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HOST–GUEST COMPLEXATION—37

SYNTHESIS AND BINDING PROPERTIES OF A TRANSACYLASE PARTIAL MIMIC WITH IMIDAZOLE AND BENZYL ALCOHOL IN PLACE

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Abstract—The design and 30-step synthesis of a transacylase partial mimic is described. The target catalyst combines a macrocyclic binding site, a hydroxymethyl group, and an imidazole group organized to act cooperatively through their attachment to a quaterphenyl support structure. The binding site is composed of three cyclic urea units in a tripod arrangement, rigidified by their incorporation into a macrocycle along with two anisyl and one *m*-xylyl spacer units. The binding and catalytic sites are complementary to amino acid ester salts. The host catalyst collects and orients through complexation the guest substrate to provide substantial rate enhancements for transacylation of amino ester salts. The free energies are reported for the host in $CDCl_3$ binding the picrate salts of Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$ and t-$BuNH_3^+$.

The design of organic compounds, of organic reactions and of synthetic sequences provides much of the challenge and attractive character of research in organic chemistry. Because of the infinite number of possible structures, the choice of synthetic target compounds must have a rationale which guides the selection. Natural product targets are provided by chemical evolution, and their syntheses enjoy the legitimacy of an association with nature. A natural product synthetic chemist "climbs the mountain because it is there", the challenge being that of getting to the top. Other researchers choose their targets precisely because "they are not there, but must be designed". In research on non-natural compounds, the targets are often moving, so a series of compounds are required. The legitimacy of the research is established by the physical, chemical or pharmacological properties that the final compounds exhibit. The challenge is to *design* and *synthesize* compounds with exciting new properties that pose and answer scientific questions or solve practical problems.

The synthesis reported here was inspired by the ability of the serine transacylases to catalyze reactions with high structural recognition at rapid rates under mild reaction conditions. The active sites of these enzymes from various organisms have in common a binding site, a serine hydroxyl, a histidine imidazole, and an aspartate carboxyl which converge on one another through their incorporation in a concave cavity of a protein support structure. These latter protein backbones from various species differ widely in their molecular weights and sequences. The active sites appear to be "evolutionary end points" that are largely preorganized to be complementary to esters and amides which are collected and oriented for reaction by complexation.[2] In our research, we assume that if a binding site and these same catalytic functional groups are preorganized by attachment to non-peptide support structures in synthetic hosts, the compounds will catalyze the reactions of complementary guests by mechanisms that resemble in part the catalysis of reactions by the transacylase enzymes.

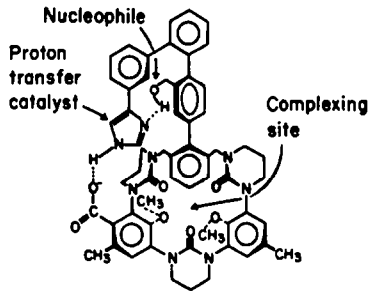
Target compounds

Through extensive examination of Corey–Pauling–Koltun models of potential transacylase mimics, we designed target catalyst **1**, possessing binding and catalytic groups preorganized to be complementary to salts of aminoesters or aminoamides. Compound **1** possesses the other desired features of relatively low molecular weight, of potential synthetic viability, and of providing an incremental approach to **1** through a series of model compounds (**2**–**4**) of successively decreasing complexity. Model host **5** was first prepared to see if it provided strong tripodal hydrogen bonding to alkylammonium salts in complexes of predictable structure. The association constant (K_a) of **5** with $(CH_3)_3CNH_3^+$ picrate in $CDCl_3$ was $K_a = 5 \times 10^9$ M^{-1}, and the crystal structure of $5 \cdot (CH_3)_3CNH_3^+$ was as anticipated from molecular model examination.[3]

Accordingly, **3** was prepared and found to react in $CDCl_3$ with **6** to give **7**, a transformation that was kinetically first order in R_3N/R_3NHClO_4 buffer ratio, where R_3N is diisopropylethylamine. The reaction showed saturation kinetics and competitive inhibition by added $NaClO_4$, whose cation **3** complexes strongly. Comparison of the second-order rate constants for acylation of **3** and the non-complexing model compound **4** showed that **3**, by collecting and orienting the reactants through complexation, provided a rate constant increase over that of **4** of $\sim 10^{11}$. The ground states in this comparison are uncomplexed **3**, **6** and **4** on the one hand, and the rate-limiting transition states for transacylation on the other.[3] These results encouraged us to prepare potential host catalyst **2**, in the hope that the imidazole group would eliminate the need for the presence of the external R_3N base, which was needed in the transacylation of **3**. This paper reports the synthesis of **2**, and companion compounds needed for rate comparisons. The kinetics will be reported elsewhere.

Synthesis

The total synthesis of **2** was accomplished in 30 steps from commercially available compounds by a highly convergent scheme. The longest linear sequence



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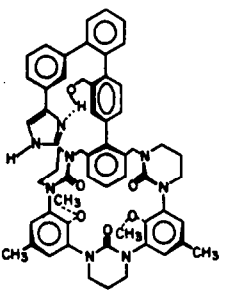

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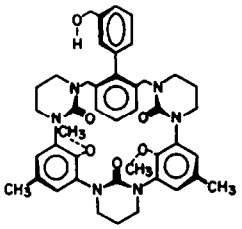

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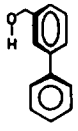

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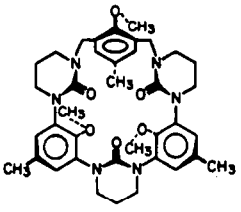

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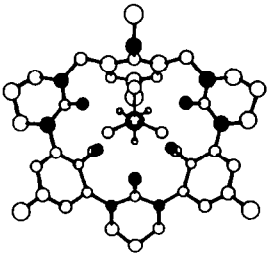
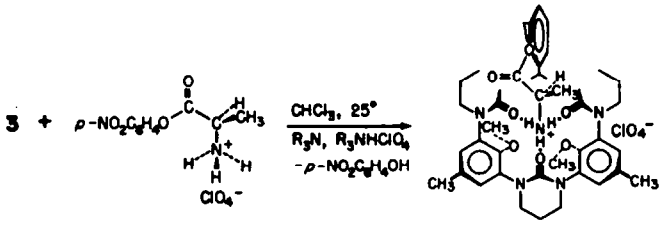


5·t-BuNH$_3^+$



6 7

involved 17 steps which provided an overall yield of 0.9%. The key macroring-closing reaction (Chart 1) involved condensation of the quateraryl dibromide **9** (whose synthesis is described here) with the previously reported quinquenuclear compound **8** (synthesis already reported†[3]) to produce **10** (68%). Mild acid treatment of **10** deprotected the imidazole to give **11**, with the hydroxyl group still protected (74%), a compound needed for kinetic comparisons. Stronger acid treatment of **10** deprotected both the imidazole and hydroxyl groups to give **2** (64%, Chart 1).‡

