Macrocycles Derived from Cinchona Alkaloids: A Thermodynamic vs Kinetic Study

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Cyclization of the quinine-derived monomer (**2a**): **HO-Cq-OMe**, under thermodynamic control, gives mainly cyclic trimer **Cq_3 (7a)**, whereas kinetic cyclization of the similar monomer **HO-Cq-OH (8)** gives a mixture of cyclic products. This difference in product distribution is attributed to predisposition of the monomer unit, which means the building block adopts a more stable conformation in cyclic trimer than it can in cyclic tetramer. The reversibility of the thermodynamic reaction was demonstrated using electrospray mass spectrometry to monitor the catalyzed mixing of the two cyclic trimers **Cq_3 (7a)** and **Cc_3 (7b)**, which results in the statistically expected 1:3:3:1 ratio of all possible cyclic trimers **Cc_3:Cc_2Cq:$CcCq_2$:Cq_3**.

Introduction

Covalent organic structures have traditionally been synthesized using kinetically controlled irreversible reactions, whereas the construction of noncovalent supramolecular assemblies generally uses thermodynamically controlled reversible interactions.[1,2] Irreversible reactions lack the ability to proofread and repair "incorrect" bond formation, while supramolecular assemblies tend to lack the robust character associated with covalent bonds, so we have been investigating the synthetic potential of covalent chemistry under reversible conditions,[3] utilizing a reversible, thermodynamically controlled macrolactonization procedure to obtain macrocycles. Macrolactonization[4] has become an important reaction in the field of natural product synthesis[5] and in the construction of large host molecules for supramolecular studies.[6] In most of these earlier studies, the product distribution has been determined kinetically, but we wished to explore the possibilities of thermodynamically templated[7] chemistry using a range of supramolecular building blocks. Thermodynamic translactonization has been used intramolecularly by Corey for the synthesis of medium ring monocyclic lactones,[8] by several groups intermolecularly for the cyclizations of β-alkanolactones,[9,10] where the ring-size distributions give good agreement with theoretical expectations,[11] as well as the synthesis of a few natural products such as Enterobactin.[12]

The chemistry we envisaged for thermodynamic cyclization of large building blocks is straightforward:

$$\mathrm{RCOOMe + R'OH \rightarrow RCOOR' + MeOH}$$

$$\mathrm{RCOOR' + R''OH \rightleftharpoons RCOOR'' + R'OH}$$

Each building block is equipped with a methyl ester group at one end and a hydroxyl group at the other. A transesterification catalyst is required, and the reaction is driven to oligomer formation by azeotropic removal into molecular sieves of the initially released methanol.[13] To test these ideas, we initially focused on cyclocholates derived from cholic acid and 7-deoxycholic acid;[3] however, to diversify the cavity size, shape, and polarity, we are now exploring other building blocks.

In designing a new building block we needed a relatively rigid, concave backbone that has a hydroxyl group

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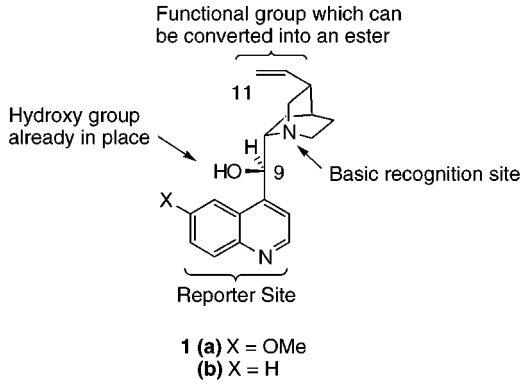
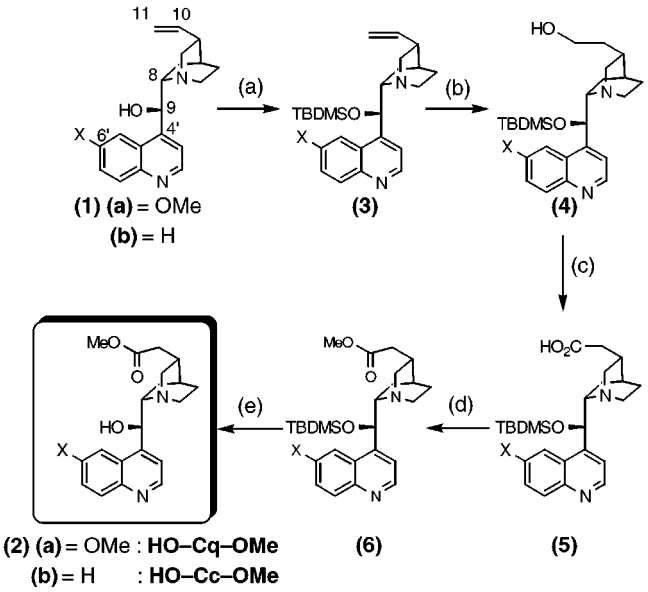


Figure 1. The quinine/cinchonidine building block core.

at one end and a methyl ester at the other. The cinchona alkaloids, quinine (**1a**) and cinchonidine (**1b**), were chosen as starting points (Figure 1). They contain a number of features which make them useful for our purposes: the quinoline ring acts as a built in spectroscopic reporter group, with quinine (X = OMe) and cinchonidine (X = H) having both different UV and mass spectra; the nitrogen in the quinuclidine ring is a basic recognition site; there is a secondary hydroxy group already in place, at position 9; and finally, the vinyl group can be converted into an ester.

Cinchona alkaloids have recently received much attention in the field of asymmetric synthesis.[14] For example, quinine and its derivatives have been used to catalyze asymmetric Michael additions,[15] cyanohydrin synthesis,[16] epoxidations,[17] thiol additions,[18] 2,2-cycloadditions, and amino acid synthesis[19] in addition to their widespread application in the Sharpless dihydroxylation reaction.[20] Quinine has also been used as a chiral solvating agent[21] and as a heterogeneous catalyst[22] after incorporation into polymers. Despite all this interest, however, there has been little use of this building block in supramolecular or macrocyclic chemistry. Notable exceptions include its use as a chiral resolution agent, where quinine forms an inclusion complex with binaphthols,[23] and as a quinine-derived macrocycle, prepared by Corey and Noe[24] for use as a more rigid ligand in the Sharpless dihydroxylation reaction. In this paper we describe the synthesis of cyclic trimers under thermodynamic conditions and prove that the conditions are truly thermodynamic both indirectly by demonstrating kinetic accessibility of other oligomers and directly by ES-MS.

Scheme 1[a]



[a] (a) TBDMSCl, Et_3N, DMAP, DMF, room temp; (b) (1) 5 equiv of BH_3·THF, diglyme, 0 °C, (2) Me_3NO, 100 °C; (c) Jones reagent, acetone, room temp; (d) MeOH, $HCl_{(concd)}$, room temp; (e) TBAF, THF, room temp.

Results and Discussion

An ester group was introduced into the cinchona alkaloid by modifying the vinyl group in five steps (Scheme 1) to give the methyl ester **HO-Cq-OMe (2a)**.[25] Starting with the natural product **1a**, the hydroxyl group at the 9 position was protected with a TBDMS group using Et_3N/DMAP and TBDMSCl to give **3a** in 99% yield. Hydroboration of the vinyl group using 5 equiv of BH_3/THF in diglyme, followed by oxidation with $Me_3NO{\cdot}2H_2O$,[26] yielded the terminal alcohol **4a** in 87% yield.[27] Subsequent oxidation of this alcohol using Jones' reagent gave the acid **5a** in 62% yield, which was esterified, using MeOH/$HCl_{(concd)}$ to furnish (**6a**) in 97% yield. Finally, deprotection of the TBDMS group using TBAF/THF yielded the monomer **HO-Cq-OMe (2a)** in 66% yield. Overall the final monomeric building block was synthesized in a 34% yield from the starting natural product. The cinchonidine monomer **HO-Cc-OMe (2b)** was prepared in an analogous manner starting from natural cinchonidine (**1b**), in 16% overall yield.

Thermodynamic cyclizations[28] of **HO-Cq-OMe (2a)** were carried out utilizing a procedure similar to that reported previously[3] (Scheme 2). The catalyst (5−10%

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(25) The following notation was used to avoid confusion during mixing experiments: The capital **C** indicates that the monomer is derived from the **C**inchona alkaloids. The second lower case letter indicates which specific monomer unit: **q** − **q**uinine derived monomer; **c** − **c**inchonidine derived monomer. The subscript denotes the number of monomer units and **HO-X-OMe** is used in the linear species.
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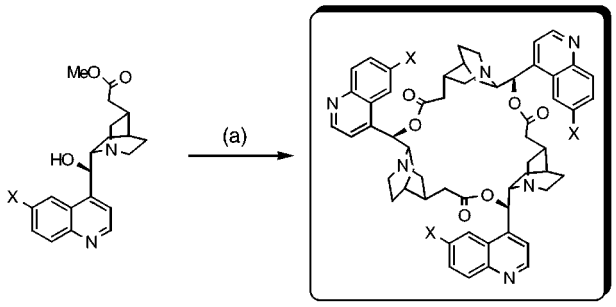
Scheme 2[a]



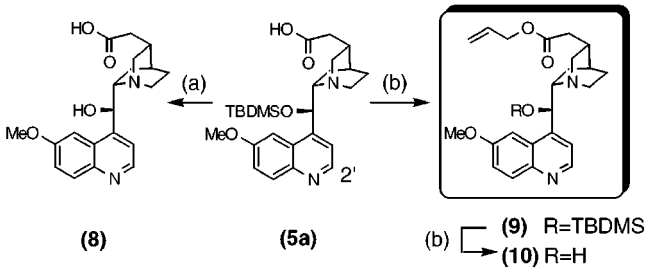
[a] (a) KOMe, 18-crown-6, toluene, reflux.

KOMe/18-crown-6) was added to a refluxing solution (5 mM) of **HO-Cq-OMe (2a)** in toluene, with azeotropic removal into molecular sieves of the methanol produced. The extent of the reaction was followed by a combination of HPLC and electrospray mass spectrometry (ESMS). Remarkably, the cyclization of **HO-Cq-OMe (2a)** gave virtually a single product (Scheme 2): the cyclic trimer **Cq_3 (7a)** was formed in high yield (>90% by NMR and 84% isolated yield). The reaction was complete after 10 min, and no further significant change in distribution was seen, even after 24 h. Monomer **HO-Cq-OMe (2a)** can be regenerated from cyclic trimer **Cq_3 (7a)** by stirring in KOMe/MeOH, indicating that the quinine building block itself was stable to the reaction conditions and no epimerization had occurred. Cyclization of the corresponding cinchonidine monomer **HO-Cc-OMe (2b)** results in the cyclic trimer **Cc_3 (7b)** again in excellent yield (>90% by NMR). Monitoring of the cyclization by ES-MS showed initial formation of some linear dimer which then disappears to give only cyclic trimer **Cq_3 (7a)**; no other linear intermediates build up significantly.

The observation of almost exclusive formation of cyclic trimer **Cq_3 (7a)** is contrary to the wide distribution we would expect from theory,[10,11] and in order to confirm that other macrocycles such as cyclic dimer or tetramer were not present, authentic samples of the cyclic oligomers (cyclic dimer−cyclic tetramer) were required. Successful preparation of these oligomers would also confirm that they are accessible kinetically and so help to demonstrate that the result of the "thermodynamic" reaction is indeed due to thermodynamics rather than a kinetic barrier preventing formation of the other oligomers. We show here that cyclic tetramer and higher oligomers are in fact accessible and that the thermodynamic approach is indeed the best for cyclic trimer.

The approach taken to obtain these cyclic oligomers was to prepare samples of the linear oligomers (monomer through tetramer) and cyclize them under kinetic conditions.[29] The acid alcohol monomer unit **8** was prepared (Scheme 3) by deprotection of the previously synthesized TBDMS protected monomer **5a**, using TBAF/ THF, in 50% yield. The other linear acid alcohol molecules were prepared by a stepwise approach. The basis of the strategy was to utilize the two differently monoprotected monomer units (**5a** (acid with protected alcohol) and (**10**) (alcohol with protected acid)). **10** was obtained as

Scheme 3[a]



[a] (a) TBAF, THF, room temp, 2−3 h; (b) 2,6-dichlorobenzoyl chloride, allyl alcohol, Et_3N, DMAP, CH_2Cl_2, room temp, 3−4 h.

outlined in Scheme 3. Starting with acid **5a**, an allyl protecting group was added using Yamaguchi esterification[30] conditions to give **9** in 90% yield. The TBDMS group could then be removed, as before, to obtain the allyl protected monomer **10** (66% yield).

