Effects of Shape on Thermodynamic Cyclizations of Cinchona Alkaloids

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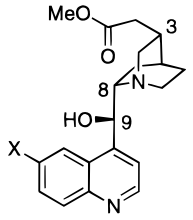
Thermodynamic cyclizations of a series of cinchona alkaloid derivatives are investigated. An extended quinine monomer **2:HO−Ce−OMe** is prepared and cyclized to produce a mixture of cyclic oligomers. Combining the extended monomer **2:HO−Ce−OMe** with the previously reported cinchonidine monomer **1b:HO−Cc−OMe** under thermodynamic control produces a library of quinine-derived macrocycles. Two quinidine-derived methyl ester monomers **10:HO−Cd−OMe** and **16:HO−Ca−OMe** are also reported. Both are preorganized to form cyclic dimers; upon carrying out the thermodynamic cyclization on a mixture of both monomers only a small percentage (5%) of the hetero-dimer is obtained. Thermodynamic cyclization of the corresponding cinchonidine derived methyl ester **1b:HO−Cc−OMe** with **10:HO−Cd−OMe** results in the self-sorting of the two diastereoisomers.

Introduction

A combinatorial library consists of many members ($\mathbf{M_1...M_n}$) each of which contains two or more building blocks (*A*, *B*, *C*...) arranged in a particular way. In a traditional combinatorial library[1] the covalent bonds between building blocks are fixed by using irreversible chemistry during synthesis, so that there can be no postsynthetic interconversion between members such as *ABC* and *ACB*. However, in a dynamic combinatorial library (DCL)[2] the connections between building blocks are reversible and in flux, continuously being made and broken; these connections may be covalent bonds such as imine,[2a] ester,[3,4] disulfide,[5] borate,[6] or alkene linkages,[7] or they may be noncovalent, utilizing metal−ligand[8] or hydrogen-bonding[9] interactions. The composition of a DCL will be dependent upon its environment, allowing thermodynamic templating to take place. For example, if a library of macrocycles is produced, then upon addition of a particular substrate, macrocycles that are strong binders of the substrate would be stabilized. This then results in the library modifying its distribution, increasing the concentration of macrocycles that are good receptors for the substrate. To be able to investigate and utilize such systems we need to understand the factors that can influence the library's diversity. We have shown that thermodynamically controlled transesterification reactions can lead to efficient synthesis of oligomeric macrocycles based on quinine alkaloids[10,11] and cholic acid.[4,12] When monomeric building blocks are suitably predisposed, a single product may dominate even when other oligomers are kinetically accessible;[13] for example, the thermodynamic cyclization of the quinine methyl ester **1a:HO−Cq−OMe** or cinchonidine methyl ester **1b: HO−Cc−OMe** gives almost exclusively the correspond-



(1a) HO–Cq–OMe: X=OMe
(1b) HO–Cc–OMe: X=H

ing cyclic trimer.[10] Predisposition must be carefully distinguished from preorganization: The latter generally refers to the ground state of a monomer whose conformation holds the reactive groups in close proximity, thereby favoring one pathway over alternatives (Figure 1a). Preorganization in covalent chemistry is therefore a kinetic process. Predisposition, on the other hand, should

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(1) Wilson, S. R.; Czarnik, A. W. *Combinatorial Chemistry. Synthesis and Application*; Wiley: New York, 1997.

(2) (a) Huc, I.; Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2106−2110. (b) Brady, P. A.; Sanders, J. K. M. *Chem. Soc. Rev.* **1997**, *26*, 327−336. (c) Rowan, S. J.; Sanders, J. K. M. *Curr. Opin. Chem. Biol.* **1997**, *1*, 483−490. (d) Timmerman, P.; Reinhoudt, D. N. *Adv. Mater.* **1999**, *11*, 71−74. (e) Ganesan, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2828−2831.

(3) Some of the extended quinine work has been reported in communication form: Rowan, S. J.; Sanders, J. K. M. *Chem. Commun.* **1997**, 1407−1408.

(4) Brady, P. A.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3237−3253.

(5) (a) Hioki, H.; Still, W. C. *J. Org. Chem.* **1998**, *63*, 904−905. (b) Tam-Chang, S.-W.; Stehouwer, J. S.; Hao, J. *J. Org. Chem.* **1999**, *64*, 334−335.

(6) Giger, T.; Wigger, M.; Audétat, S.; Benner, S. A. *Synlett* **1998**, 688−691.

(7) Kidd, T. J.; Leigh, D. A.; Wilson A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599−1600.

(8) Klekota, B.; Hammond, M. H.; Miller, B. L. *Tetrahedron Lett.* **1997**, *38*, 8639−8642.

(9) Calama, M. C.; Hulst, R.; Fokkens, R.; Nibbering, N. M. M.; Timmerman, P. Reinhoudt, D. N. *Chem. Commun.* **1998**, 1021−1022.

(10) Rowan, S. J.; Brady, P. A.; Sanders, J. K. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2143−2145.

(11) Rowan, S. J.; Hamilton, D. G.; Brady, P. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1997**, *119*, 2578−2579.

(12) Brady, P. A.; Bonar-Law, R. P.; Rowan, S. J.; Suckling, C. J.; Sanders, J. K. M. *Chem. Commun.* **1996**, 319−320.

(13) Rowan, S. J.; Brady, P. A.; Sanders, J. K. M. *Tetrahedron Lett.* **1996**, *37*, 6013−6016.

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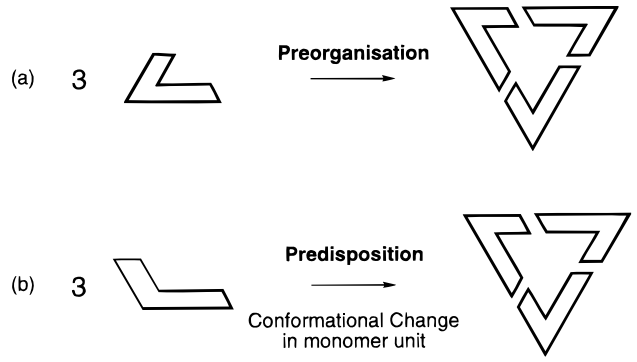


Figure 1. Schematic representation of a monomer (a) preorganized and (b) predisposed to form a cyclic trimer.

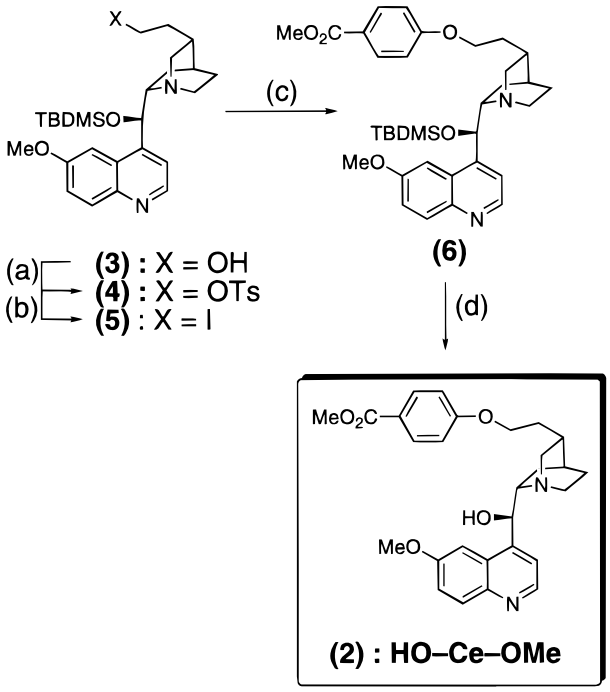
be thought of as a strong conformational or structural preference expressed by the building block once it is incorporated into a larger structure, giving rise to a thermodynamic preference for a particular product (Figure 1b). This means that the final conformation in the oligomer is not the same as, or dictated by, the ground-state conformation of the free monomer. We have also shown that such predisposition can be affected with the addition of a flexible facilitator[14] and thus increase the size of the DCL. We now report the consequences of altering the underlying alkaloid shape and geometry on this predisposition of thermodynamic cyclizations.

Results and Discussion

An Extended Quinine Building Block. Our first attempt to try to relax the predisposition of quinine[3] was the addition of an arm at the C(11) position, to give the extended quinine monomer **2:HO−Ce−OMe**. The extension, methyl 4-hydroxybenzoate, serves several functions: it is compatible with our transesterification conditions; it programs into the molecule-added length to increase the size of any cavity formed and allow access to cyclic dimer; and it also introduces a little extra flexibility, while still being rigid enough to prevent formation of cyclic lactone monomer. Synthesis of **2:HO−Ce−OMe** started from the previously prepared C(11)-alcohol **3**. This was converted into the tosylate **4** with tosyl chloride and triethylamine (77% yield), which on heating with NaI in acetone gave 9-*O*-*tert*-butyldimethylsilyl-10−11-dihydro-11-iodo quinine **5** in 86% yield. **5** was converted into **6** (75%) by stirring with methyl 4-hydroxybenzoate, 18-crown-6, and K_2CO_3, and deprotection of the TBDMS group by using TBAF/THF gave the extended monomer **2:HO−Ce−OMe** in 78% yield (Scheme 1).

The monomer was then thermodynamically cyclized by using our transesterification conditions.[10] The catalyst (5−10% KOMe/18-crown-6) was added to a solution (5 mM) of **2:HO−Ce−OMe** in toluene which was heated to reflux through 4 Å sieves in a Soxhlet extractor to effect clean macrocyclization within 10−20 min. The initial solution of monomer in toluene is heated to reflux for 30−60 min prior to the addition of the catalyst to ensure that the reaction is as dry as possible. The Soxhlet extractor apparatus permits the azeotropic removal of the methanol produced on addition of the catalyst, thereby favoring

Scheme 1[a]



[a] Reagents and conditions: (a) TsCl, Et_3N, CH_2Cl_2, rt; (b) NaI, acetone, reflux; (c) methyl-*p*-hydroxybenzoate, K_2CO_3, 18-crown-6, acetone, rt; (d) TBAF, THF, rt.

the formation of macrocyclic over linear oligomers. A range of macrocycles is observed, the mixture being dominated by cyclic dimer **(Ce_2)**:trimer **(Ce_3)**:tetramer **(Ce_4)** quinine cyclophanes (Scheme 2), with a mass ratio of 39:47:14, respectively, as observed by HPLC.[15] Even though there is still a preference for cyclic trimer, the extension unit has allowed access to cyclic dimer (not previously seen even in kinetic cyclizations of the **1a** derivative) and tetramer under thermodynamic control, demonstrating the expected relaxation of predisposition. ^{1}H NMR helps to explain this relaxation in distribution. The $^3J_{H_8H_9}$ coupling constant is particularly useful in this respect, allowing us to examine the gross conformation of the quinine unit.[16−18] $^3J_{H_8H_9}$ in the cyclic dimer **(Ce_2)** is 10.2 Hz, indicating that the quinine unit can adopt a conformation in **Ce_2** similar to that of the predisposed cyclic trimer **(Cq_3)** in which $^3J_{H_8H_9} = 10.5$ Hz. $^3J_{H_8H_9}$ in **Ce_3** and the higher cyclic oligomers is 7.8 Hz, suggesting that the quinine unit, in these molecules, can now adopt the stable conformation similar to that of linear species[18] which display similar *J* values.

