration shows a pronounced break at a ratio at two ligands: one $Mg(ClO_4)_2 \cdot 1.5\ H_2O$. Most likely 2:1 complexes form. The point was not investigated further. Similar behavior *was not* observed in the series **7**.

The conclusion that the series **31** binds more strongly is substantiated by quantitative determination of the complexation constants by conductiometric methods. The accuracy of the method was tested by comparison of determined values for 18-crown-6 with K^+ with literature data.[52] Some quantitative data are collected in Table VI. The best ligand, **31b**, as deduced from the ^{13}C measurements, indeed complexes most strongly. It shows also a relative affinity for Mg^{2+} but little for the larger cation, K^+. The 1,4-dihydropyridines illustrated, with or without bridge, all complex about equally strongly. The magnitudes compare with the reported association constant, 750 L mol^{-1}, for *N*-benzyl-1,4-dihydronicotinamide with $ZnBr_2$ in CH_3CN.[47a] There is, then, no question of significant *enhancement of binding* on bridging. There is, as a consequence, no obvious correspondence between binding ability and the degree of recognition of the prochiral carbonyl to be reduced.

Despite the modestness of the complexation constants, one should realize that at the concentrations used, 1 M, in CH_3CN, assuming a complexation constant of 750,[47a] in the initial stages of the reaction, 96% of the 1,4-dihydropyridine would be bound in a 1:1 complex. Unfortunately, there seem to be no good data that allow estimation of the complexation constant for a 1,4-dihydropyridine/Mg^{2+} complex with the α-keto acid derivative (or for a α-keto ester/Mg^{2+} complex with 1,4-dihydropyridine). If, however, the other binding constants have similar modest values, then at these high concentrations, the ternary complex will be present in significant concentration (although the chance of two-to-one ligand/Mg^{2+} complexes occurring as well as other related complexes becomes higher).

This survey of interactions is neither complete nor quantitative. However, it establishes the structural points that we wish to argue (Discussion section) in interpretation of the chiral selectivity involved. That the binding postulated here has a basis in reality is illustrated by the results summarized in eq 9. Ethyl phenylglyoxylate is reduced, albeit in poor yield, by achiral **6** in the presence of $Mg(ClO_4)_2 \cdot 1.5H_2O$ in several hours; **6** is completely oxidized to **36**. In the hope that chirality could be transferred from a Mg^{2+} selective ligand, 1 equiv of **31b** was added. After 2 days, less than 10% of **6** had reacted. Only a 7% yield of (completely racemic) ethyl mandelate was isolated. The Mg^{2+} is bound strongly and acts poorly as a catalyst, or a small amount of uncomplexed Mg^{2+} is responsible for reaction.

Discussion

These chiral macrocycles recognize quite selectively at ambient temperatures one prochiral face of a phenylglyoxylate derivative. This occurs in spite of the large structural differences among the macrocyclic systems. One may safely predict that an (*S*)-amino acid (natural configuration) containing a macrocycle of the type described here on reaction with a phenylglyoxylate will provide an excess of the *S* enantiomer of the mandelic acid derivative.[53] In terms of selectivity and mildness of reaction conditions, these reactions compare favorably with other methods for enantioselective reduction.[54]

There are, of course, limitations. In practice, these reductions are restricted to activated carbonyl groups. Moreover, the preparation of the macrocyles is not trivial although the syntheses have now been developed to a point that most representatives of the **7** (R = $(CH_3)_2CH$) group can be prepared routinely on a scale of several grams. The pyridinium salts, which are formed on reaction with a carbonyl equivalent, can be recycled to the 1,4-dihydropyridine by reduction with $Na_2S_2O_4$. There is, of course, no "turnover"; these macrocyclic 1,4-dihydropyridines are used as stoichiometric reagents.[55] The most important experimental parameter for investigation of the relationship between structure and selectivity has been the enantiomeric excess (ee) of the product alcohol. This drops, although not too drastically, as the bridge is lengthened.[58] Composition and structure of the bridge have in general a relatively minor effect on the enantiomeric excesses. This is illustrated rather qualitatively in Figure 1a in which for the series of compounds **7** (R = $CH(CH_3)_2$) with *polymethylene* bridges the ee's are plotted against the bridge length. Estimated error limits for each compound are indicated. Inspection of Table I reveals that the poly(ethylene glycol) and the majority of the branched bridges give ee's virtually identical (and, of course, same absolute configuration) *for the same bridge lengths* as indicated in Figure 1a. However, for purity of comparison, we have confined Figure 1a only to the homologous series.

The data of Figure 1a can be compared also with some properties of the macrocycles as functions of bridge length. To do so, the more stable *pyridine* precursors **11** to 1,4-dihydropyridines **7** must be used to obtain trustworthy values for analytically pure compounds. In Figure 1b, $[\alpha]^{20}_D$ is plotted as a function of bridge length, and in Figure 1c the molecular ellipticity $[\theta]$ at 20 °C for the characteristic *pyridine* $^1L_b \leftarrow {}^1A$ transition at 270 nm is plotted for the series (see ref 59 for a detailed discussion of the CD spectra). Finally, although we admit that we obtain more per-

(52) Frensdorff, H. K. *J. Am. Chem. Soc.* **1971**, *93*, 600.

(53) The relative priorities of the groups are the same in all cases, thereby allowing direct comparison of the (*R*),(*S*) nomenclatural symbols.

(54) For a leading reference to this very extensive subject, see, for example: Eliel, E. L.; Otsuka, S. "Asymmetric Reactions and Processes in Chemistry"; American Chemical Society: Washington, DC, 1982.

(55) An attractive solution to the "turnover" problem would be to use a two-phase reaction system. The macrocyclic 1,4-dihydropyridine would carry out a reduction in the organic phase, and the (positively charged) pyridinium salt formed from this reaction would shuttle to the aqueous layer, which should be a pH 7 buffered $Na_2S_2O_4$ solution. Reduction would occur, and the neutral 1,4-dihydropyridine would shuttle back again to the organic phase to carry out another reduction cycle. This chemistry has been frustrated by the need for an electrophile in the organic phase for reduction;[56] these species always dissolve selectively in the aqueous phase. Moreover, $Na_2S_2O_4$ has the ability to reduce spontaneously many carbonyl groups.[57] We have so far found no satisfactory solutions to these problems.

(56) For some potential applications in a related system, see: (a) Degani, Y.; Willner, I. *J. Chem. Soc., Chem. Commun.* **1983**, 710. (b) Degani, Y.; Willner, I. *J. Am. Chem. Soc.* **1983**, *105*, 6228.

(57) De Vries, J. G.; Kellogg, R. M. *J. Org. Chem.* **1980**, *45*, 4126.

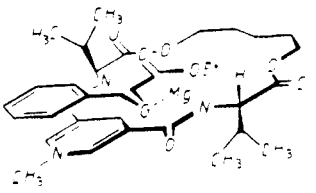
(58) For original discussion of ring size effects, see: Prelog, V. *J. Chem. Soc.* **1950**, 420.

(59) Talma, A. G.; Waninge, J. K.; Kellogg, R. M.; Snatzke, G., in preparation.

plexed amusement than enlightenment from it, a plot of melting point against bridge length is given in Figure 1d. Both Figure 1b and c reveal roughly monotonic decrease of $[\alpha]_D$ and $[\theta]$ with increasing bridge length. In ref 59, it is argued that in fact this is a consequence of the roughly equal population of several conformations of sharply differing morphologies at room temperature.[59] On the other hand, the observed ee's as a function of macrocycle size neither tend rapidly toward zero (compare Figure 1b and c) nor fluctuate irregularly (compare Figure 1d). We believe this to be a consequence of *organization* of the shapes of the macrocycles in the reductions.[60]

The relation between the conformations of these macrocycles, as determined by circular dichroism (CD) spectroscopy, and the bridge length is discussed separately.[59] Also, the quite modest complexing ability of these compounds has been discussed in the Results section together with structural reasons for the relatively weak binding. This weak complexation and our failure to obtain crystalline complexes suitable for X-ray crystallographic structure determination complicate the mechanistic analysis. However, the following conclusions seem justified on the basis of the data available. First, lone pairs of heteroatoms attached to or in the bridge itself do not act as complexing sites. This contradicts the implicit assumption in structure **7a** (M^+ – carbonyl) postulated in the introduction. The fact that polymethylene bridges act equally well as poly(ethylene glycol) bridges of the same length indicates the absence of complexation at bridge sites, which leads to reaction. Second, the amide carbonyl groups do contribute to complexation. This conclusion follows directly from the observed effects in the ^{13}C NMR spectra reported in section C.

Because there is no evidence available that dimeric, trimeric, or other aggregate forms are involved, we assume for the sake of simplicity that reduction occurs in a ternary complex in which the macrocyclic 1,4-dihydropyridine, Mg^{2+} ion, and carbonyl component are associated together. We furthermore assume that for reasons of charge repulsion, a corresponding complex after reaction, i.e., macrocyclic pyridinium salt and magnesium (mono)alkoxide, would be less stable. The complexes that lead to reaction must have stereochemical features in common. A generalized structure consistent with the stereochemical observations is that shown in **37**. The magnesium ion is coordinated



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through the amide oxygen on the least hindered side of one face of the macrocyclic system. The ^{13}C NMR results are in accord with complexation at an amide position.[47b] From ab initio calculations Welti et al.[46] conclude that the Mg^{2+} ion can best coordinate to an amide oxygen on a line that is an extension of the C–O binding axis. We assume, although the data in Table V are not unambiguous, that the adjacent carbonyl oxygen also acts as a ligand. This results in the magnesium ion being held selectively to one side, namely the least hindered, of the macrocyclic ring. On complexation of the Mg^{2+} ion, the C_2 symmetry axis is lost and the faces, as well as the reactive hydrogens of the 1,4-dihydropyridine ring, become diastereotopic. The magnesium ion on binding *organizes* the structure of the macrocycle to a more or less common morphology suitable for acceptance of the carbonyl component irregardless of the bridge.

Examination of CPK models reveals that a phenylglyoxylate can be placed on this framework only in the fashion indicated; it "sits astraddle" the chiral barrier. This is intuitively satisfying in that the remarkable effectiveness of methyl, benzyl, isopropyl, and phenyl to act as chiral barriers, all in the same stereochemical sense, is explained in terms of a tight association with the steric barriers with the same type of steric interactions pertaining in every case.

The foregoing discussion has been based on an assumed sequentiality, i.e., complexation of Mg^{2+} to the macrocycle, followed by complexation of the phenylglyoxylate derivative. The arguments remain identical, however, if, say, a Mg^{2+}–phenylglyoxylate complex were to associate with the macrocycle.

Although trustworthy kinetic data were not obtained owing to the complexities of the reaction, in particular the heterogenity in many cases, it is qualitatively clear that no great acceleration in rates is obtained on bridging the macrocycle. All these reactions, be they with bridged compounds **7** or with, for example, open analogues like **20a** and **b**, proceed to completion within about 24 h at room temperature. There are, of course, qualitatively observable differences in completion times for the reactions. It is unlikely, however, that the rates differ by more than a factor of 2 or 3. This means that any "macrocyclic effect" on the reaction manifests itself in selectivity in the chiral discrimination rather than any significant rate enhancement. In this aspect, the enzymic property of attainment of selectivity and speed simultaneously has not been achieved.

To achieve simultaneously speed and selectivity with relatively low molecular weight catalytic systems is a general problem for which, again in our opinion, no convincing practical solutions of any generality have been developed.

Grounds can doubtlessly be found to defend several mechanistic variations for the reactions observed here. These mechanisms differ chiefly in the timing by which a hydrogen from the 4-position of the 1,4-dihydropyridine is transferred. The results described here provide only insights in the geometry in which this occurs in these macrocyclic systems. The orientation of the dihydropyridine ring and carbonyl is forced chiefly by the local steric situation. There are good arguments to support the belief that the carbonyl group may be oriented differently with respect to the 1,4-dihydropyridine ring in some other nicotinamide derivatives.[45]

We do note that the model implied here implies attack of hydride roughly on the best Bürgi–Dunitz–Lehn approach line.[61] Moreover, in accord with theoretical calculation as well as some experimental evidence, the oxygen of an amide side chain points roughly parallel to the direction in which hydride will depart.[23b] This is, according to calculations, the side chain conformation that leads to the lowest enthalpy owing to strong dipole interaction of the carboxamide side chain during the hydride-transfer step.