Scheme 4 outlines the synthetic route used to obtain the desired linear oligomers. **5a** was reacted, again under Yamaguchi esterification conditions, with **10** to give, in 90% yield, the diprotected linear dimer **11**. Linear dimer **13** was prepared by di-deprotection of **11** in two steps using TBAF/THF (yields (**12**) in 81%) and $Pd(PPh_3)_4$/morpholine/THF[31] (yields (**13**) in 99% yield). Linear trimer **17** was obtained by reacting the monoprotected dimer **12** with the monomer acid unit **5a** under Yamaguchi conditions to give the diprotected linear trimer **15**. This was then deprotected as before via **16** to give **17** (in 69% and 66% yield, respectively). Finally the synthesis of linear tetramer **20** was achieved by reacting the two monoprotected dimers **14** (prepared in 69% by allyl deprotection of **11** and **12**), under Yamaguchi esterification conditions to give the diprotected linear tetramer **18** in 97% yield. **18** was then deprotected in the usual manner (via **19**, 48% yield) to give the linear tetramer (33%).

Cyclizations of the linear molecules were carried out under kinetic conditions with the aim of obtaining authentic samples of cyclic dimer, trimer, and tetramer. The cyclization conditions employed were a modification of the Yamaguchi macrolactonization method, using a small amount of DMF to help solubilize the starting materials. The reactions were carried out at 5 mM in order to ensure the formation of cyclic molecules and were monitored by electrospray mass spectrometry and ^1H NMR. Linear dimer **13** does not cyclize to give the cyclic dimer but instead gives mainly cyclic tetramer **Cq_4 (21)** with a small amount of cyclic hexamer. Forty-four percent of the linear dimer is converted into cyclic tetramer with the remainder being incorporated into a mixture of higher oligomers. For kinetic cyclizations,[32] a wide distribution of cyclic products should be obtained, starting from the smallest possible ring and going upward. This result suggests that cyclic dimer is too strained to be formed, as predicted by inspection of CPK models, and explains the lack of cyclic dimer in the thermodynamic reaction. Although it does not explain

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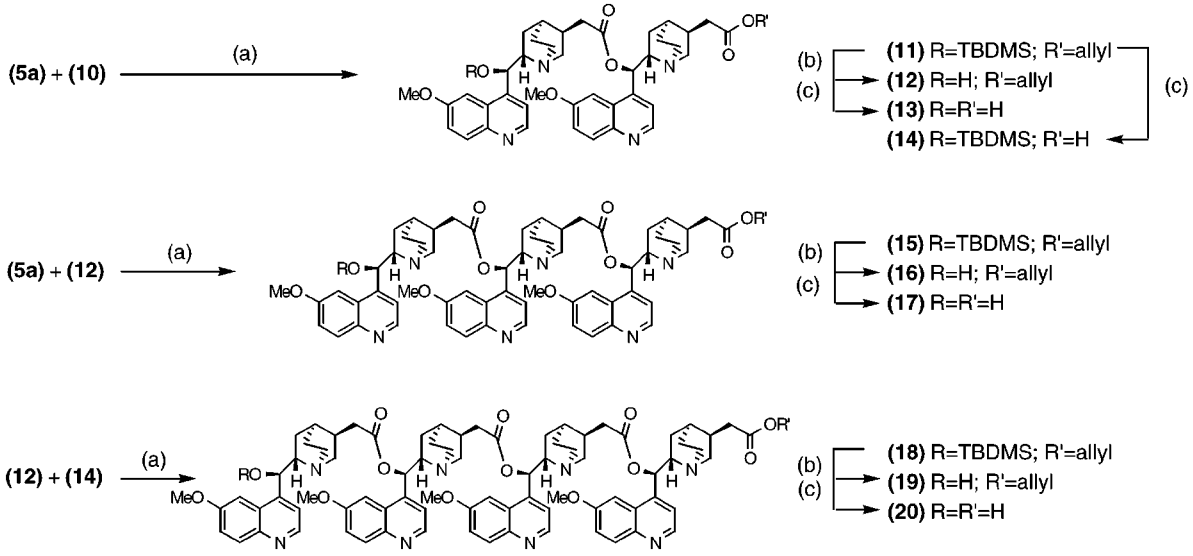
Scheme 4[a]



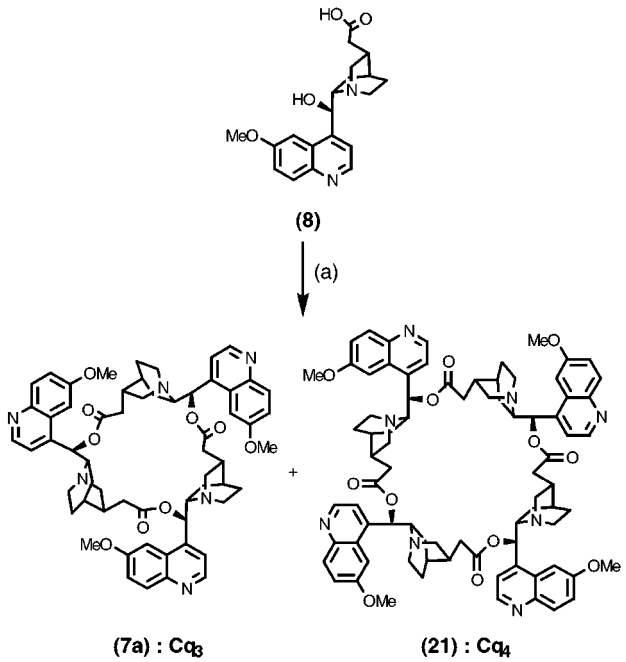
[a] (a) 2,6-Dichlorobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, room temp, 3−4 h; (b) TBAF, THF, room temp, 2−3 h; (c) $Pd(PPh_3)_4$, morpholine, THF, room temp, 1−2 h.

the absence of cyclic tetramer in the thermodynamic process, this result does show that there is no kinetic barrier to the formation of cyclic tetramer. Linear trimer **17** gave the expected cyclic trimer **Cq$_3$ (7a)** (48% of linear trimer units), the remaining products being cyclic hexamer and other higher oligomers. The isolated cyclic trimer obtained from the linear trimer reaction gave ^{1}H NMR spectra identical to the product obtained in the thermodynamic cyclization, confirming that the only significant product in that reaction is indeed cyclic trimer **Cq$_3$ (7a)**. Linear tetramer gave mainly cyclic tetramer **Cq$_4$ (21)** (45% of linear tetramer units) with the remaining material being other higher oligomers.

Kinetic cyclization of the monomer **8** (Scheme 5) gave no cyclic monomer or dimer, as predicted from the above kinetic results. The main product was cyclic trimer **Cq$_3$ (7a)**, as in the thermodynamic reaction, but here a wider distribution of cyclic products is observed. ^{1}H NMR spectra showed that monomer was converted into **Cq$_3$**:**Cq$_4$**:other higher oligomers in the proportions of 37%:23%:40%, respectively, by mass. This corresponds to a molar trimer:tetramer ratio of ca. 2:1. The kinetic results confirm that cyclic oligomers above dimer are kinetically accessible. For comparison Figure 2 shows the diagnostic parts of the ^{1}H NMR spectra from the thermodynamic and kinetic cyclizations of the monomer units **HO-Cq-OMe (2a)** and **8**, respectively. They show the narrow distribution observed in the thermodynamic cyclization (cyclic trimer) and the wider distribution (cyclic trimer, tetramer, and higher oligomers) in the kinetic cyclization.

The chemistry developed to prepare linear oligomers allowed us to synthesize the linear dimer methyl ester **HO-Cq$_2$-OMe (23)**, by coupling the alcohol protected acid (**5**) to the quinine monomer (**2a**) and removing the TBDMS group to give **HO-Cq$_2$-OMe (23)** in 51% overall yield. When **HO-Cq$_2$-OMe (23)** is submitted to our thermodynamic conditions, cyclic trimer **Cq$_3$ (7a)** is obtained (Scheme 6). This can happen in two ways: either some linear dimer is broken down into monomer which then oligomerizes and cyclizes in the usual way or linear dimer dimerizes to give cyclic and/or linear tetramer which then is converted into the most thermodynamically stable cyclic trimer releasing a monomer unit (Figure 3). ES-MS monitoring of the reaction does not give any evidence of the cyclic or linear tetramer being formed, but we do see the initial formation of monomer. This suggests that at least some of the dimer is being broken down into monomer which can then react with another dimer to give linear and then cyclic trimer. However, it is also possible that the rate of cyclization of linear tetramer to give cyclic trimer, releasing monomer, is much faster than the rate of its formation so we never "isolate" any tetramer.

Scheme 5[a]



[a] (a) (1) 2,6-Dichlorobenzoyl chloride, Et_3N, DMF; (2) DMAP, CH_2Cl_2, room temp, 18 h.

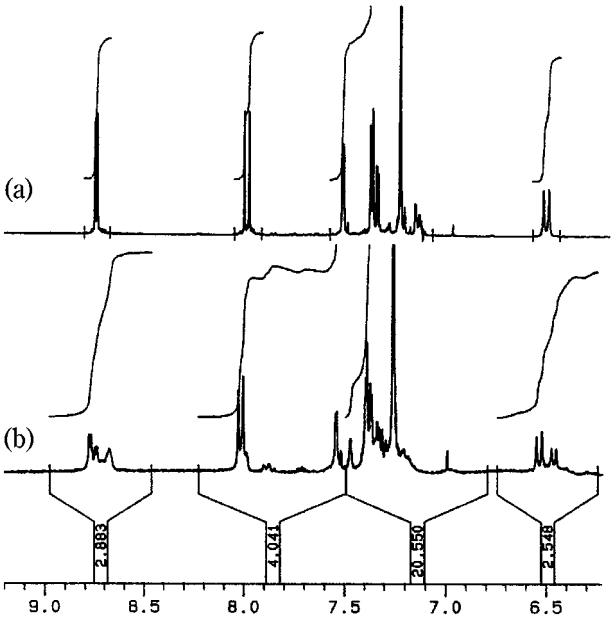


Figure 2. 400 MHz ^{1}H NMR spectra of the crude mixture of (a) the thermodynamic and (b) the kinetic cyclizations in $CDCl_3$.

Further proof was then sought to confirm that the cyclization was a reversible process. To this end, a series of mixing experiments of **Cc** and **Cq** oligomers were carried out. The monomers **HO-Cq-OMe (7a)** and **HO-Cc-OMe (7b)** were submitted to the thermodynamic conditions, and the resulting solution was assayed by ES-MS after quenching with aqueous pH 7 buffer and extraction into ethyl acetate. A statistical 1:3:3:1 ratio of the four possible trimers (**Cq_3**, **Cq_2Cc**, **$CqCc_2$**, **Cc_3**) (containing 0, 1, 2, and 3 methoxyl groups) was observed. There is an argument, however, that this distribution could be the result of a kinetic cyclization of the two monomers. The next mixing experiment carried out used the cinchonidine monomer **HO-Cc-OMe (7b)** and the linear quinine dimer **HO-Cq_2-OMe (23)**. Once again the distribution is the 1:3:3:1 ratio of the cyclic trimers, indicating that the reaction is indeed reversible. If it was irreversible than we would expect the cyclic trimer **$CcCq_2$** to dominate the products. We have shown that the cyclic trimers are thermodynamically the most stable; the final mixing experiment was designed to not only test the reversibility of the reaction but to also show that these stable cyclic trimers can indeed be opened and broken down. A mixture of the preformed trimers **Cq_3** and **Cc_3** was subjected to the reaction conditions[33] (Scheme 7), and as Figure 4 demonstrates, once again, all four possible trimers (**Cq_3**, **Cq_2Cc**, **$CqCc_2$**, **Cc_3**) are present in a 1:3:3:1 ratio. This result is consistent only with reversible breakdown and reformation of the initial trimers. The heterotrimers appear almost immediately (20 s), and after only 2 min there is already a ratio of over 2:1 (heterotrimer:homotrimer). The statistically expected 3:1 is reached within 10 min and is still present after 1 h.[34] These mixing experiments demonstrate that the final product distribution is the same irrespective of the starting oligomer, indicating that a reversible thermodynamic process is taking place.