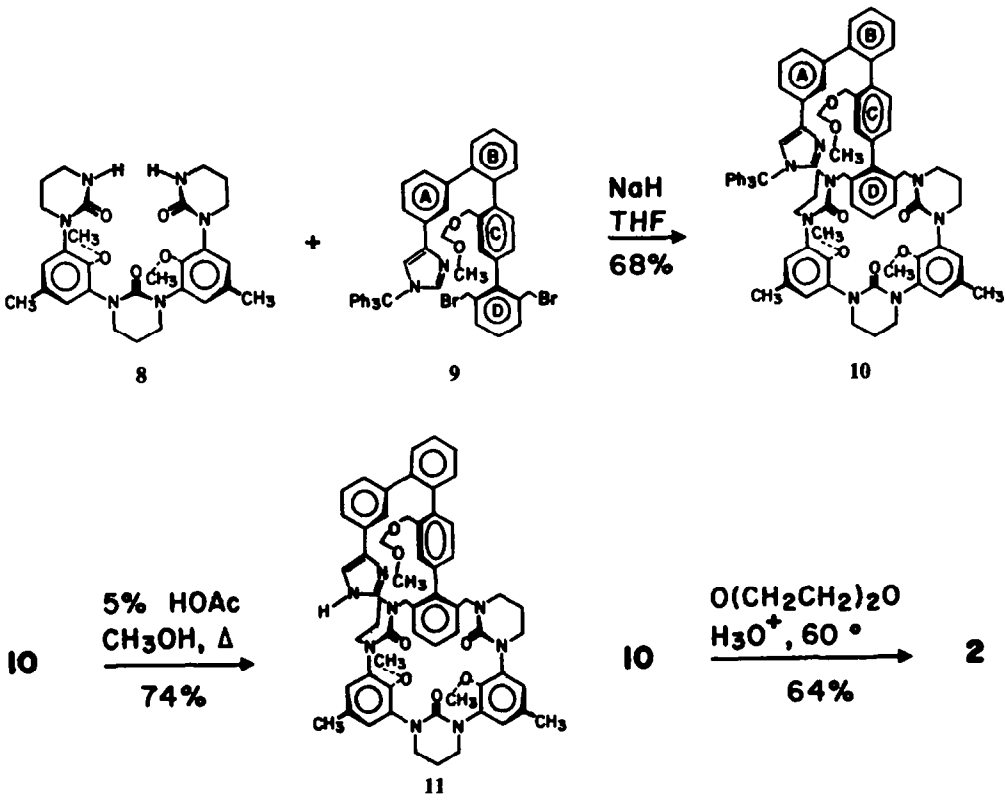
The key step in the preparation of the quateraryl bridging unit **9** was the Negishi *et al.*[4] aryl–aryl coupling of aryl iodide **12** with aryl bromide **13** to give the triply protected **14** (85%, Chart 2). The high yield to give such a hindered compound suggests that the reaction might have been templated by Pd coordinating simultaneously to the imidazole and $CH_2OCH_2OCH_3$ groups. Desilylation of **14** produced diol **15** (87%), which was converted under relatively neutral conditions to dibromide **9** (82%).[5] Models of **9** suggest its imidazole moiety might be benzylated intramolecularly. Although the geometry required for an S_N2 reaction is far from ideal, such a reaction might account for the instability of **9**. Compounds **16** and **17**, required for kinetic comparisons, were prepared from **15** by the conventional reactions outlined in Chart 2.

Chart 3 outlines the syntheses of the biphenyl unit **12**. Ketalization of commercial *m*-bromoacetophenone gave **18**[6] (89%), which was coupled to *o*-diiodobenzene by Negishi *et al.*'s method[4] to give **19**, deprotection of which provided iodoketone **20** in 35% for the two steps. This substance was α-brominated[7] to provide **21**, which without full characterization was refluxed in formamide.[8] The iodoimidazole produced (**22**) was tritylated to give the desired **12** in 32% yield for the three steps.

The second biphenyl unit, **13**, required the longest synthetic sequence. Purchasable 2,6-dimethylaniline was converted to 2,6-dimethylfluorobenzene[9a] (66%), oxidation of which with $KMnO_4$–pyridine[9b] afforded 2-fluoro-1,3-benzenedicarboxylic acid (48%).[9c] This diacid by sequential treatment with $SOCl_2$, $HOCH_2C(CH_3)_2NH_2$ and again $SOCl_2$ by a Meyers-type synthetic sequence[10] gave **23** (64% overall).[11] The two oxazolino groups of **23** activated the fluorine for nucleophilic aromatic substitution by the less hindered carbon of the double Grignard reagent prepared from 2,5-dibromotoluene, as shown in Chart 4. The reaction product was quenched with Br_2 to re-establish the bromine atom *ortho* to the methyl group in **24** (76%).

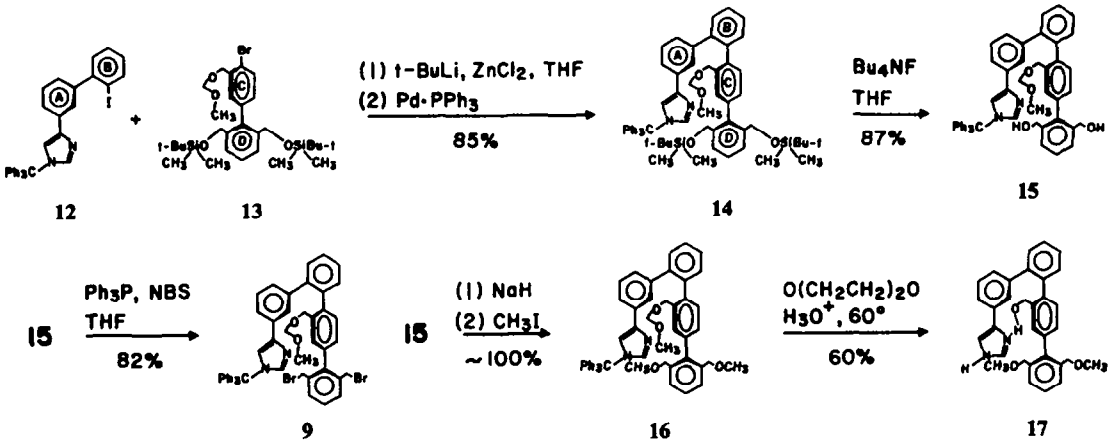
† I. B. Dicker and K. D. Stewart prepared the compound in seven steps from commercially available 2,4-dinitro-4-methylphenol.

‡ Compounds containing chiral elements such as **2**, **6**, and **7** are formulated with particular configurations for convenience of representation. Of these, **6** and **7** were enantiomerically pure, and the configuration formulated is the opposite of what was used.



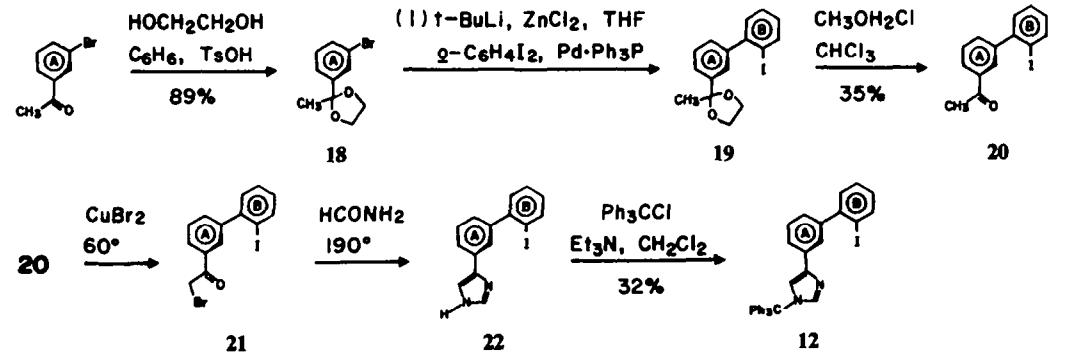
8 9 10 11

Chart 1.



12 13 14 15 9 16 17

Chart 2.



18 19 20 21 22 12

Chart 3.

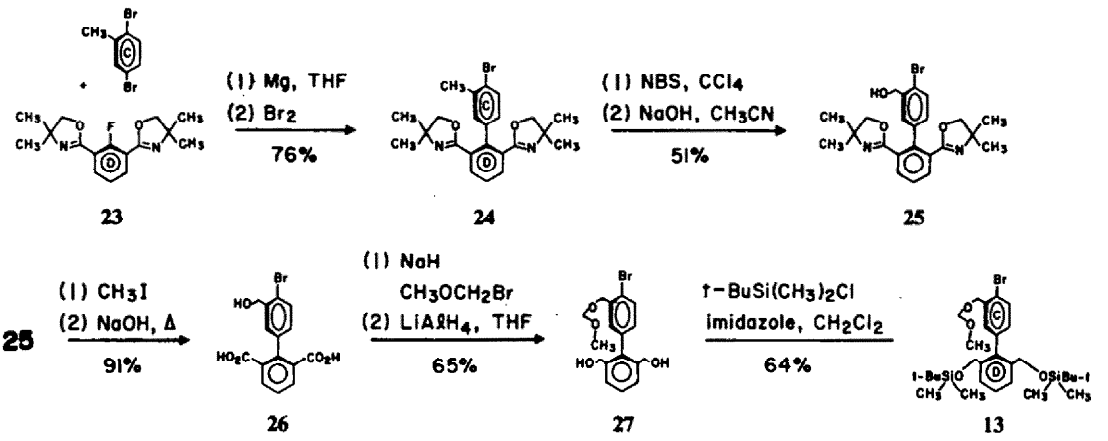


Chart 4.

