CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200800326

Tailored Polymer-Supported Templates in Dynamic Combinatorial Libraries: Simultaneous Selection, Amplification and Isolation of Synthetic Receptors

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Abstract: The thermodynamically controlled synthesis and isolation of macrocyclic receptors from dynamic combinatorial libraries has been achieved in a single step using a polymer-supported template. The templates were cinchona alkaloids which show interesting enantio- and diastereoselective molecular recognition events in libraries based on pseudo-dipeptide building blocks. The synthetic routes used to derivatise the alkaloids and attach them to polymer supports minimised any influence of the tethering linkage on the templating activity. Systematic studies have been carried out to probe how the polymer morphology and the template loading affect the selectivity and isolation yield of the macrocyclic receptors. Molecular recognition between solid-phase bound templates and selected receptors also enabled their affinity-type chromatographic separation.

Keywords: affinity chromatography · dynamic combinatorial chemistry · molecular recognition · polymer-supported templates · synthetic receptors

Introduction

In the last decade, different approaches in the field of target-guided synthesis have been developed to a point where they can now compete against the classical approach of designing, synthesising and studying a potential receptor or drug compound.[1–5] The thermodynamically controlled approach of dynamic combinatorial chemistry has been shown to be a powerful tool for the synthesis of specific macrocycles,[6–15] molecular species that can be considered to be host molecules for guest molecules in host–guest complex formation and which show potential applications ranging from catalysis[16,17] and sensors[18] to encapsulation systems[19] for drug delivery.[20] However, a limiting factor in increasing the diversity and versatility of dynamic combinatorial libraries (DCLs) in order to enhance the probability of identifying strongly binding species is the associated separation demands and the analytical chemistry. Although separation and identification of all library members is not normally necessary, the ability to isolate a potential hit (e.g., via chromatography) is essential. In this context, solid-phase bound templates[3,21–26] and building blocks[27,28] have been developed and can be used in a semi-continuous process[21,22] where synthesis and separation are performed separately. This does not take full advantage of the adaptive properties of DCLs, but can be useful in those cases where the equilibration conditions are not compatible with the target. To the best of our knowledge, Roberts et al.[26] reported the first example of simultaneous selection, amplification and isolation of a receptor (host) by an immobilised template (guest), using a commercially available quaternary ammonium resin. Severin[29] has used computer simulations to study the selection of DCL members by an immobilized target (guest) in an iterative fashion whereby equilibration and selection are performed separately or simultaneously. The simulations indicate that an evolutionary procedure can be advantageous in larger, multi building block DCLs, although a decrease in the overall yield has to be taken into consideration due to the iterative protocol.[30]

The advantage of using solid-phase templates (guests) in DCLs lies in the potential to carry out synthesis and affinity chromatography in one single step.[26] Tedious separations via chromatographic techniques can thus be avoided, which

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200800326.

would open new preparative possibilities especially in more complex libraries comprising an increased number of building blocks. The methodology would not only simplify the isolation of potentially strong macrocyclic binders but also improve the identification of hits. This can indeed be very challenging if separations of library members is already problematic on an analytical scale.

Zimmerman et al. developed an affinity-type chromatographic separation using immobilised hosts[31–33] or guests[34] on HPLC stationary phases. Only a few attempts[35–39] have been made aimed at broadening this approach of mimicking solution based host–guest interactions under heterogeneous conditions, while not all of the designs were fully successful.[40,41]

We now report the development of tailor-made polymer-supported templates. Some success with immobilised templates has already been reported,[26] but in order to obtain a generically viable procedure, a much better understanding of how polymer supports influence library behaviour at a molecular level is necessary. Resin morphology—highly cross-linked, permanently porous or lightly cross-linked swellable polymers—and template loading will be the key parameters addressed, while optimising the selective amplification and isolation of synthetic receptors.

We have chosen DCLs based on pseudo-dipeptide building blocks[42–45] (Figure 1) and cinchona alkaloids quinine and quinidine (Figure 2) as templates to be immobilised onto the stationary phases, which under homogeneous conditions have been shown to give rise to enantio- and diastereoselective molecular recognition events.[46,47] Fitted binding studies[47,48] in LL-*p*PF libraries (Figure 1) reveal high binding affinities for the quinidine-LL-pPF$_2$ and quinine-LL-pPF$_4$ pairs. In the DD-*p*PF systems the reverse selectivity is observed; quinidine binds more strongly to DD-pPF$_4$ whereas quinine shows higher affinity for DD-pPF$_2$. Unpublished fitted binding studies in *p*PV libraries (Figure 1) reveal high affinities for the quinidine-LL-pPV$_2$ and quinine-DD-pPV$_2$ complexes.

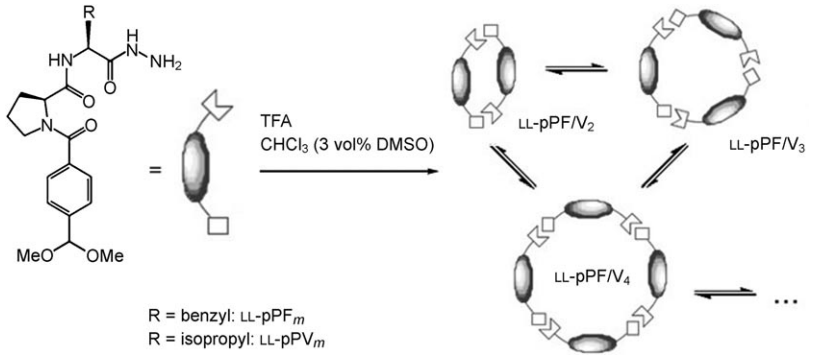


Figure 1. Pseudo-dipeptide building blocks and the macrocyclic receptors obtained in DCLs by reversible hydrazone exchange. [Nomenclature: e.g., "LL-*p*PF/V$_2$" implies that *either* the F *or* V building block is used; the subscripted number two indicates dimer.]

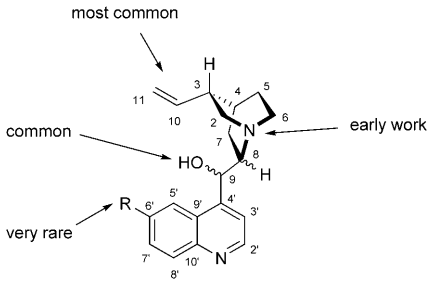


Figure 2. Derivatisation sites for attachment of cinchona alkaloids to solid-phases. (*R*/*S* configurations are obtained from references [66] and [67]).

Results and Discussion

Choice of polymer support: For applications in DCL syntheses, styrene resins were expected to be highly compatible with hydrazone-based pseudo-peptide macrocycle synthesis which takes place in $CHCl_3$.[49] A range of polymer supports with different functional group loading and polymer morphology[50] were synthesized using vinylbenzyl chloride (VBC, mixture of *meta*- and *para*-isomers) as functional co-monomer, styrene (Sty) as diluting or structural co-monomer and divinylbenzene (DVB-80) as cross-linker in a suspension-type polymerization (Figure 3). Table 1 summarizes the composition of the resins: **MA-X** are highly cross-linked macroporous (MA) resins, for which toluene was used as a porogen

Table 1. Characterisation of VBC resins: high specific surface area (SA) resins **MA-1**, **MA-2** and gel-type polymer supports **GT-1**, **GT-2**.