The narrow product distributions in these cinchona alkaloid cyclizations contrast with the broader distributions observed in the cholate series,[3] using the same cyclization conditions, a result that must be due to a different balance of the statistical and enthalpic factors in the two systems. In the cholate series, steroid cores are linked by flexible four-carbon units which apparently allow considerable dispersity in the ring size distribution (dimer, trimer, tetramer, pentamer mainly). In the cinchona series, rigid quinuclidine cores are connected by a flexible two-carbon unit (C_{10} and C_{11}), with some further rotation possible around the C_8-C_9 and $C_9-C_{4'}$ bonds. This latter rotation, however, turns out to be unexpectedly restricted: ^{1}H NMR spectra of compounds **3a**−**6a** show splitting of both the $(CH_3)_3CSi$ and CH_3Si proton resonances, suggesting hindered rotation of the bonds around the C(9) carbon, presumably due to the bulky quinoline unit. This hindered rotation gives us two distinct conformations in approximately 75:25 ratio. This is also seen in the cinchonidine series **3b**−**6b**, although broadening of these signals suggests faster rotation due to the removal of the 6′-OMe group, and ratio of the two conformers is now closer to 80:20.

We believe that the monomer unit is predisposed[35] to stabilize the cyclic trimer under our conditions. 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. Preorganization in covalent chemistry is therefore a kinetic process. Predisposition, on the other hand, should be thought of as a strong conformational or structural preference expressed by the building block once incorporated into a larger structure, giving rise to a thermodynamic preference for a particular product. We have used ^{1}H NMR to examine the gross conformation of the individual quinine units in the cyclic trimer. The coupling constant between C_8 and C_9, $^3J_{H8H9}$, in the trimer is quite diagnostic in this respect. The $^3J_{H8H9}$ coupling constant is 10.5 Hz corresponding to a "closed" conformation.,[36,37] NOE interactions observed between H_9 and $H_{5'}$, H_8 and $H_{3'}$, and H_9 and H_6 are also in agreement with this conformation. This brings out the difference between preorganization and predisposition. Quinine monomer **HO-Cq-OMe (2a)** which possesses several degrees of conformational freedom, especially round the C_8-C_9 and $C_9-C_{4'}$ bonds, has a $^3J_{H8H9}$ value of 3.4 Hz, similar to that in quinine itself which adopts a more open conformation,[36,37] while in the cyclic trimer **Cq_3 (7a)** $^3J_{H8H9}$ is 10.5 Hz, indicating that the conformational relationship between the two halves of the quinine moeity has altered substantially. Although free quinine adopts an open conformation, formation of an ester on the 9 position of the molecule forces it into a more closed conformation. We see this in the linear oligomers, so it could be argued that we have preorga-

(33) The reaction procedure is the same as before but 15 mol % catalyst was used with respect to the trimers, corresponding to 5% per monomer unit.

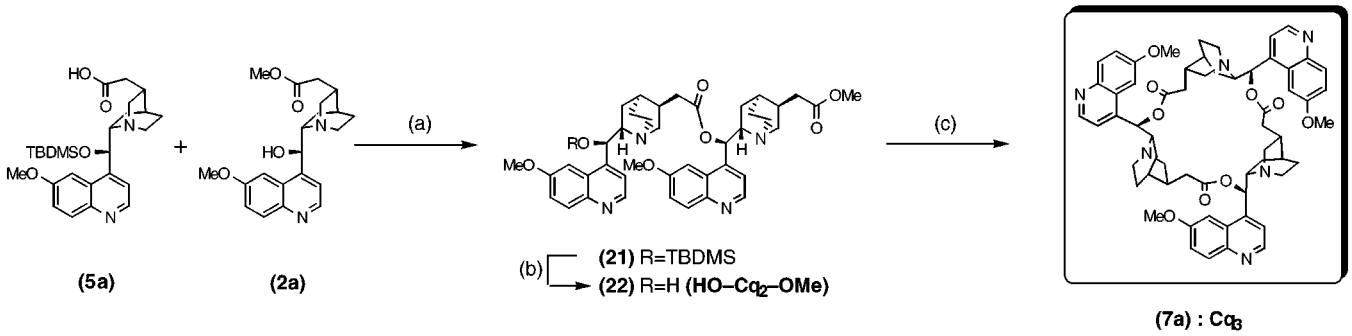
(34) For a conceptually similar experiment involving metal helicates, see Charbonnière, L. J.; Williams, A. F.; Frey, U.; Merbach, A. E.; Kamalaprija, P.; Schaad, O. *J. Am. Chem. Soc.* **1997**, *119*, 2488−2497.

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

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

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

Scheme 6[a]



[a] (a) 2,6-Dichlorobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, room temp, 3−4 h; (b) TBAF, THF, room temp, 2−3 h; (c) KOMe.18-C-6, toluene, reflux.

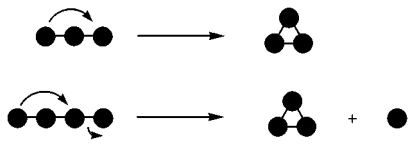


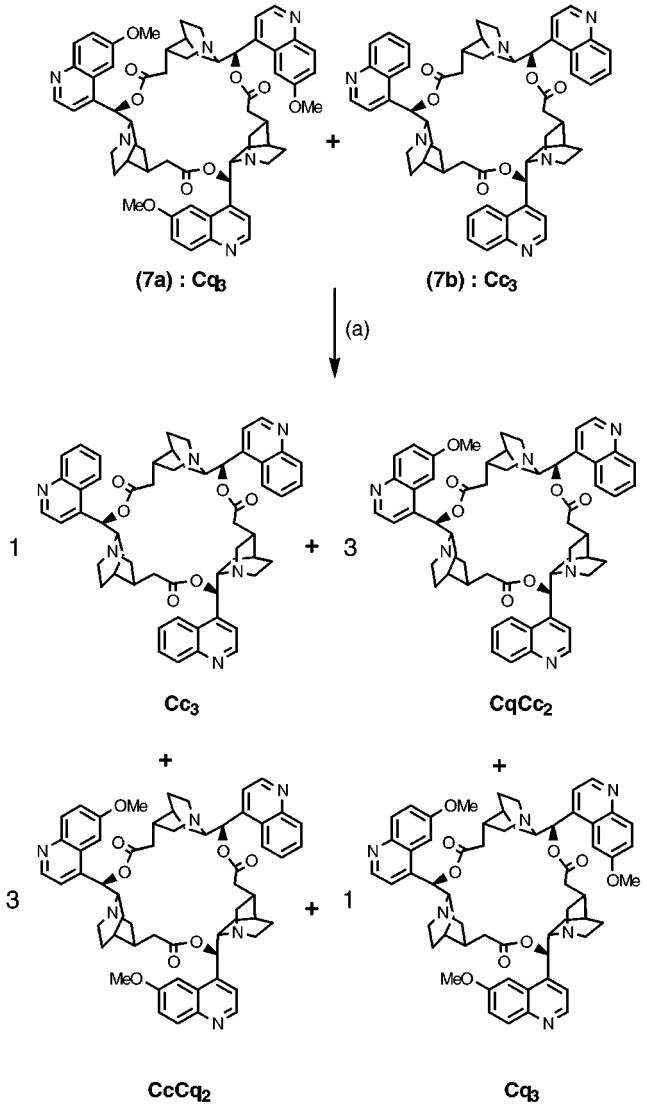
Figure 3. Schematic representation of two possible routes to cyclic trimer.

nization of the linear trimer to help cyclization; however, the $^3J_{H8H9}$ value in the linear oligomers is around 7 Hz (similar to that of 9 O-acetate derivative). This is closer to the $^3J_{H8H9}$ value adopted by the quinine in cyclic tetramer (9.3 Hz) than it is to cyclic trimer (10.5 Hz), suggesting that the linear species should be more preorganized to form cyclic tetramer over cyclic trimer neglecting entropic considerations that favor smaller rings. The NMR results demonstrate that the preferential formation of cyclic trimer cannot be due to preorganization of the monomer unit or linear trimer. The overall effect is that trimer is very much the most favored product in this reaction, with only trace amounts of the higher oligomers and no detectable dimer.

Conclusions

We have now shown that the thermodynamic transesterification reaction is applicable to systems other than cholates and that cinchona alkaloid-derived building blocks **HO-Cq-OMe (2a)** and **HO-Cc-OMe (2b)** are predisposed to give cyclic trimers.[38] We have also demonstrated that both linear and cyclic oligomeric quinine derivatives can easily be obtained. We have shown that cyclic oligomers from trimer−octamer can be prepared kinetically and in doing so we have confirmed the result of our thermodynamic cyclization where only cyclic trimer **Cq_3 (7a)** is formed. In theory, both kinetic and thermodynamic reactions should give a distribution of products. From this point of view, the kinetic reaction is well behaved, and an ever-decreasing amount of larger rings is obtained with trimer as the most abundant product (37% of monomer units). Kinetic cyclizations are dependent on the energy of the transition state, and in our system the rates of cyclization of the different linear species appear to be broadly comparable, as demonstrated by the wide distribution of the cyclic products

Scheme 7[a]



[a] (a) KOMe, 18-crown-6, toluene, reflux.

obtained. This confirms that all these cyclic products other than dimer are kinetically accessible and therefore that the absence of the larger oligomers in the thermodynamic reaction is not due to a kinetic effect. The high yield of the cyclic trimer **Cq_3 (7a)** in the thermodynamic reaction (>90% of monomer units), which should be influenced by the energy of the ring system, suggests that this is a particularly stable molecule, relative to the other

(38) A similar distribution has recently been observed by Shea and co-workers, in cyclization of their spirocatechols with phenyltriethoxysilane to give cyclic tetramer, but they did not comment on the origin of the selectivity: Small, J. H.; McCord, D. J.; Greaves, J.; Shea, K. J. *J. Am. Chem. Soc.* **1995**, *117*, 11588−11589.

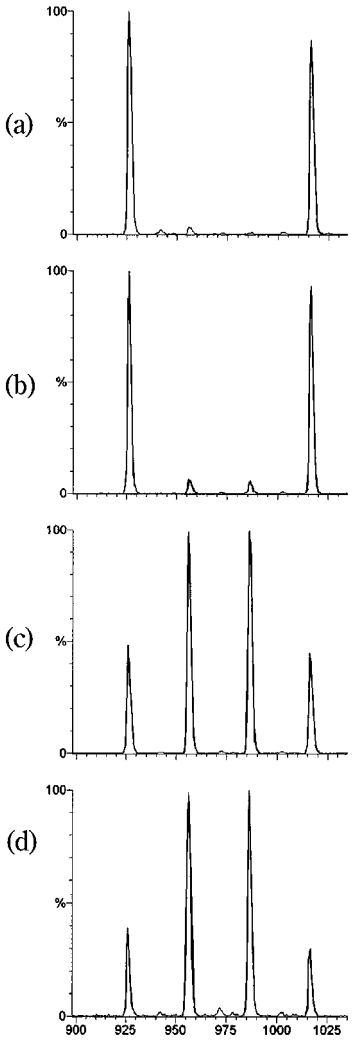


Figure 4. Molecular ion region of the ES mass spectra of the quinine trimer **Cq$_3$ (7a)** and cinchonidine trimer **Cc$_3$ (7b)** mixed reaction: (a) The reaction mixture before any catalyst was added, (b) after 20 s, (c) after 2 min, and (d) after 10 min. The four peaks correspond to trimers with zero 6′-OMe (**Cc$_3$**) (925, MH^+), one 6′-OMe (**Cc$_2$Cq**) (955, MH^+), with two 6′-OMe (**CcCq$_2$**) (985, MH^+), and with three 6′-OMe (**Cq$_3$**) (1015, MH^+). The deviation from the expected 1:1 peak intensities in (a) and from 1:3:3:1 in (c) results mainly from the slight excess of **Cc$_3$ (7b)** used (9.5 mg, 1.03×10^{-5} mol) compared to **Cq$_3$ (7a)** (9.8 mg, 9.7×10^{-6} mol).

ring systems. We believe this is due to a degree of rigidity in our molecule which predisposes it to favor the cyclic trimer **Cq$_3$ (7a)**; however, as rates of cyclization are broadly comparable (cf. kinetic cyclization) then the added stability of the trimer is probably due to decreased ring opening rate of cyclic trimer. This selectivity should be generally applicable whenever there is a thermodynamic driving force favoring a particular product. We have also recently shown that we can relax the predispositon by use of a phenoxy extension unit on the 11 position of the cinchona alkaloid.[39] Overall these results suggest that, if a particular oligomer can be stabilized by an external agent (rather than by the internal predisposition, as here), the distribution should be shifted toward that oligomer. This would be thermodynamic templating.

(39) Rowan S. J.; Sanders, J. K. M. *Chem Commun.* **1997**, 1407−1408.