This compound was contaminated with a few percent of product produced by adventitious water protonating the final Grignard reagent. The methyl group of **24** was monobrominated with NBS and the product hydrolyzed with base to produce alcohol **25** (51% overall), The oxazoline masking groups of **25** were methylated, and the resulting salt was subjected to basic hydrolysis to give diacid alcohol, **26** (91%). Treatment of **26** with NaH–CH_3OCH_2Br gave ester–ether which was directly reduced with $LiAlH_4$ to give ether diol **27** (65% overall). Silylation of the two hydroxyl groups of **27** gave the required compound, **13** (64%). Thus the reactions of Charts 1–4, together with the preparation of tris-urea compound **8**,[3] constitute a total synthesis of target compound **2** from known or purchasable compounds. A total of about 0.5 g of **2** was prepared by this route. It was fully characterized as a complex with 1 mol of water.

Conformations

The ^{1}H-NMR spectrum of **10** (**2** with Ph_3C and CH_3OCH_2 protecting groups present) indicated the compound existed in $CDCl_3$ as a 4:1 mixture of two conformers each containing a mirror plane. Thus two signals of 4:1 intensities were observed at ambient temperature for each of the following protons: $ArOC\underline{H}_3$, $ArC\underline{H}_3$ and $OCH_2OC\underline{H}_3$. Molecular model examination suggested two possible explanations: (1) one observed conformer places the CH_3OCH_2O group *syn* to the cavity opening as drawn in **10**, while the second places the CH_3OCH_2O group *anti* to the cavity opening as drawn in **10**; (2) in one conformer the CH_3OCH_2O group is *syn* to the cavity opening as in **10**, and in the second, the CH_3OCH_2O group as drawn in **10** is *anti* to the cavity opening. In the former case, rotation about the C–D rings equilibrates the two conformers; in the latter, the cyclic urea and $ArOCH_3$ units must ring invert to equilibrate the two conformers. The ^{1}H-NMR spectrum of **14** in 10% $CDCl_3$–90% C_6D_6 at ambient temperature provided calibration for how many conformers might result from rotational barriers within the quateraryl unit itself without the added complication of the macroring. The spectrum showed six kinds of methylene protons (2:1:1:1:1:2), two kinds of CH_3Si protons, and two kinds of t-Bu protons. Of the three aryl–aryl bonds (between rings A–B, B–C, and C–D), we make the reasonable assumption that the A–B rotation is fast on the NMR time scale at 30°. The observation of two kinds of t-Bu protons is consistent only with the rotations about rings B–C and C–D being slow on the NMR time scale, giving rise to two pairs of enantiomeric conformers. If rotations about C–D were slow and B–C fast, or C–D fast and B–C slow, only one kind of t-Bu proton would be observed. Unfortunately, **14** decomposed when heated in attempts to do dynamic NMR experiments. For the rotational barrier of 1,2-bis(2-methylphenyl)benzene, $T_c = 9°$ and $\Delta G_c^{\ddagger} \sim 15$ kcal mol^{-1}.[12]

The ^{1}H-NMR spectrum of target compound **2** indicates it exists in solution as one major conformer containing 14 identifiable types of protons. This conformer is dissymmetric, with six different benzylic protons, two different CH_3Ar groups, and two different $ArOCH_3$ groups, one at a normal δ 3.567 ppm, and one moved upfield to δ 3.005 ppm. The best explanation for this spectrum is that the mol of water observed in the elemental analysis of **2** is hydrogen bonded to the two urea carbonyls at 2 and 6 o'clock, and that the shielded OCH_3 group at 8 o'clock is turned inward to complete the filling of the cavity. This explanation is compatible with the shielding environment and steric requirements of such a methyl in CPK molecular models of **2**. Models also suggest the imidazole can hydrogen bond to the benzyl hydroxyl group, which in turn can hydrogen bond to the oxygen of the guest water molecule. The resulting structure in models is dissymmetric, unstrained, compact, rigid, and cavity free. Upon complexation of **2** with cations, the ^{1}H-NMR spectrum becomes more complicated, and the upfield CH_3O signal shifts to a more normal $\sim\delta$ 3.7 ppm. Thus complexation with charged guests must drive out the water and turn the methyl group outward as in the crystal structure of **5**·t-$BuNH_3^+$.

The ^{1}H-NMR spectrum of **11** in $CDCl_3$ was complicated, and indicated the presence of more than two conformers. Upon complexation with NaBr, the spectrum simplified to what is probably that of two conformers.

Binding free energies

The binding powers of our hosts in $CDCl_3$ saturated with D_2O at 25° were determined by distributing picrate salts between D_2O and $CDCl_3$ in the presence and absence of **2**, **10** and **11** by a method already described.[13] These hosts and their complexes remained

essentially completely in the organic phase at equilibrium. Table 1 reports the association constants (K_a, M^{-1}) and $-\Delta G°$ values (kcal mol^{-1}) for compounds **2**, **3**[3], and **5**[3] binding Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ picrates, for **10** binding $CH_3NH_3^+$, and for **11** binding Na^+, Rb^+, and $CH_3NH_3^+$ picrates (insufficient quantities of **10** and **11** were available for the complete series of ion binding studies).

The patterns of binding the eight guest ions are similar for **2**, **3** and **5**. The binding is strongest with K^+ and weakest with Li^+ or t-$BuNH_3^+$, but these hosts are relatively indiscriminate in their complexation with maximum $\Delta(-\Delta G°)$ values being about 5 kcal mol^{-1} for **2** and **3**, and about 3 kcal mol^{-1} for **5**. Host **5** binds all ions better than **3** by about 1 kcal mol^{-1}, which in turn binds them better than **2** by about 1.5 kcal mol^{-1}. These trends are interpreted in terms of the number of hydrogen bonds that need to be broken or at least reorganized upon complexation. All three hosts bind a mol of water, presumably hydrogen bonded by two of the three urea units.[14] In **2** and **3**, the benzylhydroxyl of the host can hydrogen bond the oxygen of the bound water. In addition, in **2**, the benzylhydroxyl oxygen can be hydrogen bonded to the imidazole. The resulting network of hydrogen bonds must be disrupted when the bound water is expelled and a guest takes its place. In concert with this interpretation, **11** binds Na^+, Rb^+ and $CH_3NH_3^+$ with $-\Delta G°$ values closer to those of **5** than to **2**, whereas **10** and **5** bind $CH_3NH_3^+$ comparably well.

As hoped, **2** is readily acylated by **6** in $CDCl_3$ without added base, and the acylated **2** in turn more slowly acylates the small amount of water in the medium. The kinetics of these reactions and those involving **3**, **4**, **10**, **11** and **17** will be described elsewhere.

Table 1. Association constants (K_a, M^{-1}) and free energies of binding ($-\Delta G°$, kcal mol^{-1}) of picrate salts at 25° in $CDCl_3$ saturated with D_2O

Host ion	2[a]		3[b]		5[b]		10[a]		11[a]	
	K_a	$-\Delta G°$	K_a	$-\Delta G°$	K_a	$-\Delta G°$	K_a	$-\Delta G°$	K_a	$-\Delta G°$
Li	5.2×10^8	11.9	9.0×10^8	12.2	7.2×10^8	12.1				
Na	9.8×10^9	13.6	1.2×10^{11}	15.0	1.6×10^{11}	15.3			1.0×10^{11}	15.0
K	2.6×10^{10}	14.2	2.1×10^{11}	15.4	2.2×10^{11}	15.5				
Rb	3.1×10^8	11.6	1.9×10^9	12.6	1.4×10^{10}	14.2			7.0×10^9	13.4
Cs	2.8×10^7	10.2	4.9×10^8	11.8	3.9×10^9	13.1				
NH_4	8.6×10^8	12.2	9.7×10^9	13.6	3.5×10^{10}	14.4				
CH_3NH_3	2.2×10^8	11.4	2.2×10^9	12.7	3.5×10^{10}	14.4	5.5×10^{10}	14.7	4.1×10^9	13.1
t-$BuNH_3$	7.2×10^6	9.4	6.3×10^7	10.6	4.5×10^9	13.1				

[a] We warmly thank Dr Siew P. Ho for determining these values.
[b] Taken from Ref. 3.