Experimental Section

General Methods. Melting points were recorded on a Mettler automatic FP-2 apparatus or on a melting block. Neither apparatus was calibrated. ^1H NMR spectra [$(CH_3)_4Si$ internal standard] were recorded on Varian, JEOL, or Perkin-Elmer instruments (60 MHz) or a Varian XL-100 (100 MHz) or Nicolet 283 A (200 MHz) instrument. ^{13}C and ^{19}F spectra were also obtained on the latter two instruments. Mass spectra were obtained with the aid of a MS-9 mass spectrometer. Medium-pressure liquid chromatography was carried out on an instrument built in these laboratories;[62] a Waters apparatus was used for analytical work. Conductivity measurements were carried out with a Wayne Kerr autobalance B642 apparatus. Microanalyses were performed by the analytical division of these laboratories.

Compounds cited without reference were either in stock or were prepared by unexceptional literature procedures. Where possible, general procedures are given for preparation and reactions of compounds of closely related structure. However, synthetic approaches that differ

(60) We imply in no way that high flexibility leads to better binding. Very strongly binding crown ethers and cryptates are distinguished by a high degree of prestructuring. What is involved here, put in simple terms, is improvement of quite poor bonding to better by allowing the ligand to attain more easily a shape in which multidentate binding is possible. See, for example: (a) Craine, L. H.; Greenblatt, J.; Woodson, S.; Hortelano, E.; Raban, M. *J. Am. Chem. Soc.* **1983**, *105*, 752. (b) Raban, M.; Greenblatt, J.; Kandil, F. *J. Chem. Soc., Chem. Commun.* **1983**, 1409.

(61) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956.

(62) Clark Still, W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

essentially in character are described in detail. For a series of compounds, only the initial example is described with any significant deviations in procedure. All other descriptions of synthetic techniques and spectral data are given in the supplementary material.

N,N'-Bis[(1S)-1-carboxy-2-methylpropyl]-3,5-bis(aminocarbonyl)pyridine (10, X = OH, R = CH(CH$_3$)$_2$). L-Valine (2.4 g, 20.3 mmol) is dissolved in 10–12 mL of 2 N KOH and cooled to 5–10 °C. To this vigorously stirred solution are added simultaneously a solution of 5 mL of 4 N KOH and a solution of 3,5-bis(chlorocarbonyl)pyridine in 10 mL of CH_2Cl_2. (This acid chloride is prepared immediately before use from the reaction of 3,5-pyridinedicarboxylic acid (1.84 g, 11 mmol) suspended in benzene (50 mL) with $SOCl_2$ (2 mL) at 50 °C. Two drops of DMF are added to catalyze the reaction. After 2 h at 50 °C, the solution becomes clear. The solvent and excess $SOCl_2$ are removed; benzene is added again, and the solution is refluxed 10 min. The solvent is removed, and 10 mL of CH_2Cl_2 is added.) If necessary, at the end of the reaction, enough KOH solution is added to bring the pH to >8. The solution is stirred in the ice bath for 30 min and at room temperature for 20 min. The CH_2Cl_2 layer is decanted, and the aqueous phase is diluted with 200 mL of H_2O. This is acidified with stirring with a solution of 3 mL of formic acid in 30 mL of H_2O. This process should be carried out with care; once some turbidity develops, the solution should be allowed to stand. The bis-amide usually precipitates within 15 min, although on occasion the process may be slower. The material is isolated by filtration, rinsed with cold H_2O, and dried in the desiccator, yield 2.5 g (6.85 mmol, 67%). When run on a 5-fold greater scale, the yield was 73%. The product has mp 217.2 °C dec. $[\alpha]^{20}_D$ +49.7° (DMF, *c* 1); ^{1}H NMR (CD_3OD) δ 1.1 (d, 12 H, $(CH_3)_2CH$), 2.35 (heptet, 2 H, $(CH_3)_2CH$), 4.6 (d, 2 H, NHC*H*), 8.6 (s, 1 H, pyr -4-H), and 9.1 (s, 2 H, pyr-2,6-*H*).

Anal. Calcd for $C_{17}H_{13}N_3O_6 \cdot H_2O$: C, 52.26; H, 6.52; N, 10.97. Found: C, 53.60; H, 6.42, N, 11.00.

N,N'-Bis[(1S)-1-((2-methyl-2-propyl)oxycarbonyl)-2-methylpropyl]-3,5-bis(aminocarbonyl)pyridine (10, X = OC(CH$_3$)$_3$, R = CH(CH$_3$)$_2$). To a well-stirred solution of L-valine *tert*-butyl ester (76.0 g, 0.44 mol) in 700 mL of benzene were added simultaneously 0.22 mol of 3,5-bis(chlorocarbonyl)pyridine in 700 mL of benzene and triethylamine (44.3 g, 0.44 mol) in 700 mL of benzene over a period of 1 h. The reaction temperature was kept at about 5 °C. After addition was complete, the solution was stirred for 2 h at room temperature. The white precipitate was filtered with suction and was washed carefully with ethyl acetate. The ethyl acetate washings were combined with the residue obtained after evaporating the benzene from the first filtrate. This solution was washed in sequence with saturated $NaHCO_3$ solution, 2 N citric acid solution, saturated $NaHCO_3$ solution, and H_2O. The organic layer was dried over Na_2SO_4, and the solvent was removed. The solid material was recrystallized from ether/petroleum ether. There was obtained 92.7 g (0.194 mol, 88% yield) of product as white crystals, mp 170.1–170.4 °C: IR (KBr) 3200–3900, 3000, 1730, 1675, 1550, 1390, and 1155 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ 9.22 (d, 2 H, pyr-2,6-*H*), 8.67 (t, 1 H, pyr-4-*H*), 8.01 (d, 2 H, N*H*), 4.56 (d of d, 2 H, *H*C–N, 1.97–2.62 (m, 2 H, $(CH_3)_2CH$), 1.49 (s, 18 H, $(CH_3)_3C$), and 1.04 (d, 12 H, $(CH_3)_2CH$); mass spectrum, *m/e* 477, calcd parent 477; $[\alpha]^{21}_D$ +37.7°, $[\alpha]^{21}_{578}$ +39.6°, $[\alpha]^{21}_{546}$ +45.8°, $[\alpha]^{21}_{436}$ +87.3°, $[\alpha]^{21}_{365}$ +165.8° (*c* 1.00, ethyl acetate).

Anal. Calcd for $C_{25}H_{39}N_3O_6$: C, 62.87; H, 8.23; N, 8.80. Found: C, 62.71; H, 8.12; N, 8.79.

N,N'-Bis[(2S)-2-((2-oxo-2-phenyl)ethoxy)-2-oxo-1-benzyl]-3,5-bis(aminocarbonyl)pyridine (10, X = CH$_2$COC$_6$H$_5$, R = CH$_2$C$_6$H$_5$). A 40% HBr solution in glacial acetic acid (40 mL) was added dropwise to a stirred solution of *N*[(benzyloxy)carbonyl]-L-phenylalanine phenacyl ester (10 g, 33 mmol) in ethyl acetate (250 mL). The hydrobromide began to precipitate after 10 min. After addition of the HBr solution was completed, ether (250 mL) was added to precipitate the HBr salt completely. This salt was filtered, washed thoroughly with ether, and dried in a desiccator. The hydrobromide (10.8 g, 29.7 mmol, 90%) was recrystallized from methanol/diethyl ether, mp 154.5–155.5 °C.

The (*tert*-butyloxy)carbonyl-protected phenacyl ester could be deprotected by the same procedure.

The crude hydrobromide obtained above (20 g, 55 mmol) and 3,5-bis(chlorocarbonyl)pyridine (4.7 g, 28 mmol) were suspended in a benzene solution (1.5 L), which was stirred and cooled to 10 °C. Triethylamine (12 mL, 0.12 mol) was added dropwise; the temperature of the solution was kept at 10–15 °C. Stirring was continued for 3 h. The benzene was evaporated, and H_2O (1 L) and CH_2Cl_2 (1 L) were added to the residual slurry. The water layer was extracted 4 times with 250-mL portions of CH_2Cl_2 and was then dried over $MgSO_4$. After removal of the solvent, the crude material was recrystallized from ethyl acetate. Material recovered from the mother liquor was recrystallized from ethyl acetate/pentane. In total there was obtained 17.6 g (25.3 mmol, 92%) of product, mp 169–171 °C: IR (Nujol) 3350, 1745, 1695, 1640, 1595, and 1530 cm^{-1}; $[\alpha]^{20}_D$ −74.8°, $[\alpha]^{20}_{578}$ −78.5°, $[\alpha]^{20}_{546}$ −89.3°, $[\alpha]^{20}_{436}$ −156.7°, and $[\alpha]^{20}_{365}$ −255.5° (*c* 0.97, CH_3CN); ^{1}H NMR ($CDCl_3$) δ 3.40 (br, 4 H, 2C*H*$_2$C), 5.0–5.9 (m, 6 H, 2C*H*$_2$O + 2C*H*), 6.9–8.0 (m, 22 H, 4C$_6$*H*$_5$ + 2N*H*), 8.15 (br, 1 H, pyr-4-*H*), and 8.75 (d, 2 H, pyr-2,6-*H*).

Anal. Calcd for $C_{41}H_{35}N_3O_8$: C, 70.58; H, 5.06; N, 6.02. Found: C, 70.38; H, 5.10; N, 5.99.

Amino Acid Derived Bridged Pyridines 11. For the series of compounds derived from the amino acid amides of pyridine-3,5-dicarboxylic acid, the same general procedure was followed, which is given here. Details for individual compounds are given chiefly in the supplementary material. Procedures that differ in essential aspects from each other are given in full here.

The bis-(L-valinamide) of pyridine-3,5-dicarboxylic acid (1.1 g, 3.01 mmol) is dissolved in CH_3OH (30 mL) with Cs_2CO_3 (950 mg, 2.0 mmol). After CO_2 evolution stops, 100 mL of DMF is added and the solvent removed under vacuum (ca. 1–2 torr), taking care that the temperature does not exceed 50 °C; the solution is concentrated until a heavy slurry remains. DMF (250 mL) is added together with the desired chain component (3 mmol) as the dibromide, and the solution is heated at 45–50 °C with stirring for 48 h. After this time, the DMF is removed under vacuum and CH_2Cl_2 (100 mL) is added. The solution is filtered to remove the CsBr, and this salt is washed thoroughly with 100 mL of CH_2Cl_2. The crude material is subjected to flash chromatography on silica gel (Merck Kieselgel 60, 0.040–0.063 mesh). Elution is carried out with CH_2Cl_2/ethyl acetate (4:1) for compounds with hydrocarbon bridges but with 1:1 CH_2Cl_2/ethyl acetate or pure ethyl acetate for more polar bridges.

(4S,14S)-4,14-Di-(2-propyl)-6,9,12,-trioxa-3,15,19-triazabicyclo-[15.3.1]heneicosa-1(21),17,19-triene-2,5,13,16-tetrone (11a, R = CH(CH$_3$)$_2$). The bis(valine-*tert*-butylamide) of pyridine-3,5-dicarboxylic acid (30.0 g, 63 mmol), prepared as described, was dissolved in 70 mL of trifluoroacetic acid (TFA). The solution was stirred with exclusion of moisture for 20 min. After removal of TFA under reduced pressure, CH_2Cl_2 was added, and the resulting slurry was homogenized in an ultrasonic bath. The solvent was removed by suction on a glass filter (P-3), and the precipitate was washed twice with CH_2Cl_2. Care was taken to keep the precipitate covered with solvent to prevent it from liquefying. Thereafter, the wet mass was dried in a vacuum desiccator for 48 h. Without further purification, the diacid was converted into its dicesium salt, following the procedure of Wang et al.[35] The dicesium salt was purified by adding dry DMF to the crude product and homogenizing the resulting slurry in an ultrasonic bath. Workup proceeded as described above for the diacid, using DMF instead of CH_2Cl_2. The bulk of DMF was removed from the wet mass by distillation under reduced pressure (oil pump, ca. 3 torr) from a water bath. The solid was then kept under vacuum for 48 h: yield 32.66 g. ^{1}H NMR spectroscopy revealed the presence of 1.2 equiv of DMF and 0.75 equiv of H_2O. Taking this into account, an overall yield of 66% was calculated; ^{1}H NMR (CD_3OD) δ 9.26 (d, 2 H), 8.82 (t, 1 H), 4.93 (br s, 3.5 H, NH + H_2O), 4.38 (d, 2 H), 2.59 (d, 7.4 H, DMF), 1.89–2.64 (m, 2 H), and 1.06 (d, 12 H).

