Building thermodynamic combinatorial libraries of quinine macrocycles

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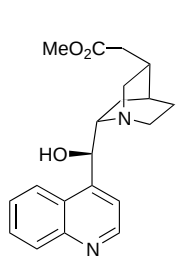
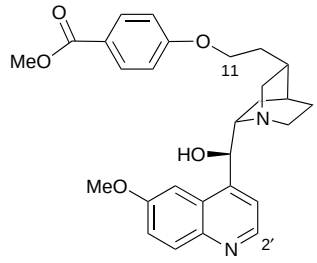
Thermodynamically-controlled transesterification of a predisposed cinchonidine building block with a more flexible extended quinine monomer leads to a combinatorial mixture of 11 macrocyclic receptors which is analysed by electrospray mass spectrometry; similar results with alkaloid–cholate mixtures demonstrate the generality of the approach.

We have recently shown that thermodynamically-controlled transesterification can lead to efficient synthesis of oligomeric macrocycles,[1,2] and that when the monomeric building blocks are suitably predisposed a single product may dominate even when other oligomers are kinetically accessible.[3] For example, the cinchonidine monomer **1** (HO–Cc–OMe) is



1 HO–Cc–OMe



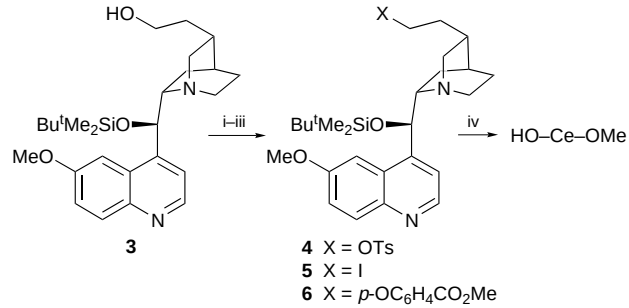
2 HO–Ce–OMe

predisposed to give almost exclusively the cyclic trimer under thermodynamic control. We now report that the extended quinine monomer **2** (HO–Ce–OMe), in which this predisposition is slightly relaxed, gives access to a wider range of homomacrocycles; more importantly it allows the development of thermodynamically-controlled receptor libraries by combination with other building blocks such as **1**.

In order to relax the predisposition of **1**, we elected to extend the cinchonidine monomer at the 11-position. The chosen extension, a methyl 4-hydroxybenzoate moiety, 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; introduces a little extra flexibility; and is still rigid enough to prevent formation of cyclic lactone monomer. Synthesis of **2** started from the previously prepared 11-alcohol **3**.[2] 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. Compound **5** was converted into **6** (75%) by stirring with methyl 4-hydroxybenzoate, 18-crown-6 and K_2CO_3, and removal of the Bu^tMe_2Si group using Bu_4NF–THF gave the extended monomer **2** in 78% yield (Scheme 1).

The result of submitting monomer **2** to transesterification under thermodynamic control[2] was a mixture of mainly cyclic dimer (Ce_2) : trimer (Ce_3) : tetramer (Ce_4) and higher oligomeric quinines, with a mass ratio of 30 : 41 : 29 respectively† (Scheme 2). Even though there is still a distinct preference for cyclic trimer,‡ the extension unit has allowed access to cyclic dimer (not previously seen even in kinetic cyclisations of **1**[4]) and tetramer under thermodynamic control, demonstrating the expected relaxation of predisposition.