EXPERIMENTAL

General. Unless otherwise specified, all NMR spectra were obtained on a 200 MHz spectrometer in $CDCl_3$, and all mass spectra were taken at 70 eV. Solvent percent compositions are by volume. Unless otherwise specified, $MgSO_4$ was used as drying agent. Column volumes are abbreviated as c.v. Gel permeation chromatography was performed at high pressure on a 20 ft by 0.375 in (O.D.) column packed with SX-12 Bio Beads (Bio-Rad, 200–400 mesh), with CH_2Cl_2 (doubly distilled) as the mobile phase.

1-(2′-*Iodo*[1,1′-*biphenyl*]-3-*yl*)*ethanone* (**20**). To a soln of 33.4 g (137 mmol) of the ethylene glycol ketal of 3-bromoacetophenone (prepared in 89% yield)[2] in 500 ml of anhyd THF stirred under argon was added dropwise (20 min) 65.5 ml (151 mmol) of 2.3 M BuLi in hexane. The soln was stirred for 40 min at −78°. A soln of 24.4 g (179 mmol) of $ZnCl_2$ (dried by heating 24 hr at 130°, then distilling from it dry benzene) in 250 ml of anhyd THF was added rapidly (20 min), and the mixture was warmed from −78° to 25° and stirred for 1 hr. Dropwise addition of 14.8 ml (14.8 mmol) of 1.0 M DIBAL in hexane to a suspension of 5.2 g (7.41 mmol) of yellow $PdCl_2 \cdot (Ph_3P)_2$ in 500 ml of dry THF at 25° under argon provided the black catalytic mixture. To this mixture was added 36.0 ml (275 mmol) of 1,2-diiodobenzene. The arylzinc chloride soln was cannulated (20 min) into the diiodide-catalyst mixture stirred at −25° under argon. The resulting mixture was stirred for 15 min at −25°, and for 14 hr at 25°. Water saturated with NH_4Cl was added, the solvent was evaporated, and the residue partitioned between ether and water. Addition of H_3OCl cleared the emulsion. The ether phase was washed (H_2O, brine), dried ($MgSO_4$) and concentrated to give 94.7 g of residue, which dissolved in a

minimal amount of CH_2Cl_2 and was passed through 700 g of SiO_2 with pentane as the mobile phase. Pentane (3.6 l) washed 54.5 g (60% recovery) of 1,2-diiodobenzene from the column, and then (1.8 l) removed 2.2 g (4%) of 1,1'-diiodobiphenyl (compared by ^{1}H-NMR and MS with an authentic sample). Pentane–CH_2Cl_2 (11 l, up to 50% of latter) eluted 27.9 g of oil, which was filtered through 250 g of SiO_2 with 10% EtOAc in hexane to give 23.0 g of a mixture of iodoketal **19** and ketone **20**. A pure sample of **19** (35%) was obtained by preparative TLC (2 mm SiO_2, 15% EtOAc–hexane, R_f 0.48) as an oil: ^{1}H-NMR δ 7.955 (dd, 1H, J = 8.1, 1.0 Hz), 7.54–7.35 (m, 6H, ArH), 7.033 (dt, 1H, J = 7.1, 2.2 Hz, ArH), 4.12–3.80 (m, 4H, CH_2CH_2), 1.705 (s, 3H, CH_3C); MS (70 eV) *m/e* 366 (M^+, 13), 351 ($M^+ - 13$, 100), exact mass calc for $C_{15}H_{12}O_2I$ ($M - 13$), 350.9883; found, 350.9983. The remainder of the mixture (21.3 g) was stirred vigorously (1 day) with 200 ml of $CHCl_3$, 150 ml of CH_3OH, and 100 ml of 15% aq HCl. The solvent was evaporated (reduced pressure). The residue was partitioned between ether and water. The ether phase was washed (5% $NaHCO_3$ in H_2O and brine), dried and evaporated (vacuum) to give 19.5 g of oil, which was distilled at 0.035 Torr to give 2.1 g (9%) of 3-butylacetophenone (^{1}H-NMR and MS), b.p. 69°, and 14.5 g (35% from **18**) of **20** as an oil, b.p. 133–135° (0.01 Torr); ^{1}H-NMR ($CDCl_3$) δ 8.05–7.90 (m, 3H, ArH), 7.55–7.28 (m, 4H, ArH), 7.06 (dt, 1H, J = 6.1, 2.1 Hz), 2.633 (s, 3H, CH_3CO); IR (neat) 1685 (s) cm^{-1}; MS exact mass calc for $C_{14}H_{11}OI$, 321.9855; found, 321.9863. (Found: C, 52.23; H, 3.39; I, 39.31. Calc for $C_{14}H_{11}OI$: C, 52.20; H, 3.44; I, 39.39%.)

1 - *Trityl* - 4 - (2' - *iodo*[1,1' - *biphenyl*] - 3 - *yl*)*imidazole* (**12**). By the general procedure of King and Ostrum,[7] 11.7 g (36.2 mmol) of iodoketone **20** was treated with 19.0 g (85.1 mmol) of $CuBr_2$ for 3 hr to give 14.0 g of a dark oil. Its ^{1}H-NMR spectrum indicated it to be 7% **20**, 14% of the α,α-dibromoketone of **20** (δ, 6.723 (s)), and 79% α-bromoketone **21**; δ 8.50–8.30 (m, 3H, ArH), 8.10–7.95 (m, 4H, ArH), 7.08 (dt, 1H, J = 7.1, 1.7 Hz, ArH), 4.487 (s, 2H, CH_2Br); IR (neat) 1680 (s) cm^{-1}; MS, exact mass calc for $C_{14}H_{10}BrIO$ (M^+), 401.8940 and 399.8959; found, *m/e* 401.8942 and 399.8961. The crude product (11.7 g) was held at reflux for 2 hr at 190° in 180 ml of $(CH_3)_2NCHO$ by modifying the general procedure of Bredereck and Theilig[8] for forming imidazoles. The hot black mixture was poured into 500 ml of hot water, the mixture was cooled, and extracted twice with CH_2Cl_2. The combined organic phases were washed (H_2O, brine) and dried with K_2CO_3. Evaporation of the solvent (vacuum) provided 8.6 g of crude **22**, a sample of which was purified by preparative TLC (0.5 mm SiO_2, 15% CH_3OH in CH_2Cl_2 with 0.1% NH_3, R_f 0.5); ^{1}H-NMR δ 7.935 (d, 1H, J = 8.1 Hz, ArH), 7.735 (s, 1H, ArH), 7.694 (s, 1H, ArH), 7.632 (s, 1H, ArH), 7.50–7.20 (m, 5H, ArH), 7.006 (t, 1H, J = 7.4 Hz, ArH), 6.5 (brs, 1H); IR (neat) 3100 (bs) cm^{-1}; MS exact mass calc for $C_{15}H_{11}N_2I$ (M^+), 345.9967; found, *m/e* 345.9952. Crude **22** (10.7 g) was stirred under argon at 25° with 12.1 g (443 mmol) of Ph_3CCl, 6.0 ml (433 mmol) of anhyd Et_3N, and 150 ml of anhyd Et_2O. The NH_4Cl that separated was filtered, the filtrate was washed (four times with H_2O, then brine), dried over K_2CO_3, and the solvent was evaporated (vacuum) to give 23.6 g of oil. Preparative HPLC (2 SiO_2 columns, 10% hexane–90% CH_2Cl_2) of this material provided 7.7 g of solid, m.p. 179–185°, which was recrystallized from 2% $CHCl_3$ in EtOH to give 6.78 g of **12** (32% based on **20**); ^{1}H-NMR δ 7.92 (d, 1H, J = 8.0 Hz, ArH), 7.76 (d, 1H, J = 8.0 Hz, ArH), 7.68 (s, 1H, ArH), 7.50 (d, 1H, J = 1.2 Hz, imidazole 2 C—H), 7.41–7.10 (m, 20 H, ArH), 7.03–6.95 (m, 1H, ArH); IR (neat) 1480, 735 cm^{-1}, characteristic of imidazole; MS (70 eV) exact mass calc for $C_{30}H_{25}IN_2$ (M^+), 588.1003; found, *m/e* 588.1030. (Found: C, 69.42; H, 4.40; I, 21.69; N, 4.68. Calc for $C_{34}H_{25}IN_2$: C, 69.39; H, 4.28; I, 21.56; N, 4.76%.)