In the thermodynamic (reversible) reaction, once a product is formed it can be reconverted into other more thermodynamically stable species, a proof-reading process. However, this is not the case in a kinetic (irreversible) reaction where once a product is formed there is no going back. We decided, therefore, to investigate the cyclization of the extended acid alcohol monomer **7** under kinetic control. **7** could easily be prepared from the

(14) Rowan, S. J.; Lukeman P. S.; Reynolds; D. J.; Sanders, J. K. M. *New J. Chem.* **1998**, *22*, 1015−1018.

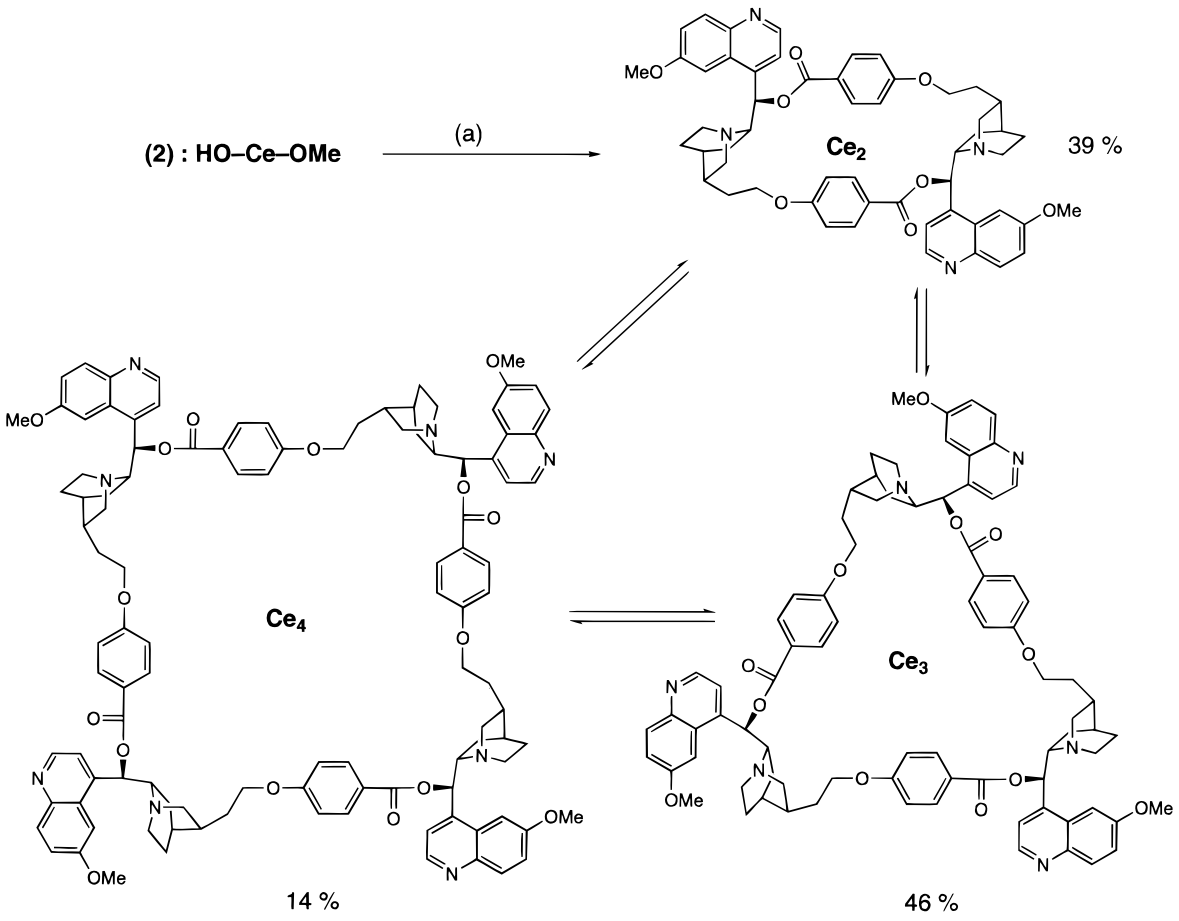
(15) Small amounts of higher oligomers are also observed.

(16) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069−8076.

(17) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *J. Org. Chem.* **1990**, *55*, 6121−6131.

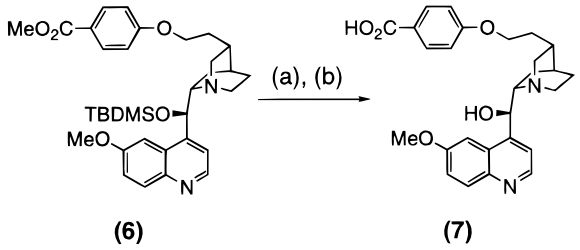
(18) Rowan, S. J.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 1536−1546.

Scheme 2[a]



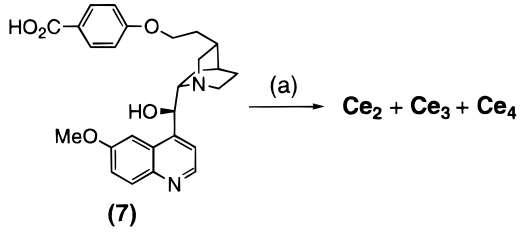
[a] Reagents and conditions: (a) KOMe, 18-crown-6, toluene, reflux.

Scheme 3[a]



[a] Reagents and conditions: (a) LiOH, THF/H_2O, rt; (b) TBAF, THF, rt.

Scheme 4[a]

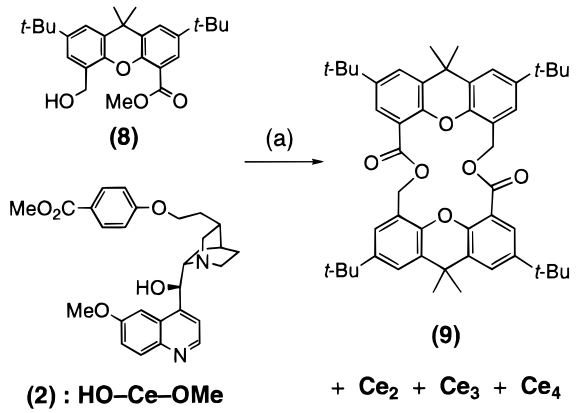


[a] Reagents and conditions: (a) 1. 2,6-dichlorobenzoyl chloride, Et_3N, DMF. 2. DMAP, CH_2Cl_2, rt, 18 h.

TBDMS-protected extended methyl ester **6** in two steps (Scheme 3). Ester hydrolysis with LiOH in THF/H_2O followed by deprotection of the TBDMS group with TBAF in THF affords **7** in a 13% overall yield for the two steps. Kinetic cyclization of this monomer was carried out, at 5 mM, using a modified Yamaguchi macrolactonization procedure[13] (Scheme 4). As in the thermodynamic cyclization, a range of macrocycles is obtained with cyclic dimer, trimer, and tetramer being the dominant products; however, the distribution is slightly different (**Ce_2**:**Ce_3**:**Ce_4** ratio is 46:43:11. cf. 39:47:14 for thermodynamic cyclizations at 5 mM). It is interesting, at this point, to compare the thermodynamic and kinetic cyclizations of both the quinine **1a:HO−Cq−OMe** and extended quinine **2:HO−Ce−OMe** derivatives. For **1a:HO−Cq−OMe** there is a large difference observed between the kinetic cyclizations (where a range of macrocycles is formed) and thermodynamic cyclizations (where mainly cyclic trimer **Cq_3** is observed). However, in the extended series **2:HO−Ce−OMe** the difference in macrocycle distribution is not so stark. These observations imply no significant destabilization of **Ce_4** and other oligomers relative to **Ce_3**, and thus no significant increase in the **Ce_4** reconversion rate under thermodynamic conditions. This is not the case with **1a:HO−Cq−OMe**, where while the cyclization rates are comparable for the **Cq** oligomers relative to **Cq_3** (this is demonstrated by the distribution observed in the kinetic formation of these macrocycles), the stability of **Cq_4** and higher oligomers is less. This results in an unzipping of the **Cq** higher oligomers (i.e., increased reconversion rate) and ultimately an increased distribution of **Cq_3**.

The xanthene hydroxy ester **8** is a molecule specifically designed to have the ester and hydroxyl functional groups arranged in a parallel fashion on a rigid framework, to

Scheme 5[a]



[a] Reagents and conditions: (a) KOMe, 18-crown-6, toluene, reflux.

give a molecule preorganized to form only cyclic dimer. Under thermodynamic control, mixtures of cinchonidine monomer **1b:HO−Cc−OMe** and preorganized xanthenes self-sort to give good yields of cyclic trimer and dimer, respectively, because the homo-products are stabilized.[11] To see if the extension unit has any effect on mixed thermodynamic cyclizations with the xanthene **8**, we submitted the xanthene monomer **8** and the extended quinine **2** to the thermodynamic cyclization (Scheme 5) at a total monomer concentration of 5 mM (2.5 mM of each monomer). Once again self-selection was observed: only the xanthene dimer and homo-extended quinine macrocycles were formed. The **Ce_2**:**Ce_3**:**Ce_4** ratio observed is 53:39:8, which is similar to the distribution observed for the cyclization of **2**, carried out at 2.5 mM (52:42:6). This change in macrocycle distribution highlights just how sensitive to concentration the final product mixture is; e.g., at 5 mM, cyclic trimer **(Ce_3)** is the slightly more favored product, but upon reducing the concentration to 2.5 mM, cyclic dimer **(Ce_2)** becomes the more favored product. Formation of larger amounts of smaller oligomers at lower concentration is predicted by theoretical considerations.[19]

Quinidine-Derived Building Blocks. Having examined the effect that an extension unit has on the product distribution of a monomer, we wanted to explore the effect of a radical shape change within the context of essentially identical chemistry. We therefore prepared the methyl ester derivative of quinidine **10:HO−Cd−OMe**. The inverted stereochemistry (Figure 2) at the C(8) and C(9) positions (but not at the C(3) position) was expected to lead to a different product distribution.

Synthesis of **10:HO−Cd−OMe** was achieved by using a procedure similar to that reported previously (Scheme 6) for the quinine derivative.[18] The C(9)-hydroxyl of quinidine **11** was protected as the TBDMS ether **12**, prepared in a 97% yield. Hydroboration of **12**, followed by oxidation with trimethylamine *N*-oxide dihydrate, gave the alcohol **10** in 81% yield.[20] Oxidation of the terminal alcohol **10** was carried out by employing Jones reagent. The resulting carboxylic acid **14**, formed in 62%

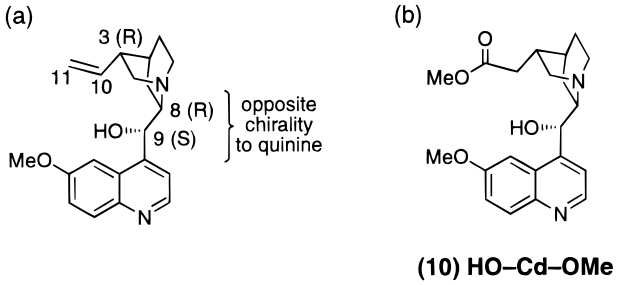
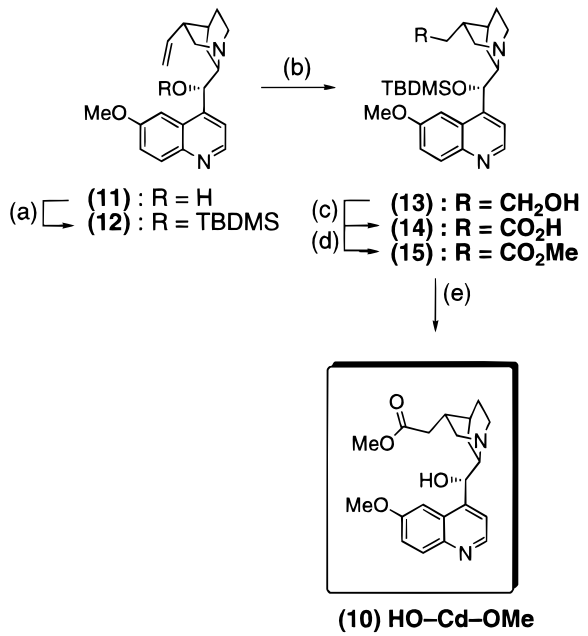


Figure 2. (a) Quinidine and (b) quinidine methyl ester **10: HO−Cd−OMe**.