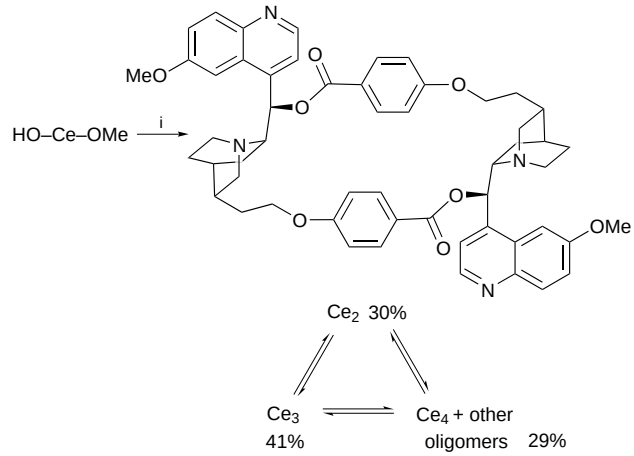
Under thermodynamic control, mixtures of cinchonidine monomer **1** and preorganised xanthenes self-sort to give good yields of cyclic trimer and dimer respectively because the homo-products are stabilised.[3] However, the relaxed constraints of the extended monomer **2** combined with predisposed **1** lead to quite a different outcome: thermodynamic transesterification of **1** and **2** under the usual conditions led to a combinatorial library of macrocycles, as observed by electrospray mass spectrometry§ (Fig. 1). The mass spectrum contains two of the three possible dimers, all possible trimers and small amounts of all the possible tetramers. It is unwise to draw precise quantitative conclusions from peak intensities since individual species have different inherent detectabilities in electrospray mass spectra, but there are systematic and interpretable deviations from the expected statistical distribution of hetero : homo oligomers. The extended quinine homo-dimer is seemingly favoured over the hetero dimer, which is not surprising given that **1** cannot form homo dimer at all. The trimers show the expected weighting towards the cinchonidine homo trimer but the more promiscuous monomer **2** gives access to two new hetero trimers. To a first approximation, it appears that the tetramers are formed in statistical proportions.



3

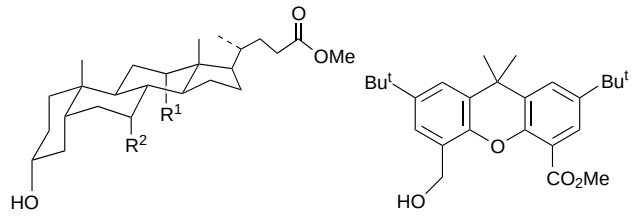
4 X = OTs
5 X = I
6 X = *p*-$OC_6H_4CO_2Me$

Scheme 1 *Reagents and conditons*: i, TsCl, Et_3N, room temp., 4 h; ii, NaI, acetone, reflux, 16 h; iii, 4-$HOC_6H_4CO_2Me$, 18-crown-6, K_2CO_3, room temp., 16 h; iv, Bu_4NF, THF, room temp., 4 h.



Scheme 2 *Reagents and conditions*: i, KOMe, 18-crown-6, toluene, reflux, 1 h.

To further examine the idea of relaxation of predisposition monomers **1** and **2** were individually mixed with the cholate monomer **7**, which has enough flexibility to allow access to a



7 **8**

R^1 = OBn
R^2 = $OCH_2OCH_2CH_2OMe$

range of cyclic oligomers.[1] Transesterification produced a cocktail of all the possible hetero oligomers of both **1** and **2** with **7**, which is consistent with the idea that if there is enough flexibility in one component then that is generally sufficient to give a range of macrocycles. We had already demonstrated that mixing of **1** with the highly preorganised xanthene monomer **8** leads to self-sorting.[3] To examine how powerfully preorganised **8** is we allowed it to react in the presence of extended quinine monomer **2**: the result was predominantly self-sorting, indicating that preorganised monomers such as **8** find it difficult to form mixtures with monomers that do not have the correct 'bite size' or flexibility.