2,2' - (4' - *Bromo* - 3' - *methyl*[1,1' - *biphenyl*] - 2,6 - *diyl*)*bis*[4,5 - *dihydro* - 4,4 - *dimethyloxazoline*] (**24**). An existing procedure was modified.[15] A soln of 23.3 g (93.1 mmol) of 2,5-dibromotoluene in 250 ml of anhyd THF was added dropwise to a mixture of 13.4 g (550 mmol) of resublimed Mg in 100 ml of THF stirred under argon over 45 min (a few drops of $BrCH_2CH_2Br$ were added to start the reaction). The mixture was refluxed for 3 hr, cooled to 25° and cannulated (tube was 1/8 in I.D.) into a soln of 8.90 g (30.7 mmol) of **23**[11] in 200 ml of dry THF stirred under argon. The mixture was stirred for 2 hr, cooled to −78°, and 8.66 ml (168 mmol) of Br_2 in 100 ml of pentane was added dropwise. After 0.5 hr at −78°, 50 ml of 5% aq $NaHSO_3$ soln was added. The mixture was warmed to 25° and the THF evaporated (vacuum). The residue was partitioned between ether and water, the aqueous phase was extracted with two fresh portions of ether (a few drops of 6% HCl aq cleared the emulsion). The combined ether phases were washed twice with water, once with brine, dried and evaporated (vacuum) to give 23.0 g of oil. This material was chromatographed by flash chromatography (700 g of SiO_2, 10 cm I.D., EtOAc, 4–7 c.v.) to give 10.3 g (76%) of crude **24**, m.p. 75–81°; ^{1}H-NMR δ 7.98 (d, 1H, J = 8.4 Hz, ArH), 7.75 (d, 2H, J = 8.0 Hz, ArH), 7.18 (d, 1H, J = 2.4 Hz, ArH), 7.00 (dd, 1H, J = 8.4, 2.4 Hz, ArH), 3.73 (s, 4H, CH_2), 2.39 (s, 3H, $ArCH_3$), 1.22 (s, 12H, 4 CH_3—C); MS exact mass calc for $C_{23}H_{25}BrN_2O_2$ (M^+), 442.1079 and 440.1100; found, *m/e* 442.1067 and 440.1082.

2,2' - (4' - *Bromo* - 3' - *hydroxymethyl*[1,1' - *biphenyl*] - 2,6 - *diyl*)*bis*[4,5 - *dihydro* - 4,4 - *dimethyloxazole*] (**25**). A mixture of 20.5 g (46.5 mmol) of **24** and 12.4 g (69.7 mmol) of NBS in 400 ml of CCl_4 was refluxed under a sunlamp for 1 hr. Dibenzoyl peroxide was added at 20 min intervals (a total of 450 mg). The mixture was cooled, filtered, and washed with 5% $NaHCO_3$ aq, 5% $Na_2S_2O_3$ aq, water and brine. The solvent was evaporated (vacuum) to give 27.4 g of the crude benzyl bromide as an oil. A pure sample was prepared by preparative TLC (0.5 mm SiO_2, 50% acetone in CH_2Cl_2, R_f 0.25), m.p. 175–185°; ^{1}H-NMR δ 7.80 (d, 2H, J = 7.6 Hz, ArH), 7.54 (d, 1H, J = 8.2 Hz), 7.442 (t, 1H, J = 7.6 Hz, ArH), 7.371 (d, 1H, J = 2.2 Hz, ArH), 7.103 (dd, 1H, J = 8.2, 2.2 Hz), 4.599 (s, 2H, $ArCH_2$), 3.770 (s, 4H, CCH_2), 1.218 (s, 12H, CH_3C); MS exact mass calc for $C_{23}H_{29}O_2N_2Br$ (M^+), 441.1005 and 439.1010; found, *m/e* 441.1014 and 439.1003. The crude benzyl bromide was dissolved in 1.5 l of CH_3CN, and 0.5 l of sat $NaHCO_3$ aq was added. The mixture was heated to reflux for 5 hr, and the solvent was evaporated (vacuum). The residue was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 phase was washed with H_2O and brine, dried and evaporated (vacuum) to give 20.1 g of oil, which was flash chromatographed (SiO_2, 10 cm I.D. column, 45% acetone in CH_2Cl_2 with 0.01% Et_3N; 9–16 c.v.) to provide 10.9 g (51% from **24**) of **25**, m.p. 163–167°; ^{1}H-NMR ($CDCl_3$) δ 7.752 (d, 2H, J = 7.8 Hz, ArH), 7.489 (d, 1H, J = 8.1 Hz, ArH), 7.429 (d, 1H, J = 2.4 Hz, ArH), 7.411 (t, 1H, J = 7.8 Hz, ArH), 7.076 (dd, 1H, J = 8.1, 2.4 Hz, ArH), 4.685 (s, 2H, Ar—CH_2O), 3.738 (s, 4H, CH_2C), 3.399 (s, 1H, OH), 1.191 (s, 12H, CH_3C); MS exact mass calc for $C_{23}H_{25}O_3BrN_2$ (M^+), 458.1029 and 456.1049; found, *m/e* 458.0991 and 456.1007. (Found: C, 60.20; H, 5.36; Br, 17.35; N, 6.05. Calc for $C_{23}H_{25}O_3BrN_2$: C, 60.40; H, 5.51, Br, 17.47; N, 6.12%.)

4' - *Bromo* - 3' - *hydroxymethyl* - 1,1' - *biphenyl* - 2,6 - *dicarboxylic acid* (**26**). A soln of 7.2 g (15.8 mmol) of **25** and 80 ml of CH_3I in 150 ml of CH_3NO_2, 150 ml of acetone and 200 ml of CH_3OH was held at reflux for 4 hr. More CH_3I (100 ml) was added when TLC showed that 30% of the original **25** was present. After refluxing for a total of 12 hr, the solvent was evaporated (chased with toluene), and to the residue was added 150 ml of 15% NaOH aq. The mixture was refluxed for 1 day, cooled and filtered. The filtrate was washed with Et_2O, cooled to 0°, and acidified to pH 1 with concentrated HCl aq. The insoluble diacid that separated was extracted with three portions of Et_2O, the ether layer was washed with 5% $NaHSO_3$ aq, water and brine, and dried. The soln was evaporated (vacuum) to give 5.05 g (91%) of **26**, m.p. 225–227°; ^{1}H-NMR ($(CD_3)_2SO$) δ 7.813 (d, 2H, J = 7.6 Hz, ArH), 7.540 (t, 1H, J = 7.6 Hz, ArH), 7.52 (d, 1H, J = 8.0 Hz, ArH), 7.331 (d, 1H, J = 2.7 Hz, ArH), 7.001 (dd, 1H, J = 8.0, 2.7 Hz, ArH), 5.490 (br t, 1H, OH), 3.312 (br d, 2H, CH_2O); IR (neat) 3350 (br s), 2900 (br s), 1700 (s) cm^{-1}; MS exact mass calc for $C_{15}H_{11}O_5Br$ (M^+), 351.9773; found, *m/e* 351.9772. (Found: C, 51.32; H, 3.24; Br, 22.57. Calc for $C_{15}H_{11}O_5Br$: C, 51.31; H, 3.16; Br, 22.76%.)