Scheme 6[a]



[a] Reagents and conditions: (a) TBDMSCl, Et_3N, DMAP, DMF, rt; (b) BH_3.THF (5 equiv), diglyme, 0 °C then $Me_3NO{\cdot}2H_2O$, 100 °C; (c) Jones reagent, acetone, rt; (d) $HCl_{(concentrated)}$, MeOH, rt; (e) TBAF, THF, rt.

yield, was esterified with MeOH/HCl to give the methyl ester **15** (92%). Finally, the protecting group was removed by using TBAF/THF to yield the monomer **10:HO−Cd−OMe** in 67% yield. The overall yield for the five steps is 30%. As in the quinine series,[18] the C(9) position in the quinidines seems to be rather hindered as indicated by the ^{1}H NMR spectra of the TBDMS ether intermediates: the TBDMS *tert*-butyl group resonance is split into two peaks, indicative of two slowly interconverting conformations, of relative populations of approximately 3:1. Once the bulky TBDMS group is removed only one conformation is observed.

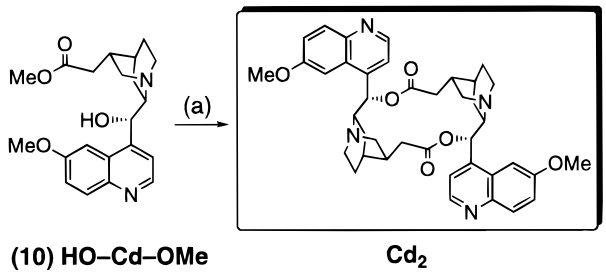
Using a method similar to that used before, the monomer **10** was thermodynamically cyclized (Scheme 7). The catalyst (5−10% KOMe/18-crown-6) was added to a solution (5 mM) of **10:HO−Cd−OMe** in refluxing toluene. Electrospray mass spectrometry (ES-MS) was used to follow the extent of the reaction, and by HPLC analysis the reaction appears to have yielded almost exclusively cyclic dimer **Cd_2**, although up to 5% of cyclic trimer **Cd_3** is observed in both the ES-MS and HPLC.

The $^3J_{H_8H_9}$ coupling observed in the ^{1}H NMR spectra of **10:HO−Cd−OMe** and **Cd_2** is less than 3 Hz, which is indicative of a dihedral angle that does not change

(19) (a) Ercolani, G.; Mandolini, L.; Mencarelli, P.; Roelens, S. *J. Am. Chem. Soc.* **1993**, *115*, 3901−3908. (b) Ercolani, G. *J. Phys. Chem. B* **1998**, *102*, 5699−5703.

(20) Commercial quinidine from Aldrich or Lancaster contains 10% dihydroquinidine. The yields reported are based on the actual amounts of quinidine used.

Scheme 7[a]



[a] Reagents and conditions: (a) KOMe, 18-crown-6, toluene, reflux.

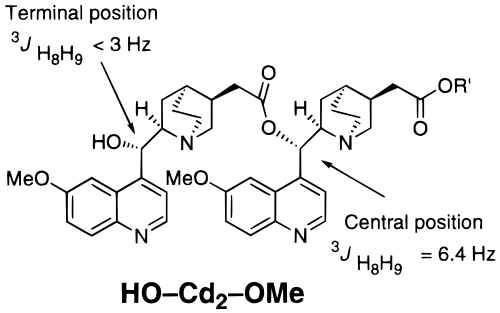


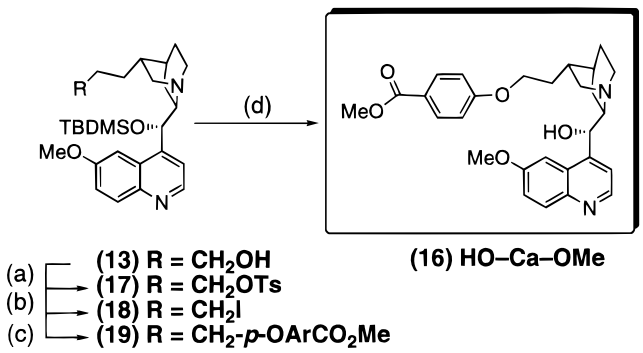
Figure 3. The two different $^3J_{H_8H_9}$ values in **HO−Cd$_2$−OMe**.

dramatically from around 90° on macrocyclization. In other words, the conformation that the quinidine unit adopts in the macrocycle is similar to that in the monomer, so that it might not seem too surprising then that the dimer is very much preferred in this case. It should be noted, however, that there are two different $^3J_{H_8H_9}$ values in the linear quinidine dimer **HO−Cd$_2$−OMe** (Figure 3), which is, presumably, the species which undergoes the cyclization to form cyclic dimer **Cd$_2$**. The $^3J_{H_8H_9}$ at the terminal alcohol has a value similar to that of the quinidine monomer **10:HO−Cd−OMe**, whereas the $^3J_{H_8H_9}$ at the central ester has now changed to 6.4 Hz. This change in conformation of the quinidine unit containing an ester on the C(9)-hydroxyl is to be expected (*cf.* quinidine acetate $^3J_{H_8H_9}$ ca. 7 Hz).[16] This would imply that upon cyclization a conformational change in one of the quinidine units is required, which would not be the case if the quinidine linear dimer **HO−Cd$_2$−OMe** was preorganized.

The result of the cyclization of monomer **10:HO−Cd−OMe** implies that this molecule is more preorganized to give cyclic dimer. In an attempt to create a more promiscuous monomer, that is, capable of the required diversity, we added the phenoxy extension group to give an extended quinidine monomer. The required monomer **16:HO−Ca−OMe** was prepared in a way similar to that used before (Scheme 8), using the terminal alcohol **13** as a starting point. The primary alcohol was converted into the tosylate **17**, in 77% yield. The tosylate was subsequently displaced by iodide to form intermediate **18** (79%). Combination of **18** with methyl 4-hydroxybenzoate and potassium carbonate gave **19** (98%), which upon deprotection with TBAF yielded the monomer **16:HO−Ca−OMe** (45%). The overall yield from the quinidine natural product was 21% for the six steps.

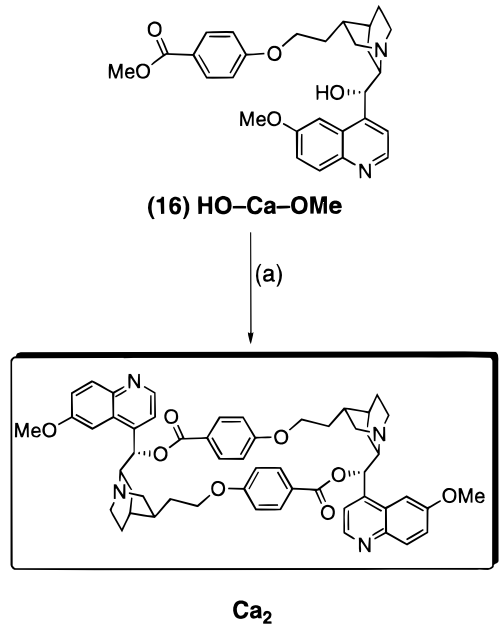
Once again, the NMR spectra of compounds **17**−**19** were complicated by the appearance of two conformational isomers, probably resulting from the steric bulk

Scheme 8[a]



[a] Reagents and conditions: (a) Tosyl chloride, Et_3N, rt 4 h; (b) NaI, acetone, reflux, 16 h; (c) methyl 4-hydroxybenzoate, 18-crown-6, K_2CO_3, rt, 16 h; (d) TBAF, THF, rt, 4 h.

Scheme 9[a]

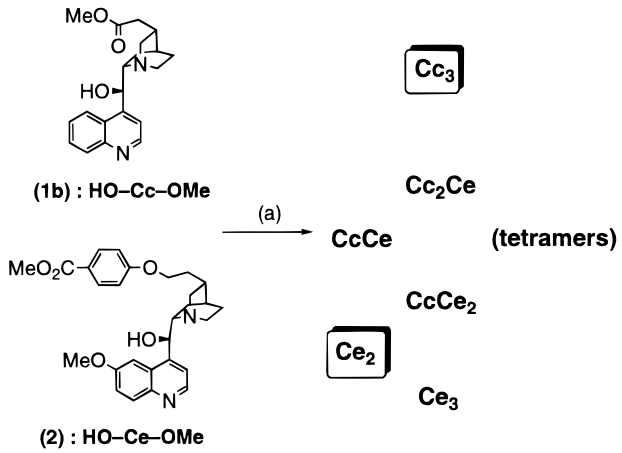


[a] Reagents and conditions: (a) KOMe, 18-crown-6, toluene, reflux.

of the quinoline unit and the TBDMS group. These were exacerbated by the addition of the tosylate/extension unit, where the resonance of the C(9) proton becomes so broad that it nearly disappears in the spectra of **17** and **19**; again, this is believed to be an exchange phenomenon. As before, deprotection at the C(9)-hydroxyl resulted in a much sharper proton spectrum, as the previously split peaks coalesced to give rotationally averaged signals.

Cyclization of **16:HO−Ca−OMe** was carried out as before and the reaction mixture was analyzed by HPLC. Despite the extra flexibility and size of **16:HO−Ca−OMe**, the cyclization yielded almost exclusively dimer **Ca$_2$** (>85% of the cyclized material), as shown in Scheme 9; again, the rest of the material is thought to be cyclic trimer (which is observed by ES-MS). This does not mirror the results obtained for the quinine derivatives described above, where the extension unit allowed a large relaxation of the predisposition properties of **1a:HO−Cq−OMe**. Thus, it would appear that **16:HO−Ca−OMe** is also preorganized to give the dimeric macrocycle; in this case the phenoxy unit does not confer enough extra conformational freedom to overcome the strong prefer-

Scheme 10[a]



[a] Reagents and conditions: (a) KOMe, 18-crown-6, toluene, reflux.

ence to form dimer, and the product distribution is not greatly altered. In retrospect, this observation may not be too surprising since the phenoxy unit acts primarily as an extension to C(11), adding extra length in the form of the aromatic ring; there is only one extra degree of freedom (the C(11)−O bond) in **16:HO−Ca−OMe** as compared to **10:HO−Cd−OMe**.