To a solution of 1,5-dibromo-3-oxapentane (9.37 g, 40 mmol) in 2 L of dry DMF in a wide-mouthed glass kettle, 40 mmol of the dicesium salt, prepared as described above, was added. The mixture was agitated with a vibromixer for 24 h, while the temperature was maintained at 40 °C. The solvent was then evaporated (0.05 torr), and dioxane was added to the residue. After the mixture was stirred for 1 h, the precipitate was filtered with suction and washed several times with dioxane. Most of the solvent was evaporated from the filtrate, and acetone was added. Amost immediately a crystalline precipiate formed. This was filtered with suction and washed with a small amount of cold acetone. A second crop of crystals was obtained by washing the dioxane-insoluble residue with water. The cesium salts are thus washed out, and pure product remains

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on the filter. The two crops were combined and crystallized from CH_2Cl_2–petroleum ether: yield 7.45 g. The combined acetone and CH_2Cl_2–petroleum ether mother liquors were evaporated, and the residue was subjected to preparative HPCL (Water Assoc. Preppak 500 silica cartridge; 2:1 CH_2Cl_2–dioxane as eluent) to yield another 1.05 g of product, total yield 8.50 g (19.3 mmol, 48%), as white crystals: mp 251.4–254.3 °C; IR (KBr) 3450, 3370, 3000, 1735, 1670, 1550, and 1280 cm^{-1}; ^1H NMR (CD_3SOCD_3) δ 8.99 (d, 2 H, pyr-2,6-*H*), 8.73 (d, 2 H, N*H*), 8.22 (t, 1 H, pyr-4-*H*), 4.38 (d of d, 2 H, NHC*H*), 4.10–4.40 (m, 4 H, CO_2CH_2), 3.60–3.92 (m, 4 H, $CO_2CH_2CH_2O$), 1.87–2.47 (m, 2 H, $(CH_3)_2CH$), and 0.94 (d, 12 H, $(CH_3)_2CH$); ^{13}C NMR (CD_3SOCD_3) δ 170.6 (s), 166.5 (s), 149.9 (d), 134.6 (d), 130.7 (d), 69.3 (t), 65.0 (t), 58.5 (d), 30.2 (d), 19.0 (q), and 18.4 (q); mass spectrum, *m/e* 435, calcd parent 435; m_r (osmometric in dioxane) 454.6, calcd for $C_{21}H_{29}N_3O_7$ 435.5; $[\alpha]^{20}_D$ −126.8°, $[\alpha]^{20}_{578}$ −134.5°, $[\alpha]^{20}_{546}$ −160.1°, $[\alpha]^{20}_{436}$ −355.7° $[\alpha]^{20}_{365}$ −840.8° (*c* 1.02, DMF).

Anal. Calcd for $C_{21}H_{29}N_3O_7$: C, 57.92; H, 6.71; N, 9.65. Found: C, 57.76; H, 6.64; N, 9.75.

Cesium Thiophenolate. Cesium carbonate (8.5 g, 2.6 mol) was suspended in CH_3OH (50 mL). Thiophenol (5.5 g, 50 mmol) was added dropwise; CO_2 was evolved. The solution was stirred for 15 min and was then filtered through Celite. The solvent was removed until a slurry remained, and enough CH_3OH was added to dissolve the cesium thiophenolate; diethyl ether was then added until the salt began to crystallize. The crystals were filtered off, washed with ether, and dried in a desiccator. Yields were 70–80%. The salt was stored at −40 °C under dry conditions.

(4*S*,14*S*)-4,14-Dibenzyl-6,9,12-trioxa-2,5,13,16-tetraoxo-3,15,19-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (11a, R = $CH_2C_6H_5$). The bis phenacyl ester **10** (X = $CH_2COC_6H_5$, R = $CH_2C_6H_5$) (3 g, 4.3 mmol) and cesium thiolate (4.5 g, 17.2 mmol) were stirred in DMF (50 mL) for 30 min. The solution was filtered through Celite, and acetone was added slowly to the filtrate to precipitate the bis-cesium salt (3 g, 4.14 mmol, 96%), which was used immediately for the ring closure, owing to its instability.

The bis-cesium salt (3 g, 4.14 mmol) and 3-oxa-1,5-dibromopentane (1 g, 4.3 mmol) in DMF (250 mL) were heated at 50 °C for 48 h. The reaction mixture was cooled to room temperature, and H_2O (200 mL) and CH_2Cl_2 (200 mL) were added. The organic layer was dried over $MgSO_4$. The solvent was removed and after recrystallization from CH_2Cl_2/diethyl ether, there was obtained 670 mg of **11a** (R = $CH_2C_6H_5$). From the mother liquor after three recrystallizations there was obtained an additional 250 mg of product. In total 920 mg (1.73 mmol, 41%) was obtained, mp 250–252 °C: IR (Nujol) 3250, 1725, 1640, and 1550 cm^{-1}; $[\alpha]^{22}_{578}$ −179.2°, $[\alpha]^{22}_{546}$ −209.9°, $[\alpha]^{22}_{436}$ −423.1°, and $[\alpha]^{22}_{365}$ −860.5° (*c* 1.06, 96% EtOH); ^1H NMR ($CDCl_3$) δ 3.15 (br d, *J* = 5.5 Hz, 4 H, $2CH_2$), 3.55 (m, 4 H, CH_2OCH_2), 4.28 (m, 4 H, $2COOCH_2$), 4.90–5.30 (m, 2 H, 2C*H*), 7.15 (s, 10 H, $2C_6H_5$), 7.60 (br s, 2 H, 2N*H*), 7.75 (br s, 1 H, pyr-4*H*), and 8.35 (br s, 2 H, pyr-2,6*H*).

Anal. Calcd for $C_{29}H_{29}N_3O_7$: C, 65.53; H, 5.50; N, 7.90. Found: C, 64.99; H, 5.51; N, 7.83.

Alkylation of Pyridines. Two essentially different procedures, designated A and B as described below, were followed in many cases. Representative examples are given, and the details for all other compounds are given in the supplementary material.

(4*S*,14*S*)-4,14-Di-(2-propyl)-19-methyl-6,9,12-trioxa-3,15-diaza-19-azoniabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,5,13,16-tetraone Perchlorate (12a, R = $CH(CH_3)_2$). Method A. This pyridinium salt was prepared from **11a** (R = $CH(CH_3)_2$) (2.50 g, 5.75 mol), which was dissolved in dry CH_2Cl_2 (125 mL). To this stirred solution was added methyl fluorosulfonate (6.5 mL, CAUTION!). After evaporation of the solvent, the residue was crystallized from CH_3CN/diethyl ether. There was obtained 2.47 g (4.5 mmol, 80% yield) as white crystals. For purposes of identification, the crystalline perchlorate was obtained by anion exchange. The fluorosulfonate salt was dissolved in a minimal amount of water, and a saturated solution of $NaClO_4$ was added. A white crystalline precipitate formed, which was collected by filtration, washed with cold water, and dried in vacuo. Recrystallization from CH_3OH afforded analytically pure material, melting point decomposition: IR (KBr) 3380, 3070, 2950, 1725, 1670, 1545, 1275, and 1090 cm^{-1}; ^1H NMR (CD_3SOCD_3) δ 9.42 (d, 2 H, pyr-2,6-*H*), 9.33 (d, 2 H, N*H*), 8.70 (t, 1 H, pyr-4-*H*), 4.58 (d of d, 2 H, NHC*H*), 4.44 (s, 3 H, NCH_3), 4.08–4.42 (m, 4 H, CO_2CH_2), 3.56–3.95 (m, 4 H, $CO_2CH_2CH_2O$), 1.78–2.56 (m, 2 H, $(CH_3)_2CH$), and 0.94 (d of d, 12 H, $(CH_3)_2CH$); UV (CH_3OH) λ_{max} 242 (ϵ 5300) and 266 nm (ϵ 4700); $[\alpha]^{23}_D$ −81.5°, $[\alpha]^{23}_{578}$ −86.8°, $[\alpha]^{23}_{546}$ −104.5°, $[\alpha]^{23}_{436}$ −250.4°, $[\alpha]^{23}_{365}$ −639.2 (*c* 1.00, DMF).

Anal. Calcd for $C_{22}H_{32}ClN_3O_{11}$: C, 48.05; H, 5.86; N, 7.64; Cl, 6.45. Found: C, 47.65; H, 5.75; N, 7.65; Cl, 6.37.

(4*S*,14*S*)-4,14-Diisopropyl-6,12-dioxa-3,15-diaza-19-azonia-19-methylbicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,5,13,16-tetrone Perchlorate (12f, R = $CH(CH_3)_2$). Method b. A mixture of pyridine **11a** (R = $CH(CH_3)_2$) (1 mmol), $Mg(ClO_4)_2 \cdot 1.5H_2O$ (1 mmol), and 1 mL of CH_3I in 50 mL of CH_3CN was stirred at 50 °C overnight. The solution became orange–red. The solvent was evaporated, and the remaining sticky mass was flash chromatographed (column 10 cm × 2.5 cm Kieselgel Merck 60, 200–400-mesh ASTM) with CH_2Cl_2 followed by CH_2Cl_2/CH_3CN (1:1) as eluents. The product was isolated almost quantitatively as a white solid. Stripping with absolute alcohol was often used to induce crystallization of the glassy material isolated after removal of the CH_2Cl_2/CH_3CN: ^1H NMR (CD_3CN) δ 0.95 (d, 12 H), 1.7 (m, 6 H), 2.2 (heptet, 2 H), 4.1 (m, 4 H), 4.4 (s, 3 H), 4.6 (dd, 2 H), 7.6 (d, 2 H), 8.6 (s, 1 H), and 8.95 (s, 2 H).

(4*S*,14*S*)-4,14-Di-(2-propyl)-19-methyl-6,9,12-trioxa-3,15,19-triazabicyclo[15.3.1]heneicosa-17,20-diene-2,5,13,16-tetrone (7a, R = $CH(CH_3)_2$). The fluorosulfonate salt of **12a** (R = $CH(CH_3)_2$) (550 mg, 1.0 mmol) was dissolved in 17 mL of Merck Puffer–titrisol, pH 7.00, phosphate. After addition of $Na_2S_2O_4$ (1.0 g, 5.74 mmol), the solution was stirred for 15 min. The solution was put in an ice bath and stirred another 15 min. The yellow precipitate was isolated by filtration with suction, washed with cold water, and dried in vacuo. There was obtained 442 mg (0.98 mmol, 98% yield) of product as a yellow powder, mp 140.5–142.2 °C: IR (KBr) 3520, 3450, 2965, 2930, 1740, 1695, 1585, 1530, and 1265 cm^{-1}; ^1H NMR (CD_3CN) δ 6.86 (s, 2 H, pyr-2,6-*H*), 6.21 (d, 2 H, N*H*), 4.42 (d of d, 2 H, NHC*H*), 4.09–4.44 (m, 4 H, CO_2CH_2), 3.54–3.83 (m, 4 H, $CO_2CH_2CH_2O$), 3.32 (s, 2 H, pyr-4-*H*,*H*), 3.09 (s, 3 H, NCH_3), 2.00–2.48 (m, 2 H, $(CH_3)_2CH$), and 0.95 (d of d, 12 H, $(CH_3)_2CH$); exact mass spectrum, *m/e* calcd for $C_{22}H_{33}N_3O_7$ 451.23, found 451.24; $[\alpha]^{25}_D$ −133.9°, $[\alpha]^{25}_{578}$ −143.6°, $[\alpha]^{25}_{546}$ −178.2° (*c* 1.04, CH_3CN); UV (CH_2Cl_2) λ_{max} 352 nm (ϵ 2500).