Transesterification is, of course, not the only reaction which offers the prospect of efficient covalent synthesis under thermodynamic conditions. Imine formation[40] and olefin metathesis[41] have also been used in the same way. Indeed, it appears that synthesis of thermodynamically privileged structures under reversible conditions must surely always be better than kinetic synthesis.

Experimental Section

NMR spectra were recorded on Bruker WM-250 or AM-400 spectrometers. Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer. Fast atom bombardment (FAB) mass spectra were obtained using a *m*-nitrobenzyl alcohol matrix on a Kratos MS-50 instrument. Positive-ion electrospray mass spectra (ES-MS) were obtained on a VG BioQ triple quadrupole apparatus using conditions previously reported.[28] HPLC separations were carried out using either dichloromethane/methanol/triethylamine (1% in methanol) mixtures with a 25 cm × 4 mm Spherisorb S5W normal phase column or acetonitrile/*n*-hexylamine, H_3PO_4 buffer (pH = 3) mixtures with a 300 × 3.9 mm Waters μBondapak C_{18} column on a Hewlett-Packard 1050 system, and detection by a Hewlett-Packard HP1050 diode array UV detector.

Preparation 9-*O*-(*tert*-Butyldimethylsilyl)quinine (3a). To a solution of quinine (2 g, 6.17×10^{-3} mol) in DMF (10 mL) were added Et_3N (4.3 mL, 3.1×10^{-2} mol), DMAP (75 mg, 6.15×10^{-4} mol), and TBDMSCl (1.4 g, 9.30×10^{-3} mol). The solution was allowed to stir for 2−3 h and worked up by adding toluene and washing with water. The toluene was removed under vacuum and the remaining oil purified by flash column chromatography, ethyl acetate/methanol (9:1), to yield the product (2.62 g, 97%). TLC ethyl acetate/methanol (8:2) $R_f = 0.43$. ^{1}H NMR (250 MHz, $CDCl_3$)[42] δ = 8.68 (d, J = 4.5 Hz, 1H), 7.96 (d, J = 9 Hz, 1H), 7.46 (d, J = 4.5 Hz, 1H), 7.30 (dd, J = 2.5, 9 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 5.66 (brs, 1H), 5.57 (m, 1H), 4.71−4.94 (m, 2H), 3.90 (s, 3H), 3.51 (m, 1H), 3.00−3.10 (m, 1H), 2.93 (m, 1H), 2.62−2.67 (m, 2H), 2.20 (m, 1H), 1.62−1.86 (m, 3H), 1.30−1.51 (m, 2H), 0.91 (s, 9H), 0.10 (s, 3H), −0.44 (s, 3H); ^{13}C NMR (62 MHz, $CDCl_3$) δ = 158.2 (s), 147.2 (s,d), 144.4 (s), 142.2 (d), 131.9 (d), 126.2 (s), 121.5 (d), 118.7 (d), 114.1 (t), 100.5 (d), 71.6 (d), 61.1 (d), 57.0 (t), 56.1 (q), 43.2 (t), 39.9 (d), 27.2 (t), 25.9 (q), 25.7 (d), 21.0 (t), 18.0 (s), −4.2 (q), −5.0 (q). υ_{max} ($CHCl_3$) 2952, 2860, 1621, 1509, 1472, 1256, 1107, 839 cm^{-1}. MS (FAB) 439.27630 ($C_{26}H_{39}O_2N_2Si$ requires 439.27806), 423.5, 381, 303, 184, 173, 160, 136, 108, 73, 59.

Preparation of 9-*O*-(*tert*-Butyldimethylsilyl)cinchonidine (3b). A similar procedure was used for the preparation of **3b** with the following alterations: Cinchonidine (10 g, 3.4×10^{-2} mol), Et_3N (21.5 mL, 0.15 mol), DMAP (415 mg, 3.4×10^{-3} mol), and TBDMSCl (7.16 g, 4.8×10^{-2} mol) in DMF (50 mL) was stirred for 1 day. The mixture was worked up and columned as before to yield the product (13.54 g, 97%). TLC ethyl acetate/methanol (8:2) $R_f = 0.41$. ^{1}H NMR (400 MHz, $CDCl_3$)[42] δ = 8.87 (d, J = 4 Hz, 1H), 8.12 (d, J = 8 Hz, 1H), 8.04 (d, J = 8 Hz, 1H), 7.70 (m, 1H), 7.50−7.60 (m, 2H), 5.72 (brs, 1H), 5.66 (m, 1H), 4.81−4.91 (m, 2H), 3.46 (m, 1H), 3.05 (m, 1H), 2.90 (m, 1H), 2.63−2.69 (m, 2H), 2.20 (m, 1H), 1.79−1.87 (m, 2H), 1.68 (m, 1H), 1.41−1.48 (m, 2H), 0.95 (s, 9H), 0.12 (s, 3H), −0.42 (s, 3H); ^{13}C NMR (62 MHz, $CDCl_3$) δ = 149.9 (d), 149.8 (s), 148.2 (s), 142.0 (d), 130.5 (d), 129.0 (d), 126.8 (d), 125.4 (s), 122.5 (d), 118.5 (d), 114.3 (t), 72.5 (d), 61.8 (d), 57.4 (t), 43.2 (t), 40.1 (d), 28.0 (d), 27.9 (t), 25.9 (q), 21.1 (t), 18.1 (s), −4.2 (q), −5.1 (q). υ_{max} ($CHCl_3$) 2955, 1592, 1463, 1259, 1108, 839 cm^{-1}. MS (FAB) 409.26450 ($C_{25}H_{37}ON_2Si$ requires 409.26750), 351, 307, 273, 168, 154.

(40) Goodwin, J. T.; Lynn, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 9197−9198. Lindsey, J. S.; Mauzerall, D. C. *J. Am. Chem. Soc.* **1982**, *104*, 4498−4500.

(41) Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1997**, *36*, 1101−1103.

(42) Major conformer only.

Preparation of 9-*O*-(*tert*-Butyldimethylsilyl)-10,11-dihydro-11-hydroxyquinine (4a). 3a (10 g, 2.28×10^{-2} mol) was dissolved in diglyme (80 mL) in a flask equipped with a condenseer under an inert atmosphere. The solution was cooled to 0 °C and BH_3·THF (1 M in THF, 114 mL, 0.114 mol) 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 (38.3 g, 0.345 mol) was then added and the mixture gently refluxed at 100 °C for 2 h. Ethyl acetate was then added to the mixture and the organic layer washed with water (×3) and dried over magnesium sulfate. The ethyl acetate was then removed to yield an oil which was purified by flash column chromatography ethyl acetate/methanol (10:0, 9:1, 8:2,...0.1:1) to yield a white foam 9.40 g (90%). TLC ethyl acetate/methanol (7:3) $R_f = 0.33$. ^{1}H NMR (250 MHz, $CDCl_3$)[42] $\delta = 8.66$ (d, $J = 4.5$ Hz, 1H), 7.98 (d, $J = 9$ Hz, 1H), 7.48 (d, $J = 4.5$ Hz, 1H), 7.32 (dd, $J = 2.5$, 9 Hz, 1H), 7.20 (d, $J = 2.5$, 1H), 5.58 (brs, 1H), 3.90 (s, 3H), 3.41−3.55 (m, 4H), 2.97 (m, 1H), 2.83 (m, 1H), 2.57 (m, 1H), 2.36 (m, 1H), 1.82 (m, 1H), 1.18−1.70 (m, 7H), 0.86 (s, 9H), 0.09 (s, 3H), −0.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 158.1$ (s), 148.2 (s), 147.2 (d), 144.2 (s), 131.6 (d), 126.2 (s), 121.8 (d), 118.7 (d), 100.6 (d), 72.5 (d), 60.7 (d), 60.4 (t), 58.7 (t), 55.9 (q) 43.2 (t), 38.1 (t), 31.9 (d), 28.3 (t), 26.0 (q), 25.7 (d), 20.5 (t), 18.0 (s), −4.2 (q), −5.2 (q). υ_{max} ($CHCl_3$) 3689, 2932, 1621, 1509, 1472, 1235, 1111, 1036, 839 cm^{-1}. MS (FAB) 457.28810 ($C_{26}H_{41}O_3N_2Si$ requires 457.28863), 441.5, 339.5, 325, 303, 186, 173, 126, 73, 59.

Preparation of 9-*O*-(*tert*-Butyldimethylsilyl)-10,11-dihydro-11-hydroxycinchonidine (4b). A similar procedure was used for the preparation of **4b** with the following alterations: **3b** (14 g, 3.43×10^{-2} mol), BH_3·THF (171 mL, 0.171 mol), triethylamine *N*-oxide dihydrate (57.45 g, 0.375 mol) in diglyme (120 mL). The mixture was worked up and columned as before to yield the product (7.20 g, 54%). TLC ethyl acetate/methanol (7:3) $R_f = 0.24$. ^{1}H NMR (250 MHz, $CDCl_3$)[42] $\delta = 8.86$ (d, $J = 4$ Hz, 1H), 8.11 (d, $J = 8$ Hz, 1H), 8.03 (d, $J = 8$ Hz, 1H), 7.69 (m, 1H), 7.54 (m, 2H), 5.70 (brs, 1H), 3.35−3.52 (m, 3H), 3.03 (m, 1H), 2.87 (m, 1H), 2.63 (m, 1H), 2.43 (m, 2H), 1.85 (m, 1H), 1.64−1.76 (m, 3H), 1.34−1.49 (m, 3H), 0.95 (s, 9H), 0.11 (s, 3H), −0.43 (s, 3H); ^{13}C NMR (62 MHz, $CDCl_3$) $\delta = 149.8$ (s,d), 148.1 (s), 130.4 (d), 129.0 (d), 126.8 (d), 125.3 (s), 122.5 (d), 118.4 (d), 72.5 (d), 61.4 (d), 60.8 (t), 58.6 (t), 43.1 (t), 38.0 (d), 32.0 (d), 28.3 (t), 26.0 (q), 25.9 (t), 20.7 (t), 18.0 (s), −4.2 (q), −5.2 (q). MS (FAB) 427.2743 ($C_{25}H_{39}O_2N_2Si$ requires 427.2781), 411, 381, 369, 286, 273, 228, 200, 154.

Preparation of 9-*O*-(*tert*-Butyldimethylsilyl)-10,11-dihydroquinine-11-carboxylic Acid (5a). 4a (1 g, 2.19×10^{-3} mol) was dissolved in acetone (100 mL). Jones reagent was then added drop by drop until the dark brown color persists (ca. 10 mL). The mixture was then neutralized with sat. $NaHCO_3$, extracted with ethyl acetate, and dried over magnesium sulfate. It is then flash-columned ethyl acetate/methanol (7:3, 6:4,...0.0:10) to yield a white foam (0.64 g, 62%). TLC ethyl acetate/methanol (1:1) $R_f = 0.14$. ^{1}H NMR (250 MHz, CD_3OD)[42] $\delta = 8.67$ (d, $J = 4.5$ Hz, 1H), 7.98 (d, $J = 9$ Hz, 1H), 7.66 (d, $J = 4.5$ Hz, 1H) 7.46 (m, 2H), 5.99 (brs, 1H), 3.93 (s, 3H), 3.71 (m, 1H), 3.30 (m, 1H), 3.19 (m, 1H), 2.96 (m, 1H), 2.72 (m, 1H), 1.92−2.38 (m, 4H), 1.72 (m, 1H), 1.54 (m, 1H), 1.01 (s, 9H), 0.19 (s, 3H), −0.39 (s, 3H); ^{13}C NMR (62 MHz, CD_3OD) $\delta = 180.5$ (s), 160.3 (s), 148.5 (s), 147.8 (d), 144.9 (s), 131.7 (d), 127.5 (s), 123.6 (d), 120.7 (d), 102.2 (d), 71.6 (d), 61.6 (d), 58.4 (t), 56.7 (q) 44.1 (t), 43.4 (t), 33.5 (d), 27.8 (t), 26.4 (q), 26.2 (d), 20.7 (t), 18.9 (s), −4.1 (q), −4.8 (q). υ_{max} ($CHCl_3$) 3306, 2955, 1730, 1621, 1592, 1509, 1433, 1257, 1104, 1035, 840 cm^{-1}. MS (FAB) 471.26580 ($C_{26}H_{39}O_4N_2Si$ requires 471.26789), 413.5, 337, 339, 316, 303, 186, 173, 154, 122, 73, 59.