Mixing Experiments

We now had four cinchona alkaloid derivatives for thermodynamic mixing experiments. We have already carried out a mixing experiment using two cinchona alkaloids; upon transesterification of **1a:HO−Cq−OMe** and **1b:HO−Cc−OMe**, each 2.5 mM, we observe all four possible cyclic trimers, **Cc_3**, **Cc_2Cq**, **$CcCq_2$**, **Cq_3**, in the expected 1:3:3:1 ratio.[10] We, therefore, could now examine the effect that addition of an extension unit and/or change of shape has on the product distribution by mixing either **1a** or **1b** with one of the other cinchona alkaloid monomers. Combination of extended monomer **2:HO−Ce−OMe** with predisposed **1b:HO−Cc−OMe** allowed us to examine the effect of the extension unit. Thermodynamic transesterification of **2:HO−Ce−OMe** and **1b:HO−Cc−OMe**, under the usual conditions, led to a combinatorial library of macrocycles (Scheme 10), as observed by electrospray mass spectrometry (Figure 4). The mass spectrum contains two of the three possible dimers, all possible trimers and small amounts of all the possible tetramers. However, it is unwise to draw precise quantitative conclusions from peak intensities since individual species have different inherent detectabilities in electrospray mass spectra,[21] but there are systematic and interpretable deviations from the expected 2:1 statistical distribution of hetero:homooligomers. The extended quinine homodimer is seemingly favored over the heterodimer, which is not surprising given that **1b:HO−Cc−OMe** cannot form the homodimer. The trimers show the expected weighting toward the cinchonidine homotrimer but the more relaxed monomer **2:HO−Ce−OMe** gives access to two new heterotrimers. To a first approximation, it appears that the tetramers are formed in statistical proportions. It is important, however, to note that

(21) Brady, P. A.; Sanders, J. K. M. *New J. Chem.* **1998**, *22*, 411−417.

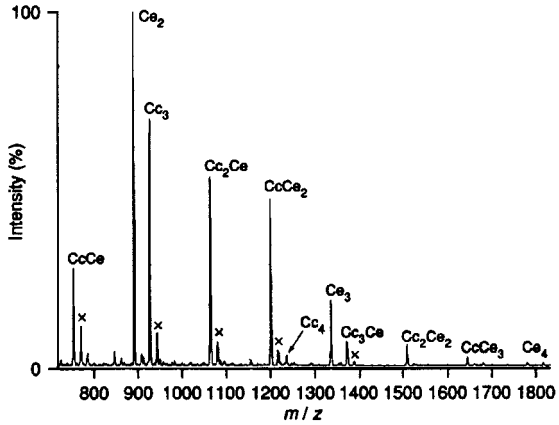
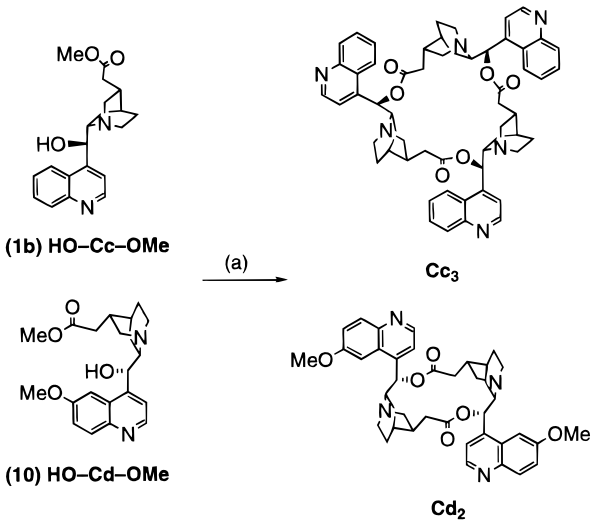


Figure 4. Electrospray mass spectra of the thermodynamic cyclization of **2b: HO−Cc−OMe** and **22:HO−Ce−OMe**. Peaks marked (X) are NH_4^+ adducts of molecular ions.

Scheme 11[a]



[a] Reagents and conditions: (a) KOMe, 18-crown-6, toluene, reflux, 1 h.

from the electrospray data alone we cannot tell the relative quantities of cyclic dimers, trimers, or tetramers.

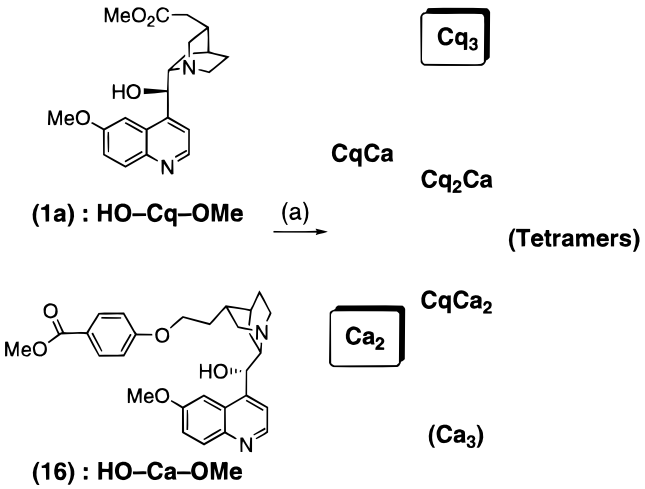
These results demonstrate that it is possible to generate combinatorial libraries of macrocyclic receptors, even when one of the building blocks is predisposed to produce just a single product when cyclized alone. By mixing only two monomers we observe eleven cyclic products, indicating that large libraries of macrocycles can be obtained quickly from a small number of monomers.

We also examined the effect that shape change has on the product distribution by mixing the two diastereoisomers. When cinchonidine **1b:HO−Cc−OMe** and quinidine **10:HO−Cd−OMe** monomers are cyclized together, they self-sorted into the cinchonidine cyclic trimer **Cc_3** and quinidine dimer **Cd_2** (Scheme 11).

This could be thought of as diastereomeric self-sorting and emphasizes the importance of shape in thermodynamic chemistry.

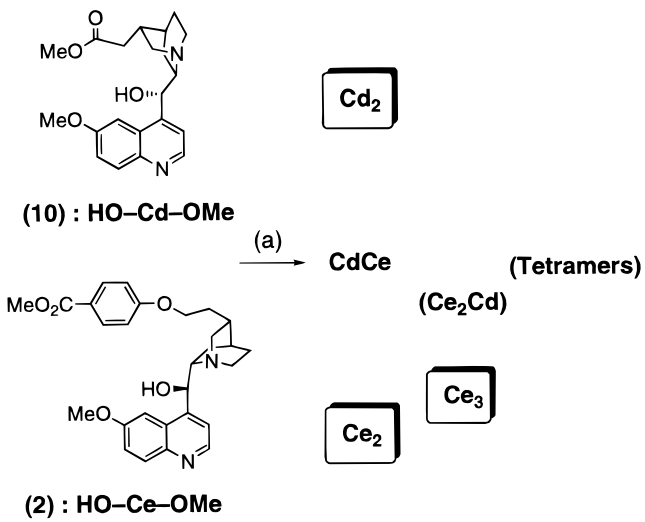
Mixing quinine **1a:HO−Cq−OMe** with extended quinidine **16:HO−Ca−OMe** allowed us to examine what would happen to the diversity when an extension unit was put on the quinidine monomer. The result was that **Ca_2** and **Cq_3** were the major products, although the extension allowed access to reasonable amounts of the

Scheme 12[a]



Reagents and conditions: (a) KOMe, 18-crown-6, toluene, reflux.

Scheme 13[a]



[a] Reagents and conditions: (a) KOMe, 18-crown-6, toluene, reflux, 1 h.

heterodimer and trimers, as well as detectable amounts of $\mathbf{Ca_3}$ and tetramers (Scheme 12). This might be due to the fact that one monomer is predisposed to form trimer, while the other prefers to form dimer. This, along with the slight relaxation of dimer formation in the extended quinidine, results in less preference for dimer formation and allows access to a slightly wider range of macrocycles.

Mixing of the apparently more promiscuous extended quinine **2:HO−Ce−OMe** with the quinidine **10:HO−Cd−OMe** gave access to only a small amount of mixing. The major products are the two homodimers $\mathbf{Ce_2}$ and $\mathbf{Cd_2}$, and it could be argued that because both monomers prefer dimer, this limits the stability of other mixed, nondimeric products. In fact, the other major products are the heterodimer **CdCe** and the two cyclic trimers that contain high proportions of the extended quinine, $\mathbf{Ce_3}$ and $\mathbf{Ce_2Cd}$ (Scheme 13). It is interesting to note that, while putting the extension on either cinchona alkaloid increases diversity, in both reactions, the degree of mixing is different. This might be due to the quinidine unit being too preorganized to encourage diversity.

Finally, we then examined the thermodynamic cyclization of a mixture of both quinidine monomers **10:HO−Cd−OMe** and **16:HO−Ca−OMe** under the conditions used for the previous cyclization reactions. The cyclization reaction involving both **10:HO−Cd−OMe** and **16:HO−Ca−OMe** was found to give the two homodimers as the major product, but about 5% of the heterodimer was detected by HPLC analysis, as depicted in Scheme 14. The rest of the material is believed to correspond to the cyclic homotrimers. A similar ratio of homodimer to homotrimer is observed in both the mixing and single monomer experiments for each of the quinidine monomers.

In both of our previous cases of self-sorting, the **1b:HO−Cc−OMe** monomer unit with either the xanthene building block[11] or the quindine monomer **10:HO−Cd−OMe**, the individual monomers cyclized to yield different oligomers: **1b:HO−Cc−OMe** yields trimer, while the xanthene and quinidine monomer both yield dimer. This, combined with the relative rigidity of the monomers, results in a greater stability of the two homooligomers relative to that of the heterodimers or trimers, dictating that very little of the latter would survive the proofreading (or reconverting) process. In the case of **10:HO−Cd−OMe** and **16:HO−Ca−OMe** the similarity of the two monomer units means that both favor cyclic dimer formation. The slight relaxation of rigidity in **16:HO−Ca−OMe** has reduced the difference in thermodynamic stability between the homo- and heterodimers, thereby hindering total self-sorting. However, the different bite-sizes of these monomers prevent a statistical distribution being observed.