(4*S*,17*S*)-4,17-Di-(2-propyl)-22-methyl-6,9,12,15-tetraoxa-2,5,16,19-tetraoxo-3,18,22-triazabicyclo[18.3.1]tetraeicosa-1(23),20(21)-diene (7b, R = $CH(CH_3)_2$). The bis-cesium salt of the bis(valinamide) of pyridine-3,5-dicarboxylic acid (629 mg, 1 mmol) in DMF (100 mL) was allowed to react with 1,8-dibromo-3,6-dioxaoctane (275 mg, 1 mmol) at 50 °C for 48 h. The solvent was removed under vacuum, and the residue was taken up in dioxane; the solid salt was washed well with dioxane. The salts were dissolved in H_2O, and the remaining solid was isolated by filtration and then dissolved. The dioxane solution was concentrated, and sufficient acetone was added to cause precipitation of **11b** (R = $CH(CH_3)_2$). After two recrystallizations from CH_2Cl_2/diethyl ether, there was obtained 250 mg (0.52 mmol, 52%) of product, mp 204–205 °C: IR (Nujol) 3300, 3000, 1710, 1640, 1600, and 1535 cm^{-1}; $[\alpha]^{21}_{578}$ −25.2°, $[\alpha]^{21}_{546}$ −29.5°, $[\alpha]^{21}_{456}$ −55.9°, and $[\alpha]^{21}_{365}$ −102.2° (*c* 0.49, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.95 (d, *J* = 7 Hz, 12 H, $4CH_3$), 1.9–2.6 (m, 2 H, 2C*H*), 3.50–3.90 (m, 8 H, $CH_2O(CH_2)_2OCH_2$), 4.10–4.45 (m, 4 H, $2CO_2CH_2$), 4.55–4.95 (m, 2 H, 2C*H*), 7.1–7.4 (br, 2 H, 2N*H*), 8.50 (br s, 1 H, pyr-4*H*), and 9.10 (br s, 2 H, pyr-2,6-*H*); mass spectrum, *m/e* (parent) 479, calcd for $C_{23}H_{33}N_3O_8$ 479.

The above material (200 mg, 0.42 mmol) was dissolved in CH_3I (25 mL) and stirred for 48 h. The excess CH_3I was evaporated, and the crude pyridinium salt was reduced without further characterization with $Na_2S_2O_4$ (500 mg, 2.87 mmol) in buffer solution. There was obtained 195 mg (0.39 mmol, 94% yield) of **7b** (R = $CH(CH_3)_2$), which was used immediately for reductions: ^1H NMR (CD_3CN) δ 0.95 (d, *J* = 7 Hz, 12 H, $4CH_3$), 2.20–2.45 (m, 2 H, 2C*H*), 3.05 (s, 3 H, CH_3), 3.22 (s, 2 H, pyr-CH_2), 3.40–3.75 (m, 8 H, $CH_2O(CH_2)_2OCH_2$), 4.00–4.50 (m, 6 H, 2C*H* + $2CO_2CH_2$), 6.00–6.35 (br, 2 H, 2N*H*), and 6.85 (s, 2 H, pyr-2,6-*H*).

(4*S*,14*S*)-4,14-Dibenzyl-19-methyl-6,9,12-trioxa-2,5,13,16-tetraoxo-3,15,19-triazabicyclo[15.3.1]heneicosa-17,20-diene (7a, R = $CH_2C_6H_5$). The pyridine **11a** (R = $CH_2C_6H_5$) (500 mg, 0.94 mmol) was dissolved in ca. 10 mL of $CHCl_3$. Methyl fluorosulfonate (0.5 mL, excess, CAUTION. DANGEROUS CHEMICAL) was added, and the solution was stirred overnight. A white precipitate formed. The solution was evaporated, and CH_2Cl_2 was added and evaporated again to remove the last traces of methyl fluorosulfonate. The pyridinium salt in this case was not characterized but was dissolved immediately in 50 mL of pH 7 buffer solution to which sodium dithionite (1 g, 5.75 mmol) was added. The solution was stirred for 15 min after which time the dihydropyridine began to precipitate. The solid was collected, and the aqueous phase was extracted with CH_2Cl_2 and then dried over $MgSO_4$. After evaporation of the solvent, the solids were combined and recrystallized carefully from CH_2Cl_2/diethyl ether to give 435 mg (0.80 mmol, 85%) of **7a** (R = $CH_2C_6H_5$). A satisfactory melting point could not be obtained owing to decomposition: IR (Nujol) 3300, 3000, 1750, 1695, and 1580 cm^{-1}; $[\alpha]^{20}_D$ −134.1°, $[\alpha]^{20}_{578}$ −146.1°, and $[\alpha]^{20}_{546}$ −192.5° (*c* 1.39, $CHCl_3$); ^1H NMR (CD_3CN) δ 3.08 (s, 3 H, CH_3), 3.0–3.2 (br, 6 H, $2CH_2$/s, DHP-CH_2), 3.25–3.50 (m, 4 H, CH_2OCH_2) 3.90–4.20 (m, 4 H, $2CO_2CH_2$), 4.60–4.80 (m, 2 H, 2C*H*), 6.85 (s, 2 H, DHP-2,6-C*H*), 5.80–6.25 (br, 2 H, 2N*H*), and 7.15 (br, 10 H, $2C_6H_5$). Owing to

instability, this material was used immediately for reductions; no attempt was made to obtain an analysis.

To determine the optical purity of **7a** (R = $CH_2C_6H_5$), a sample (0.984 mg, 1.806×10^{-3} mmol) was hydrolyzed for 24 h at 105 °C in 5.7 N HCl. The hydrolyzate was evaporated to dryness in a desiccator over P_2O_5 and NaOH pellets. Digestion was carried out in 0.5 mL of 0.36 M Tris–HCl buffer, 0.02 mL of 2 N LiOH, and 2.3 mg of L-amino acid oxidase, Type 4 obtained from Sigma Chemicals Co. By analysis, 3.604×10^{-3} mmol (99.8% recovery) of L-amino acid was measured.

18-Aza-3,14-dioxabicyclo[14.3.1]eicosa-1(19),16,17-triene-2,15-dione (13). A solution of 3,5-pyridinedicarboxylic acid (2.0 g, 12 mmol), 1,10-dibromodecane (3.65 g, 2 mmol), and Cs_2CO_3 (4.08 g, 12.5 mmol) in 1 L of DMF was stirred for 72 h at 70–80 °C. The DMF was evaporated, to the residue was added hot CH_2Cl_2, and the CsBr was filtered off. The crude product was flash-chromatographed over Kieselgel (Merck 60, 230–400-mesh ASTM, column length ~10 cm × 25 mm) with CH_2Cl_2 and $CH_2Cl_2/C_2H_5O_2CCH_3$ (1:1) (product) as eluents. The product was recrystallized from CH_2Cl_2/CH_3OH (1:30): yield 2.8 g (9.15 mmol, 75% yield); ^1H NMR ($CDCl_3$) δ 1.2–2.0 (m, 16 H), 4.3 (t, 4 H) 8.6 (s, 1 H), and 9.24 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 164.06 (s), 154.74 (d), 136.58 (d), 125.71 (s), 66.30 (t), 28.06 (t), 27.72 (t), 27.19 (t), and 26.59 (t); mass spectrum, *m/e* 305 (parent), calcd 305.

3,14-Dioxa-18-methyl-18-azoniabicyclo[14.3.1]eicosa-1(19),16,17-triene-2,15-dione perchlorate was synthesized by method B on a 3 mmol scale. Recrystallization from CH_3OH yielded 65%; ^1H NMR (CD_3CN) δ 1.3–1.8 (m, 16 H), 4.4 (m, 4 H), 4.5 (s, 3 H), 9.1 (s, 2 H), and 9.25 (s, 2 H).

18-Aza-3,14-dioxa-18-methylbicyclo[14.3.1]eicosa-1,16-diene-2,15-dione was synthesized as described for **7a**, on a 1 mmol scale: ^1H NMR (CD_3CN) δ 1.2–1.9 (m, 16 H), 3.0 (s, 3 H), 3.25 (s, 2 H), 4.1 (m, 4 H), and 6.85 (s, 2 H).

(5*S*,15*S*)-5,15-Diisopropyl-3,17-dioxa-6,10,14,21-tetraazatricyclo-[17.3.1.1^{8,12}]tetracosa-1(22),8,10,12,19,20-hexaene-4,7,13,16-tetrone (15) was synthesized as described for **12a** (R = $CH(CH_3)_2$) from the diacid (740 mg, 2.3 mmol), Cs_2CO_3 (excess), and 3,5-bis(bromomethylene)-pyridine in DMF (0.5 L). The product after recrystallization from $CHCl_3$/ether/CH_3OH was obtained as a white solid (600 mg, 1.28 mmol, 58% yield) mp 264–266 °C: $[\alpha]^{20}_D$ −200° (*c* 0.2, DMF); ^1H NMR ($CDCl_3/CD_3OD$) δ 1.05 (dd, 12 H), 2.0–2.5 (m, 2 H), 4.62 (d, 2 H), 5.20 (q-AB system, 4 H), 7.85 (s, 1 H), 8.05 (s, 1 H), 8.50 (s, 2 H), and 8.80 (s, 2 H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 169.77 (s), 166.44 (s), 149.85 (d), 137.62 (d), 132.52 (d), 130.93 (s), 129.62 (s), 63.89 (t), 58.79 (d), 30.56 (d), 18.69 (q), and 17.87 (q); IR (KBr) 3550, 3450, 3050, 1760, and 1665 cm^{-1}; exact mass spectrum *m/e* calcd for $C_{24}H_{25}N_4O_6$ 468.203, found 468.201.

***N*,*N*′-Bis[(1*S*)-1-carboxy-2-methylpropyl]-2,6-bis(aminocarbonyl)-pyridine.** Starting from 22 g (131 mmol) of pyridine-2,6-dicarboxylic acid, 34 g (81 mmol, 62% yield) of product was isolated. The product contains three molecules of water; mp 179–180 °C: ^1H NMR (CD_3OD) (H_2O peak set at 4.8 ppm) δ 0.9 (d, 12 H, *J* = 6, 3 Hz), 1.9–2.45 (m, 2 H), 4.45 (d, 2 H, *J* = 6.3 Hz), and 8.35 (m, 3 H); exact mass spectrum, *m/e* calcd for $C_{17}H_{23}N_3O_6$ 365.159, found 365.158; ^{13}C NMR (CD_3OD) δ 18.24 (q), 19.57 (q), 31.90 (d), 58.93 (d), 126.06 (d), 140.57 (d), 149.51 (s), 165.03 (s), and 174.19 (s); $[\alpha]^{20}_D$ +37.6° (*c* 0.9, CH_3OH).

(4*S*,14*S*)-4,14-Diisopropyl-6,9,12-trioxa-3,15,21-triazabicyclo-[15.3.1]heneicosa-1(21),17,19-triene-2,5,13,16-tetrone (17a). Starting from 3.1 g (7.4 mmol) of the previously described diacid, 1.6 g (3.6 mmol, 45% yield) of product was isolated by using the cesium salt method for ring closure, mp 163 °C: ^1H NMR ($CDCl_3$) δ 0.95 (dd, 12 H, *J* = 6 Hz), 2.25 (m, 2 H), 3.35–4.25 (m, 6 H), 4.50–4.70 (dd, 2 H), 4.70–5.05 (dd, 2 H), and 7.85–8.40 (m, 5 H); exact mass spectrum, *m/e* calcd for $C_{21}H_{29}N_3O_7$ 435.206, found 435.202; ^{13}C NMR ($CDCl_3$) δ 16.11 (q), 16.70 (q), 30.74 (d), 56.12 (d), 63.27 (t), 66.99 (t), 123.39 (d), 137.12 (d), 146.65 (s), 160.67 (s), and 166.99 (s); $[\alpha]^{20}_D$ −70.1° (*c* 0.99, CH_2Cl_2).