Resin	Extent of cross-linking[a]	Specific SA [$m^2 g^{-1}$]	Solvent up-take [$g g^{-1}$]		Cl loading [$mmol g^{-1}$]
			$CHCl_3$	*n*-hexane	
MA-1	60 wt % DVB	506	1.3	0.6	1.30 ± 0.09
MA-2		520	1.6	0.7	0.51 ± 0.09
GT-1	2 wt % DVB	<5	4.0	0.1	1.63 ± 0.09
GT-2		<5	4.7	0.0	0.56 ± 0.09

[a] The table shows the wt % of divinylbenzene actually present in the monomer feed rather than the wt % of "monomer as supplied". The grade of the cross-linking reagent used was DVB-80, containing 80 wt % DVB (mixture of *meta*- and *para*-isomers) and 20 wt % ethyl styrene (mixture of *meta*- and *para*-isomers).

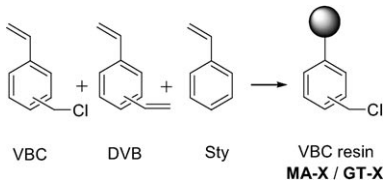
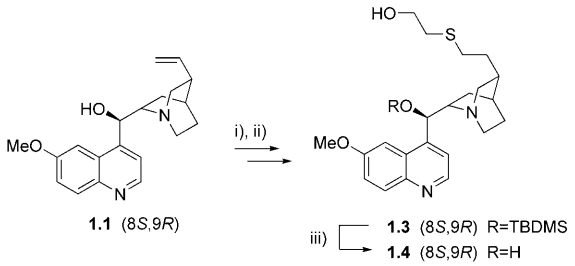


Figure 3. Synthesis of VBC resins **MA-X** and **GT-X**.

during the polymerization to create high specific surface areas (SA).[50,51] **GT-X** are typical Merrifield resins;[52] no porogen was used and, in combination with the low cross-linking, this results in the formation of gel-type (GT) resins having no porous structure in the dry state.[50,53] Solvent uptake data for a thermodynamically good solvent ($CHCl_3$) and *n*-hexane as bad solvent, presented in Table 1, show the swelling nature of gel-type resins. Each resin type was prepared with two different levels of functionalisation.

Cinchona alkaloid derivatisation: The tremendous interest in polymer-supported cinchona alkaloids is as a result of rapid development in two main areas: a) chiral stationary phases in chromatographic separation techniques[54,55] and b) chiral polymer-supported catalysts.[56–60] The skeleton of cinchona alkaloids offers up to four potential sites for polymer attachment (Figure 2). The secondary alcohol at C-9 and the nitrogen on the quinuclidine moiety of the alkaloid appeared unsuitable because of their close proximity to the stereogenic centres, which are crucial for templating activity and selectivity. The double bond of the quinuclidine group has been explored extensively in the past for cinchona alkaloid immobilisation (for reviews see references [60–62]), whereas the isoquinoline moiety has been used only very rarely for polymer attachment.[63–65]

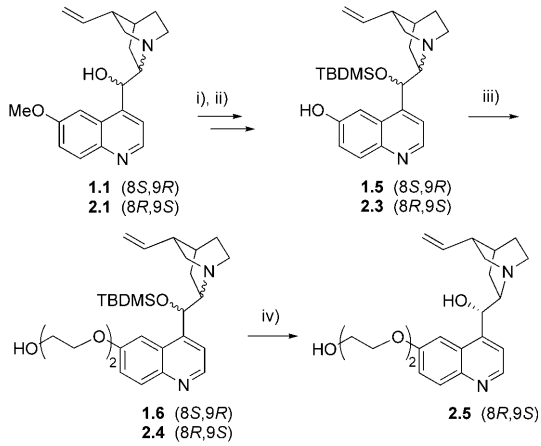
For the immobilisation of quinine and quinidine onto the pre-synthesised polymer resins the attachment of choice was selected as the stable ether linkage to the VBC-containing resin, including a spacer which preferably would be variable in length. The relatively straightforward linker attachment to the vinylic double bond on the quinuclidine moiety of the alkaloid (using quinine in this case, Scheme 1) was carried out first. *tert*-Butyldimethylsilyl ether was selected as protecting group[68] (97%), followed by the radical addition of mercaptoethanol to the double bond in good yield (77%),



Scheme 1. Functionalisation Route 1 leading to quinine derivates **1.*x***: i) TBDMSCl, DMAP, NEt_3, DMF, 12 h, RT; ii) Mercaptoethanol, AIBN, $CHCl_3$, 48 h, reflux; iii) TBAF, THF, 12 h, RT.

as described by Oda et al.[69] and Salvadori et al.[70] Deprotection of compound **1.3** gives quinine derivative **1.4** (26%), which turned out to lose all of its templating activity compared to quinine itself in the synthesis of LL-*p*PF libraries, very probably because of steric hindrance arising from the newly attached spacer group being in close proximity to the stereogenic carbons on the quinuclidine moiety of the template (Figure 4). In contrast, during synthesis of DD-*p*PF libraries (Figure 5), no loss of templating activity was observed.

The sole remaining functionalisation was derivatisation via the quinoline moiety of the alkaloid (Scheme 2). The secondary alcohol of the cinchona alkaloid was protected in high yield as the *tert*-butyldimethylsilyl ether.[68] For the demethylation, the classical cleavage with aqueous hydrogen



Scheme 2. Functionalisation Route 2 leading to quinine derivates **1.*x*** and quinidine derivates **2.*x***: i) TBDMSCl, DMAP, NEt_3, DMF, 12 h, RT; ii) L-Selectride, THF, 48 h, reflux; iii) chloroethoxyethanol, K_2CO_3, cat. NaI, CH_3CN, 4d, reflux; iv) TBAF, THF, 12 h, RT.

bromide[71,72] could not be used as HBr would add to the vinyl bond of the alkaloid and cleave the silyl ether protecting group. Apart from common demethylation reagents, such as the $BBr_3{\cdot}S(CH_3)_2$ complex,[73] relatively mild reaction conditions and promising yields were reported by Majetich and co-workers[74] using L-Selectride in THF. Indeed, good yields (>70%) were obtained for quinine derivative **1.5** and quinidine derivative **2.3**. Finding a suitable linker for the next step proved tedious, but 2-(2-chloroethoxy)ethanol was eventually attached in moderate yields. The overall yields for products **1.6** and **2.4** were 37 and 39%, respectively. In order to perform some dynamic combinatorial library syntheses under homogenous conditions, with the aim of assessing any attenuation of templating activity due to the described derivatisation work, product **2.4** was deprotected using TBAF in THF. The previous purification procedure that led to low isolation yields of quinine **1.4** (Scheme 1) was improved slightly to 48%, by using a relatively high amount of magnesium sulphate as drying agent in the reaction work-up, which adsorbs phase transfer catalysts such as quaternary ammonium salts.