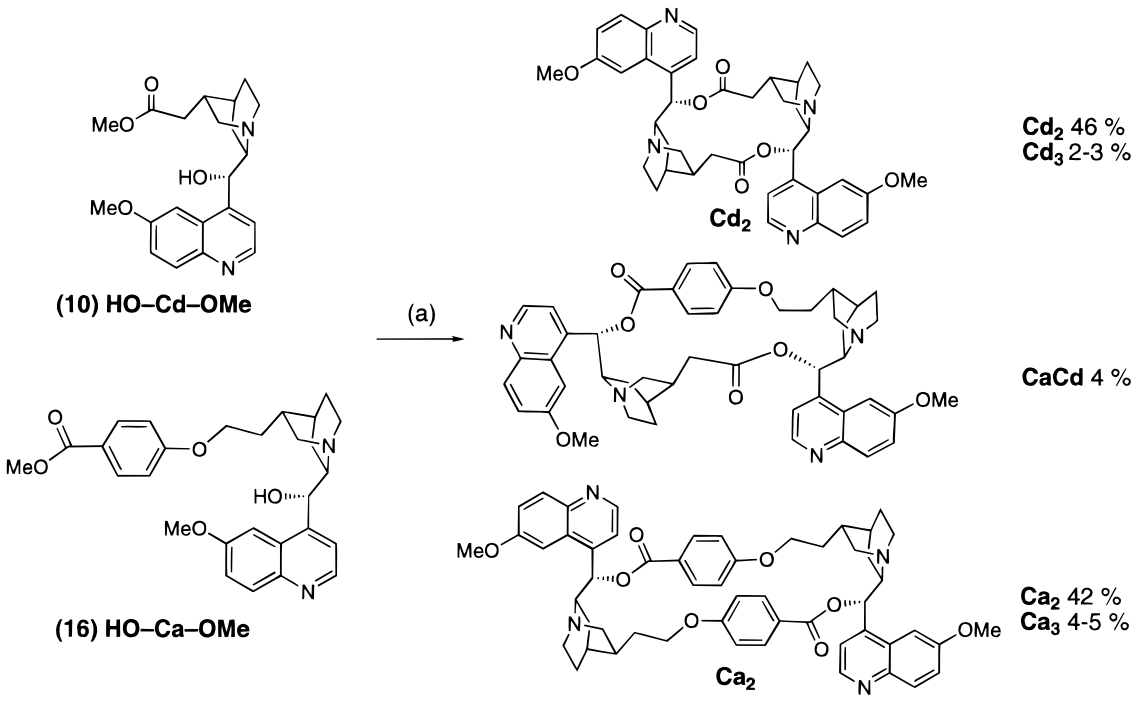
The cinchona alkaloid mixing experiments highlight a range of diversity that can be achieved in the thermodynamic cyclization of two monomers, ranging from self-sorting (as observed with **1b:HO−Cc−OMe** and **10:HO−Cd−OMe**) to complete mixing (as observed, for example, with **2:HO−Ce−OMe** with **1b:HO−Cc−OMe**). The degree of mixing will obviously rely upon the conformational stability of the heterooligomers when compared to that of the homooligomers. Furthermore, mixing will also be dependent on the bite-size of the monomer.[22] The question of bite-size is illustrated in Figure 5. If the monomers are too rigid and have different bite-sizes, then strain will be observed in any mixed oligomers, thus rendering such heterooligomers thermodynamically unfavorable and inducing self-sorting. In contrast, if the bite-sizes of the two monomers are similar, then mixing will occur. One way to overcome the bite-size problem is to increase the amount of flexibility in at least one of the monomers. Flexibility helps with diversity in at least two ways. First, it bestows greater freedom to any heterodimer, allowing it to adopt a more energetically favorable conformation. Moreover, flexibility permits the bite-size of the monomer to alter without paying too much of a penalty in energy, and in both scenarios mixing is facilitated.

Conclusions

We have now succeeded in showing that the quinidine derivatives can be synthesized and cyclized under the transesterification conditions described. The results contrast with those previously obtained for the diastereoisomer quinine, in that now the predominant cyclic species formed is the cyclic dimer. Furthermore, and

(22) A similar argument based upon bite-angle can also be invoked here.

Scheme 14[a]



[a] Reagents and conditions: (a) KOMe, 18-crown-6, toluene, reflux, 1 h.

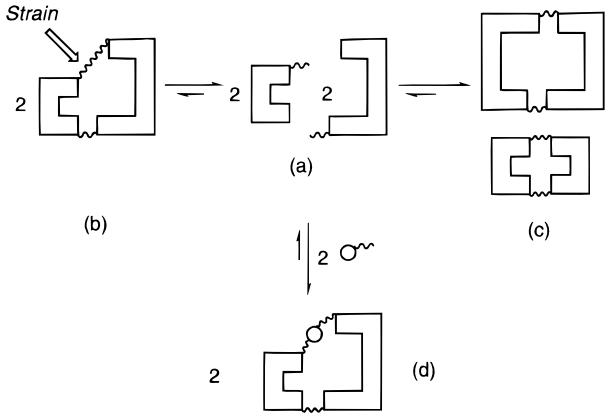


Figure 5. Schematic representation of how incompatible "bite size" can lead to self-sorting of building blocks in thermodynamically controlled chemistry: (a) a mixture of large and small building blocks, (b) mixed dimer exhibiting bond and/or angle strain, (c) self-sorted mixture of strain-free dimers, and (d) the use of a small diversifier to facilitate formation of mixed oligomers.

perhaps more significantly, there appears to be little or no conformational change on macrolactonization suggesting these quinidine derivatives are more preorganized, rather than predisposed. We have also demonstrated that thermodynamic cyclization of cinchonidine **1b:HO−Cc−OMe** and quinidine **10:HO−Cd−OMe** leads to self-sorting into cinchonidine trimer $\mathbf{Cc_3}$ and quinidine dimer $\mathbf{Cd_2}$−diastereomeric sorting. Finally, we have demonstrated that this predisposition can be reduced to give mixtures of oligomers, with addition of an extension unit to the quinine molecule (which results in **2:HO−Ce−OMe**) and that libraries of cinchona alkaloid macrocycles can be quickly generated. However, a more general solution to the diversity problem may lie in the use of small facilitator molecules.[14]

Experimental Section

None of the yields have been optimized. ^{1}H NMR and ^{13}C NMR were obtained at either 250 or 400 and 63 or 100 MHz, respectively. Fast atom bombardment (FAB) mass spectra were obtained using a *m*-nitrobenzyl alcohol matrix and positive-ion electrospray mass spectra (ES-MS) were obtained using 80 V sampling cone voltage (V_c). Samples were introduced into the mass spectrometer source with an LC pump and a flow rate of 4 mL min^{-1} of MeCN/H_2O (1:1). HPLC separations were carried out on a μBondapak C_{18} 3.9 × 300 mm reverse phase column using a mobile phase with a flow rate of 1 mL min^{-1}, pump A 0.05 M *n*-hexylamine, H_3PO_4 (pH = 3), pump B MeCN and detection by a diode array UV detector.

9-*O*-*tert*-Butyldimethylsilyl-10-11-dihydro-11-tosyl-quinine (4). To a solution of the alcohol **3** (3.0 g, 6.8 mmol) in DCM (20 mL) was added tosyl chloride (1.94 g, 10.2 mmol) and Et_3N (1.75 mL, 12.6 mmol). The solution was allowed to stir overnight and worked up by adding ethyl acetate, washing with water (×3), and drying over magnesium sulfate. The ethyl acetate was removed under vacuum and the remaining oil purified by flash column chromatography ethyl acetate/methanol (10:0, 9:1, ..., 6:4) to yield the product (3.09 g, 77%). TLC ethyl acetate/methanol (8:2) R_f = 0.51. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.72 (d, J = 4.4 Hz, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.58 (m, 1H), 7.47 (d, J = 4.5 Hz, 1H), 7.36 (dd, J = 2.5, 9.6 Hz, 1H) 7.29 (d, J = 8.2 Hz, 2H), 6.50 (brs, 1H), 4.01 (s, 3H), 3.89 (m, 2H), 3.49 (m, 1H), 3.17 (m, 2H), 2.80 (m, 1H), 2.41 (s, 3H), 1.81−2.35 (m, 5H), 1.80 (m, 1H), 1.57 (m, 2H), 1.41 (m, 1H) 0.98 (s, 9H), 0.27 (s, 3H), −0.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.4 (s), 146.7 (d), 145.3 (s), 144.6 (s), 140.2 (s), 132.5 (s), 131.9 (d), 130.0 (d), 127.8 (d), 125.7 (s), 123.4 (d), 118.9 (d), 100.2 (d), 67.8 (t), 67.3 (t), 60.4 (d), 57.5 (q), 56.1 (t), 42.9 (t), 33.2 (t), 30.3 (d), 25.9 (q), 24.7 (d), 21.7 (q) 18.1 (t), 18.0 (s), −4.7 (q), −5.2 (q). (Due to different conformations, the C(9) carbon was too broad to be observed). MS (FAB) 611.29480 ($C_{33}H_{47}O_5N_2$-SiS requires 611.2975).

9-*O*-*tert*-Butyldimethylsilyl-10-11-dihydro-11-iodo-quinine (5). 4 (2.0 g, 3.28 mmol) was dissolved in acetone (15 mL) in a flask equipped with a condenser under an inert atmosphere and NaI (1.0 g, 6.67 mmol) added. The solution

was then heated to reflux for 2−3 h. The mixture was worked up by adding ethyl acetate, washing with water (×3), and drying over magnesium sulfate. The ethyl acetate was removed under vacuum and the remaining oil purified by flash column chromatography ethyl acetate/methanol (9:1) to yield the product (1.6 g, 86%). TLC ethyl acetate/methanol (8:2) R_f = 0.67. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.71 (d, J = 4.5 Hz, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.47−7.49 (m, 2H), 7.38 (dd, J = 2.5, 9.2 Hz, 1H), 6.62 (brs, 1H), 4.12 (s, 3H), 4.05 (m, 1H), 3.54 (m, 1H), 3.23−3.40 (m, 2H), 2.97−3.02 (m, 2H), 2.78 (m, 1H), 1.80−2.40 (m, 5H), 1.68 (m, 2H), 1.20 (m, 1H), 0.97 (s, 9H), 0.38 (s, 3H), −0.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.5 (s), 146.6 (d), 144.7 (s), 143.6 (s), 132.0 (d), 125.6 (s), 123.4 (d), 119.2 (d), 100.4 (d), 67.8 (d), 60.6 (d), 59.3 (q), 56.0 (t), 43.2 (t), 37.1 (t), 34.2 (d), 26.0 (q), 24.8 (t), 24.5 (d), 19.0 (s*), 18.0 (t*), −3.6 (q), −4.2 (q). (Due to different conformations, the C(9) carbon was to broad to be observed). MS (FAB) 567.1898 ($C_{26}H_{40}O_2N_2SiI$ requires 567.19055).

Methyl 9-*O*-*tert*-Butyldimethylsilyl-10-11-dihydroquinine-11-(phenoxy-*p*-carboxylate) (6). To a solution of **5** (0.5 g, 0.88 mmol) in acetone (5 mL) was added methyl-4-hydroxybenzoate (0.269 g, 1.77 mmol), 18-crown-6 (0.466 g, 1.77 mmol) and K_2CO_3 (0.244 g, 1.77 mmol), and the mixture was left to stir overnight. To work up the reaction ethyl acetate was added, and the solution was washed with water (×3) and then dried over magnesium sulfate. The ethyl acetate was removed under vacuum and the remaining oil purified by flash column chromatography ethyl acetate/methanol (9:1) to yield the product (0.39 g, 76%). TLC ethyl acetate/methanol (8:2) R_f = 0.53. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.74 (d, J = 4.5 Hz, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.91 (d, J = 8.9 Hz, 2H), 7.51 (d, J = 4.5 Hz, 1H), 7.37 (dd, J = 2.4, 9.2 Hz, 1H), 7.18 (brs, 1H), 6.78 (d, J = 8.9 Hz, 2H), 5.64 (brs, 1H), 4.02 (m, 3H), 3.89 (m, 2H), 3.84 (s, 3H), 1.50−3.50 (m, 13H), 0.94 (s, 9H), 0.18 (s, 3H), −0.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.8 (s), 162.7 (s), 156.6 (s), 147.4 (d), 147.2 (s), 144.5 (s), 131.9 (d), 131.6 (d), 126.1 (s), 122.6 (s), 121.4 (d), 118.8 (d), 113.9 (d), 100.5 (d), 72.1 (br), 66.5 (t), 60.7 (d), 57.9 (t), 55.4 (q), 51.8 (q), 43.1 (t), 34.1 (t), 32.2 (d), 28.7 (t), 26.0 (q), 25.7 (d), 21.0 (t), 18.0 (s), −4.7 (q), −5.2 (q). MS (FAB) 591.32540 ($C_{34}H_{47}O_5N_2Si$ requires 591.3254).