***N*,*N*′-Bis[(1*S*)-1-carboxy-2-methylpropyl]1,3-bis(aminocarbonyl)-benzene.** Starting from 23.3 g (140 mmol) of isophthalic acid, 32 g (78.2 mmol, 56% yield) of product was isolated, mp 132–133 °C: ^1H NMR ($CD_3OD/CDCl_3$) δ 1.05 (d, 12 H, *J* = 6.2 Hz), 2.0–2.5 (m, 2 H), 4.35–4.6 (d, 2 H, *J* = 5 Hz), and 7.25–8.3 (m, 4 H); exact mass spectrum, *m/e* calcd for $C_{18}H_{24}N_2O_6$ 364.163, found 364.163; ^{13}C NMR (CD_3OD) δ 22.56 (q), 23.52 (q), 35.63 (d), 64.10 (d), 136.16 (d), 133.50 (d), 135.29 (d), 139.61 (s), 173.24 (s), and 179.34 (s); $[\alpha]^{20}_D$ +22.8° (*c* 0.90, MeOH).

(4*S*,14*S*)-4,14-Diisopropyl-6,9,12-trioxa-3,15-diazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,5,13,16-tetrone (16a). Starting from 4.8 g (11.7 mmol) of diacid, 1.7 g (3.9 mmol, 33% yield) of product was isolated, mp 242.0–243.5 °C: ^1H NMR ($CDCl_3$) δ 1.09 (d, 12 H, *J* = 6 Hz), 2.05–2.65 (m, 2 H), 3.82–4.01 (m, 4 H), 4.28–4.61 (m, 4 H), 4.83–4.99 (dd, 2 H, *J* = 5.9 Hz), and 6.95–7.95 (m, 5 H); exact mass spectrum, *m/e* calcd for $C_{22}H_{29}N_2O_7$ 434.205, found 434.205; ^{13}C NMR ($CDCl_3$) δ 17.66 (q), 18.23 (q), 31.32 (d), 57.58 (d), 64.22 (t), 68.72 (t), 123.56 (d), 127.72 (d), 129.56 (d), 133.67 (s), 167.33 (s), 169.90 (s); $[\alpha]^{20}_D$ −138.4° (*c* 1.14, CH_2Cl_2).

(7*S*,17*S*)-25-Methyl-9,12,15-trioxa-2,8,16,22-tetraoxo-3,21,25-triazatetracyclo[21.3.1.0^{3,7}.0^{17,21}]heptaeicosa-1(26),23(24)-diene (19a). The bis-phenacyl ester of the bis(prolinamide) of pyridine-3,5-dicarboxylic acid (2.5 g, 4.2 mmol), prepared as described above, was allowed to react with cesium thiophenolate (4.05 g, 16.4 mmol) in 75 mL of DMF as described for phenylalanine. The dicesium salt (2.2 g, 3.5 mmol, 84%) was suspended in dry DMF (250 mL) and allowed to react with 1,5-dibromo-3-oxopentane (820 mg, 3.5 mmol) at 50 °C for 48 h. The crude material was chromatographed over a 130-mm DEAE cellulose column which was eluted with cyclohexane/CH_2Cl_2 (3:1). There was obtained 450 mg (1.04 mmol, 34% based on cesium salt of **14a**), mp 228–231 °C; $[\alpha]^{20}_D$ −68.1°; $[\alpha]^{20}_{578}$ −71.8°, $[\alpha]^{20}_{546}$ −82.8°, $[\alpha]^{20}_{436}$ −157.6°, and $[\alpha]^{20}_{365}$ −297.9° (*c* 0.68, 96% EtOH); ^1H NMR ($CDCl_3$) δ 1.7–2.5 (m, 8 H, $2CH_2CH_2$), 3.2–3.8 (m, 8 H, $CH_2OCH_2 + 2CH_2N$), 4.0–4.4 (m, 4 H, $2CO_2CH_2$), 4.70 (t, *J* = 6 Hz, 2 H, 2 $CHCO_2$), 8.00 (br s, 1 H, pyr-4*H*), and 8.80 (br s, 2 H, pyr-2,6*H*); exact mass spectrum, *m/e* calcd for $C_{21}H_{25}N_3O_7$ 431.168, found 431.168.

Anal. Calcd for $C_{21}H_{25}N_3O_7$: C, 58.5; H, 5.8; N, 9.7. Found: C, 57.8; H, 5.9; N, 9.6.

The above material (200 mg, 0.46 mmol) was alkylated with methyl fluorosulfonate (0.5 mL) in CH_2Cl_2. The pyridinium salt was not isolated but was reduced immediately with $Na_2S_2O_4$ (500 mg, 2.87 mmol) as described for phenylalanine. The 1,4-dihydropyridine **19a** was isolated as a solid (200 mg, 0.45 mmol, 97%). The material was recrystallized from CH_2Cl_2/diethyl ether, but a satisfactory melting point was not obtained, owing to rapid oxidation of the solid: IR (Nujol) 3000, 1745, and 1655 cm^{-1}; $[\alpha]^{20}_D$ +11.9°, $[\alpha]^{20}_{578}$ +14.3°, and $[\alpha]^{20}_{546}$ +25.2° (*c* 0.2, $CHCl_3$); ^1H NMR (CD_3CN) δ 1.6–2.0 (m, 8 H, $2CH_2CH_2$), 3.2–3.6 (m, 10 H, pyr-CH_2 + CH_2OCH_2 + $2CH_2N$), 3.65 (s, 3 H, CH_3), 3.8–4.1 (m, 4 H, $2CO_2CH_2$), 4.65 (br t, 2 H, $CHCO_2$), and 6.85 (s, 2 H, pyr-2,6-*H*).

***N*,*N*′-Bis[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]-3,5-bis(aminocarbonyl)-1,4-dihydro-1-benzylpyridine (20a, R^1 = $CH_2C_6H_5$).** L-Valine methyl ester was prepared from the HCl salt in 91% yield. This was immediately coupled with pyridine-3,5-bis(carbonyl chloride) as described for the L-valine *tert*-butyl ester. From L-valine methyl ester (2.14 g, 1.6 mmol), there was obtained 2.39 g (0.61 mmol, 75% yield) of amide, which was crystallized from ethyl acetate/benzene to give white crystals, mp 148.7–152.1 °C: IR (KBr) 3360, 3090, 2980, 1745, 1680, 1650, 1565, and 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.10 (d, 2 H, pyr-2,6-*H*), 8.46 (t, 1 H, pyr-4-*H*), 7.22 (d, 2 H, N*H*), 4.78 (d of d, 2 H, NHC*H*), 3.78 (s, 6 H, OCH_3), 1.78–2.68 (m, 2 H, $(CH_3)_2CH$), and 1.01 (d, 12 H, $(CH_3)_2CH$); $[\alpha]^{28}_D$ +27.6°, $[\alpha]^{28}_{578}$ +29.2°, $[\alpha]^{28}_{546}$ +34.2°, $[\alpha]^{28}_{436}$ +70.6°, $[\alpha]^{28}_{365}$ +151.6° (*c* 1.00, $CH_3CO_2C_2H_5$).

Anal. Calcd for $C_{19}H_{27}N_3O_6$: C, 58.00; H, 6.92; N, 10.68. Found: C, 58.14; H, 6.95; N, 10.54.

The above pyridine (2.00 g, 5.1 mmol) was allowed to react with benzyl bromide (6.00 g, 35 mmol) in 25 mL of CH_2Cl_2. Reaction was complete after 24 h. Ether was added, and the precipitate was filtered with suction and washed several times with ether. There was obtained 2.78 g (4.9 mmol, 97% yield) of pyridinium bromide as white crystals which, after two crystallizations from ethanol/petroleum ether, had mp 190.0–191.1 °C: IR (KBr) 3410, 3200, 2970, 1735, 1675, 1555, and 1220 cm^{-1}; ^1H NMR (CD_3OD) δ 9.67 (d, 2 H, pyr-2,6*H*), 9.47 (t, 1 H, pyr-4*H*), 7.55 (br s, 5 H, C_6H_5), 6.08 (s, 2 H, N*H*), 4.72 (s, 2 H, CH_2N), 4.49 (d, 2 H, NHC*H*), 3.76 (s, 6 H, OCH_3), 1.92–2.17 (m, 2 H, $(CH_3)_2CH$), and 1.07 (dd, 12 H, $(CH_3)_2CH$); $[\alpha]^{22}_D$ −0.8°, $[\alpha]^{22}_{578}$ −0.4°, $[\alpha]^{22}_{546}$ +0.5°, $[\alpha]^{22}_{436}$ +16.7° (*c* 1.00, CH_3OH).

Anal. Calcd for $C_{26}H_{34}BrN_3O_6$: C, 55.32; H, 6.07; N, 7.44, Br, 14.16. Found: C, 55.35; H, 6.01; N, 7.35; Br, 13.95.

The above pyridinium salt (1.23 g, 2.2 mmol) yielded 0.99 g (2.0 mmol, 92% yield) of **20a** (R^1 = $CH_2C_6H_5$) when reduced under the conditions described for compounds **7**. The compound was obtained as a yellow powder, mp 63.6–76.3 °C: IR (KBr) 3380, 2960, 1735, 1890, 1580, 1530, and 1190 cm^{-1}; ^1H NMR (CD_3CN) δ 7.92 (s, 5 H, C_6H_5), 6.98 (s, 2 H, pyr-2,6-*H*), 6.24 (d, 2 H, N*H*), 4.43 (s, 2 H, $CH_2C_6H_5$), 4.32 (d of d, 2 H, NHC*H*), 3.61 (s, 6 H, OCH_3), 3.26 (s, 2 H, pyr-4,4-*H*), 1.80–2.32 (m, 2 H, $(CH_3)_2CH$), and 0.90 (d, 12 H, $(CH_3)_2CH$); exact mass spectrum, *m/e* calcd for $C_{26}H_{35}N_3O_6$ 485.252, found 485.257.

The material appeared to contain some unreduced pyridinium salt that could not be removed readily. The compound was therefore used as such.

The corresponding 2-methoxyethyl ester **20b** (R^1 = CH_3) was prepared in an analogous manner and was characterized on the basis of its ^{13}C NMR spectrum: ^{13}C NMR ($CDCl_3/CD_3CN$) δ 172.35 (s), 167.03 (s), 137.46 (d), 104.75 (s), 70.29 (t), 63.94 (t), 58.81 (d), 57.42 (q), 41.04 (q), 31.32 (d), 21.91 (t), 19.01 (q), and 18.14 (q).

3-(Chlorocarbonyl)pyridine. Nicotinic acid (5 g, 40.6 mmol) was refluxed for 3 h in $SOCl_2$ (20 mL) with a few drops of DMF. The $SOCl_2$ was distilled off, and the HCl form of the acid chloride was suspended in CH_2Cl_2 (50 mL) and used as such.

***N*-[(1*S*)-1-(Methoxycarbonyl)-2-methylpropyl]-3-(aminocarbonyl)-pyridine (21).** To a cooled (0 °C), stirred suspension of the above acid chloride (4.23 g, 30 mmol) in 50 mL of CH_2Cl_2 was added slowly L-valine methyl ester (3.93 g, 30 mmol) in CH_2Cl_2 and excess $(C_2H_5)_3N$ in CH_2Cl_2 at the same time. After addition, the mixture was stirred for 1 h. The CH_2Cl_2 was extracted with H_2O and brine and dried over $MgSO_4$. The crude product (3.2 g, 13.6 mmol, 45% yield) was recrystallized from CH_2Cl_2/ether (1:5); mp 100–101 °C; $[\alpha]^{20}_D$ +13.3° (*c* 0.9, DMF); exact mass spectrum, *m/e* calcd for $C_{12}H_{16}N_2O_3$ 236.116, found 236.115; ^1H NMR ($CDCl_3$) δ 1.0 (d, 6 H), 2.0–2.7 (m, 1 H), 3.7 (s, 3 H), 4.7 (dd, 2 H), 6.7 (d, 1 H) 7.3 (m, 1 H), 8.0 (d, 1 H), 8.6 (s, 1 H), and 8.9 (s, 1 H); ^{13}C NMR ($CDCl_3$) 171.86 (s), 165.38 (s), 151.44 (d), 147.91 (d), 134.60 (d), 129.27 (s), 122.62 (d), 57.37 (d), 51.47 (q), 30.44 (d), 18.43 (q), and 17.63 (q); IR (KBr) 3400, 3000, 1740, 1650, 1540, and 1200 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.01; H, 6.83; N, 11.86. Found: C, 60.77; H, 6.84; N, 12.01.