The results presented in Figure 4 and Table 2, which relate to homogeneous DCL syntheses, allow an approximate quantification of the loss of templating activity due to the derivatisation of the quinoline moiety of the alkaloid. In the synthesis of the LL-*p*PF library, it appears that in order to achieve the same amplification yield of the dimer, a 1.5- to 2-fold increase in the amount of template **2.5** is necessary compared to quinidine **2.1**. When the same functionalised templates were used to synthesise the enantiomeric DD-*p*PF library, no loss of activity was observed (Figure 5). Apparently, DD-*p*PF based receptors are more tolerant to small changes in the structure of the complexed guest molecules.

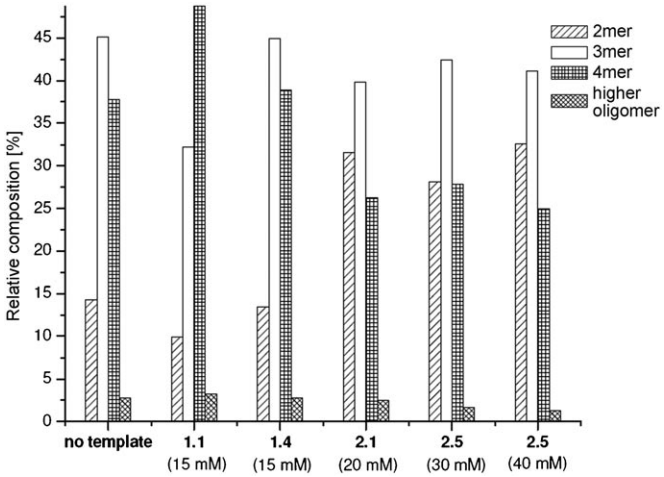


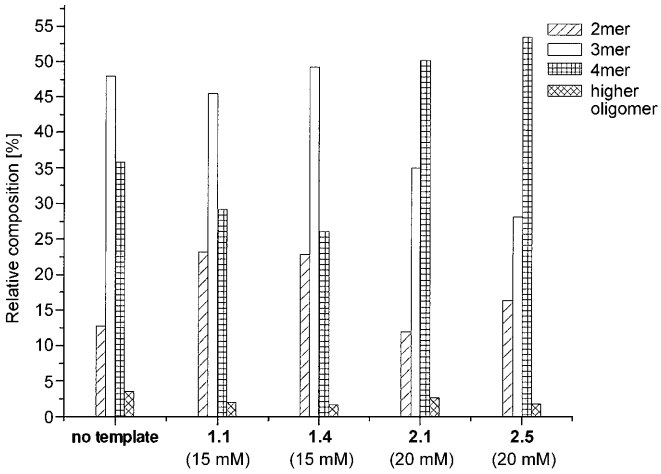
Figure 4. Templating activity of the parent quinine **1.1** and quinidine **2.1** compared to their derivatives **1.4** and **2.5** [LL-*p*PF$_m$ library (2 mM)]. Amplification factor is defined as the ratio of host present in the templated library to host in the non-templated library.

Table 2. See Figure 4 for heading.

Guest	Host	Amplification factor
1.1 (15 mM)	LL-*p*PF$_4$	1.4
1.4 (15 mM)	LL-*p*PF$_4$	1.0
2.1 (20 mM)	LL-*p*PF$_2$	2.2
2.5 (30 mM)	LL-*p*PF$_2$	1.9
2.5 (40 mM)	LL-*p*PF$_2$	2.3

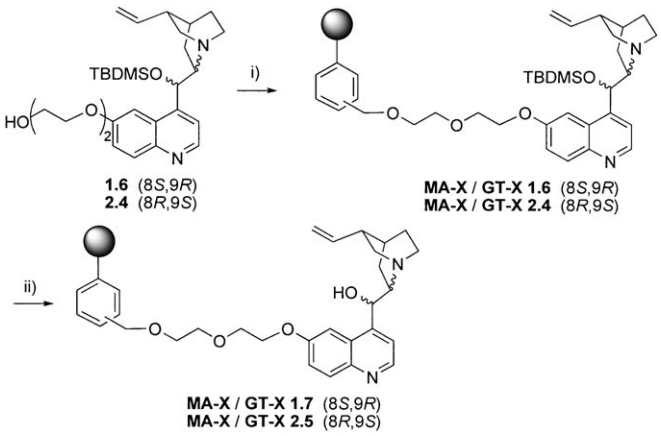
Template attachment to pre-formed polymer resins: In the next step the functionalised protected quinine **1.6** and quinidine **2.4** were attached via an ether linkage to the in-house prepared VBC-containing resins (Scheme 3).[50,51,53,75] The use of microwave reactor vessels proved advantageous for small scale reactions, while for larger scale reactions (>500 mg) a classical experimental set up[76–78] using a three-necked, round-bottomed flask with nitrogen inlet, condenser and mechanical stirrer was a better choice. Cleavage of the *tert*-butyldimethylsilyl ether was carried out at room temperature in sealed glass vials on flatbed rollers for 24 h.

Yields for the attachment reactions were calculated based on elemental microanalytical data. Under optimized conditions gel-type VBC resins **GT-X** gave quantitative conversion of benzyl chloride groups to the ether linked cinchona alkaloids. For macroporous resins **MA-X** lower conversions were obtained, most probably due to their heavily cross-linked network, which reduces the accessibility of functional groups. (All details on calculation of the conversions and FTIR data are presented in the Supporting Information.) The deprotection step on the polymer supports followed in high yields, as evident from the appearance of the OH absorption band around 3400 cm^{-1} in FT-IR spectroscopic analysis, due to cleavage of the *tert*-butyldimethylsilyl ether protecting group. The spherical form of the polymer beads was not affected during the attachment and deprotection reactions as shown by optical microscope photographs (Figure 6) obtained in the dry state.



Guest	Host	Amplification factor
1.1 (15 mM)	DD-*p*PF$_2$	1.8
1.4 (15 mM)	DD-*p*PF$_2$	1.8
2.1 (20 mM)	DD-*p*PF$_4$	1.4
2.5 (20 mM)	DD-*p*PF$_4$	1.5

Figure 5. Templating activity of the parent quinine **1.1** and quinidine **2.1** compared to their derivatives **1.4** and **2.5** [DD-*p*PF$_m$ library (2 mM)].



Scheme 3. Quinine and quinidine derivative attachment to polymer supports, followed by deprotection of the alcohol: i) NaH, **MA-X** or **GT-X**, THF, 72 h, reflux; ii) TBAF, THF, 24 h, RT.