Methyl 10-11-Dihydroquinine-11-(phenoxy-*p*-carboxylate) (2). 6 (77 mg, 0.13 mmol), TBAF (60 μL, 1M in THF, 0.6 mmol), and THF (1 mL) were stirred overnight. The THF was then removed under vacuum, and the resulting oil was dissolved in dichloromethane and washed with water. Upon removal of the dichloromethane the remaining oil was purified by flash column chromatography ethyl acetate/methanol (9:1, 8:2, 7:3) to yield the product (39 mg, 63%). TLC ethyl acetate/methanol (6:4) R_f = 0.23. HPLC (reverse phase: time/%pump A = 0/90, 40/60) R_t = 20.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.65 (d, J = 4.5 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.93 (d, J = 8.9 Hz, 2H), 7.50 (d, J = 4.5 Hz, 1H), 7.31 (dd, J = 2.6, 9.2 Hz, 1H), 7.21 (d, J = 2.6 Hz, 1H), 6.82 (d, J = 8.9 Hz, 2H), 5.55 (d, J = 3.8 Hz, 1H), 3.93 (t, J = 6.2 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.49 (m, 2H), 3.14 (m, 2H), 2.66 (m, 1H), 2.49 (m, 1H), 1.68−1.80 (m, 5H), 1.47−1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.8 (s), 162.6 (s), 157.8 (s), 147.6 (d), 147.4 (s), 144.3 (s), 131.7 (d), 131.6 (d), 126.6 (s), 122.5 (s), 121.5 (d), 118.4 (d), 113.9 (d), 101.2 (d), 72.1(d), 66.4 (t), 59.8 (d), 58.4 (t), 55.7 (q), 51.9 (q), 43.2 (t), 34.2 (t), 32.5 (d), 28.1 (t), 26.0 (d), 21.5 (t). MS (FAB) 477.2369 ($C_{28}H_{33}O_5N_2$ requires 477.2390).

Thermodynamic Cyclization of Quinine Extended Monomer (2). Sample preparation of KOMe catalyst. KOMe in methanol (0.513 mL, 0.78 M, 0.40 mmol), freshly prepared from potassium metal and methanol, was added to 18-crown-6 (106 mg, 0.40 mmol). Dried toluene (1 mL) was then added and the mixture condensed under reduced pressure to ca. 0.5 mL. More toluene (1 mL) was added, and the mixture was again condensed under reduced pressure to 0.5 mL. This was repeated once more to make sure all of the methanol had been removed azeotropically. The catalyst mixture was then diluted with toluene (ca.1.5 mL) and the solution filtered under an inert atmosphere to give a KOMe·18-C-6 toluene solution of ca. 0.015−0.03 M as determined by titration.

Cyclization of Monomer. 2 (11.2 mg, 2.35×10^{-5} moles) was added to a round-bottomed flask attached to a Soxhlet extractor which contained molecular sieves (4 Å) and then dissolved in toluene (4.7 mL). This was heated to reflux for 30 min to remove all of the water from the system, and then the KOMe·18-C-6 catalyst solution (18 μL, 0.066 M, 1.18×10^{-6} moles) was added. To work up the reaction, the mixture was added to aqueous pH 7 buffer and extracted with ethyl acetate. The organic solvent was then removed and the resulting mixture analyzed by HPLC and ES-MS, indicating the presence of mainly cyclic dimer, trimer, and tetramer. After purification by column chromatography ethyl acetate/methanol (10:0, 9:1, ..., etc.) samples of dimer and trimer could be isolated. HPLC (reverse phase: time/%pump A = 0/80, 25/30) R_t = 12.874, 14.573, 15.762 (main peaks); ES-MS 889 (**Ce$_2$**, MH^+), 1333 (**Ce$_3$**, MH^+), 1777 (**Ce$_4$**, MH^+).

Cyclic dimer (Ce$_2$): TLC ethyl acetate/methanol (1:1) R_f = 0.22. HPLC (reverse phase: time/%pump A = 0/80, 25/30) R_t = 12.87; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (d, J = 4.6 Hz, 2H), 8.01 (d, J = 9.2 Hz, 2H), 8.00 (d, J = 8.9 Hz, 4H), 7.60 (d, J = 2.6 Hz, 2H), 7.46 (d, J = 4.6 Hz, 2H), 7.36 (dd, J = 2.6, 9.2 Hz, 2H), 6.96 (d, J = 8.9 Hz, 4H), 6.52 (d, J = 10.2 Hz, 2H), 4.26 (m, 4H), 3.90 (s, 6H), 3.63 (m, 2H), 3.15 (m, 2H), 3.03 (dd, J = 9.6, 13.6 Hz, 2H), 2.67 (m, 2H), 2.27 (m, 2H), 1.97−2.25 (m, 4H), 1.86 (m, 2H), 1.451.75 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =165.6 (s), 162.4 (s), 157.8 (s), 147.5 (d), 144.9 (s), 131.8 (d), 127.8 (s), 122.1 (s), 121.5 (d), 114.6 (d), 102.0 (d), 73.4 (d), 67.4 (t), 60.2 (d), 57.6 (t), 55.6 (q), 42.0 (t), 33.8 (d), 32.8 (t), 28.2 (t), 24.4 (t), 24.4 (d). ES-MS 889 (MH^+).

Cyclic trimer (Ce$_3$): TLC ethyl acetate/methanol (1:1) R_f = 0.19. HPLC (reverse phase: time/%pump A = 0/80, 25/30) R_t = 14.57; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (d, J = 4.5 Hz, 3H), 7.99−8.03 (m, 9H), 7.55 (d, J = 2.6 Hz, 3H), 7.44 (d, J = 4.5 Hz, 3H), 7.36 (dd, J = 2.6, 9.2 Hz, 3H), 6.90 (d, J = 8.9 Hz, 6H), 6.70 (d, J = 7.8 Hz, 2H), 3.98−4.03 (m, 6H), 3.97 (s, 9H), 3.53 (m, 3H), 3.09−3.20 (m, 6H), 2.68 (m, 3H), 2.36 (m, 3H), 1.44−2.03 (m, 30H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =165.4 (s), 163.1 (s), 158.0 (s), 147.5 (d), 144.9 (s), 131.8 (d), 127.3 (s), 122.1 (s), 121.8 (d), 114.2 (d), 101.7 (d), 73.4 (d), 66.9 (t), 59.7 (d), 58.1 (t), 55.7 (q), 42.4 (t), 33.6 (d), 32.9 (t), 28.2 (t), 26.7 (t), 24.2 (d). ES-MS 1333 (MH^+).

10-11-Dihydro-11-(phenoxy-*p*-carboxy)-quinine (7). To a solution of **6** (5 g, 8.47 mmol) in THF/methanol (66 mL/20 mL) was added an aqueous solution of LiOH (1 g in 22 mL H_2O). After the reaction was stirred at room temperature for 24 h, the mixture was carefully neutralized and extracted into ethyl acetate (×3). The organic solvent was then removed, and the product could be purified by column chromatography ethyl acetate/methanol (10:0, 9:1, 8:2, ..., 0:10) to yield a white solid (2.44 g, 50%) which could be crystallized from chloroform/methanol mixtures. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.74 (d, J = 4.0 Hz, 1H), 7.96−8.02 (m, 3H), 7.49−7.53 (m, 2H), 7.34 (m, 1H), 6.73 (m, 2H), 6.27 (brs, 1H), 3.85 (m, 2H), 3.80 (s, 3H), 3.53 (m, 1H), 3.08−3.20 (m, 2H), 2.79 (m, 1H), 1.40−2.20 (m, 9H), 0.97 (s, 9H), 0.20 (s, 3H), −0.37(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.0 (s), 160.8 (s), 158.8 (s), 146.9 (d), 146.0 (s), 144.4 (s), 131.8 (d), 131.4 (d), 128.1 (s), 125.9 (s), 122.5 (d), 118.9 (d), 113.3 (d), 100.4 (d), 69.4 (d), 65.5 (t), 59.8 (d), 56.5 (t), 56.2 (q), 42.1 (t), 34.1 (t), 31.5 (d), 26.4 (t), 26.0 (q), 25.8 (d), 18,9 (t), 18.0 (s), −4.1 (q), −5.2 (q). ES-MS 577 (MH^+). The TBDMS was removed in the usual way. TBDMS-protected quinine (0.42 g, 0. 73 mmol) and TBAF (2 mL, 1 M in THF, 2 mmol) in THF (10 mL) was stirred overnight. The mixture was worked up by removal of the THF, followed by trituation with diethyl ether to yield **7** as a white powder (83 mg, 25%). ^{1}H NMR (400 MHz, CD_3SOCD_3, C_5D_5N) δ = 8.83 (d, J = 4.5 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 9.2 Hz, 2H), 7.68−7.73 (m, 2H), 7.41 (dd, J = 2.6, 9.2 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 5.70 (d, J = 5.4 Hz, 1H), 3.98 (m, 2H), 3.88 (s, 3H), 3.38 (m, 1H), 3.35 (m, 1H), 3.03 (m, 1H), 2.61 (m, 1H), 1.86 (m, 1H), 1.65−1.73 (m, 7H), 1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2 (s), 161.9 (s), 157.2 (s), 147.6 (d), 144.3 (s), 131.4 (d), 127.1 (s), 121.0 (d), 119.1 (d), 113.9 (d), 102.5 (d), 70.5 (d), 66.3 (t), 60.3 (d), 57.1 (t), 55.3 (q), 42.0 (t), 33.6 (t), 31.9 (d), 27.6 (t), 25.8 (d), 22.6 (t). MS (FAB) 463 (MH^+).

9-*O*-*tert*-Butyldimethylsilylquinidine (12). To a solution of quinidine **11** (10 g, 30.8 mmol) in DMF (50 mL) was added Et_3N (8.6 mL, 61.6 mmol), DMAP (0.75 g, 6.2 mmol), and TBDMSCl (6.97 g, 46.2 mmol). The solution was allowed to stir overnight and worked up by adding toluene and washing with water (×3). The toluene was removed under vacuum and the remaining oil purified by flash column chromatography, ethyl acetate/methanol (9:1) to yield the product (13.15 g, 97%). TLC ethyl acetate/methanol (8:2) R_f = 0.43. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.73 (d, J = 4.5 Hz, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.54 (d, J = 4.5 Hz, 1H), 7.36 (dd, J = 2.6, 9.2 Hz, 1H), 7.15 (brs, 1H), 5.9−6.1 (m, 1H), 5.59 (brs, 1H), 5.08 (d, J = 9.0 Hz,1H), 5.03 (d, J = 15 Hz, 1H) 3.92 (s, 3H), 3.26 (m, 1H), 2.5−3.0 (m, 5H), 2.21 (m, 1H), 2.05 (m, 1H), 1.75 (m, 1H), 1.46 (m, 1H), 1.11 (m, 1H), 0.92 (s, 9H), 0.10 (s, 3H), −0.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.9 (s), 148.2 (s), 147.5 (d), 144.4 (s), 140.6 (d), 131.9 (d), 126.4 (s), 121.5 (d), 118.9 (d), 114.6 (t), 100.5 (d), 73.0 (d), 61.1 (d), 55.7 (q), 50.4 (t), 49.5 (t), 40.4 (d), 28.1 (d), 26.7 (q), 22.4 (t), 21.0 (t), 18.1 (s), −4.6 (q), −5.2 (q). MS (FAB) 439.27880 ($C_{26}H_{39}O_2N_2Si$ requires 439.27806).