Preparation of 9-*O*-(*tert*-Butyldimethylsilyl)-10,11-dihydrocinchonidine-11-carboxylic Acid (5b). A similar procedure was used for the preparation of **5b** with the following alterations: **4b** (1 g, 2.35×10^{-3} mol) yields 0.575 g (56%) of **5b**. TLC ethyl acetate/methanol (1:1) $R_f = 0.07$. ^{1}H NMR (250 MHz, CD_3OD)[42] $\delta = 8.87$ (d, $J = 4$ Hz, 1H), 8.27 (d, $J = 8$ Hz, 1H), 8.10 (d, $J = 8$ Hz, 1H) 7.81 (m, 1H), 7.64−7.73 (m, 2H), 6.02 (brs, 1H), 3.68 (m, 1H), 3.30 (m, 1H), 2.94 (m, 1H), 2.73 (m, 1H), 2.30 (m, 2H), 2.00−2.15 (m, 4H), 1.94 (m, 1H), 1.60−1.71 (m, 2H), 0.99 (s, 9H), 0.18 (s, 3H), −0.40 (s, 3H); ^{13}C NMR (62 MHz, CD_3OD) $\delta = 181.0$ (s), 150.7 (d), 150.0 (s), 148.9 (s), 131.1 (d), 128.9 (d), 127.4 (s), 123.9 (d), 120.6 (d), 71.4 (d), 62.2 (d), 61.5 (d), 58.4 (t), 44.1 (t), 43.1 (t), 33.3 (d), 27.6 (t), 27.0 (q), 26.2 (d), 20.9 (t), 18.9 (s), −4.1 (q), −4.8 (q). MS (FAB) 441.25580 ($C_{25}H_{37}O_3N_2Si$ requires 441.25733), 347, 286, 273, 168, 143.

Preparation of Methyl 9-*O*-(*tert*-Butyldimethylsilyl)-10,11-dihydroquinine-11-carboxylate (6a). To a solution of **5a** (0.90 g, 1.91×10^{-3} mol) in methanol (50 mL) was added a few drops of concentrated HCl and left to stir overnight. The solution was then neutralized with sodium bicarbonate (sat.), the methanol removed under vacuum, and the resulting oil dissolved in ethyl acetate and washed with water (×3) and dried over magnesium sulfate. Once the ethyl acetate was removed the compound was purified by flash column ethyl acetate/methanol (10:0, 9:1, 8:2,...0.1:1) to yield a clear oil (0.90 g, 97%). TLC ethyl acetate/methanol (9:1). $R_f = 0.50$. ^{1}H NMR (250 MHz, $CDCl_3$)[42] $\delta = 8.71$ (d, $J = 4.5$ Hz, 1H), 8.00 (d, $J = 9$ Hz, 1H), 7.48 (d, $J = 4.5$ Hz, 1H) 7.34 (dd, $J = 2.5$, 9 Hz, 1H), 7.20 (m, 1H), 5.66 (brs, 1H), 3.93 (s, 3H), 3.55 (s, 3H), 3.51 (m, 1H), 3.16 (m, 1H), 2.88 (m, 1H), 2.71 (m, 1H), 2.43 (m, 1H), 2.05−2.10 (m, 3H), 1.75−1.94 (m, 3H), 1.28−1.68 (m, 2H), 0.94 (s, 9H), 0.12 (s, 3H), −0.42 (s, 3H); ^{13}C NMR (62 MHz, $CDCl_3$) $\delta = 172.2$ (s), 158.0 (s), 146.8 (s, d), 144.1 (s), 131.5 (d), 125.7 (s), 121.6 (d), 118.4 (d), 100.2 (d), 71.7 (d), 60.6 (d), 57.4 (t), 55.9 (q), 51.2 (q), 42.6 (t), 38.6 (t), 31.4 (d), 27.1 (t), 25.6 (q), 25.4 (d), 19.8 (t), 17.7 (s), −4.6 (q), −5.4 (q). MS (FAB) 485.28220 ($C_{27}H_{41}O_4N_2Si$ requires 485.28354), 427, 303, 258, 198, 173, 136.

Preparation of Methyl 9-*O*-(*tert*-Butyldimethylsilyl)-10,11-dihydrocinchonidine-11-carboxylate (6b). A similar procedure was used for the preparation of **6b** with the following alterations: **5b** (300 mg, 6.8×10^{-4} mol) yields 279 mg (90%) of **6b**. TLC ethyl acetate/methanol (8:2). $R_f = 0.47$. ^{1}H NMR (250 MHz, $CDCl_3$)[42] $\delta = 8.87$ (d, $J = 4.4$ Hz, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 8.04 (d, $J = 8.3$ Hz, 1H) 7.70 (m, 1H), 7.51−7.60 (m, 2H), 5.74 (brs, 1H), 3.56 (s, 3H), 3.47 (m, 1H), 3.21 (m, 1H), 2.87 (m, 1H), 2.68 (m, 1H), 2.42 (m, 1H), 2.15−2.19 (m, 2H), 2.00−2.09 (m, 1H), 1.89 (m, 1H), 1.75 (m, 2H), 1.49 (m, 1H), 1.35 (m, 1H), 0.94 (s, 9H), 0.12 (s, 3H), −0.44 (s, 3H); ^{13}C NMR (62 MHz, $CDCl_3$) $\delta = 173.0$ (s), 149.9 (d), 148.4 (s), 148.2 (s), 130.5 (d), 129.1 (d), 126.9 (d), 125.3 (s), 122.5 (d), 118.4 (d), 72.2 (d), 61.5 (d), 58.0 (t), 51.5 (q), 42.9 (t), 39.1 (t), 32.1 (d), 28.0 (t), 26.1 (d), 25.9 (q), 20.6 (t), 18.0 (s), −4.6 (q), −5.4 (q). MS (FAB) 455.26950 ($C_{26}H_{39}O_3N_2Si$ requires 455.27298), 397, 286, 273, 228, 182, 143.

Preparation of Methyl 10,11-Dihydroquinine-11-carboxylate (2a). To a solution of **6a** (0.99 g, 2.05×10^{-3} mol) in THF (20 mL) was added TBAF (1 M in THF, 6.1 mL, 6.1×10^{-3} mol). Once this had stirred for 2 h, ethyl acetate was added to the solution which was then washed with brine (×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,..0.6:4), to yield a white foam (0.50 g, 66%). TLC ethyl acetate/methanol (6:4) $R_f = 0.27$. HPLC (reverse phase: 90:10.0.60:40 0.05 M $HexNH_3$ (pH = 3 with H_3PO_4):AcCN) $t_R = 7.673$; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.40$ (d, $J = 4.5$ Hz, 1H), 7.83 (d, $J = 9$ Hz, 1H), 7.42 (d, $J = 4.5$ Hz, 1H) 7.22 (dd, $J = 2.5$, 9 Hz, 1H), 7.15 (d, $J = 2.5$, 1H), 5.38 (d, $J = 3.4$ Hz, 1H), 3.82 (s, 3H), 3.57 (m, 3H), 3.46 (m, 1H), 3.09 (dd, $J = 10$, 13.7 Hz, 1H), 2.99 (m, 1H), 2.58 (m, 1H), 2.35 (m, 1H), 2.17−2.20 (m, 2H), 2.02 (m, 1H),1.69−1.80 (m, 3H), 1.46 (m, 1H), 1.34 (m, 1H); ^{13}C NMR (62 MHz, $CDCl_3$) $\delta = 172.9$ (s), 157.8 (s), 147.6 (s), 147.3 (d), 143.9 (s), 131.3 (d), 126.4 (s), 121.5 (d), 118.4 (d), 101.1 (d), 71.0 (d), 59.8 (d), 57.7 (t), 55.7 (q), 51.6 (q), 43.1 (t), 39.0 (t), 31.9 (d), 27.6 (t), 26.1 (d), 20.7 (t). υ_{max} ($CHCl_3$) 3288, 2947, 1731, 1620, 1505, 1433, 1241, 1092, 1026 cm^{-1}. MS (FAB) 371.20020 ($C_{21}H_{27}O_4N_2$ requires 371.19707), 301, 182, 154.

Preparation of Methyl 10,11-Dihydrocinchonidine-11-carboxylate (2b). A similar procedure was used for the

preparation of **2b** with the following alterations: **6b** (590 mg, 1.29×10^{-3} mol), TBAF (3.87×10^{-3}, 1 M, 3.87 mL) in THF (10 mL). The reaction mixture was worked up and columned as before. The resulting product was then recrystallized from acetone/diethyl ether to yield fine white needles (270 mg, 61%) of (**2b**). TLC ethyl acetate/methanol (6:4). R_f =0.14. HPLC (reverse phase: 90:10.0.60:40 0.05M $HexNH_3$ (pH = 3 with H_3PO_4):AcCN) $t_R = 6.004$; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.80$ (d, $J = 4.5$ Hz, 1H), 8.07 (d, $J = 8$ Hz, 1H), 7.94 (d, $J = 8$ Hz, 1H) 7.64 (ddd, $J = 1$, 7, 8 Hz, 1H), 7.55 (d, $J = 4.5$ Hz, 1H), 7.40 (m, 1H), 5.62 (d, $J = 3.8$ Hz, 1H), 3.98 (brs, 1H), 3.59 (s, 3H), 3.44 (m, 1H), 3.11 (dd, $J = 10$, 14 Hz, 1H), 3.04 (m, 1H), 2.59 (m, 1H), 2.37 (m, 1H), 2.22 (dd, $J = 2$, 8 Hz, 2H), 2.04 (m, 1H), 1.94 (m, 1H), 1.70−1.82 (m, 2H), 1.39−1.50 (m, 2H); ^{13}C NMR (62 MHz, $CDCl_3$) $\delta = 173.1$ (s), 150.1 (d), 149.2 (s), 148.2 (s), 130.3 (d), 129.1 (d), 126.7 (d), 125.6 (s), 122.9 (d), 118.1 (d), 72.0 (d), 60.2 (d), 58.0 (t), 51.6 (q), 43.0 (t), 39.1 (t), 32.2 (d), 28.0 (t), 26.2 (d), 21.2 (t). MS (FAB) 341.18950 ($C_{20}H_{25}O_3N_2$-Si requires 341.18650), 307, 289, 165, 154, 136.

Preparation of 10,11-Dihydroquinine-11-carboxylic Acid (8). To a solution of **5** (820 mg, 1.7×10^{-3} mol) in THF (10 mL) was added TBAF (1 M in THF, 7 mL, 7.0×10^{-3} mol). Once this had stirred for 2 h, ethyl acetate was added to the solution and a white precipitate was formed, which was filtered off and washed with more ethyl acetate and dried under vacuum to yield a white powder (310 mg, 50%). ^{1}H NMR (250 MHz, CD_3OD) $\delta = 8.72$ (d, $J = 4.5$ Hz, 1H), 7.99 (d, $J = 9$ Hz, 1H), 7.76 (d, $J = 4.5$ Hz, 1H) 7.47 (dd, $J = 2.5$, 9 Hz, 1H), 7.38 (d, $J = 2.5$, 1H), 5.89 (brs, 1H), 4.15 (m, 1H), 3.94 (s, 3H), 3.56 (m, 2H), 3.20 (m, 1H), 3.01 (m, 1H), 2.25 (m, 1H), 2.06−2.14 (m, 4H), 2.00 (m, 1H), 1.87 (m, 1H),1.60 (m, 1H); ^{13}C NMR (62 MHz, $CDCl_3$) $\delta = 179.4$ (s), 160.1 (s), 148.3 (s), 147.3 (d), 144.9 (s), 131.8 (d), 127.6 (s), 123.2 (d), 120.5 (d), 102.5 (d), 69.0 (d), 61.2 (d), 57.8 (t), 56.5 (q), 45.0 (t), 42.5 (t), 32.8 (d), 26.9 (d), 26.1 (t), 19.7 (t). MS (FAB) 357.18440 ($C_{20}H_{25}O_3N_2Si$ requires 357.18142), 307, 289, 165, 154, 136.