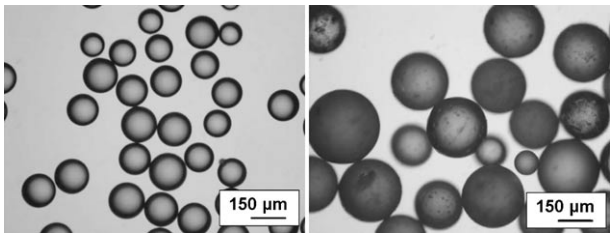
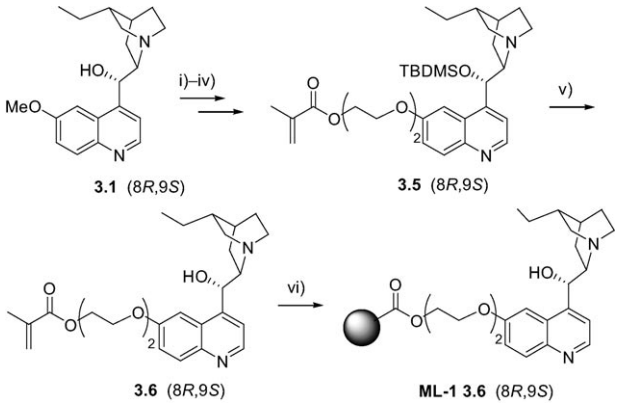


Figure 6. Transmission optical microscope photographs at a magnification of X8. Left: High surface area polymer-supported quinidine **MA-1 2.5B**; Right: Gel-type polymer-supported quinidine **GT-2 2.5**.

Polymerisable template: Attachment of a polymerisable methacrylate group to the derivatised template was also explored and has the advantage that standard solution state analysis can be performed up to the final synthetic step before polymerization. Furthermore, the resulting polymer-supported templates are likely to be free of impurities and by-products. Scheme 4 shows the route chosen for the synthesis of a polymerisable dihydroquinidine derivative **3.6**. The first three steps of protection, demethylation and attachment of the linker were performed as described previously, in an overall yield of 41%. The esterification with methacroyl chloride and the subsequent deprotection had to be performed carefully, since the resulting methacrylates can be polymerised easily. The protected methacrylate **3.5** was obtained in a good yield of 77% and the final deprotected polymerisable template **3.6** in a yield of 62%.



Scheme 4. Polymer-supported dihydroquinidine synthesis via a polymerisable template derivative: i) TBDMSCl, DMAP, NEt_3 in DMF, 12 h, RT; ii) L-Selectride in THF, N_2, 48 h, reflux; iii) 2-(2-chloroethoxy)ethanol, K_2CO_3, cat. NaI in CH_3CN, N_2, 4 d, reflux; iv) methacroyl chloride, DMAP, NEt_3, THF, N_2, 12 h, RT; v) TBAF, THF, 12 h, RT; vi) Sty, DVB-80, AIBN, 80°C, 24 h.

We considered three different polymerisation methods: bulk polymerisation, suspension polymerisation using an oscillatory baffled reactor[79] and precipitation polymerisation.[80,81] The two latter methods were deemed less suitable because in order to obtain spherical particles of suitable morphology the compositions of the polymerisation media have to be adapted very carefully. This tends to be time and material consuming. Therefore, a gel-type polymer was synthesised in a bulk type polymerisation, using 1.6 wt% cross-linker DVB-80, in combination with styrene (81.3 wt%) to adjust the loading of the template **3.6** (16.7 wt%) on the final polymer. The targeted template loading of 0.45 mmol g^{-1} was similar to the other polymer-supported templates described above (see Table 3). The loading level obtained (0.33 mmol $g^{-1} \pm 0.11$) was indeed relatively close to the monomer feed and the yield of product was high (>80%). The only disadvantage of the bulk polymerisation was the fact that the final gel-type polymer needed to be crushed into smaller particles.

Table 3. Summary of loadings achieved in attachment and deprotection reactions on high surface area resins **MA-1** and **MA-2**, and gel-type resins **GT-1** and **GT-2**.

Resin	N content [%][a]	Template loading [mmol g^{-1}][b]
MA-1[a,b]	4.62±0.3	1.30±0.09
MA-1 2.4A	1.23±0.3	0.44±0.11
MA-1 2.5A	1.31±0.3	0.47±0.10
MA-1 2.4B[c]	0.57±0.3	0.20±0.11
MA-1 2.5B	0.64±0.3	0.23±0.10
MA-1 1.6	1.03±0.3	0.37±0.11
MA-1 1.7	0.96±0.3	0.34±0.11
MA-2[a,b]	1.81±0.3	0.51±0.09
MA-2 2.4	0.48±0.3	0.17±0.11
MA-2 2.5	0.50±0.3	0.18±0.11
MA-2 1.6	0.47±0.3	0.17±0.11
MA-2 1.7	0.42±0.3	0.15±0.11
GT-1[a,b]	5.77±0.3	1.63±0.09
GT-1 2.4	2.12±0.3	0.76±0.10
GT-1 2.5	2.15±0.3	0.77±0.10
GT-2[a,b]	2.00±0.3	0.56±0.09
GT-2 2.4	1.01±0.3	0.36±0.11
GT-2 2.5	0.98±0.3	0.35±0.11
GT-2 1.6	0.93±0.3	0.33±0.11
GT-2 1.7	0.91±0.3	0.32±0.11

[a] Cl content for resins **MA-1**, **MA-2**, **GT-1** and **GT-2**, and N content for all other products. [b] Cl loading for resins **MA-1**, **MA-2**, **GT-1** and **GT-2**, and template loading for all other products. [c] For resin **MA-1 2.4B** the reaction time for the template attachment was only 48 h, whereas for **MA-1 2.4A** and all other resins the reaction was allowed to proceed for 72 h.

Simultaneous selection, amplification and isolation in DCLs: **Experimental procedure**: The initial experimental conditions for running dynamic combinatorial libraries using polymer-supported templates were the same as those reported previously for homogeneous[47] or heterogeneous conditions.[26] Building blocks were dissolved in $CHCl_3$ (3 vol% DMSO), followed by the addition of trifluoroacetic acid (TFA) and polymer-supported templates. In order to improve the dispersion of the floating polymer beads in chloroform, the reaction vials were put on a horizontal shaker. After four days the resins were filtered off through syringe filters (10 μm polypropylene frits), the vial rinsed with a small amount of $CHCl_3$ which was then filtered also through the syringe filter, and both filtrates combined. The beads were then washed repeatedly using 2×2.5 mL of each of two different solvents (Figure 7): $CHCl_3$ (3 vol% DMSO) for the non-disruptive wash which removes unselectively bound oligomers; MeOH for the disruptive wash or elution, which

releases selectively amplified and bound receptors by disrupting non-covalent interactions between host and guest or receptor and template bound on the polymer support. Three drops of triethylamine were added to each solution in order to quench the trifluoroacetic acid and hence terminate the hydrazone exchange, together with an internal standard. Toluene was found to be suitable as such a reference.

Figure 7 shows the selective amplification, binding and isolation of the dimer LL-pPF$_2$ (trace E) using quinidine supported on a gel-type polymer. As all integrated HPLC peak areas have to be corrected using the internal standard, presenting the data in a tabular fashion makes the direct comparison of different solutions more accurate (Figure 8). The conditions used were already optimised, the different steps of which will be explained in more detail below.