9-*O*-*tert*-Butyldimethylsilyl-10-11-dihydro-11-hydroxyquinidine (13). 12 (12.15 g, 27.7 mmol) was dissolved in diglyme (100 mL) in a flask equipped with a condenser under an inert atmosphere. The solution was cooled to 0 °C, and BH_3·THF (1 M in THF, 139 mL, 139 mmol) was added via syringe and left stirring for 30 min. The mixture was allowed to warm to room temperature and the THF removed under vacuum. Triethylamine *N*-oxide dihydrate (46.17 g, 415 mmol) was then added, and the mixture was gently heated at 100 °C for 1 h. Ethyl acetate was then added, to the mixture, and the organic layer was washed with water (×3) and dried over magnesium sulfate. The ethyl acetate was then removed to yield an oil which was purified by recrystallization from DCM/ethyl acetate to yield white crystals (9.22 g, 81%). TLC ethyl acetate/methanol (7:3) R_f = 0.18. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.73 (d, J = 4.5 Hz, 1H), 8.03 (d, J = 9.2 Hz, 1H), 7.55 (d, J = 4.5 Hz, 1H), 7.38 (dd, J = 2.5, 9.2 Hz, 1H), 7.16 (d, J = 2.5 Hz, 1H), 5.63 (d, J = 2.4 Hz, 1H), 3.93 (s, 3H), 3.67 (m, 2H), 2.57−2.95 (m, 4H), 2.04 (brs, 1H), 2.02 (m, 1H), 1.64−1.78 (m, 5H), 1.44 (m, 2H), 0.94 (s, 9H), 0.12 (s, 3H), −0.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.9 (s), 148.1 (s), 147.4 (d), 144.3 (s), 131.9 (d), 126.2 (s), 121.6 (d), 118.8 (d), 100.5 (d), 73.3 (d), 61.0 (t), 60.8 (d), 55.8 (q), 51.2 (t) 50.5 (t), 36.2 (t), 32.2 (d), 27.4 (d), 27.1 (t), 26.3 (q), 20.2 (t), 18.1 (s), −4.6 (q), −4.8 (q). MS (FAB) 457.28690 ($C_{26}H_{41}O_3N_2Si$ requires 457.28863).

9-*O*-*tert*-Butyldimethylsilyl-10-11-dihydroquinidine-11-carboxylic acid (14). 13 (1.0 g, 2.19 mmol) was dissolved in acetone (100 mL). Jones reagent was then added drop by drop until the dark brown color persisted (ca.10 mL). The mixture was then neutralized with saturated $NaHCO_3$, extracted with ethyl acetate, and dried over magnesium sulfate. It was then flash-columned ethyl acetate/methanol (8;2, 7:3, 6:4, ..., 0.0:10) to yield a white foam (0.64 g, 62%). TLC ethyl acetate/methanol (1:1) R_f = 0.12. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.71 (brs, 1H), 8.03 (d, J = 9.2 Hz, 1H), 7.49 (brs, 1H) 7.37 (d, J = 9.2 Hz, 1H), 7.10 (brs, 1H), 5.72 (brs, 1H), 3.93 (s, 3H), 1.24−3.39 (brm, 13H), 0.97 (s, 9H), 0.08 (s, 3H), −0.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.0 (s), 158.2 (s), 148.0 (s), 147.4 (d), 144.4 (s), 132.0 (d), 126.1 (s), 121.5 (d), 118.7 (d), 100.7 (d), 73.0 (d), 61.0 (d), 60.4 (t), 55.9 (q), 55.5 (d), 32.9 (t), 26.7 (q), 26.1 (d), 25.7 (d), 18.0 (s), −4.6 (q), −4.8 (q). MS (FAB) 471.26400 ($C_{26}H_{39}O_4N_2Si$ requires 471.26789).

Methyl 9-*O*-*tert*-Butyldimethylsilyl-10-11-dihydroquinidine-11-carboxylate (15). To a solution of **14** (0.84 g, 1.79 mmol) in methanol (40 mL) was added a few drops of concentrated HCl and left to stir overnight. The solution was then neutralized with sodium bicarbonate (saturated) and the methanol removed under vacuum. The resulting oil was dissolved in DCM, washed with water (×3), and dried over magnesium sulfate. Once the DCM had been removed, the compound was purified by flash column chromatography ethyl acetate/methanol (9:1) to yield a clear oil (0.80 g, 92%). TLC ethyl acetate/methanol (9:1). R_f = 0.50. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.73 (d, J = 4.5 Hz, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.53 (d, J = 4.5 Hz, 1H), 7.38 (dd, J = 2.5, 9.2 Hz, 1H), 7.20 (m, 1H), 5.66 (brs, 1H), 4.03 (s, 3H), 3.69 (s, 3H), 2.75−3.50 (brm, 4H), 2.52 (m, 2H), 2.14−2.40 (m, 2H), 2.01 (m, 1H), 1.52−2.00 (m, 4H), 0.94 (s, 9H), 0.23 (s, 3H), −0.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.3 (s), 157.8 (s), 147.4 (s), 147.0 (d), 144.5 (s), 131.9 (d), 125.9 (s), 121.3 (d), 118.8 (d), 100.4 (d), 73.1 (d), 60.4 (t), 60.2 (d), 55.8 (q), 55.5 (q) 51.8 (t), 49.2 (t), 36.7 (t), 26.9 (q), 26.5 (d), 25.8 (d), 18.0 (s), 14.2 (d), −4.6 (q), −4.7 (q). MS (FAB) 485.2842 ($C_{27}H_{41}O_4N_2Si$ requires 485.2835).

Methyl 10-11-Dihydroquinidine-11-carboxylate (10). To a solution of **15** (0.80 g, 1.65 mmol) in THF (15 mL) was added TBAF (1 M in THF, 3.3 mL, 3.3 mmol). Once this had stirred overnight, ethyl acetate was added to the solution which was then washed with water (×3) and dried over magnesium sulfate. The ethyl acetate was then removed under vacuum and the resulting oil purified by flash column chromatography, ethyl acetate/methanol (10:0, 9:1, ..., 6:4) to yield a white foam (0.41 g, 67%). TLC ethyl acetate/methanol (6:4) R_f = 0.16. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.60 (d, J = 4.5 Hz, 1H), 7.90 (d, J = 9.2 Hz, 1H), 7.55 (d, J = 4.5 Hz, 1H) 7.23 (dd, J = 2.5, 9.2 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 5.78 (brs, 1H), 4.71 (brs, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 3.42 (m, 1H), 3.10 (m, 2H), 2.96 (m, 1H), 2.86 (m, 1H), 2.60 (dd, J = 8.2, 15.8 Hz, 1H), 2.50 (dd, J = 6.8, 15.8 Hz, 1H), 2.00−2.13 (m, 2H), 1.70 (m, 1H), 1.57 (m, 1H), 1.50 (m, 1H), 1.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.3 (s), 157.8 (s), 147.5 (d), 147.0 (s), 144.0 (s), 131.5 (d), 126.1 (s), 121.7 (d), 118.3 (d), 100.8 (d), 70.9 (d), 59.5 (d), 55.8 (q), 51.7 (q), 50.3 (t), 49.9 (t), 37.0 (t), 31.7 (d), 27.5 (t), 26.2 (d), 19.7 (t). MS (FAB) 371.19350 ($C_{21}H_{27}O_4N_2$ requires 371.19707).

Thermodynamic Cyclization of (10), Cyclic Dimer Ca_2. 10 (10.3 mg, 2.78×10^{-5} moles) was added to a round-bottomed flask attached to a Soxhlet extractor which contained molecular sieves (4 Å) and then dissolved in toluene (5.6 mL). The reaction was heated at reflux for 60 min to remove all of the water from the system, and then the KOMe·18-C-6 catalyst solution (23 μL, 0.06 M, 1.39×10^{-6} moles) was added. To work up the reaction, the mixture was added to aqueous pH 7 buffer and extracted with ethyl acetate, and the solvent was removed to give the product which was immediately submitted for NMR. TLC ethyl acetate/methanol (6:4) R_f = 0.22. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (d, J = 4.5 Hz, 2H), 8.02 (d, J = 9.2 Hz, 2H), 7.41 (dd, J = 2.65, 9.2 Hz, 2H), 7.31 (d, J = 4.5 Hz, 2H), 7.16 (d, J = 2.63 Hz, 2H), 6.82 (s, 2H), 3.96 (s, 6H), 3.30 (d, J = 12.7 Hz, 2H), 3.25 (d, J = 12.7 Hz, 2H), 3.14 (m, 4H), 2.90 (m, 4H), 2.85 (m, 4H), 2.55 (dd, J = 3.1, 15.2 Hz, 2H), 2.22 (m, 4H), 1.72 (m, 2H), 1.57 (m, 2H), 1.46 (m, 2H), 1.14−1.23 (m, 4H). ES-MS 677 (**Cd_2H^+**).

Linear Quinidine Dimer HO−Cd_2−OMe. The linear quinidine dimer was prepared in the same manner as that for the previously published linear quinine dimer[18] with the following alterations: quinidine acid **14** (103 mg, 0.22 mmol) and the quinidine monomer **10:HO−Cd−OMe** (81 mg, 0.22 mmol) were reacted with 2,6-dichlorobenzoyl chloride (44 μL, 0.33 mmol), triethylamine (61 μL, 0.44 mmol), and DMAP (6 mg, 0.44 mmol) in DCM (4.6 mL). After stirring overnight, the reaction was worked up and purified as before, to yield a white foam (132 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.70−8.74 (m, 2H), 8.01 (d, J = 9.0 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.53 (d, J = 4.5 Hz, 1H), 7.05−7.40 (m, 5H), 6.48 (d, J = 7.5 Hz, 1H), 5.64 (brs, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.62 (s, 3H), 2.42−3.40 (m, 12H), 1.39−2.19 (m, 16H), 0.94 (s, 9H), 0.09 (s, 3H), −0.3 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0 (s), 171.9 (s), 157.9 (s), 147.4 (d), 144.8 (s), 144.4 (s), 131.9 (d), 127.0 (s), 126.0 (s), 121.8 (d), 118.7 (d), 101.5 (d), 100.4 (d), 73.8 (d), 58.9 (d), 55.7(q), 55.6 (q), 51.7 (q), 50.0 (t), 49.6 (t), 37.3 (t), 32.5 (d), 32.3 (d), 26.8 (t), 26.6 (d), 26.1 (q), 25.8 (d), 23.6 (t), 19.5 (t), 18.1 (s), −4.7 (q), −5.1 (q). MS (FAB) 823.4171 ($C_{47}H_{62}O_7N_2Si$ requires 823.41735). The TBDMS group was removed in a similar way to that used before with the following amounts of material. The linear TBDMS-protected quinidine dimer (100 mg, 0.12 mmol) was reacted with TBAF (0.243 mL, 1 M in THF, 0.24 mmol) in THF (1.5 mL). After stirring overnight, the reaction was worked up and purified as before, to yield **HO−Cd_2−OMe** as a clear oil (73 mg, 81%). ^{1}H NMR

(400 MHz, $CDCl_3$) δ = 8.61−8.65 (m, 2H), 7.96 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 7.53 (d, J = 4.5 Hz, 1H), 7.13−7.32 (m, 5H), 6.48 (d, J = 6.4 Hz, 1H), 5.59 (s, 1H), 4.48 (brs, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.69 (s, 3H), 3.22 (m, 1H), 2.64−3.00 (m, 9H), 2.42−2.56 (m, 2H), 2.00−2.21 (m, 4H), 1.35−1.76 (m, 8H), 1.30−1.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.3 (s), 172.2 (s), 158.0 (s), 157.8 (s), 147.9 (s), 147.6 (d), 147.3 (d), 144.6 (s), 144.2 (s), 143.9 (s), 131.7 (d), 131.6 (d), 126.9 (s), 126.4 (s), 121.8 (d), 121.5 (d), 118.3 (d), 118.1 (d), 101.5 (d), 101.2 (d), 73.7 (d), 72.3 (d), 59.5 (d), 58.9 (d), 55.6 (q), 51.8 (q), 50.6 (t), 50.1 (t), 50.0 (t), 49.7 (t), 37.7 (t), 37.5 (t), 32.0 (d), 32.2 (d), 26.9 (t), 26.8 (t, d), 26.7 (d), 22.9 (t), 20.0 (t). MS (FAB) 709.3636 ($C_{41}H_{49}O_7N_4$ requires 709.3601).