Preparation of Allyl 9-*O*-(*tert*-Butyldimethylsilyl)-10,11-dihydroquinine-11-carboxylate (9). To a solution of **5** (1.33 g, 2.83×10^{-3} mol) in DCM (30 mL) were added Et_3N (787 μL, 5.66×10^{-3} mol), allyl alcohol (232 μL, 3.24×10^{-3} mol), DMAP (70 mg, 5.74×10^{-3} mol), and 2,6-dichlorobenzoyl chloride (570 μL, 4.25×10^{-3} mol) and stirred for 2−3 h. DCM was then added to the reaction mixture which was then washed with water (×3). After removal of the solvent under vacuum, the oily product was purified by flash column chromatograhy ethyl acetate/methanol (10:0, 9:1, 8:2, 7:3) to yield a clear oil (1.3 g, 90%). TLC ethyl acetate/methanol (9:1) R_f = 0.41. ^{1}H NMR (250 MHz, $CDCl_3$)[42] $\delta = 8.71$ (d, $J = 4.5$ Hz, 1H), 8.00 (d, $J = 9.2$ Hz, 1H), 7.49 (d, $J = 4.5$ Hz, 1H) 7.35 (dd, $J = 2.5$, 9.2 Hz, 1H), 7.21 (m, 1H), 5.80 (m, 1H), 5.65 (brs, 1H), 5.12−5.29 (m, 2H), 4.47 (d, $J = 5.75$ Hz, 2H), 3.93 (s, 3H), 3.49 (m, 1H), 3.17 (m, 1H), 2.91 (m, 1H), 2.57 (m, 1H), 1.92−2.53 (m, 6H), 1.77 (m, 1H), 1.53 (m, 1H), 1.31 (m, 1H), 0.95 (s, 9H), 0.13 (s, 3H), −0.41 (s, 3H); ^{13}C NMR (62 MHz, $CDCl_3$) $\delta = 172.2$ (s), 158.1 (s), 147.3 (s, d), 144.4 (s), 131.9 (d), 126.2 (s), 121.7 (d), 118.7 (d), 118.3 (t), 100.5 (d), 72.2 (d), 65.1 (t), 60.7 (d), 58.0 (t), 56.0 (q), 42.9 (t), 39.3 (t), 32.2 (d), 28.0 (t), 25.9 (q), 25.7 (d), 20.5 (t), 18.0 (s), −4.2 (q), −5.1 (q). MS (FAB) 511.30180 ($C_{29}H_{43}O_4N_2Si$ requires 511.29919), 485.5, 453, 316, 303, 253, 208, 186, 173, 136.

Preparation of Allyl 10,11-Dihydroquinine-11-carboxylate (10). To a solution of **9** (850 mg, 1.67×10^{-3} mol) in THF (15 mL) was added TBAF (1 M in THF, 3.34 mL, 3.34×10^{-3} mol). Once this had stirred for 2 h, ethyl acetate was added to the solution which was then washed with brine (×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,..0.6:4), to yield a clear oil (450 mg, 66%). TLC ethyl acetate/methanol (6:4) $R_f = 0.28$. ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 8.40$ (d, $J = 4.5$ Hz, 1H), 7.83 (d, $J = 9.2$ Hz, 1H), 7.42 (d, $J = 4.5$ Hz, 1H) 7.21 (dd, $J = 2.5$, 9.2 Hz, 1H), 7.13 (m, 1H), 5.81 (m, 1H), 5.49 (d, $J = 3.3$ Hz, 1H), 5.13−5.33 (m, 2H), 4.48 (dt, $J = 1.3$, 5.75 Hz, 2H), 3.81 (s, 3H), 3.47 (m, 1H), 3.10 (dd, $J = 10$, 13.7 Hz, 1H), 2.98 (m, 1H), 2.58 (m, 1H), 2.36 (m, 1H), 2.36 (1H), 2.22 (m, 2H), 2.04 (m, 1H), 1.65−1.85 (m, 3H), 1.49−1.28 (m, 2H); ^{13}C NMR (62 MHz, $CDCl_3$) $\delta = 172.3$ (s), 157.7 (s), 148.1 (s), 147.3 (d), 143.9 (s), 132.0 (d), 131.2 (d), 126.5 (s), 121.4 (d), 118.4 (d), 118.3 (t), 101.3 (d), 71.6 (d), 65.0 (t), 59.7 (d), 57.9 (t), 55.6 (q), 42.9 (t), 39.3 (t), 32.1 (d), 27.9 (t), 26.2 (d), 21.0 (t).

Linear TBDMS Allyl Protected Dimer 11. To a solution of **5** (0.300 g, 7.6×10^{-4} mol) and **10** (0.356 g, 7.6×10^{-4} mol) in DCM (15 mL) were added Et_3N (105 μL, 1.52×10^{-3} mol), DMAP (19 mg, 1.52×10^{-4} mol), and 2,6-dichlorobenzoyl chloride (102 μL, 1.14×10^{-3} mol) and stirred for 2−3 h. DCM was then added to the reaction mixture which was then washed with water (×3). After removal of the solvent under vacuum the oily product was purified by flash column chromatography, ethyl acetate/methanol (10:0, 9:1,...0.1:1), to yield a clear oil. TLC ethyl acetate/methanol (8:2) $R_f = 0.26$. ^{1}H NMR (250 MHz, $CDCl_3$)[42] $\delta = 8.72$ (d, $J = 4.5$ Hz, 1H), 8.66 (d, $J = 4.5$ Hz, 1H) 8.02 (d, $J = 9.2$ Hz, 1H), 7.97 (d, $J = 9.2$ Hz, 1H), 7.48 (d, $J = 4.5$ Hz, 1H), 7.18−7.35 (m, 5H), 6.40 (d, 7.4 Hz, 1H), 5.84 (m, 1H), 5.64 (brs, 1H), 5.16−5.29 (m, 2H), 4.46 (d, $J = 5.75$ Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 1.73−3.45 (m, 38H), 0.94 (s, 9H), 0.12 (s, 3H), −0.41 (s, 3H); ^{13}C NMR (62 MHz, $CDCl_3$) $\delta = 172.1$ (s), 171.5 (s), 158.2 (s), 157.9 (s), 147.3 (s, d), 144.7 (s), 144.4 (s), 143.5 (s), 132.0 (d), 131.9 (d), 126.9 (s), 126.1 (s), 121.8 (d), 121.2 (d), 118.7 (d), 118.4 (t), 101.3 (d), 100.5 (d), 73.6 (d), 72.0 (d), 65.1 (t), 61.0 (d), 58.9 (d), 58.0 (t), 57.6 (t), 55.9 (q), 55.6 (q), 42.8 (t), 42.1 (t), 39.5 (t), 39.3 (t), 32.0 (d), 28.1 (t), 27.8 (t), 25.9 (q), 25.8 (d), 25.7 (d), 24.2 (t), 20.4 (t), 18.0 (s), −4.2 (q), −5.2 (q). MS (FAB) 849.46810 ($C_{49}H_{65}O_7N_4Si$ requires 849.46222), 792, 764, 718, 691, 642, 606, 577.5, 526.5, 471.5, 453, 425, 397, 379, 339, 316, 303, 253, 213, 186, 173, 160.

Linear Allyl Protected Dimer 12. To a solution of **11** (200 mg, 2.36×10^{-4} mol) in THF (2 mL) was added TBAF (0.472 mL, 1 M in THF, 4.72×10^{-4} mol). Once this had stirred for 2 h, ethyl acetate was added to the solution which was then washed with brine (×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,..0.0:10) to yield a clear oil (140 mg, 81%). TLC ethyl acetate/methanol (6:4) $R_f = 0.13$. ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 8.58$ (d, $J = 4.5$ Hz, 1H), 8.54 (d, $J = 4.5$ Hz, 1H), 7.94 (d, $J = 9.2$ Hz, 1H), 7.87 (d, $J = 9.2$ Hz, 1H), 7.45 (d, $J = 4.5$ Hz, 1H), 7.17−7.33 (m, 4H), 7.05 (d, $J = 2.5$ Hz, 1H), 6.38 (d, 7 Hz, 1H), 5.83 (m, 1H), 5.58 (d, $J = 2$ Hz, 1H), 5.15−5.28 (m, 2H), 4.89 (brs, 1H), 4.50 (dt, $J = 1.25$, 5.75 Hz, 2H), 3.87 (s, 3H), 3.71 (s, 3H), 3.58 (m, 1H), 2.93−3.25 (m, 15H), 1.21−1.86 (m, 10H); ^{13}C NMR (62 MHz, $CDCl_3$) $\delta = 172.1$ (s), 171.5 (s), 158.0 (s), 157.7 (s), 147.6 (s), 147.4 (d), 144.6 (s), 144.0 (s), 143.5 (s), 132.0 (d), 131.7 (d), 131.4 (d), 126.9 (s), 126.3 (s), 121.8 (d), 121.5 (d), 118.6 (d), 118.4 (t), 101.4 (d), 101.0 (d), 73.6 (d), 70.7 (d), 65.1 (t), 59.7 (d), 58.9 (d), 57.5 (t), 55.6 (q), 42.8 (t), 42.1 (t), 39.2 (t), 39.2 (t), 31.9 (d), 28.1 (t), 27.3 (t), 26.0 (d), 25.8 (d), 24.1 (t), 20.3 (t). υ_{max} ($CHCl_3$) 3666, 3602, 3170, 2942, 1729, 1620, 1594, 1511, 1473, 1453, 1434, 1364, 1299, 1165, 1094, 1030, 985, 852 cm^{-1} MS (FAB) 735.37450 ($C_{43}H_{51}O_7N_4$ requires 735.37575), 546.5, 401, 379, 307, 208.

Linear Acid Alcohol Dimer 13. To a solution of **12** (337 mg, 4.59×10^{-4}) in THF (1 mL) were added $Pd(PPh_3)_4$ (53 mg, 4.59×10^{-5}) and morpholine (400 μL, 4.59×10^{-3}). This was allowed to stir for 1−2 h. Diethyl ether was then added to the reaction, and the resulting precipitate was filtered and washed with more diethyl ether and dried to yield a white powder (316 mg, 99%). TLC ethyl acetate/methanol (3:7) R_f = 0.10. ^{1}H NMR (400 MHz, CD_3OD) $\delta = 8.68$ (d, $J = 4.5$ Hz, 1H), 8.59 (d, $J = 4.5$ Hz, 1H), 7.97 (d, $J = 9.4$ Hz, 1H), 7.95 (d, $J = 9.4$ Hz, 1H), 7.64 (d, $J = 4.5$ Hz, 1H), 7.35−7.49 (m, 5H), 6.49 (d, 4.8 Hz, 1H), 5.68 (d, $J = 2$ Hz, 1H), 3.90−3.98 (m, 7H), 3.75 (m, 1H), 2.98−3.37 (m, 6H), 2.31−2.65 (m, 6H) 1.49−2.13 (m, 12H); ^{13}C NMR (62 MHz, $CDCl_3$) $\delta = 172.8$ (s), 159.8 (s), 149.2 (s), 148.2 (d), 148.0 (d), 145.0 (s), 144.8 (s), 131.7 (d), 131.5 (d), 128.1 (s), 127.8 (s), 123.7 (d), 123.2 (d), 120.4 (d), 120.2 (d), 102.4 (d), 102.2 (d), 70.8 (d), 60.9 (d), 59.8 (d), 58.6 (t), 58.0 (t), 56.4 (q), 56.3 (q), 45.8 (t), 45.0 (t), 43.6 (t), 43.2 (t),

32.9 (d), 32.6 (d), 28.5 (t), 27.4 (d), 26.9 (d), 24.1 (t), 20.5 (t), 19.9 (t). MS (FAB) 695.3448 ($C_{40}H_{47}O_7N_4$ requires 695.3445), 371, 357, 339, 307, 279, 242, 184, 154, 136.

TBDMS Protected Linear Dimer Carboxylic Acid 14. To a solution of **11** (369 mg, 4.35×10^{-4}) in THF (1 mL) were added $Pd(PPh_3)_4$ (50 mg, 4.33×10^{-5}) and morpholine (380 μL, 4.35×10^{-3}). This was allowed to stir for 1−2 h. The THF was removed, diethyl ether was then added and the resulting precipitate was filtered and washed with more diethyl ether and dried to yield a white powder (243 mg, 69%). ^{1}H NMR (250 MHz, CD_3OD)[42] δ = 8.68 (d, J = 4.5 Hz, 1H), 8.59 (d, J = 4.5 Hz, 1H) 7.92−8.00 (m, 2H), 7.71 (d, J = 4.5 Hz, 1H), 7.39−7.49 (m, 5H), 6.47 (d, J = 4.7 Hz, 1H), 5.74 (brs, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 1.30−3.67 (m, 26H), 0.98 (s, 9H), 0.18 (s, 3H), −0.39 (s, 3H); ^{13}C NMR (62 MHz, CD_3OD) δ = 181.2 (s), 173.0 (s), 160.1 (s), 159.8 (s), 149.9 (s), 148.0 (d), 147.9 (d), 145.8 (s), 145.0 (s), 144.9 (s), 131.7 (d), 131.5 (d), 128.1 (s), 127.7 (s), 123.7 (d), 123.6 (d), 120.4 (d), 120.0 (d), 102.5 (d), 101.9 (d), 75.2 (d), 72.9 (d), 61.8 (d), 59.7 (d), 58.8 (t), 58.7 (t), 56.6 (q), 56.4 (q), 43.9 (t), 43.6 (t), 40.0 (t), 34.0 (d), 33.2 (d), 28.9 (t), 28.6 (t), 27.3 (d), 27.1 (d), 26.3 (q), 24.0 (t), 21.3 (t), 18.9 (s), −4.1 (q), −4.8 (q).