Influence of morphology of polymer support and template loading in *p*PF libraries: Several optimisation steps were necessary in order to achieve selective isolation of an amplified receptor in the highest possible yield. It was shown earlier (Figure 4) that the templating activity of the guests can be affected to some extent by the chemical derivatisation. Also, the quantity of polymer-attached template can be expected to influence the efficiency of the solid-phase templating. In order to assess how large excesses of solid-phase bound template affect selectivity and isolation yields, several experiments were carried out by increasing the relative amount of template used, bound on the high surface area macroporous and the gel-type resins. In Figures 9 and 10 the composition of the elution step is shown together with the overall dimer isolation yield. In both cases, considerable improvements were achieved as the excess of template used was increased. The increased yield and selectivity are correlated intimately, since increasing relative amounts of amplified dimer pre-disposes the system to show improved selectivity in the separation process.

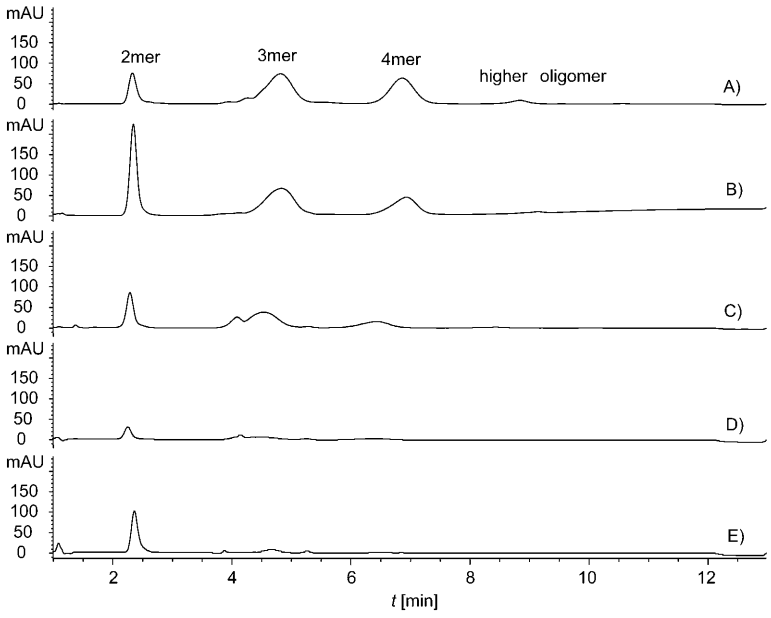


Figure 7. HPLC traces of libraries prepared from the LL-pPF$_m$ building block (2 mM): A) library without template; B) in the presence of quinidine **2.5** (50 mM); in the presence of polymer-supported quinidine **GT-2 2.5** (25 equivalent): C) filtrate, (D) $CHCl_3$ wash, (E) elution with MeOH.

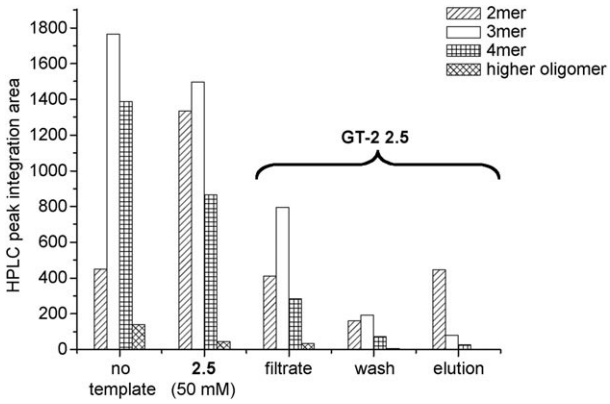


Figure 8. LL-pPF$_m$ building block (2 mM) based libraries: comparison between the untemplated library and libraries templated by derivatised quinidine **2.5** (50 mM) and polymer-supported quinidine **GT-2 2.5** (25 equivalent).

It is clear from these data that lightly cross-linked gel-type polymer supports out-perform highly cross-linked high surface area resins in terms of isolation yield and selectivity. This is probably due to the swellable nature of gel-type materials, allowing better access of incoming interacting receptors to the templates. Due to the very low cross-link ratio of the gel-type polymer the swelling solvent places the template into a more "solution-like environment" compared to the highly cross-linked macroporous resins. Although the latter materials show better mechanical stability for potential chromatographic applications, their more heavily cross-linked networks are more rigid and appear to reduce accessibility.

However, it is not only the morphology of the polymeric support that is crucial for their application in DCLs, but also the template loading. Figure 11 compares the isolation yields of different receptors to template loading, at the same overall "template concentration". Two trends seem obvious: a decrease in template loading on the polymer support is favourable regarding the yield of isolation of a selectively amplified receptor. Secondly, the results confirm that gel-type resins are more suitable as polymeric supports than macroporous resins. It was hoped that using gel-type polymer-supported template **ML-1 3.6** obtained via the "cleaner" polymerisable template route would give rise to further improvements. However, due to

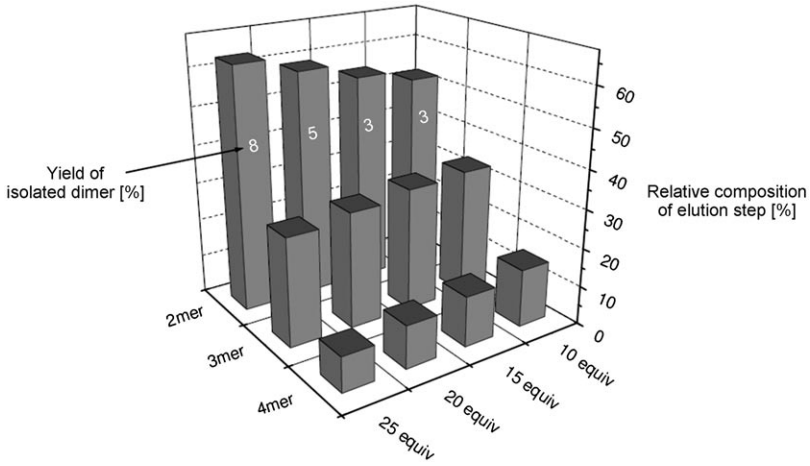


Figure 9. Yield and selectivity of isolated LL-pPF$_2$ obtained for different solid-phase template/building block mole ratios by increasing the amount of high surface area macroporous polymer-supported template **MA-1 2.5**, using a fixed concentration of LL-pPF$_m$ (2 mM).