***N*-[(1*S*)-Methoxycarbonyl)-2-methylpropyl]-3-(aminocarbonyl)-1,4-dihydro-1-methylpyridine (21).** Alkylation was carried out on a 4 mmol scale by method B; the pyridinium perchlorate was obtained in 90% yield: ^1H NMR ($CDCl_3$) δ 1.0 (d, 6 H, $CH(CH_3)_2$), 2.3 (h, 1 H, $CH(CH_3)_2$), 3.8 (s, 3 H, NCH_3), 4.5 (s, 3 H, OCH_3), 4.6 (dd, 1 H, CHCO), 7.7 (d, 1 H, pyr-2-*H*), 8.1 (t, 1 H, pyr-5-*H*), and 8.65–9.1 (m, 3 H, pyr-4,6-*H* + N*H*).

This pyridinium salt was reduced in 68% yield by the method of Ohno:[25b] ^1H NMR ($CDCl_3$) δ 0.9 (d, 6 H, $CH(CH_3)_2$), 2.1 (h, 1 H, $CH(CH_3)_2$), 2.9 (s, 3 H, NCH_3), 3.15 (d, 2 H, CH_2), 3.7 (s, 3 H, OCH_3), 4.6 (m, 2 H, CHCO + N*H*), 5.5 (s, 1 H, pyr-5/6-*H*), 5.7 (s, 1 H, pyr-5/6-*H*), and 6.9 (s, 1 H, pyr-2-*H*).

Phenylglyoxylate Esters (22). Ethyl phenylglyoxylate was prepared by the method described by Kindler et al.[63] During the Friedel–Craft acylation, some ethylation at the para position of the benzene ring took place. This was due to the ethyl chloride that was formed on the preparation of the acid chloride and which was not removed quantitatively upon distillation. The mixture was saponified by boiling in a 10% KOH solution. The new esters were made by dissolving the phenylglyoxylic acid in an alcohol and leading HCl gas through. After 2-h reflux, the alcohol was distilled off, and the esters were purified by distillation where necessary.

Acid Chlorides (26) and Adipic Monoacid Chloride–Monomethyl Ester. A solution/suspension of diacid in dry C_6H_6 was refluxed with excess of $SOCl_2$ and a few drops of DMF for 3 h. The solvent and excess $SOCl_2$ were evaporated, and the diacid chlorides were dissolved in ether. The diacid chlorides were used as such assuming 100% conversion.

D-Tartaric acid chloride–cyclohexanone acetal was prepared by heating the diacid with PCl_5 followed by evaporation of the $POCl_3$.

***N*,*N*′-Bis[((1*S*)-1-methoxycarbonyl)-2-methylpropyl]-1,3-bis(aminocarbonyl)propane (27, X = CH_2, Z = OCH_3).** To a cooled (ice/salt, −5 °C), stirred solution of L-valine methyl ester (4 g, 30.5 mmol) and an excess of $(C_2H_5)_3N$ in ether (100 mL) was added slowly a solution of glutaryl chloride (15.1 mmol) in ether (50 mL). The temperature was kept below 0 °C. The solution was allowed to come to room temperature. Water was added, and the organic material was extracted with CH_2Cl_2. Workup gave a crude yellowish solid, which was recrystallized from $C_2H_5O_2CCH_3/C_6H_{12}$ (1:5) to give **27** (4.3 g, 12.0 mmol, 80% yield), mp 100–102 °C: $[\alpha]^{20}_D$ −21.8° (*c* 0.9, MeOH); ^1H NMR ($CDCl_3$) δ 0.9 (dd, 12 H), 1.9–2.4 (m, 8 H), 3.65 (s, 6 H), 4.55 (dd, 2 H), and 7.35 (d, 2 H); ^{13}C NMR (CD_3CN) δ 174.06 (s), 173.84 (s), 58.61 (d), 52.59 (q), 35.14 (t), 31.09 (d), 23.05 (t), 19.42 (q), and 18.48 (q); IR (Nujol) 3310, 1740, 1640, and 1540 cm^{-1}; exact mass spectrum, *m/e* calcd for $C_{17}H_{30}N_2O_6$ 358.210, found 358.211.

Anal. Calcd for $C_{17}H_{30}N_2O_6$: C, 56.98; H, 8.38; N, 7.82. Found: C, 56.56; H, 8.43; N, 7.80.

***N*,*N*′-Bis[(1*S*)-1-(ethoxycarbonyl)-2-methylpropyl]1,3-bis(aminocarbonyl)-2,2-dimethylpropane (27, X = $C(CH_3)_2$, Z = OC_2H_5)** was prepared as described above from L-valine ethyl ester (5.5 g, 38 mmol) and β,β-dimethylglutaryl chloride (18.8 mmol). Recrystallization from $C_2H_5O_2CCH_3$/methylcyclohexane (1:5) gave 5.0 g (12.1 mmol, 64% yield) of the product as a white solid, mp 119–121 °C: $[\alpha]^{20}_D$ −19.3° (*c* 0.65, MeOH); ^1H NMR ($CDCl_3$) δ 0.95 (dd, 12 H), 1.10 (s, 6 H), 1.25 (t, 6 H), 2.30 (A,B quartet, 4 H), 1.9–2.5 (m, 2 H), 4.10 (q, 4 H), 4.40 (dd, 2 H), and 7.30 (d, 2 H); ^{13}C NMR (CD_3CN) δ 173.11 (s), 172.75 (s), 61.61 (t), 58.78 (d), 46.79 (t), 34.59 (s), 31.10 (q), 29.47 (d), 19.53 (q), 18.34 (q), and 14.57 (q); exact mass spectrum, *m/e* calcd for $C_{21}H_{38}N_2O_6$ 414.275, found 414.274; IR (KBr) 3350, 3000, 1740, 1660, 1630, and 1550 cm^{-1}.

Anal. Calcd for $C_{21}H_{38}N_2O_6$: C, 60.87; H, 9.18; N, 6.76. Found: C, 60.81; H, 9.30; N, 6.76.

***N*,*N*′-Bis[(1*S*)-1-(ethoxycarbonyl)-2-methylpropyl]-1,3-bis(aminocarbonyl)-2-oxapropane (27, Z = OC_2H_5, X = O).** This compound was prepared as described above from 6.5 g (44.8 mmol) of L-valine ethyl ester and diglycolic acid chloride (22.4 mmol). This compound was isolated as an oil which was purified by column chromatography (flash) (column 10 cm × 25 mm diameter, Kieselgel (Merck 60, 230–400-mesh ASTM) using CH_2Cl_2 (major) and $CH_2Cl_2/C_2H_5O_2CCH_3$(1:1) (minor fraction) as eluents): yield 7 g (19.4 mmol, 87% yield) of a slightly yellow oil; $[\alpha]^{20}_D$ −20.2° (*c* 0.64, MeOH); ^1H NMR ($CDCl_3$) δ 0.92 (dd, 12 H), 1.20 (t, 6 H), 1.9–2.6 (m, 6 H), 4.15 (q, 4 H), 4.05 (s, 4 H), 4.50 (dd, 2 H), and 6.8 (d, 2 H); ^{13}C NMR (CD_3CN) δ 172.35 (s), 170.18 (s), 71.54 (t), 61.89 (t), 58.12 (d), 31.55 (d), 19.34 (q), 18.29 (q), and 14.53 (q); IR (KBr) 3400, 3000, 1740, 1690, 1545, 1210, and 1160 cm^{-1}; exact mass spectrum, *m/e* calcd for $C_{16}H_{28}N_2O_7$ 360.190, found 360.189.

General Procedure for Hydrolysis of 27. This is illustrated for *N*,*N*′-bis[(1*S*)-1-carboxy-2-methylpropyl]-1,3-bis(aminocarbonyl)propane (**28**, X = CH_2, Z = OH). A solution of 1.5 g (4.2 mmol) of diester **27** (X = CH_2, Z = OCH_3) in 100 mL of a 0.1 N NaOH solution in C_2H_5OH/H_2O (1:1) was stirred overnight at room temperature. The solution was neutralized with dilute HCl (±1 N) and evaporated. The resulting crystalline material was stripped with absolute C_2H_5OH to remove the water. The crude diacid was not purified, and the NaCl formed was not removed. After ^1H NMR (D_2O) identification (loss of ester groups), the diacid was used as such for the cyclization step: ^1H NMR (D_2O) δ 1.0 (dd, 12 H), 1.8–2.7 (m, 2 H), 4.1–4.3 (d, 2 H), and 4.8 (H_2O).

***N*,*N*′-Bis[(1*S*)-1-carboxy-2-methylpropyl]-1,3-bis(aminocarbonyl)-2,2-dimethylpropane (28, X = $C(CH_3)_2$, Z = OH).** Saponification was as described above: ^1H NMR (D_2O) δ 1.1 (d, 12 H), 1.2 (s, 6 H), 2.0–2.7 (m, 2 H), 2.6 (s, 4 H), 4.3 (d, 2 H), and 4.8 (H_2O).

***N*,*N*′-Bis[(1*S*)-1-carboxy-2-methylpropyl]-1,3-bis(aminocarbonyl)-2-oxopropane (28, Z = OH, X = O).** Saponification was as described above: ^1H NMR (D_2O) δ 1.1 (dd, 12 H), 2.0–2.6 (m, 2 H), 4.1–4.5 (m, 6 H), and 4.8 (H_2O).

(3*S*, 11*S*)-3,11-Diisopropyl-1,13-dioxa-4,10-diazacyclooctadecane-2,5,9,12-tetrone (31a, X = CH_2, Y = CH_2). A suspension of diacid **28** (1.39 g, 4.2 mmol), Cs_2CO_3 (2.4 g, 7 mmol), and 1,5-dibromopentane (1 g, 4.3 mmol) in 0.5 L of dry DMF was stirred for 72 h at 70–80 °C. The DMF was evaporated as well as possible, and the residue was dissolved in hot CH_2Cl_2. The hot solution was filtered over a P-4 glass filter to separate the NaCl and CsBr. After evaporation of the solvent, the crude product was column chromatographed (flash, Kieselgel, Merck 60, 230–400-mesh ASTM, length 10 cm × 25 mm diameter) with CH_2Cl_2 (gave DMF) and $CH_2Cl_2/C_2H_5O_2CCH_3$ (1:1) (gave product) as eluents. Evaporation of the solvent gave the product as a solid. Recrystallization from CH_2Cl_2/petroleum ether (40:60) gave 0.8 g (2.61 mmol, 48% yield) of product as white crystals, mp 174–176 °C: $[\alpha]^{20}_D$ −84.7° (*c* 1.7, MeOH); ^1H NMR ($CDCl_3$) δ 0.95 (d, 12 H), 1.4–2.6 (m, 14 H), 4.05 (m, 4 H), 4.4 (d, 2 H), and 6.4 (d, 2 H); ^{13}C NMR (CD_3CN) δ 174.29 (s) 172.54 (s), 66.02 (t), 59.32 (d), 35.51 (t), 31.20 (d), 29.45 (t), 24.67 (t), 23.15 (t), 19.43 (q), and 18.49 (q); IR (KBr) 3350, 3000, 1725, and 1550 cm^{-1}; exact mass spectrum, *m/e* calcd for $C_{20}H_{34}N_2O_6$ 398.242, found 398.244.

D-Tartaric acid–cyclohexanone acetal diacid chloride was prepared from the D-diethyltartaric acid by the method of Tsuzuki,[64] yield 32%, bp 130 °C (0.01 torr). Saponification of the diester of the method of Tsuzuki[64] gave the desired product in 83% yield. Treatment with PCl_5 gave the crude diacid chloride, which was used without purification.