2,6 - *Bis*(*hydroxymethyl*) - 4' - *bromo* - 3' - *meth-*

oxymethoxymethyl - 1,1′ - *biphenyl* (**27**). A soln of 5.05 g (14.4 mmol) of diacid **26** in 50 ml of anhyd THF was added to a suspension of 3.5 g (71.9 mmol) of 50% NaH in mineral oil (removed by THF washing) stirred in 20 ml of THF under argon. The mixture was refluxed for 2 hr, cooled to −78°, and 5.29 ml (64.7 mmol) of bromomethyl methyl ether was added dropwise. The mixture was slowly warmed to 25°, allowed to stand for 14 hr, and then carefully neutralized with 5% HCl in water. The solvent was evaporated (vacuum), and the residue was partitioned between ether and water. The ether phase was washed with water, brine, dried, and evaporated (vacuum) to give 6.2 g of diester-ether; MS exact mass calc for $C_{21}H_{23}O_8Br$, 484.0576 and 482.0576; found, 484.0479 and 482.0544. This crude material (6.5 g) was dissolved in 150 ml of anhyd Et_2O and treated with 1.5 g (41 mmol) of $LiAlH_4$ in 150 ml of anhyd Et_2O under argon. The mixture was refluxed for 2 hr and quenched with EtOAc. The ether phase was washed with 5% Na_2CO_3 aq, and brine, dried, and evaporated (vacuum) to give 4.87 g of oil. This material was filtered through 25 g of SiO_2 (30% ether–70% CH_2Cl_2; 2–6 c.v.) to give 3.43 g (59% based on **26**) of **27**, m.p. 80–85°; ^{1}H-NMR δ 7.60 (d, 1H, J = 8.0 Hz, ArH), 7.461–7.40 (A_2B, 3H, J = ~8.5 Hz, ArH), 7.341 (d, 1H, J = 2.2 Hz), 7.00 (dd, 1H, J = 8.0, 2.2 Hz); IR (neat) 3350 (br s) cm^{-1}; MS exact mass calc for $C_{15}H_{13}O_2Br$ (M^+), 306.0080 and 304.0098; found, *m/e* 306.0071 and 304.0071.

2,6 - *Bis*(t - *butyldimethylsilyloxy*) - 4′ - *bromo* - 3′ - *methoxymethoxymethyl* - 1,1′ - *biphenyl* (**13**). By a modified procedure,[16] a soln of 3.43 g (9.35 mmol) of diol **27** and 3.82 g (56.1 mmol) of imidazole in 25 ml of anhyd DMF (dried with 3 Å molecular sieves) was cooled in ice under argon and 4.23 g (28.0 mmol) of t-butyldimethylsilyl chloride was added. The yellow soln was stirred at 25° for 1 day, and diluted with ether. The soln was washed three times with water, once with brine, and the solvent was evaporated (vacuum) to give 6.2 g of oil. This material was filtered through 60 g of SiO_2 (25% CH_2Cl_2–hexane; 6–8 c.v.) to give 3.54 g (64%) of **13**, m.p. 61–62°; ^{1}H-NMR δ 7.619 (d, 1H, J = 8.1 Hz, ArH), 7.538–7.438 (A_2B, 3H, J = 7.9 Hz, ArH), 7.354 (d, 1H, J = 2.1 Hz, ArH), 7.015 (dd, 1H, J = 8.1, 2.1 Hz, ArH), 4.769 (s, 2H), 4.729 (s, 2H), 4.387 (s, 4H, $ArCH_2OSi$), 3.430 (s, 3H, OCH_3), 0.912 (s, 18H, CH_3C), 0.007 (s, 12H, CH_3Si); MS exact mass calc for $C_{25}H_{38}BrO_4Si_2$ (M^+ − t-Bu), 539.1396 and 537.1492; found, *m/e* 539.1384 and 537.1471. (Found: C, 58.42; H, 7.78; Br, 13.44; Si, 9.35. Calc for $C_{29}H_{47}BrO_4Si_2$: C, 58.47; H, 7.95; Br, 13.41; Si, 9.43%.)

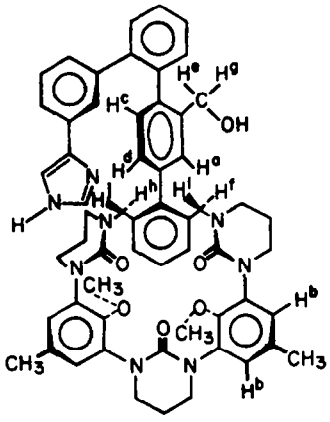
1 - *Trityl* - 4 - (2‴,6‴ - *bis*[*hydroxymethyl*] - 2″ - *methoxymethoxymethyl*[1,1′:2′,1″:4″:1‴ - *quaterphenyl*] - 3-*yl*)*imidazole* (**15**). By a modified procedure,[4] 2.90 ml (7.92 mmol) of 2.73 M t-BuLi in hexane was added dropwise to a soln of 2.19 g (3.60 mmol) of silylether **13** in 20 ml of anhyd THF stirred at −78° under argon. The soln was stirred at −78° for 20 min and 736 mg (5.40 mmol) of anhyd $ZnCl_2$ (dried at 130° for 14 hr followed by azeotropic drying with anhyd benzene just prior to use) in 10 ml of THF was added dropwise. The mixture was stirred for 20 min more, warmed to 25°, and stirred for 1 hr. Following the same procedure as in the synthesis of **19**, this mixture was treated with 0.018 mmol of Pd catalyst and 2.12 g (3.6 mmol) of tritylimidazole iodide **12** in 45 ml of THF. The reaction was quenched with 20 ml of 5% $NaHCO_3$ aq, and the solvent evaporated (vacuum). The residue was partitioned between Et_2O and water. The ether layer was washed with 3 ml of ethylenediamine in 100 ml of H_2O, with water 3 times, brine, dried and evaporated (vacuum) to give 3.57 g of a black oil. This material was filtered through 36 g of SiO_2 (20% ether–80% hexane, 40 c.v.) to give 3.00 g (85%) of **14** as a light yellow foam. A pure sample was prepared by preparative TLC (2 mm SiO_2, 0.1% Et_3N in 40% ether–60% hexane, R_f 0.43); ^{1}H-NMR ($CDCl_3$) δ 7.723 (s, 1H, ArH), 7.60–7.05 (m, 26H, ArH), 7.478 (d, 1H, J = 1.2 Hz, imidazole 2C—H), 7.089 (d, 1H, J = 1.2 Hz, imidazole 5C—H); ^{1}H-NMR (10% $CDCl_3$–90% C_6D_6) δ 8.10–6.80 (m, 31H, ArH and imidazole —H), 4.633 (s, 2H, $ArCH_2$), 4.483 (s, 1H, CH), 4.440 (br, s, 2H, CH), 4.367 (s, 1H, CH), 4.328 (s, 2H, CH_2), 2.985 (s, 3H, OCH_3), 1.035 (s, 9H, t-Bu), 0.987 (s, 9H, t-Bu), 0.084 (s, 6H, $SiCH_3$), 0.001 (s, 6H, $SiCH_3$); MS (70 eV) exact mass calc for $C_{49}H_{57}O_4N_2Si_2$ ($M^+ - Ph_3C$), 733.3857; found, *m/e* 733.3863. Compound **14** (3.00 g, 0.00307 mmol) was desilylated with 4.00 g (0.0126 mmol) of $Bu_4NF \cdot 3H_2O$ in 30 ml of anhyd THF (0.5 hr). The reaction was quenched with 10 ml of 5% $NaHCO_3$ aq, the solvent was evaporated, the residue was dissolved in a large quantity of CH_2Cl_2 (the product is only slightly soluble), and the mixture was shaken with water. The water phase was thoroughly washed with two portions of CH_2Cl_2, and the combined organic phases were washed three times with 1% $NaHCO_3$ aq, brine, and evaporated (vacuum) to give 3.00 g of oil. This material was filtered through 35 g of SiO_2 (12 c.v. of CH_2Cl_2 for impurities, 24 c.v. of 80% ether–20% CH_2Cl_2 for product) to give 2.00 g (87%) of white solid. An analytical sample of **15** was recrystallized from THF–Et_2O, m.p. 169–173°; ^{1}H-NMR δ 7.587 (td, 1H, J = 7.3, 1.2–1.7 Hz, ArH), 7.469 (d, 1H, J = 1.2 Hz), 7.452 (d, 1H, J = 1.7 Hz, imidazole 2CH), 7.44–7.02 (m, 25H, ArH), 7.065 (d, 1H, J = 1.7 Hz, imidazole 5C—H), 6.966 (d, 1H, J = 1.2 Hz, ArH), 6.856 (d,d, 1H, J = 7.8–1.7 Hz, ArH), 4.482 (s, 1H, CH), 4.453 (s, 1H, CH), 4.3898–4.3519–4.3190–4.2860 (ABq, 2H, J = 6.6 Hz, CH_2), 4.256 (s, 1H, CH), 3.840–3.818 (bs, 2H, OH), 3.047 (s, 3H, OCH_3); MS exact mass calc for $C_{32}H_{29}O_4N_2$ ($M^+ - Ph_3C$), 505.2127; found, *m/e* 505.2150. (Found: C, 81.55; H, 6.08; N, 3.60. Calc for $C_{51}H_{44}O_4N_2$: C, 81.79; H, 5.92; N, 3.74%.)