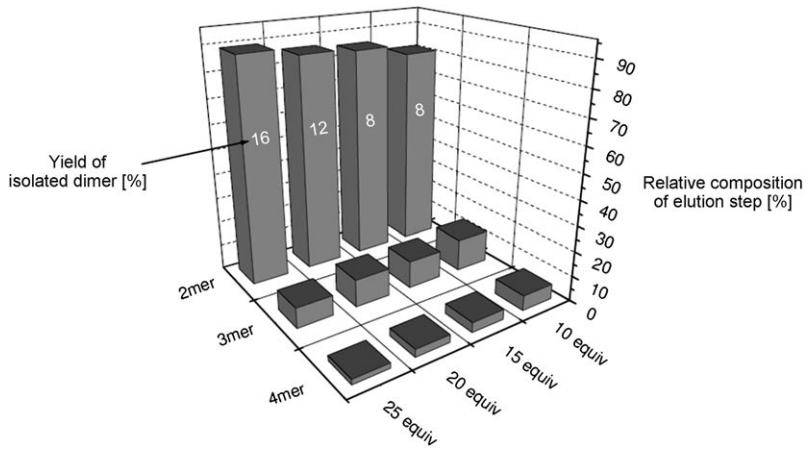


Figure 10. Yield and selectivity of isolated LL-pPF$_2$ obtained for different solid-phase template/building block mole ratios by increasing the amount of gel-type polymer-supported template **GT-2 2.5**, using a fixed concentration of LL-pPF$_m$ (2 mM).

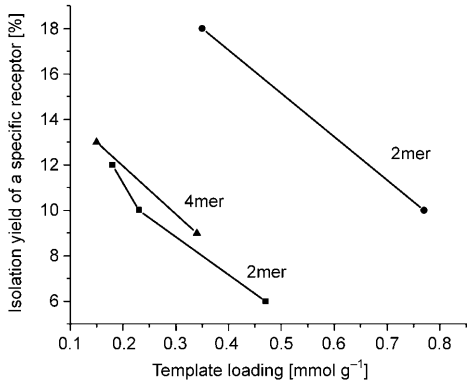


Figure 11. Increase of isolation yields of specific receptor with decreasing template loading on the various polymer supports (■: quinidine on macroporous resins **MA-X 2.5**, ▲: quinine on macroporous resins **MA-X 1.7**, ●: quinidine on gel-type resins **GT-X 2.5**), all synthesised using the same solid-phase template/building block mole ratio of 25.

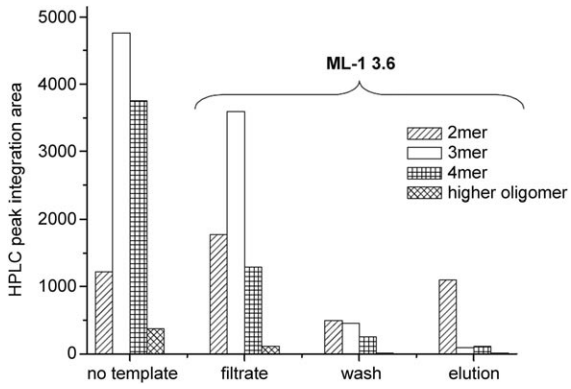


Figure 12. Gel-type polymer-supported dihydroquinidine **ML-1 3.6** in syntheses using LL-pPV$_m$ building block (2 mM), and a solid-phase template/building block mole ratio of 18.5.

the very high swelling of **ML-1 3.6** the mole ratio of solid-phase template/building block was limited to 18.5 in order to prevent the solution being totally imbibed by the polymer (Figure 12). This limitation makes **ML-1 3.6** less suitable than the GT resin, which gives superior results when used at higher template/building block ratio.

Simultaneous selection, amplification and isolation in DCLs: *p*PV libraries: All studies described so far have been performed using the pPF$_m$ building block in library syntheses. The results suggest strongly that gel-type swellable resins and low template loadings favour host–guest interactions in DCLs compared with their macroporous counterparts, enabling selective and efficient isolations of synthetic receptors. To demonstrate the generality of this observation we decided to use the "best performing" resin **GT-2 2.5** in library syntheses using the pPV$_m$ building block (Figure 13). Figure 14 shows that for this system also a member of a library can be amplified and isolated in high yield and selectivity using a solid-state bound template.

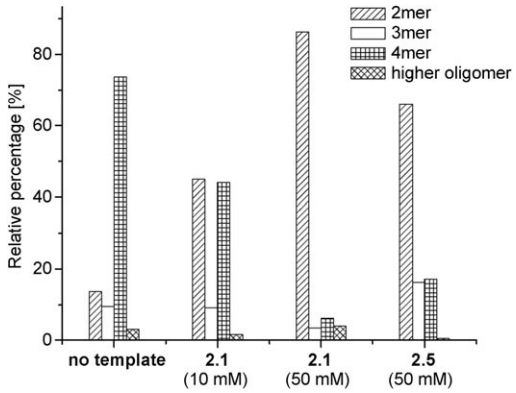


Figure 13. Templating activity of the parent quinidine **2.1** compared to its derivative **2.5** [LL-pPV$_m$ library (2 mM)].

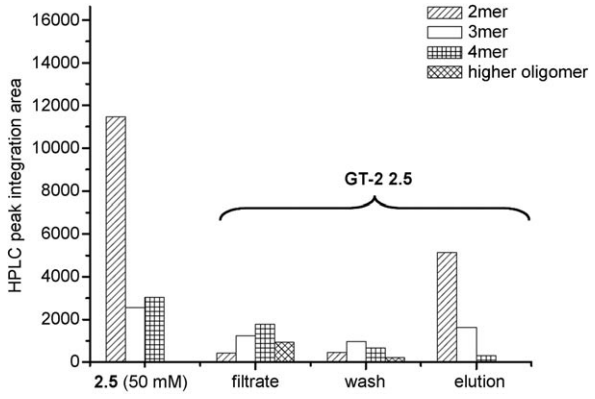


Figure 14. Gel-type polymer-supported quinidine **GT-2 2.5** in syntheses using LL-pPV$_m$ building block (2 mM), and a solid-phase template/building block mole ratio of 25.

Polymer-supported cinchona alkaloids in affinity chromatography: ***p*PV libraries**: Polymer-supported templates can be applied not only in DCL synthesis in order to carry out selection, amplification and isolation of strongly binding receptors in one single synthetic step, but also in another potential application where they can be used as a stationary phase in the separation of a static mixture of macrocyclic receptors via affinity-type chromatography. The aim of this study was not only to prove this principle, but also to evaluate whether this approach would be useful in improving the selectivity in the elution step for the isolation of amplified synthetic receptors, which is still far from perfected.

The initial work was carried out using pPV libraries because high affinities were observed between polymer-supported cinchona alkaloids and macrocyclic hosts as discussed previously in DCLs templated under heterogeneous conditions. pPV libraries behave quite differently to their published pPF based counterparts.[46,47] Fitted binding studies[48] in pPV libraries reveal high binding affinities only for the quinidine-LL-pPV$_2$ and quinine-DD-pPV$_2$ pairs (Table 4).