***N*,*N*′-Bis[(1*S*)-1-(ethoxycarbonyl)-2-methylpropyl]-(1*R*,2*R*)-1,2-bis(aminocarbonyl)-1,2-(1,1-cyclohexanediyldioxy)ethane** was prepared as described for **27a** from L-valine ethyl ester (8.5 g, 17.5 mmol) and diacid chloride (2.31 g, 8.7 mmol) prepared as described above. Flash chromatography was used to isolate the product, using CH_2Cl_2 and CH_2Cl_2/CH_3OH (3:1) as eluents; the product was obtained as the last fraction (2.4 g, 5.3 mmol, 61% yield) as a slightly yellow oil: ^1H NMR ($CDCl_3$) δ 0.95 (d, 12 H), 1.2 (t, 6 H), 2.7 (m, 10 H), 1.9–2.5 (m, 2 H), 4.1 (q, 4 H), 4.45 (dd, 2 H), 4.6 (s, 2 H), and 7.25 (d, 2 H).

***N*,*N*′-Bis[(1*S*)-1-carboxy-2-methylpropyl]-(1*R*,2*R*)-1,2-bis(aminocarbonyl)-1,2-(1,1-cyclohexanediyldioxy)ethane.** Saponification was carried out as described for **28a**: ^1H NMR (D_2O) δ 1.1 (d, 12 H), 1.5–2.9 (m, 12 H), and 4.8 (H_2O + 4 H).

(3*S*,10*S*)-3,10-Diisopropyl-6,7-(1,1-cyclohexanediyldioxy)-1,12-dioxa-4,9-diazacycloheptadecane-2,5,8,11-tetrone (32). Synthesized as described for **34a** from the above diacid (1.43 g, 3.6 mmol), Cs_2CO_3 (1.8 g, 5.5 mmol), and 1,5-dibromopentane (850 mg, 3.7 mmol) in DMF (500 mL). Flash chromatography with CH_2Cl_2 (to remove DMF) and $CH_2Cl_2/C_2H_5O_2CCH_3$ (1:1) gave the product as a slightly yellow oil (900 mg, 1.81 mmol, 50% yield); $[\alpha]^{20}_D$ −9.7° (*c* 1.4, MeOH); ^1H NMR

($CDCl_3$) δ 0.95 (d, 12 H), 1.2–2.5 (m, 18 H), 3.7–4.3 (m, 8 H), and 7.3 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 172.07 (s), 171.66 (s), 113.92 (s), 77.58 (d), 65.92 (t), 59.82 (d), 36.10 (t), 31.15, 30.27 (d), 25.87 (t), 24.67 (t), 24.30 (t), 19.43 (q), and 18.57 (q); IR (neat) 3400, 3000, 1740, 1680, and 1540 cm^{-1}; exact mass spectrum, *m/e* calcd for $C_{25}H_{40}N_2O_8$ 496.278, found 496.280.

***N,N'*-Bis[(1*S*)-1-(ethoxycarbonyl)-2-methylpropyl] Bis(aminooxalate).** This was prepared as described for **27a**, from L-valine ethyl ester (2.25 g, 50 mmol) and oxalyl chloride (3.15 g, 24 mmol). Recrystallization from C_2H_5OH/H_2O gave 3.6 g (10.5 mmol, 44% yield) of a white solid compound, mp 73–75 °C: $[\alpha]^{20}_{578}$ −27.9° (*c* 0.53, MeOH); ^1H NMR ($CDCl_3$) δ 1.0 (d, 12 H), 1.30 (t, 6 H), 1.8–2.6 (m, 2 H), 4.25 (q, 4 H), 4.50 (dd, 2 H), and 7.85 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 170.10 (s), 158.95 (s), 61.02 (t), 57.44 (d), 30.96 (d), 18.57 (q), 17.37 (q), and 13.82 (q); exact mass spectrum, *m/e* calcd for $C_{16}H_{28}N_2O_6$ 344.195, found 344.196; IR (KBr) 3400, 3050, 1740, 1680, and 1530 cm^{-1}.

Dimethyl Ester: yield 34%, $[\alpha]^{20}_D$ −28.41° (*c* 0.33, MeOH), mp 106–106.5 °C; ^1H NMR ($CDCl_3$) δ 1.0 (d, 12 H), 1.8–2.5 (m, 2 H), 3.7 (6 H), 4.4 (dd, 2 H), and 7.8 (d, 2 H); exact mass spectrum, *m/e* calcd for $C_{14}H_{24}N_2O_6$ 316.160, found 316.160.

***N,N'*-Bis[(1*S*)-1-carbonyl-2-methylpropyl]Bis(aminooxalate).** Saponification as previously described: ^1H NMR (D_2O) δ 1.1 (d, 12 H), 1.9–2.5 (m, 2 H), 4.2 (d, 2 H), and 4.8 (H_2O).

(2*S*,7*S*)-2,7-Diisopropyl-9,12,15,18-tetraoxa-3,6-diazacyclooctadecane-1,4,5,8-tetrone (33). This was prepared as described from the diacid (1.3 g, 5 mmol), 3,6-dioxaoctyl 1,8-dimesylate (1 g, 5 mmol), and Cs_2CO_3 (3 g, 9 mmol) in 0.25 L of DMF. Flash chromatography (CH_2Cl_2 (DMF); $CH_2Cl_2/C_2H_5O_2CCH_3$ (1:1)) gave the product as a white solid, 300 mg (0.75 mmol, 15% yield), mp 167.5–168 °C: $[\alpha]^{20}_{578}$ −130.6° (*c* 0.25, MeOH); ^1H NMR ($CDCl_3$) δ 1.05 (d, 12 H), 2.0–2.6 (m, 2 H), 3.4–3.8 (m, 8 H), 4.0–4.6 (m, 6 H), and 7.5 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 169.80 (s), 159.32 (s), 70.68 (t), 68.69 (t), 65.02 (t), 58.41 (d), 30.09 (d), 19.06 (q), and 17.67 (q); IR (KBr) 3450, 3050, 1750, 1670, and 1530 cm^{-1}; exact mass spectrum, *m/e* calcd for $C_{18}H_{30}N_2O_8$ 402.200, found 402.199.

(5*S*,13*S*)-5,13-Diisopropyl-3,15-dioxa-6,12,19-triazabicyclo[15.3.1]-heneicosa-1(21),17,19-triene-4,7,11,14-tetrone (34). This was prepared from diacid **28**, (X = CH_2, Z = OH) (650 mg, 2.1 mmol) Cs_2CO_3 (1.8 g, 4 mmol), and 3,5-bis(bromomethylene)pyridine (560 mg, 2.1 mmol) in DMF (250 mL). Flash chromatography with CH_2Cl_2 removed DMF, and CH_2Cl_2/C_2H_5OH gave the product as slightly yellow crystals (460 mg, 1.06 mmol, 51% yield), mp 204.5–206 °C: $[\alpha]^{20}_D$ −78.5° (*c* 0.16, MeOH); ^1H NMR ($CDCl_3$) δ 0.95 (d, 12 H), 1.6–2.9 (m, 8 H), 4.33 (dd, 2 H), 5.1 (q-AB system, 4 H), 7.0 (d, 2 H), 7.7 (s, 1 H), and 8.35 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 173.41 (s), 171.03 (s), 148.92 (d), 135.73 (d), 131.48 (s), 63.36 (t), 58.06 (d), 34.45 (t), 30.43 (d), 22.17 (t), 19.00 (q), and 18.00 (q); IR (KBr) 3400, 3050, 1750, 1660, and 1560 cm^{-1}; exact mass spectrum, *m/e* calcd for $C_{22}H_{31}N_3O_6$ 433.221, found 433.220.

3,5-Bis(ethylcarbamido)pyridine (35).[65] To a cooled (0 °C) solution of 6.12 g (30 mmol) of pyridine-3,5-dicarbonyl chloride in CH_2Cl_2 (100 mL) was added dropwise 11 mL of ethylamine (170 mmol). The temperature was kept at 0 °C. After the addition was finished, the solution was stirred at room temperature for 2 h. The CH_2Cl_2 layer was washed with brine, dried over $MgSO_4$, and evaporated. The crude crystalline material was recrystallized from isopropyl alcohol/cyclohexane and gave 6.14 g (27.3 mmol, 91% yield) of white crystals, mp 158–160 °C: ^1H NMR ($CDCl_3$) δ 1.23 (t, 6 H, *J* = 7 Hz), 3.48 (dq, 4 H, *J* = 7 Hz), 7.95 (t, 2 H, *J* = 7 Hz), 8.55 (t, 1 H, *J* = 1.5 Hz), and 9.10 (d, 2 H, *J* = 1.5 Hz).

General Procedure for Reductions. This is given in detail for **7f** (R = $CH(CH_3)_2$); other reductions were carried out in a similar manner. A solution of **7f** (R = $CH(CH_3)_2$) (1 mmol), $Mg(ClO_4)_2 \cdot 1.5H_2O$ (1 mmol), and ethyl phenylglyoxylate (1.2 mmol) in $CH_3CN/CHCl_3$ (2:1, 10 mL) was deoxygenated with N_2 or Ar. The clear yellow solution was stored in the dark for 3–5 days. The reduction was followed by TLC (CH_2Cl_2, 5% MeOH), until the green spot from 1,4-dihydropyridine had almost disappeared. To the solution was added 1 mL of water. After evaporation of the solvent, the residue was treated with hot CH_2Cl_2 and filtered over silica gel (Merck 60) and washed with ether. The crude mixture of alcohol and ketone was separated by thick-layer chromatography (Kieselgel, GF_{254}) with ether/petroleum ether (40:60, 1:1) as eluent (R_f(ketone) = 0.52, R_f(alcohol) = 0.30). The alcohol and ketone were isolated by Soxlett extraction with ether and distilled in a Kugelrohr apparatus (bp 80–90 °C (0.03 torr)). The purity was established by ^1H NMR spectroscopy. The optical purity of ethyl mandelate was calculated from the rotation ($[\alpha]^{24}_D$ −126.2° ($CHCl_3$) or $[\alpha]^{24}_D$ −104° (EtOH) for the pure *R* enantiomer), $[\alpha]^{20}_D$ +94.1° (*c* 0.6, EtOH), yield 70%, optical yield 90° (*S*).

The enantiomeric excesses measured for several mandelate esters were calculated from the ^{19}F NMR spectra from the "Mosher ester" derivatives, synthesized as described by Mosher and co-workers[42] in quantitative yields (within the limits of the measurements, i.e., ±5%).

7a, R = $CH(CH_3)_2$: yield 61%; $[\alpha]^{20}_D$ +89.9 (*c* 0.76, EtOH); optical yield 86% (*S*); ^{19}F NMR ($CDCl_3$) δ 72.26 (*R,R*), 72.48 (*R,S*) (ppm relative to $CFCl_3$), in relative proportion of 9:91, ee 82% (*S*).

7b, R = $CH(CH_3)_2$: yield 50%; $[\alpha]^{20}_D$ +44.7° (*c* 0.92, EtOH); optical yield 43% (*S*).

7c, R = $CH(CH_3)_2$: yield 60%; $[\alpha]^{20}_D$ +56° (*c* 0.8, EtOH); optical yield 54% (*S*).

7e, R = $CH(CH_3)_2$: yield 50–75%; $[\alpha]^{20}_D$ +58–75° (*c* 0.5, EtOH); optical yield 55–70% (*S*).

7g, R = $CH(CH_3)_2$: yield 80%; $[\alpha]^{20}_D$ +91° (*c* 0.6, EtOH); optical yield 88% (*S*).

7g, R = $CH(CH_3)_2$, D-valine: yield 80%; $[\alpha]^{20}_D$ −87.5° (*c* 0.7, EtOH); optical yield 87% (*R*).

7h, R = $CH(CH_3)_2$: yield 75%; $[\alpha]^{20}_D$ +85° (*c* 0.6, EtOH); optical yield 85% (*S*).

7i, R = $CH(CH_3)_2$: yield 75%; $[\alpha]^{20}_D$ +57° (*c* 0.5, EtOH); optical yield 55% (*S*).

7j, R = $CH(CH_3)_2$: yield 65%; $[\alpha]^{20}_D$ +42° (*c* 0.3, EtOH); optical yield 42% (*S*).