9-*O*-*tert*-Butyldimethylsilyl-10-11-dihydro-11-tosyl-quinidine (17). To a solution of **13** (1.5 g, 3.42 mmol) in DCM (10 mL) was added tosyl chloride (1.28 g, 6.72 mmol) and Et_3N (0.915 mL, 6.58 mmol). The solution was allowed to stir overnight and worked up by adding ethyl acetate, washing with water (×3), and drying over magnesium sulfate. The ethyl acetate was removed under vacuum and the remaining oil purified by flash column chromatography ethyl acetate/methanol (10:0, 9:1, ..., 6:4) to yield the product (1.62 g, 77%). TLC ethyl acetate/methanol (7:3) R_f = 0.54. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.73 (d, J = 4.5 Hz, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 4.5 Hz, 1H), 7.36 (d, J = 8.2 Hz, 3H), 7.13 (s, 1H), 5.61 (brs, 1H), 4.04 (m, 2H), 3.93 (s, 3H), 2.61−3.04 (brm, 5H), 2.44 (s, 3H), 1.97 (m, 1H), 1.79 (m, 2H), 1.61 (m, 2H), 1.23 (m, 2H), 0.94 (s, 9H), 0.084 (s, 3H), −0.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.9 (s), 147.3 (d), 144.9 (s), 144.4 (s), 133.0 (s), 131.9 (d), 131.5 (d), 129.9 (d), 127.9 (d), 126.0 (s), 121.8 (d), 118.7 (d), 100.3 (d), 79.6 (d), 68.9 (t), 60.8 (q), 55.4 (d), 50.2 (t), 32.1 (d), 32.0 (d), 31.4 (q), 26.4 (d), 25.9 (q), 25.8 (d), 21.7 (d), 18.0 (s), −4.7 (q), −5.2 (q). MS (FAB) 611.29160 ($C_{33}H_{47}O_5N_2SiS$ requires 611.2975).

9-*O*-*tert*-Butyldimethylsilyl-10-11-dihydro-11-iodo-quinidine (18). (17) (2.0 g, 3.28 mmol) was dissolved in acetone (20 mL) in a flask equipped with a condenser under an inert atmosphere and NaI (2.0 g, 13 mmol) added. The solution was heated at reflux at 60 °C overnight and then left to cool. The mixture was worked up by adding ethyl acetate, washing with water (×3), and drying over magnesium sulfate. The ethyl acetate was removed under vacuum and the remaining oil purified by flash column chromatography ethyl acetate/methanol (9:1) to yield the product (1.47 g, 79%). TLC ethyl acetate/methanol (8:2) R_f = 0.48. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.74 (d, J = 4.5 Hz, 1H), 8.03 (d, J = 9.2 Hz, 1H), 7.54 (d, J = 4.5 Hz, 1H), 7.37 (dd, J = 2.5, 9.2 Hz, 1H), 7.15 (brs, 1H), 5.64 (brs, 1H), 3.95 (s, 3H), 3.14 (m, 3H), 2.48−2.81 (m, 5H), 2.01 (m, 4H), 1.72 (m, 1H), 1.46 (m, 1H), 0.96 (s, 9H), 0.15 (s, 3H), −0.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.4 (s), 147.4 (d), 147.3 (s), 144.4 (s), 131.5 (d), 126.0 (s), 121.3 (d), 118.8 (d), 100.4 (d), 79.6 (d), 60.4 (d), 55.4 (q), 50.5 (t), 49.4 (t), 36.4 (t), 26.9 (d), 25.9 (q), 25.8 (d), 21.1 (d), 18.1 (s), −4.6 (q), −4.8 (q). MS (FAB) 567.18580 ($C_{26}H_{40}O_2N_2SiI$ requires 567.1906).

Methyl 9-*O*-*tert*-Butyldimethylsilyl-10-11-dihydroquinidine-11-(phenoxy-*p*-carboxylate) (19). To a solution of **18** (0.4 g, 0.70 mmol) in acetone (4 mL) was added methyl 4-hydroxybenzoate (0.21 g, 1.4 mmol), 18-crown-6 (0.37 g, 1.4 mmol), and K_2CO_3 (0.19 g, 1.4 mmol), and the mixture was left to stir overnight. To work up the reaction, ethyl acetate was added, and the solution was washed with water (×3) and then dried over magnesium sulfate. The ethyl acetate was removed under vacuum and the remaining oil purified by flash column chromatography ethyl acetate/methanol (9:1) to yield the product (0.41 g, 98%). TLC ethyl acetate/methanol (8:2) R_f = 0.48. ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.74 (d, J = 7.45 Hz, 1H), 8.06 (d, J = 9.2 Hz, 1H), 7.99 (d, J = 7.22 Hz, 2H), 7.54 (d, J = 4.5 Hz, 1H), 7.36 (dd, J = 2.5, 9.2 Hz, 1H), 7.18 (brs, 1H), 6.88 (d, J = 7.1 Hz, 2H), 5.64 (brs, 1H), 4.02 (m, 2H), 3.95 (s, 3H), 3.87 (s, 3H), 2.54−3.30 (brm, 3H), 1.94 (m, 4H), 1.78 (m, 2H), 1.52 (m, 2H), 1.02 (m, 1H), 0.94 (s, 9H), 0.16 (s, 3H), −0.31 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ = 166.8 (s), 162.7 (s), 158.1 (s), 156.6 (s), 147.3 (d), 144.4 (s), 131.9 (d), 131.6 (d), 126.1 (s), 122.6 (s), 121.3 (d), 118.8 (d), 114.0 (d), 100.5 (d), 79.7 (d), 66.5 (t), 60.9 (d), 60.7 (d), 55.4 (q), 51.8 (q), 50.3 (t), 49.7 (t), 49.4 (t), 32.5 (d), 31.9 (t), 26.9 (d), 26.0 (q), 21.0 (d), 19.9 (t), 18.0 (s), −4.7 (q), −5.2 (q). MS (FAB) 591.32550 ($C_{34}H_{47}O_5N_2Si$ requires 591.3254).

Methyl 10-11-Dihydroquinidine-11-(phenoxy-*p*-carboxylate) (16). Deprotection of the C(9)-hydroxyl was carried out utilizing a modified procedure for the preparation of **6**. **19** (1.17 g, 1.98 mmol), TBAF (5.94 mL, 1 M, 5.94 mmol), and THF (30 mL) was stirred overnight. Work up was accomplished as before with the remaining oil purified by flash column chromatography ethyl acetate/methanol (9:1, 8:2, 7:3) to yield the product (0.422 g, 45%). TLC ethyl acetate/methanol (6:4) R_f = 0.20. ^{1}H NMR (400 MHz, $CDCl_3$ + drop CD_3OD) δ = 8.50 (d, J = 4.6 Hz, 1H), 7.83 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 9.5 Hz, 1H), 7.51 (d, J = 4.6 Hz, 1H), 7.20 (dd, J = 2.5, 9.5 Hz, 1H), 7.08 (d, J = 2.5 Hz, 1H), 6.77 (d, J = 8.5 Hz, 2H), 5.46 (d, J = 1 Hz, 1H), 3.91 (t, J = 6.4 Hz, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 3.33 (m, 1H), 2.70−2.84 (m, 3H), 2.66 (m, 1H), 2.02 (m, 1H), 1.84−2.00 (m, 2H), 1.68 (m, 1H), 1.60 (brs, 1H), 1.32−1.43 (m, 2H), 0.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.8 (s), 162.4 (s), 158.0 (s), 147.1 (d), 144.4 (s), 143.8 (s), 131.7 (d), 131.4 (d), 125.3 (s), 122.9 (s), 122.1 (d), 118.4 (d), 114.1 (d), 99.6 (d), 65.6 (t), 60.0 (d), 56.5 (q), 51.9 (q), 50.0 (t), 49.6 (t), 31.4 (t), 30.8 (d), 25.9 (d), 24.4 (t), 18 0.2 (t). MS (FAB) 477.24260 ($C_{28}H_{32}O_5N_2$ requires 477.2390).

Thermodynamic Cyclization of (16), Cyclic Dimer Ca_2. KOMe catalyst was prepared as for the thermodynamic cyclization of **2**. Thermodynamic cyclization of monomer **16** was carried out as for monomer **2** with the following quantities of reagents: **16** (10.6 mg, 2.22 × 10^{-5} moles), toluene (4.45 mL), and the KOMe·18-crown-6 catalyst solution (19 μL, 0.06 M, 1.11 × 10^{-6} moles). The reaction was worked up as before and the solvent removed to give the product which was immediately submitted for NMR. TLC ethyl acetate/methanol (6:4) R_f = 0.24. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.73 (d, J = 4.5 Hz, 2H), 8.14 (d, J = 8.8 Hz, 4H), 8.03 (d, J = 9.2 Hz, 2H), 7.48 (d, J = 4.5 Hz, 2H), 7.42 (d, J = 2.5, 9.2 Hz, 2H), 7.30 (d, J = 2.5 Hz, 2H), 7.07 (s, 2H), 6.86 (d, J = 8.8 Hz, 4H), 3.96 (s, 6H), 3.85 (m, 2H), 3.64 (m, 2H), 3.47 (m, 2H), 3.23 (t, J = 9.2 Hz, 2H), 3.05 (m, 2H), 2.87 (m, 4H), 2.39 (m, 4H), 2.04 (m, 4H), 1.76 (m, 2H), 1.65 (m, 2H), 1.52 (m, 2H), 1.09 (m, 1H). ES-MS 889 (**Ca_2**H^+).

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Supporting Information Available: ^{1}H NMR, HPLC, and UV of **2**; ^{1}H NMR **10**, **16**, **Ce_2**, **Ce_2** + **Ce_3**, **HO**−**Ca_2**−**OMe**; ^{1}H NMR, ES-MS, HPLC, and UV of the thermodynamic cyclization of **2** and **10**; ES-MS, HPLC, and UV of the thermodynamic cyclization of **16**; ^{1}H NMR, HPLC, and UV of the thermodynamic cyclization of **10** with **16**; ES-MS of the thermodynamic cyclization of **1b** with **10**; **1a** with **16**; **1b** with **2** and **10** with **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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