The mixture selected for affinity chromatography studies was a LL-pPV$_m$ or DD-pPV$_m$ (5 mM) untemplated library in equilibrium, quenched and subsequently spiked with isolated dimer LL-pPV$_2$ or DD-pPV$_2$ to obtain an adequate composition for a test solution. A successful experimental set-up was as follows: polymer-supported quinidine **GT-2 2.5** (400 mg) or quinine **GT-2 1.7** (450 mg) were introduced into a solid-phase extraction (SPE) cartridge fitted with a 0.45 μm cellulose membrane filter at the bottom. This made sure that the flow of the eluent running through the column was very slow without having to apply pressure from the top or vacuum from the bottom. In order to protonate and "activate" the template bound on the solid-phase, 15 mL of 150 mM TFA in chloroform (3 vol% DMSO) solution was allowed to run through the swollen polymer resins, followed by chloroform (15 mL, 3 vol% DMSO) to remove excess acid. Not only were the beads highly swollen in chloroform, they also floated. The resins were therefore pressed down very slightly using a frit at the top, without rupturing the pre-conditioned column packing. After the acid removal washing steps, 100 μL of the prepared test solution was applied to the column, followed by an appropriate number of 1 mL chloroform (3 vol% DMSO) and 1 mL methanol (3 vol% DMSO) elution steps.

Table 4. Fitted binding affinities between protonated cinchona alkaloids and enantiomeric pPV$_m$ based synthetic receptors.

ΔG [kJ mol^{-1}]	LL-pPV$_2$	LL-pPV$_3$	LL-pPV$_4$
quinidine–H$^+$	−14.6	−7.4	>-2
ΔG [kJ mol^{-1}]	DD-pPV$_2$	DD-pPV$_3$	DD-pPV$_4$
quinine–H$^+$	−13.4	−5.8	>-2

Comparing the results obtained for polymer bound quinidine **GT-2 2.5** and quinine **GT-2 1.7** (middle and bottom chart in Figure 15) to blank polymer **GT-2** (top chart in Figure 15) clearly shows that the dimers LL-pPV$_2$ and DD-pPV$_2$ are retained very selectively on their respective polymer-supported guest (template) to an extent that they have to be eluted with a very polar solvent, methanol. The isolation yield is high, and the selectivity in LL- or DD-pPV mixtures is in accordance with the outcome that the fitted binding affinities between template and synthetic receptor had predicted.

Polymer-supported cinchona alkaloids in affinity chromatography: ***p*PF libraries**: The fitted binding affinities in cinchona alkaloid templated LL- and DD-pPF libraries reveal enantio- and diastereoselective host–guest interactions (Table 5).[47]

The mixtures to be separated in the pPF system were equilibrated and quenched 5 mM LL-pPF and DD-pPF non-templated libraries. The potentially strongly binding dimeric and tetrameric species were already present in sufficient amounts so that the spiking of particular receptors was not necessary. Figure 16 shows the diastereoselective separation of LL-pPF$_2$ and LL-pPF$_4$ by quinidine and quinine-based polymer supports, respectively. Reversed selectivity was achieved in the DD-pPF system (Figure 17): quinidine showed affinity for the tetramer DD-pPF$_4$ and quinine for the dimer DD-pPF$_2$.

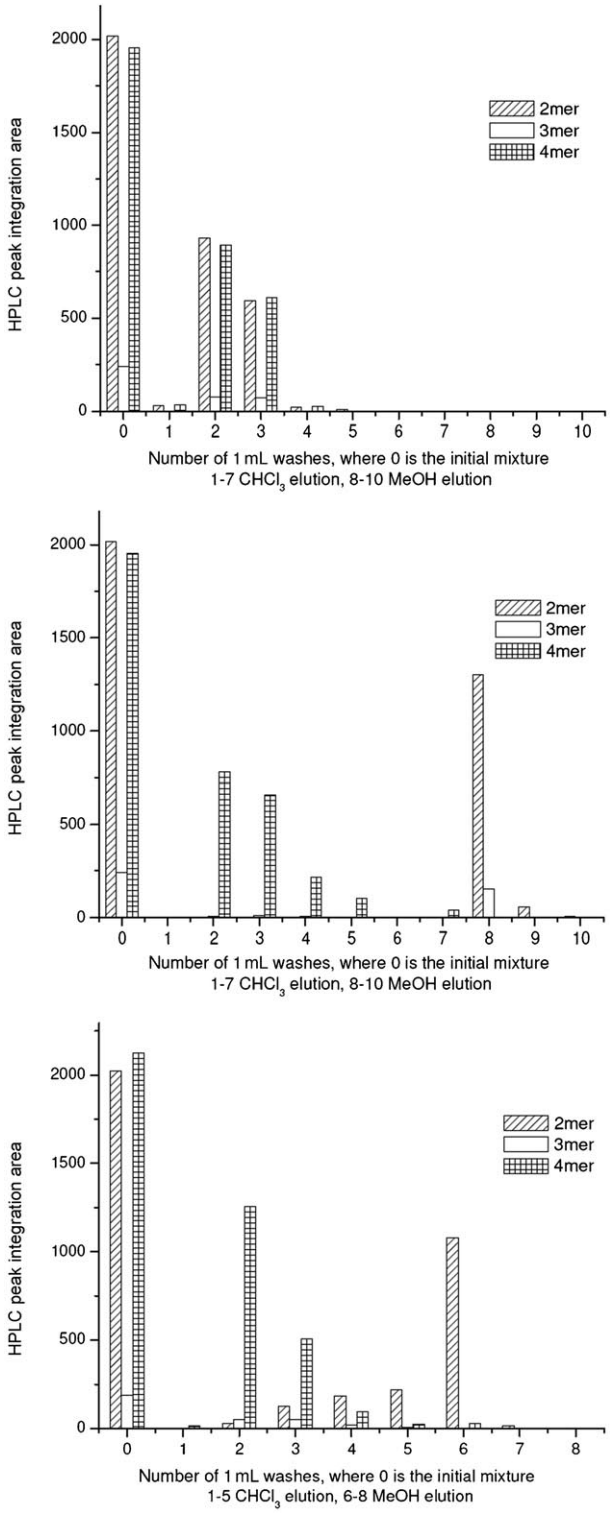


Figure 15. Composition of elution steps in affinity-type chromatographic separation involving LL-*p*PV and DD-*p*PV mixtures using: top: LL-*p*PV mixture (100 μL, 5 mM, spiked with LL-pPV_2) on gel-type polymer **GT-2** (blank polymer, 400 mg); middle: LL-*p*PV mixture (100 μL, 5 mM, spiked with LL-pPV_2) on gel-type polymer-supported quinidine **GT-2 2.5** (400 mg); bottom: DD-*p*PV mixture (100 μL, 5 mM, spiked with DD-pPV_2) on gel-type polymer-supported quinine **GT-2 1.7** (450 mg).