36 - (2 - *Methoxymethoxymethyl* - 3″ - (1 - *tritylimidazole*) - 4 - *yl*[1,1′:2′,1″ - *terphenyl*] - 4 - *yl*) - 33,35,37 - *trioxo* - 34,38 - *dimethoxy* - 4,26 - *dimethyl* - 1,7,11,19,23,29 - *hexaazaheptacyclo*[27 . 3 . 1 . $1^{2,6}$. $1^{7,11}$. $1^{13,17}$. $1^{19,23}$. $1^{24,28}$]*octaconta* - 34(2),3,5,36(13),14,16,38(24),25,27 - *nonaene* (**10**). By a modified procedure,[5] a soln of 2.42 g (9.21 mmol) of Ph_3P in 20 ml of anhyd THF was added dropwise to a vigorously stirred soln of 1.86 g (10.4 mmol) of N-bromosuccinimide (NBS) in 50 ml of THF under argon at 0°. More NBS was added if TLC showed the presence of Ph_3P. The yellow suspension was warmed to 25°, stirred for 10 min and cooled to 0°. A soln of 1.30 g (1.74 mmol) of bisalcohol **15** (dried with 3 Å molecular sieves in THF) in 75 ml of anhyd THF was slowly cannulated into the stirred mixture. After the addition was complete, the mixture was stirred at 25° for 3 hr. More brominating agent was added if TLC (SiO_2, 30% acetone–CH_2Cl_2) showed the presence of either **15** or half brominated **15**. The product was poured onto a mixture of ice and 1 ml of H_2O saturated with $NaHCO_3$. The THF was evaporated (vacuum), and the residue was partitioned between CH_2Cl_2 and water. The water phase was extracted twice with CH_2Cl_2. The combined CH_2Cl_2 phases were washed three times with slighly basic water ($NaHCO_3$), brine (slightly basic) and dried at 0° with $MgSO_4$. The soln was concentrated (vacuum) at 25° and immediately subjected to flash chromatography (SiO_2, 5 in column, 5 cm I.D.; 2.5% ether–CH_2Cl_2, 0.5–3.5 c.v.). The column was first deactivated with 20% ether–CH_2Cl_2, and rinsed with CH_2Cl_2. Dibromide **9** was put on the column in CH_2Cl_2 (CH_2Cl_2 was the initial developing solvent), and the contact time with SiO_2 was minimized. The instability of **9** required it to be stored in CH_2Cl_2 over $MgSO_4$ at −70°. The mixture was filtered and evaporated (vacuum, low temp) to dryness just prior to use to give 1.25 g (82%) of **9** as a yellow foam. In soln, 10% of **9** decomposed in 2 days at 25°; ^{1}H-NMR δ 7.70–7.10 (m, 30H, ArH), 6.893 (dd, 1H, J = 7.8, 1.2 Hz), 4.404 (s, 1H), 4.387 (s, 1H), 4.317 (s, 2H), 4.300 (s, 2H), 3.872 (s, 2H), 3.097 (s, 3H).

Following our general procedure for forming tris-urea hosts,[3] a suspension of 882 mg (1.64 mmol) of quinquenuclear **8**[3] and 2.75 g (57.2 mmol) of 50% NaH in mineral oil (removed with THF wash) in 1.7 l of anhyd THF was refluxed for 4 hr. The grayish mixture (dianion) was cooled to −78°, and a soln of 1.25 g (1.43 mmol) of **9** (dried in anhyd THF with NaH for 45 min before using) in 50 ml of THF was added. The mixture was allowed to warm slowly to 25° over a 14 hr period. After standing for 1–5 days, TLC (SiO_2) showed the absence of **17**. The mixture was acidified with 25% HBr aq to ~pH 10, the THF was evaporated (vacuum), and the residue was partitioned by stirring in a CH_2Cl_2–20% NaBr–H_2O soln for 1 hr. The organic phase was evaporated (vacuum) to give 1.92 g

of crude **10** which was filtered through 19 g of Waters Reverse Phase SiO_2–C18 (50–125 μm) in a sintered glass funnel. The pad was prewashed successively with CH_2Cl_2, CH_3OH, and 92% CH_3OH–H_2O (1% NaBr) facilitated by a mild pressure gradient. The product was eluted with 92% CH_3OH–H_2O (1% NaBr). The CH_3OH was evaporated (vacuum), and the residue was extracted with CH_2Cl_2 to give, upon evaporation (vacuum), 1.32 g (68%) of **10**·NaBr as a foam. An analytical sample was obtained by dissolving the product from the middle fraction in 50% THF–50% CH_2Cl_2, and precipitating with ether to give **10**·NaBr as a white solid, m.p. 220–228° (dec); ^{1}H-NMR δ 7.80–6.75 (m, 35H, ArH), 4.55–3.600 (m, 23H, C—CH—C), 2.930 (s, 0.8H), 2.790 (s, 0.2H), 2.50–2.10 (m, 12H); IR (neat) 1625 (s), 1485 (s, imidazole), 7.30 (s, imidazole) cm^{-1}; MS, *m/e* 990 ($M^+ - Ph_3C - CH_3$, 0.5), 244 (100). (Found: C, 69.06; H, 5.70. Calc for $C_{79}H_{76}O_7N_8 \cdot NaBr \cdot H_2O$: C, 69.24; H, 5.74%.) When heated to 80° for 1 day under high vacuum, **10**·NaBr decomposed slightly. When cyclization was attempted with the dichloride corresponding to dibromide **9**, the yield was 31%.