7k, R = $CH(CH_3)_2$: yield 65%; $[\alpha]^{20}_D$ +90° (*c* 0.33, EtOH); optical yield 86% (*S*).

7l, R = $CH(CH_3)_2$: yield 50%; $[\alpha]^{20}_D$ +63° (*c* 1, EtOH); optical yield 60% (*S*); ^{19}F NMR ($CDCl_3$) δ −72.23 (*R,R*), −72.48 (*R,S*), in relative proportion of 17:83, ee 66% (*S*).

7m, R = $CH(CH_3)_2$: yield 64%; ^{19}F NMR ($CDCl_3$) δ −72.30 (*R,R*), −72.64 (*R,S*), in relative proportion of 31:69, ee 38% (*S*).

7n, R = $Ch(CH_3)_2$: yield 46%; $[\alpha]^{20}_D$ +47° (*c* 0.5, EtOH); optical yield 45% (*S*).

7o, R = $CH(CH_3)_2$: yield 80%; ^{19}F NMR ($CDCl_3$) δ −72.20 (*R,R*), −72.65 (*R,S*); in relative proportion of 37:63, ee 26% (*S*).

7p, R = $CH(CH_3)_2$: yield 50%; $[\alpha]^{20}_D$ +65° (*c* 1, EtOH); optical yield 63% (*S*); ^{19}F NMR ($CDCl_3$) δ −72.21 (*R,R*), −72.55 (*R,S*); in relative proportion of 18:82, ee 64% (*S*).

7a, R = CH_3: yield 62%; $[\alpha]^{20}_D$ +66° (*c* 0.5, EtOH); optical yield 65% (*S*); ^{19}F NMR ($CDCl_3$) δ −72.25 (*R,R*), −72.50 (*R,S*), in relative proportion of 17:83, ee 66% (*S*).

7a, R = $CH_2C_6H_5$: yield 50%; $[\alpha]^{20}_D$ +90° (*c* 0.62, EtOH); optical yield 87% (*S*).

7f, R = $CH_2C_6H_5$: yield 70%; $[\alpha]^{20}_D$ +83° (*c* 0.2 (EtOH); optical yield 80% (*S*).

7o, R = $CH_2C_6H_5$: yield 60%; $[\alpha]^{20}_D$ +58° (*c* 0.6, EtOH); optical yield 55% (*S*).

7q, R = $CH(CH_3)_2$. The insoluble coupled 1,4-dihydropyridine was suspended in CH_3CN, and $Mg(ClO_4)_2 \cdot 1.5H_2O$ was added. After addition of the perchlorate, the 1,4-dihydropyridine dissolved. The reaction was followed by ^1H NMR. The 1,4-dihydropyridine signals disappeared in time (≃6 days), and the pyridinium salt was formed. To the mixture was added 10 mL of 96% EtOH and a drop HCl, and the mixture was boiled for 0.5 h. After the workup procedure, no ethyl mandelate could be isolated, even after several attempts and workup procedures. Only a small amount of a white crystalline material (45 mg) could be isolated. This compound was not soluble in H_2O, ether, or CH_2Cl_2, has a mp 230–231 °C, a mass peak at *m/e* 224, and the following IR: IR (Nujol) 3225, 2950, 1625, 1575, 1530, 1310, 1245, 1090, and 900 cm^{-1}. The structure could not be resolved.

19a: yield 55%; $[\alpha]^{20}_D$ +2.8° (*c* 1, EtOH); no induction.

20b: yield 70%; $[\alpha]^{20}_D$ −20° (*c* 0.2, EtOH); optical yield 18% (*R*).

6: yield 40%.

13. The 1,4-dihydropyridine dissolved poorly in $CH_3CN/CDCl_3$. The yield of ethyl mandelate was only 6%.

21: yield of ethyl mandelate 58%; $[\alpha]^{20}_D$ −5° (*c* 0.2, EtOH); optical yield 5% (*R*).

Reduction of ketopantolactone by **7f** (R = $CH(CH_3)_2$) was carried out as described for ethyl phenylglyoxylate: yield 24%; $[\alpha]^{20}_D$ +20.6° (*c* 0.43, H_2O); optical yield 41% (*S*) ($[\alpha]^{20}_D$ 50.7° (H_2O) for the pure *S* enantimer[66]).

Reductions of Phenylglyoxylate Esters (22) by 7f (R = $CH(CH_3)_2$) to the Corresponding Mandelate Esters. Reactions were carried out as described for ethyl phenylglyoxylate. Data for the alcohols follow.

23 (R^1 = C_6H_5, R^2 = $CO_2CH(CH_3)_2$): yield 67%, bp 100 °C (0.2 torr); ^1H NMR ($CDCl_3$) δ 1.3 (d, 6 H), 3.5 (br s, 1 H), 5.05 (s, 1 H), 5.1 (h, 1 H), and 7.3 (s, 5 H); ^{19}F NMR ($CDCl_3$) δ −71.75 (*R,R*), −72.16 (*S,R*), in relative proportion of 22:78, ee 56% (*S*).

23 ($R^1 = C_6H_5$, $R^2 = CO_2CH_3$): yield 80%, bp 120 °C (0.2 torr), $[\alpha]^{20}_D$ +150.5° (*c* 0.5, C_6H_6); optical yield 84% (*S*) ($[\alpha]^{20}_D$ 174.8° (C_6H_6) for the pure *S* enantiomer[67]); ^1H NMR ($CDCl_3$) δ 3.3 (br s, 1 H), 3.75 (s, 3 H), 7.3 (s, 5 H); ^{19}F NMR ($CDCl_3$) δ −72.07 (*R,R*), −72.21 (*R,S*), in relative proportion of 10:90, ee 80% (*S*).

23 ($R^1 = C_6H_5$, $R^2 = CO_2(CH_2)_2OCH_3$): yield 61%; ^1H NMR ($CDCl_3$) δ 3.15 (s, 3 H), 3.4 (m, 3 H), 4.1 (m, 2 H), 5.0 (s, 1 H), 7.2 (s, 5 H); ^{19}F NMR ($CDCl_3$) δ −71.97 (*R,R*), −72.70 (*R,S*), in relative proportion of 25:75, ee 50% (*S*).

23 ($R^1 = 4\text{-}C_2H_5C_6H_4$, $R^2 = CO_2CH(CH_3)_2$): yield 55%, bp 110 °C (0.2 torr); ^1H NMR ($CDCl_3$) δ 1.4 (d, 6 H), 1.6 (q, 2 H), 3.4 (br s, 1 H), 5.1 (s, 1 H), 5.1 (h, 1 H), 7.2–7.5 (m, 4 H); ^{19}F NMR ($CDCl_3$) δ −71.81 (*R,R*), −72.17 (*S,R*), in relative proportion of 26:74, ee 48% (*S*).

Reductions of Activated Ketones 22 by 7a, R = $CH(CH_3)_2$, to the Corresponding Alcohols. 23 ($R^1 = C_6H_5$, $R^2 = CF_3$): yield 58%; $[\alpha]^{22}_D$ +9.7° (*c* 0.2, EtOH); optical yield 68% (*S*) ($[\alpha]^{24}_D$ +14.2° (C_6H_6) for pure *S* enantiomer[68]).

23 ($R^1 = C_6H_5$, $R^2 = CONHC_2H_5$): yield 37%; $[\alpha]^{20}_D$ +26.5° (*c* 0.58, EtOH); optical yield 78% (*S*) ($[\alpha]^{16}_D$ −34.4 (EtOH) for the pure *R* enantiomer[69,70]).

23 ($R^1 = C_6H_5$, $R^2 = CONH_2$): yield 69%; $[\alpha]^{9}_D$ +47.8° (*c* 0.55, CH_3COCH_3); optical yield 64% (*S*) ($[\alpha]^{9}_D$ +74.4° (CH_3COCH_3) for the pure *S* enantiomer[70,71]).

Reductions of Activated Ketones 22 by 7a, R = $CH_2C_6H_5$, to the Corresponding Alcohols 23. 23 ($R^1 = C_6H_5$, $R^2 = CONHC_2H_5$): yield 30%; $[\alpha]^{16}_D$ +29.1° (*c* 0.43, EtOH); optical yield 85% (*S*).

23 ($R^1 = 3\text{-}C_6H_5OC_6H_4$, $R^2 = CO_2CH_3$): yield 55%; $[\alpha]^{20}_D$ +45.8° (*c* 0.36, EtOH); optical yield 60% (*S*) ($[\alpha]^{25}_D$ +75.9° (MeOH) for the pure *S* enantiomer[72]).

23 ($R^1 = 3\text{-}C_6H_5OC_6H_4$, $R^2 = CONH_2$): yield 58%; $[\alpha]^{20}_D$ +6.3° (*c* 1.2, CH_3OH); optical yield 21% (*S*) ($[\alpha]^{25}_D$ +30.3° for the pure *S* enantiomer[73]).

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Supplementary Material Available: Details of synthesis, melting points, NMR spectra, mass spectra, and optical rotations of the compounds not listed belonging to the series **10**, **11**, **12**, **14**, **17**, **19**, **20**, **21**, **26**, **27**, and **31** together with other necessary synthetic information and references (43 pages). Ordering information is given on any current masthead page.

Substituent and Conformational Effects on the Ring Current in 9-Arylmethylenecyclooctatrienyl Anions

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Abstract: Treatment of *anti*-9-[1-(4-X-phenyl)]-*cis*-bicyclo[6.1.0]nona-2,4,6-trienes (**4a–e**) (X = OCH_3, CH_3, H, Cl, and Br) with lithium amide in liquid ammonia causes formation of the corresponding 9-[1-(4-X-phenyl)]methylenecyclooctatrienyl anions (**1a–e**). A conformational analysis based on their ^1H NMR spectra led to the conclusion that electron acceptors cause an increase in the angle (θ) formed by the planes of the two rings in **1a–e** and that θ is smaller than in the corresponding (9-[1-(4-X-naphthyl)]methylenecyclooctatrienyl)lithiums (**2a–d**) (X = OCH_3, CH_3, H, and Cl). The chemical shifts of the eight-membered ring protons in **1a–e** and **2a–d** in liquid ammonia (as well as in hexamethylphosphoramide for **2a–d**) exhibit an inverse substituent effect when plotted against Hammett σ parameters. This effect arises from a decreased paramagnetic contribution to the ring current in the eight-membered ring as π-electron donors cause an increase in the energy gap between occupied and unoccupied orbitals, particularly the HOMO and LUMO. This conclusion is supported by ring current calculations based on the London–McWeeny formalism. Comparison of the ^1H NMR spectra of **1c**, **2c**, and 9-(2-naphthyl)methylenecyclooctatrienyl anion (**3**) demonstrates a dependence of the ring current in the eight-membered ring on θ. The relationship between Hückel molecular orbital parameters and the paramagnetic component of the ring current is also discussed.

The existence of a "ring current" in planar, cyclic, delocalized molecules perturbed by an external magnetic field has been inferred from the enhanced diamagnetic susceptibility (diamagnetic susceptibility exhaltation)[2,3] exhibited by these compounds as well as from their unique shielding and deshielding effects on nearby magnetic nuclei (most commonly protons) as determined by NMR spectrometry. The ring current model has been the target of some criticism[4,5] (which has in each case been answered[6,7]) and is now generally accepted.[8]

Ring currents can, in principal, be understood on the basis of the Ramsey screening tensor,[9] which is the sum of a diamagnetic (σ_d) and a paramagnetic term (σ_p), the average values of which are given by

$$\sigma_d = \frac{e^2}{3mc^2} \langle \psi_0 | \sum_i \mathbf{r}_i^{-1} | \psi_0 \rangle \quad (1)$$

and

$$\sigma_p = -\frac{e^2}{3mc^2} \sum_n (\epsilon_n - \epsilon_0)^{-1} \langle \psi_0 | \sum_i \mathbf{L}_i r_i^{-3} | \psi_n \rangle \langle \psi_n | \sum_i \mathbf{L}_i | \psi_0 \rangle + \text{c.c.} \quad (2)$$

In these equations, the wave functions for the ground state (ψ_0) and excited states (ψ_n) have eigenvalues ϵ_0 and ϵ_n, respectively,

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