Linear TBDMS Allyl Trimer 15. To a solution of **5** (128 mg, 2.72×10^{-4} mol) and **12** (200 mg, 2.72×10^{-4} mol) in DCM (5 mL) were added Et_3N (76 μL, 5.5×10^{-4} mol), DMAP (7 mg, 5.7×10^{-5} mol), and 2,6-dichlorobenzoyl chloride (55 μL, 4.1×10^{-4} mol) and stirred for 2−3 h. DCM was then added to the reaction mixture which was then washed with water (×3). After removal of the solvent under vacuum, the oily product was purified by flash column chromatography, ethyl acetate/methanol (10:0, 9:1,...0.1:1), to yield a clear oil (0.2462 g, 76%). ^{1}H NMR (250 MHz, $CDCl_3$)[42] δ = 8.65−8.73 (m, 3H), 7.96−8.04 (m, 3H), 7.48 (d, J = 4.5 Hz, 1H), 7.15−7.39 (m, 8H), 6.43 (d, 7.3 Hz, 1H), 6.38 (d, J = 7 Hz, 1H), 5.86 (m, 1H), 5.60 (brs, 1H), 5.16−5.30 (m, 2H), 4.49 (d, J = 5.7 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 2.82−3.41 (m, 9H), 2.50−2.65 (m, 3H), 2.21−2.41 (m, 9H), 1.94−2.10 (m, 3H), 1.41−1.89 (m, 15H), 0.94 (s, 9H), 0.11 (s, 3H), −0.41 (s, 3H); ^{13}C NMR (62 MHz, $CDCl_3$) δ = 172.1 (s), 171.5 (s), 158.1 (s), 158.0 (s), 147.8 (s), 147.3 (d), 144.8 (s), 144.4 (s), 143.5 (s), 132.0 (d), 131.9 (d), 127.0 (s), 126.9 (s), 126.2 (s), 121.7 (d), 121.86 (d), 121.2 (d), 118.7 (d), 118.4 (t), 101.4 (d), 101.3 (d), 100.5 (d), 73.6 (d), 72.3 (d), 65.1 (t), 61.0 (d), 59.0 (d), 58.9 (d), 58.0 (t), 57.5 (t), 55.7 (q), 55.6 (q), 42.7 (t), 42.1 (t), 39.5 (t), 39.3 (t), 32.2 (d), 32.0 (d), 28.2 (t), 28.0 (t), 26.1 (d), 25.9 (q), 25.8 (d), 24.3 (t), 23.7 (t), 20.5 (t), 18.0 (s), −4.2 (q), −5.2 (q). MS (FAB) 1187.6360 ($C_{69}H_{87}O_{10}N_6Si$ requires 1187.6253), 1158, 1130, 884.7, 810, 763, 718, 642, 546.5, 471.5, 453, 425, 379, 339, 316, 303, 253, 198, 173, 160, 136.

Linear Allyl Trimer 16. To a solution of **15** (246 mg, 2.08 × 10^{-4} mol) in THF (3 mL) was added TBAF (4.15 mL, 1M in THF, 4.15×10^{-3} mol). Once this had stirred for 2 h, ethyl acetate was added to the solution which was then washed with brine (×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,..0.0:10), to yield a clear oil (153 mg, 69%). TLC ethyl acetate/methanol (1:1) R_f = 0.14. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.57−8.62 (m, 3H), 7.91−7.96 (m, 3H), 7.44 (d, J = 4.5 Hz, 1H), 7.16−7.34 (m, 8H), 6.41 (d, J = 7.8 Hz, 1H), 6.38 (d, J = 5.6 Hz, 1H), 5.84 (m, 1H), 5.45 (d, J = 3.5 Hz, 1H), 5.17−5.27 (m, 2H), 4.51 (d, J = 5.7 Hz, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.40 (m, 1H), 3.17−3.27 (m, 2H), 2.92−3.11 (m, 6H), 2.51 (m, 3H), 2.20−2.31 (m, 9H), 2.00 (m, 3H), 1.19−1.79 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1 (s), 171.7 (s), 171.6 (s), 158.0 (s), 157.7 (s), 149.4 (d), 148.1 (s), 147.6 (d), 147.3 (d), 144.7 (s), 144.3 (s), 143.6 (s), 132.0 (d), 131.8 (d), 131.6 (d), 127.0 (s), 126.9 (s), 126.6 (s), 121.8 (d), 121.4 (d), 118.8 (d), 118.6 (t), 118.5 (d), 101.5 (d), 101.4 (d), 73.6 (d), 71.9 (d), 65.2 (t), 59.9 (d), 59.0 (d), 58.9 (d), 57.9 (t), 57.5 (t), 55.6 (q), 42.8 (t), 42.1 (t), 39.4 (t), 39.3 (t), 39.0 (t), 32.3 (d), 32.1 (d), 28.2 (t), 28.0 (t), 26.2 (d), 25.8 (d), 24.3 (t), 23.8 (t), 21.3 (t). MS (FAB) 1073.5426 ($C_{63}H_{73}O_{10}N_6$ requires 1073.53878), 710, 649.4, 546.5, 397, 379, 339, 307, 242, 213, 189.

Linear Acid Alcohol Trimer 17. To a solution of **16** (153 mg, 1.43×10^{-4} mol) in THF (1.5 mL) were added $Pd(PPh_3)_4$ (17 mg, 1.5×10^{-5} mol) and morpholine (124 μL, 1.43×10^{-3} mol). This was allowed to stir for 1−2 h. Diethyl ether was then added to the reaction, and the resulting precipitate was filtered, washed with more diethyl ether, and dried to yield a white powder (97 mg, 66%). ^{1}H NMR (250 MHz, CD_3OD) δ = 8.65 (d, J = 4 Hz, 1H), 8.56 (d, J = 4.5 Hz, 2H), 7.92 (d, J = 9 Hz, 2H), 7.90 (d, J = 9 Hz, 1H), 7.68 (d, J = 4.5 Hz, 1H), 7.36−7.48 (m, 8H), 6.50 (d, J = 4.8 Hz, 1H), 6.45 (d, J = 5 Hz, 1H), 5.75 (brs, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 1.43−3.76 (m, 37H); ^{13}C NMR (100 MHz, CD_3OD) δ = 172.9 (s), 172.8 (s), 159.8 (s), 159.7 (s), 149.3 (s), 148.1 (d), 148.0 (d), 145.7 (s), 145.5 (s), 145.0 (s), 144.7 (s), 131.5 (d), 128.1 (s), 127.8 (s), 123.6 (d), 123.2 (d), 120.2 (d), 102.5 (d), 70.4 (d), 60.8 (d), 59.7 (d), 58.6 (t), 58.2 (t), 57.8 (t), 56.5 (q), 56.4 (q), 44.1 (t), 43.5 (t), 43.3 (t), 39.6 (t), 39.4 (t), 33.8 (d), 33.0 (d), 32.5 (d), 27.2 (t), 27.1 (d), 27.0 (d), 26.9 (d), 23.7 (t), 20.3 (t).

Linear TBDMS Allyl Tetramer 18. To a solution of **14** (304 mg, 3.76×10^{-4} mol) and **12** (280 mg, 3.47×10^{-4} mol) in DCM (8 mL) were added Et_3N (105 μL, 5.7×10^{-3} mol), DMAP (10 mg, 8×10^{-5} mol), and 2,6-dichlorobenzoyl chloride (76 μL, 5.7×10^{-4} mol) and stirred for 2−3 h. DCM was then added to the reaction mixture which was then washed with water (×3). After removal of the solvent under vacuum, the oily product was purified by flash column chromatography ethyl acetate/methanol (10:0, 9:1,...0.1:1) to yield a clear oil (512 mg, 97%). ^{1}H NMR (250 MHz, $CDCl_3$)[42] δ = 8.6−8.72 (m, 4H), 7.81−8.02 (m, 4H), 7.06−7.48 (m, 12H), 6.35−6.44 (m, 3H), 5.75−5.92 (m, 1H), 5.53 (brs, 1H), 5.14−5.28 (m, 2H), 4.50 (d, J = 6 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 6H), 3.83 (s, 3H), 1.21−3.38 (m, 56H), 0.92 (s, 9H), 0.09 (s, 3H), −0.42 (s, 3H); ^{13}C NMR (62 MHz, $CDCl_3$) 172.1 (s), 171.6 (s), 171.6 (s), 171.5 (s), 157.9 (s), 147.9 (s), 147.3 (d), 144.8 (s), 144.3 (s), 143.5 (s), 143.4 (s), 132.0 (d), 131.9 (d), 127.0 (s), 126.9 (s), 126.8 (s), 126.2 (s), 121.7 (d), 121.6 (d), 118.7 (d), 118.4 (t), 101.4 (d), 100.5 (d), 73.5 (d), 72.5 (d), 65.1 (t), 61.1 (d), 59.0 (d), 58.9 (d), 58.2 (t), 57.5 (t), 55.7 (q), 55.6 (q), 55.4 (q), 42.8 (t), 42.1 (t), 39.5 (t), 39.3 (t), 32.3 (d), 32.0 (d), 28.2 (t), 28.0 (t), 26.1 (d), 25.9 (q), 25.8 (d), 24.4 (t), 23.9 (t), 23.7 (t), 20.7 (t), 18.0 (s), −4.2 (q), −5.2 (q).

Linear Allyl Tetramer 19. To a solution of **18** (376 mg, 2.47×10^{-4} mol) in THF (3 mL) was added TBAF (0.74 mL, 1 M in THF, 7.4×10^{-4} mol). Once this had stirred for 2 h, ethyl acetate was added to the solution which was then washed with brine (×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,..0.0:10), to yield a clear oil (167 mg, 48%). TLC ethyl acetate/methanol (3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.64−8.68 (m, 4H), 7.96−8.00 (m, 4H), 7.46 (d, J = 4.5 Hz, 1H), 7.31−7.36 (m, 7H), 7.19−7.25 (m, 4H), 6.38−6.45 (m, 3H), 5.85 (m, 1H), 5.51 (brs, 1H), 5.18−5.29 (m, 2H), 4.52 (dt, J = 1, 5 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 2.97−3.28 (m, 12H), 2.53−2.59 (m, 4H), 2.23−2.40 (m, 12H), 2.03 (m, 4H), 1.37−1.75 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.1 (s), 171.7 (s), 171.5 (s), 158.0 (s), 157.8 (s), 147.6 (d), 147.3 (d), 147.3 (d), 144.7 (s), 144.4 (s), 143.5 (s), 132.0 (d), 131.9 (d), 131.7 (d), 126.9 (s), 126.7 (s), 121.8 (d), 121.5 (d), 118.7 (d), 118.5 (t), 118.3 (d), 101.3 (d), 73.6 (d), 72.0 (d), 65.2 (t), 59.9 (d), 59.0 (d), 57.9 (t), 57.6 (t), 55.7 (q), 55.7 (q), 53.9 (t), 42.8 (t), 42.1 (t), 39.5 (t), 39.3 (t), 32.3 (d), 32.1 (d), 32.0 (d), 28.2 (t), 28.0 (t), 26.1 (d), 24.3 (t), 23.9 (t), 21,4 (t), 20.8 (t). FAB MS 1411 (MH^+), 1035, 736, 678, 650, 379, 339, 281.

Linear Acid Alcohol Tetramer 20. To a solution of **19** (165 mg, 1.17×10^{-4}) in THF (1 mL) was added $Pd(PPh_3)_4$ (14 mg, 1.21×10^{-5} mol) and morpholine (102 μL, 1.17×10^{-3} mol). This was allowed to stir for 1−2 h. Diethyl ether was then added to the reaction, and the resulting precipitate was filtered, washed with more diethyl ether, and dried to yield a white powder (54 mg, 34%). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.65 (d, J = 4 Hz, 1H), 8.55−8.58 (m, 3H), 7.91−7.97 (m, 4H), 7.61−7.69 (m, 2H), 7.38−7.49 (m, 10H), 6.43−6.47 (m, 3H), 5.61−5.63 (m, 1H), 3.92 (s, 3H), 3.90 (s, 6H), 3.88 (s, 3H), 1.26−

3.68 (m, 52H); ^{13}C NMR (100 MHz, CD_3OD) δ = 180.9 (s), 173.1 (s), 159.9 (s), 148.1 (d), 145.1 (s), 131.6 (d), 128.3 (s), 123.7 (d), 120.2 (d), 102.6 (d), 72.0 (d), 60.3 (d), 59.9 (d), 58.3 (t), 56.4 (q), 42.8 (t), 39.8 (t), 33.1 (d), 28.5 (t), 27.0 (d), 19.1 (s).