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. By mixing only two monomers we observe 11 cyclic products, showing how large libraries of macrocycles can be

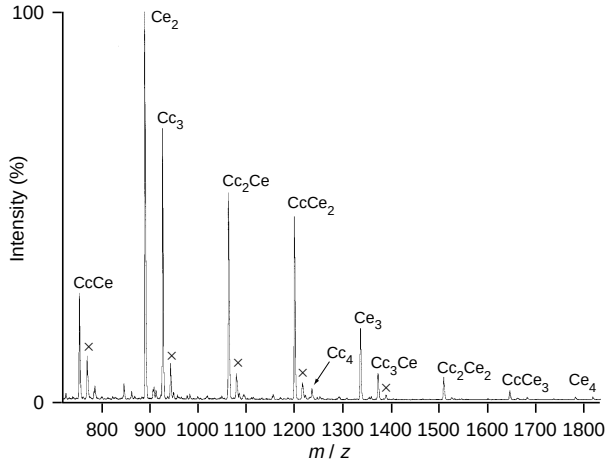


Figure 1 Electrospray mass spectrum of the thermodynamic cyclisation reaction mixture of **1** (HO–Cc–OMe) and **2** (HO–Ce–OMe). Peaks marked (×) are NH_4^+ adducts of molecular ions.

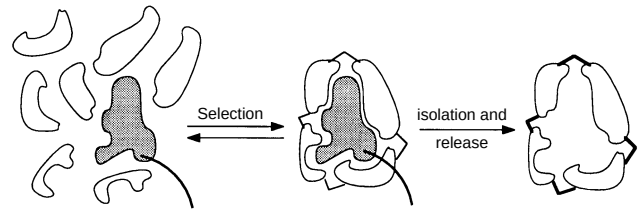


Fig 2 Schematic representation of a thermodynamic selection approach to receptors

obtained quickly from a small number of monomers. The way is now open for creating thermodynamically controlled macrocyclic receptor libraries (Fig. 2), with the possibility of thermodynamic templating to bias the library towards robust, covalent receptors with good binding properties.[5-7] If the guest is tethered in some way it should also be possible to isolate the receptors from an otherwise hopelessly complex mixture.

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Footnotes

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† Determined by 400 MHz ^{1}H NMR spectroscopy of the reaction mixture after work up and dissolution in $CDCl_3$: The chemical shifts for $H_{2'}$ were: dimer (Ce_2: δ 8.77), trimer (Ce_3: δ 8.74) and higher oligomers (Ce_{4+}: δ 8.70–8.73).

‡ In the absence of significant enthalpic differences in the stability of oligomers, simple entropic considerations lead to an expected order of abundance monomer > dimer > trimer > tetramer *etc*.

§ ES-MS were obtained on a VG BioQ triple quadrupole apparatus (VG Bio Tech Ltd, Altrincham, UK). The electrospray source was heated to 70 °C and the sampling cone voltage (V_c) was 105 V. Samples were introduced into the mass spectrometer source with an LC pump (Shimadzu LC-9A LC pump) at a flow rate of 4 μl min^{-1} of MeCN–H_2O (1 : 1). Calibration was performed using protonated horse myoglobin. Scanning was performed from *m/z* 200 to 2000 in 10 s. The data system was operated as a multichannel analyser, and several scans were summed to obtain the final spectrum. No hetero oligomers are detected in the electrospray mass spectra of control mixtures of homo oligomers.

References

1 P. A. Brady, R. P. Bonar-Law, S. J. Rowan, C. J. Suckling and J. K. M. Sanders, *Chem. Commun.*, 1996, 319.
2 S. J. Rowan, P. A. Brady and J. K. M. Sanders, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2143.
3 S. J. Rowan, D. G. Hamilton, P. A. Brady and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1997, **119**, 2578.
4 S. J. Rowan, P. A. Brady and J. K. M. Sanders, *Tetrahedron Lett.*, 1996, **37**, 6013.
5 W. C. Still, P. Hauck and D. Kempf, *Tetrahedron Lett.*, 1987, **28**, 2817.
6 A. V. Eliseev and M. I. Nelen, *J. Am. Chem. Soc.*, 1997, **119**, 1147.
7 I. Huc and J.-M. Lehn, *Proc. Natl. Acad. Sci. USA*, 1997, **94**, 2106 and references cited therein.

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