36 - (2 - *Hydroxymethyl* - 3" - *imidazole* - 4 - *yl*[1,1':2',1" - *terphenyl*] - 4 - *yl*) - 33,35,37 - *trioxo* - 34,38 - *dimethoxy* - 4,26 - *dimethyl* - 1,7,11,19,23,29 - *hexaazaheptacyclo* - [27 . 3 . 1 . $1^{2,6}$. $1^{7,11}$. $1^{13,17}$. $1^{19,23}$. $1^{24,28}$]*octaconta* - 34(2),3,5,36(13),14,16,38(24),25,27 - *nonaene* (**2**). A soln of 0.920 g (0.864 mmol) of **10**·NaBr in 25 ml of a 15% HCl aq soln in 50 ml of purified dioxane was heated at 60° for 4 hr. The soln was cooled, neutralized with $NaHCO_3$, and the dioxane was evaporated (vacuum). The residue was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 phase was washed three times with ion-free H_2O by stirring 7 hr each time (the redistribution of NaBr into the aqueous phase was slow). The CH_2Cl_2 was evaporated (vacuum) to give 897 mg of yellow foam, which was submitted to gel permeation chromatography in three runs to give 552 mg of beige foam. The foam was dissolved in CH_2Cl_2 and washed four times with ion-free water (stirring 7 hr per time) to wash out complexed salt. In the last washing, a few drops of Et_3N (distilled from TsCl and CaH_2, successively) were added to insure the imidazole was acid free. The organic layer was evaporated (vacuum), and the residue was dissolved in 10 ml of CH_2Cl_2 and 5 ml of THF. Ether (65 ml) was added dropwise to give 161 mg of the first crop of **2** (isolated by centrifugation, decantation and ether washing). Addition of 20 ml more Et_2O gave 244 mg of analytically pure **2**. Upon evaporation (vacuum) and an additional precipitation, 10 mg of additional **2** was obtained. The material in the combined filtrates was submitted to gel permeation chromatography–precipitation to give a total of 531 mg of pure **2** (64%), m.p. 270–290° (dec); ^{1}H-NMR δ 7.933 (br s, 1H, H^a), 7.52–6.80 (m, 13H),



6.94 (s, 4H, H^b), 6.516 (d, 1H, J = 7.6 Hz, H^c), 6.340 (dd, 1H, J = 7.6, 1.5 Hz, H^d), 4.950 (d, 1H, J = 12.4 Hz, H^e), 4.622 (d, 1H, J = 15.0 Hz, H^f), 4.519 (d, 1H, J = 12.4 Hz, H^g), 4.40–4.20 (m, 1H), 4.20–4.00 (m, 1H), 3.860 (d, 1H, J = 19.9 Hz, H^a), 3.80–3.40 (m, 12H), 3.567 (s, 3H, $ArOCH_3$), 3.493 (d, 1H, J = 15.0 Hz, H^i), 3.005 (s, 3H, $ArOCH_3$), 2.730 (d, 1H, J = 19.9 Hz, H^j), 2.30–2.10 (m, 6H), 2.328 (s, 3H, $ArCH_3$), 2.256 (s, 3H, $ArCH_3$); IR (neat) 3350 (br s), 1640 (s), 1490 (s), 1440 (s), 1300 (s), 1200 (s), 760 (m), 720 (m) cm^{-1}; FAB MS (Xe), Cu in probe, *m/e* 1025 ($M + Cu^+$, 32), 1000 (21), 985 ($M + Na^+$, 100), 963 ($M + H^+$, 35), 945 ($M + H^+ - H_2O$, 21), 931 ($M + H^+ - CH_3OH$, 21). (Found: C, 71.25; H, 6.30. Calc for $C_{58}H_{58}N_8O_6 \cdot H_2O$: C, 71.00; H, 6.16%.) Solubility of **2**: 28 mg dissolves in 22 ml of 45% CD_3CN in D_2O; or in 23 ml of 57% CH_3OH in D_2O (more D_2O causes cloudiness).

Upon complexation of **2** with t-$BuNH_3^+$ picrate$^-$, alaninamide·HBr, $NaClO_4$, NaBr or NaCl in $CDCl_3$, the ^{1}H-NMR spectrum of **2** became more complicated, pointing to the presence of at least two major conformeric complexes. Attempts at forming the complex of **2** and *l*-alanine in $CDCl_3$ failed due to the insolubility of $CH_3CH(NH_3^+)CO_2^-$ in $CDCl_3$.

36 - (2 - *Methoxymethoxymethyl* - 3" - *imidazole* - 4 - *yl*[1,1':2',1" - *terphenyl*] - 4 - *yl*) - 33,35,37 - *trioxo* - 34,38 - *dimethoxy* - 4,26 - *dimethyl* - 1,7,11,19,23,29 - *hexaazaheptacyclo*[27 . 3 . $1^{2,6}$. $1^{7,11}$. $1^{13,17}$. $1^{19,23}$. $1^{24,28}$]*octaconta* - 34(2),3,5,36(13),14,16,38(24),25,27 - *nonaene* (**11**). A soln of 0.40 g (0.30 mmol) of **10**·NaBr·H_2O was refluxed in 50 ml of 5% HOAc in CH_3OH for 10 hr. The soln was cooled, neutralized with 15% NaOH aq, the CH_3OH was evaporated (vacuum) and the same isolation procedure was followed as applied to **2** to give 0.22 g (74%) of **11** as a white powder, m.p. 235–255° (dec); ^{1}H-NMR (more than two conformers) δ 8.10–6.40 (m, 20H), 4.90–3.30 (m, ~26H), 3.09 (s, 1.5–2.0H), 2.84 (s, 1.5–2.0H), 2.40–2.10 (m, 12H); MS *m/e* 1006.5 (M^+, 89), 975.6 ($M^+ - CH_3O$, 22), 944.6 ($M^+ - CH_3OCH_2OH$, 25), 439 ($M^+ - 8 - CH_3O$, 12). (Found: C, 70.64; H, 6.29. Calc for $C_{60}H_{62}N_8O_7 \cdot H_2O$: C, 70.29; H, 6.29%.) Upon complexation with NaBr in $CDCl_3$, the ^{1}H-NMR spectrum simplified to give what is probably two conformeric complexes.

1 - *Trityl* - 4 - (2"',6"' - *bis*[*methoxymethyl*] - 2" - *methoxymethoxymethyl*[1,1':2',1":4":1"' - *quaterphenyl*] - 3 - *yl*)*imidazole* (**16**) *and* 4 - (2"',6"' - *bis*[*methoxymethyl*] - 2" - *hydroxymethyl*[1,1':2',1":4",1"' - *quaterphenyl*] - 3 - *yl*)*imidazole* (**17**). A soln of 40 mg (0.0535 mmol) of bis-alcohol **15** was treated with 25.7 mg (0.535 mmol) of 50% NaH in mineral oil (removed by THF washing) in 2 ml of anhyd THF for 1 hr under argon. The mixture was cooled to 0° and 14.0 μl (0.0224 mmol) of CH_3I was added. After standing 1 hr at 25°, the mixture was quenched with CH_3OH. The solvent was evaporated (vacuum) at 25°, and the residue was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 phase was twice washed with H_2O, brine, dried and evaporated to give 42 mg (~100%) of **16** as a white foam: ^{1}H-NMR δ 7.626 (d, 1H, J = 7.3 Hz, ArH), 7.50–7.00 (m, 29H, ArH), 6.90 (d, 1H, J = 7.8 Hz, ArH), 4.40–4.30 (m, 4H), 4.207 (s, 2H), 3.735 (s, 2H), 3.284 (s, 3H), 3.046 (s, 3H), 2.967 (s, 3H); MS exact mass calc for $C_{34}H_{33}N_2O_4$ ($M^+ - Ph_3C$), 533.2441; found, *m/e* 533.2451.

The protecting Ph_3C and CH_3OCH_2 groups of **16** were removed to give **17** following the procedure applied to **10** → **2**. Preparative TLC (2 mm SiO_2, 50% acetone–49% CH_2Cl–1% Et_3N, R_f 0.15) of the product gave 16 mg (60%) of **17**: ^{1}H-NMR δ 7.55–7.00 (m, 15H, ArH), 6.887 (dd, 1H, J = 7.8, 2.7 Hz), 4.540 (d, 2H, J = 1.7 Hz), 4.153 (s, 2H), 3.720–3.655–3.630–3.580 (ABq, 2H, J = 13.0 Hz), 3.235 (s, 3H), 2.7801 (s, 3H); MS exact mass calc for $C_{32}H_{30}N_2O_3$ (M^+), 490.2256; found *m/e* 490.2261. (Found: C, 78.40; H, 6.70. Calc for $C_{32}H_{30}O_3N_2$: C, 78.34; H, 6.16%.)

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