Thermodynamic Cyclization of Quinine Monomer: Trimer 7a. 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 the methanol had been removed azeotropically. The catalyst mixture was then diluted with toluene (ca. 1.5 mL) and the solution filtered under 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: 2a (10 mg, 2.703×10^{-5} mol) was added to a round-bottomed flask attached to a Soxhlet extractor which contained molecular sieves (4 Å) and then dissolved in toluene (5.4 mL). This was refluxed for 30 min to remove all water from the system and then the KOMe•18-C-6 catalyst solution (45 μL, 0.03 M, 1.35×10^{-6} mol) was added. To work up the reaction, the mixture was added to aqueous pH 7 buffer and extracted with ethyl acetate. The compound was purified by graduated silica column ethyl acetate/methanol (10:0, 9:1, 8:2,...etc.) to obtain cyclic trimer. Yield: 7.7 mg (84%). TLC ethyl acetate/methanol (1:1) R_f = 0.17. HPLC (reverse phase: 90:10.0.60:40 0.05 M $HexNH_3$ (pH = 3 with H_3PO_4):AcCN) t_R = 10.426; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (d, J = 4.5 Hz, 3H), 8.01 (d, J = 9 Hz, 3H), 7.53 (d, J = 2.5 Hz, 3H), 7.37 (m, 6H), 6.53 (d, J = 10.5 Hz, 3H), 3.97 (s, 9H), 3.43 (m 3H), 3.11 (m 3H), 2.99 (m, 3H), 2.62 (m, 6H), 2.24 (m, 3H), 1.97−2.18 (m, 9H), 1.90 (m, 3H), 1.76 (m, 3H), 1.57 (m, 3H), 1.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =171.9 (s), 157.9 (s), 147.6 (d), 144.9 (s), 143.7 (s), 131.9 (d), 127.8 (s), 121.2 (d), 119.6 (d), 102.3 (d), 72.1 (d), 59.4 (d), 56.7 (t), 55.7 (q), 41.8 (t), 38.5 (t), 32.0 (d), 28.2 (t), 25.8 (t), 24.4 (d). FAB-MS 1015.49840 ($C_{60}H_{67}O_9N_6$ requires 1015.4984).

Thermodynamic Cyclization of Cinchonidine Monomer: Trimer 7b. The above procedure was repeated using **2b** to yield **7b**. TLC ethyl acetate/methanol (1:1) R_f = 0.17. HPLC (reverse phase: 90:10.0.60:40 0.05 M $HexNH_3$ (pH = 3 with H_3PO_4):AcCN) t_R = 7.17; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.90 (d, J = 4.5 Hz, 3H), 8.32 (d, J = 8 Hz, 3H), 8.12 (d, J = 8.5 Hz, 3H), 7.71 (ddd, J = 1, 7, 8 Hz, 3H), 7.59 (ddd, J = 1, 7, 8.5 Hz, 3H), 7.41 (d, J = 4.5 Hz, 6H), 6.50 (d, J = 10.5 Hz, 3H), 3.47 (m, 3H), 3.11 (m, 3H), 2.95 (m, 3H), 2.51−2.64 (m, 6H), 2.09−2.30 (m, 12H), 1.89 (brs, 3H), 1.75 (m, 3H), 1.56 (m, 3H), 1.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8 (s), 150.0 (d), 148.8 (s), 145.1 (s), 130.6 (d), 129.2 (d), 126.8 (d), 126.6 (s), 123.4 (d), 119.7 (d), 73.2 (d), 59.7 (d), 56.7 (t), 41.6 (t), 38.5 (t), 32.0 (d), 28.1 (t), 26.2 (t), 24.4 (d). FAB-MS (MH^+) 925.4640 ($C_{57}H_{61}O_6N_6$ requires 925.4652).

Kinetic Cyclization of Quinine Monomer. To a stirred mixture of **8** (20 mg, 5.6×10^{-5} mol) in DMF (1.2 mL) were added triethylamine (16 μL, 1.15×10^{-4} mol) and 2,6-dichlorobenzoyl chloride (12 μL, 8.9×10^{-5} mol). This was then stirred at room temperature for 30 min, until all the starting material has dissolved. The reaction mixture was diluted to 5 mM with DCM (10 mL), and DMAP (27 mg, 2.2×10^{-4} mol) was added. The reaction was then stirred for a further 16 h and worked up by washing with water. The organic solvent was then removed, under vacuum, and the sample was analyzed by ^{1}H NMR and electrospray mass spectrometry and HPLC. HPLC (reverse phase: 90:10.0.60:40 0.05M $HexNH_3$ (pH = 3 with H_3PO_4):AcCN) t_R = 10.482, 12.892, 15.921 (main peaks); ESMS 508 (**Cq$_3$**, MH^{2+}), 678 (**Cq$_4$**, MH^{2+}) 846 (**Cq$_5$**, MH^{2+}), 1015 (**Cq$_3$**, MH^+), 1353 (**Cq$_4$**, MH^+), 1691 (**Cq$_5$**, MH^+).

Kinetic Cyclization of Quinine Dimer: Tetramer 21. To a stirred mixture of **13** (50 mg, 7.2×10^{-5} mol) in DMF (1.55 mL) were added triethylamine (20 μL, 1.44×10^{-4} mol) and 2,6-dichlorobenzoyl chloride (15 μL, 1.08×10^{-4} mol). This was then stirred at room temperature for 30 min, until all the starting material has dissolved. The reaction mixture was diluted to 5 mM with DCM (12.85 mL), and DMAP (35 mg, 2.87×10^{-4} mol) was added. The reaction was then stirred for a further 16 h and worked up by washing with water. The organic solvent was then removed, under vacuum to give an oil which was purified by flash column ethyl acetate/methanol (10:0, 9:1....0.1:9, 0:10) to yield a clear oil (9.2 mg, 19%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.73 (d, J = 4.5, 4H), 8.01 (d, J = 9.2 Hz, 4H), 7.47 (d, J = 2.5 Hz, 4H), 7.38 (dd, J = 2.5, 9.2 Hz, 4H), 7.32 (d, J = 4.5 Hz, 4H), 6.46 (d, J = 9.3 Hz, 4H), 3.94 (s, 12H), 3.41 (m, 4H), 3.02 (m, 4H), 2.92 (m, 4H), 2.56 (m, 4H), 2.53 (m, 4H), 2.41 (m, 4H), 2.17 (m, 4H), 2.11 (m, 4H), 1.95 (m, 4H), 1.88 (m, 4H), 1.76 (m, 4H), 1.55 (m, 4H), 1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9 (s), 157.9 (s), 147.5 (d), 144.9 (s), 143.2 (s), 132.1 (d), 127.4 (s), 121.3 (d), 119.2 (d), 102.0 (d), 73.1 (d), 59.1 (d), 56.9 (t), 55.7 (q), 41.8 (t), 39.3 (t), 32.1 (d), 28.2 (t), 25.7 (d), 25.6 (t). ES-MS 1353 (MH^+).

TBDMS Methyl Ester Linear Dimer 22. A similar procedure to the synthesis of **11** was used to prepare **22**, using **2a** (100 mg, 2.7×10^{-4} mol), **5** (127 mg, 2.72×10^{-4} mol), 2,6-dichlorobenzyl chloride (60 μL, 4.1×10^{-4} mol), triethylamine (83 μL, 6.0×10^{-4} mol), DMAP (8 mg, 6.6×10^{-5} mol) and DCM (4 mL). The reaction was worked up and columned as before to yield a clear oil (0.167 g, 75%). TLC ethyl acetate/methanol (8:2), R_f = 0.31. ^{1}H NMR (400 MHz, $CDCl_3$)[42] δ = 8.73 (d, J = 4.5 Hz, 1H), 8.68 (d, J = 4.5 Hz, 1H) 8.03 (d, J = 9 Hz, 1H), 8.00 (d, J = 9 Hz, 1H), 7.57 (d, J = 4.5 Hz, 1H), 7.33−7.40 (m, 3H) 7.19−7.29 (m, 2H), 6.41 (d, J = 7 Hz, 1H), 5.69 (brs, 1H), 3.89 (s, 6H), 3.62 (s, 3H), 2.56−3.47 (m, 8H), 2.19−2.42 (m, 6H), 2.03 (m, 2H), 2.01 (m, 2H), 1.28−1.65 (m, 8H), 0.96 (s, 9H), 0.07 (s, 3H), −0.4 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.9 (s), 171.5 (s), 158.0 (s), 147.4 (d), 144.8 (s), 144.4 (s), 131.9 (d), 126.9 (s), 126.0 (s), 121.8 (d), 118.8 (d), 101.3 (d), 100.4 (d), 73.8 (d), 60.4 (d), 58.9 (d), 57.5 (t), 56.1 (q), 51.7 (q), 42.5 (t), 42.1 (t), 39.1 (t), 32.0 (d), 28.1 (t), 26.0 (q), 25.8 (d), 24.1 (t), 22.6 (t), 18.0 (s), −4.2 (q), −5.1 (q). υ_{max} ($CHCl_3$) 2948, 1729, 1620, 1505, 1473, 1434, 1363, 1292, 1261, 1158, 1107, 1036, 902, 837 cm^{-1}. ESMS 823 (MH^+).

Methyl Ester Linear Dimer 23. A similar procedure to the synthesis of **12** was used to prepare **23**, using **22** (154 mg, 1.87×10^{-4} mol) and TBAF (0.51 mL, 1.1M, 5.67×10^{-4} mol) in THF (2 mL) and worked up and columned as before to yield a colorless oil (91 mg, 68%). TLC ethyl acetate/methanol (7:3), R_f = 0.15. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.61 (d, J = 4.5 Hz, 1H), 8.57 (d, J = 4.5 Hz, 1H) 7.96 (d, J = 9 Hz, 1H), 7.92 (d, J = 9 Hz, 1H), 7.45 (d, J = 4.5 Hz, 1H), 7.31 (m, 1H), 7.25−7.29 (m, 2H), 7.20 (d, J = 4.5 Hz, 1H), 7.12 (d, J = 2.5 Hz, 1H), 6.40 (d, J = 7 Hz, 1H), 5.52 (d, J = 3 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.61 (s, 3H), 3.45 (m, 1H), 3.21 (m, 1H), 2.91−3.08 (m, 4H), 2.49−2.62 (m, 2H), 2.21−2.33 (m, 6H), 2.01 (m, 2H), 1.57−1.82 (m, 6H), 1.30−1.45 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0 (s), 171.6 (s), 158.0 (s), 157.8 (s), 147.7 (s), 147.5 (d), 147.3 (d), 144.6 (s), 144.1 (s), 143.6 (s), 131.7 (d), 131.5 (d), 127.0 (s), 126.5 (s), 121.8 (d), 121.5 (d), 118.7 (d), 118.4 (d), 101.4 (d), 101.2 (d), 73.6 (d), 71.4 (d), 59.8 (d), 58.9 (d), 57.8 (t), 57.3 (t), 55.7 (q), 51.7 (q), 42.9 (t), 42.1 (t), 39.3 (t), 39.1 (t), 32.1 (d), 32.0 (d), 28.1 (t), 27.7 (t), 26.1 (d), 25.8 (d), 24.1 (t), 20.8 (t). υ_{max} ($CHCl_3$) 3673, 3602, 3201, 2953, 1733, 1622, 1592, 1500, 1474, 1433, 1363, 1207, 1261, 1159, 1087, 1033, 853 cm^{-1}. MS (FAB) 709.3641 ($C_{41}H_{49}O_7N_4$ requires 709.3601), 353, 307, 242, 184, 142.

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Supporting Information Available: ^{1}H NMR, HPLC, UV spectra of **2a**, **2b**, **7a**, **7b**; ^{1}H NMR, HPLC, UV, ESMS of the thermodynamic cyclization of **2a** and kinetic cyclization of **8**; the ^{1}H NMR of **10**, **12**, **16**, **19**, **21**, **22** and the kinetic cyclizations of **13**, **17**, and **20** (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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