Table 5. Fitted binding affinities between protonated cinchona alkaloids and enantiomeric pPF_m based synthetic receptors.[47]

ΔG [kJ mol^{-1}]	LL-pPF_2	LL-pPF_3	LL-pPF_4
quinidine–H^+	−11.0	> −2	> −2
quinine–H^+	−10.5	−11.2	−14.7
ΔG [kJ mol^{-1}]	DD-pPF_2	DD-pPF_3	DD-pPF_4
quinidine–H^+	−9.9	−11.8	−15.4
quinine–H^+	−9.3	> -2	> −2

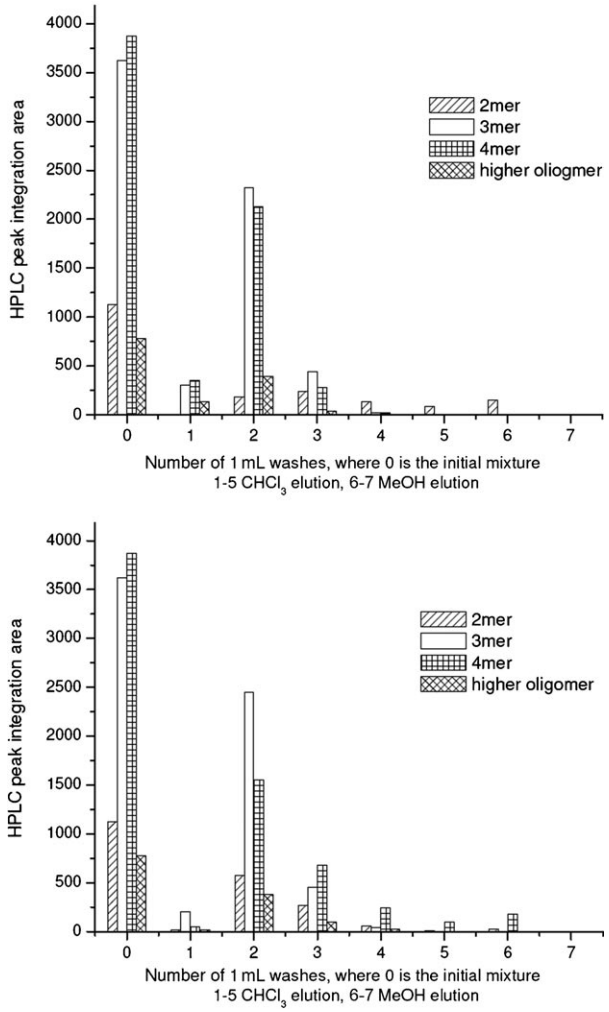


Figure 16. Composition of elution steps in affinity type chromatographic separation involving a LL-*p*PF mixture (100 μL, 5 mM) using: top: gel-type polymer-supported quinidine **GT-2 2.5** (400 mg); bottom: gel-type polymer-supported quinine **GT-2 1.7** (450 mg).

The selectivity in retention of specific macrocycles is in good agreement with the binding affinities in Table 5. However, with the exception of the highly efficient separation of DD-pPF_4 using polymer-supported quinidine **GT-2 2.5**, the retention yields were disappointingly low. Comparing separations achieved with the *p*PV and *p*PF libraries it seems that, under the present conditions, efficient retention on a solid-phase bound guest seems possible only when the host–guest binding affinity is higher than ≈ 13 kJ mol^{-1} (assuming

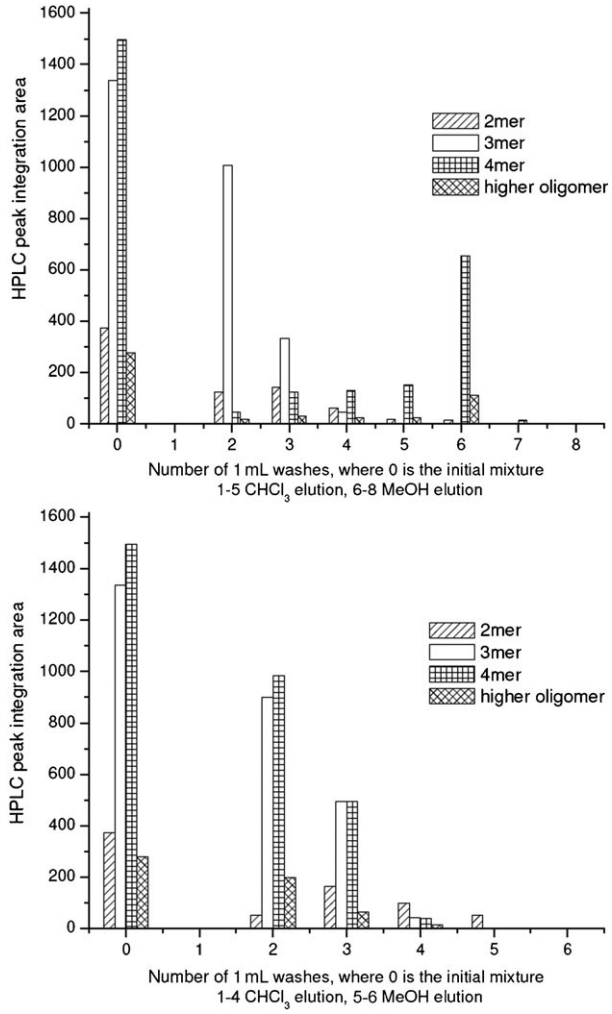


Figure 17. Composition of elution steps in affinity type chromatographic separation involving a DD-*p*PV mixture (100 μL, 5 mM) using, top: gel-type polymer-supported quinidine **GT-2 2.5** (400 mg); bottom: gel-type polymer-supported quinine **GT-2 1.7** (450 mg).

affinities of the solid-phase templates are comparable to the parent compounds in solution). In terms of selectivity, differences of up to about 4 kJ mol^{-1} in binding affinity give rise to successful separation under a competitive binding regime.

Conclusion

The cinchona alkaloids quinine and quinidine were derivatised in order to offer functional groups that would allow the attachment of the alkaloids to vinylbenzyl chloride containing resins. Dynamic combinatorial library experiments prior to polymer attachment were used to determine whether the tethering of a linker or derivatisation had any detrimental effects on the templating activity of the template. Derivatisation via the quinoline moiety of the cinchona alkaloid affects the activity of the template to only a small extent compared with the parent template.

In order to explore how the morphology of the polymer support and template loading affects templating efficiency and selectivity, a range of polymer-supported templates was synthesised. The appropriate polymer morphology was found to be crucial for achieving selective amplification and isolation of a particular member of a dynamic combinatorial library. Gel-type resins considerably out-perform their macroporous counterparts. Templates linked to a swollen polymeric network provide an environment that is sterically more accessible to incoming synthetic receptors compared to rigid polymer networks of highly cross-linked resins, hence supramolecular binding interactions can occur unhindered.

By lowering the template loading on the polymer supports, whilst keeping the overall amount of template used in the DCL fixed, yields and selectivity are improved. Again, because of steric reasons host–guest interactions are favoured at the solid-liquid interface, by "diluting" the solid-phase bound template along the polymer backbone.

By using polymer-supported templates in DCL syntheses significant improvements in selectivity in the isolation or elution step have been achieved compared to the amplification under standard homogeneous conditions. Using an affinity chromatography protocol efficient and selective separations were obtained, provided that the binding affinities are in the order of 13 kJ mol^{-1} or higher, while differences in binding affinities as small as 4 kJ mol^{-1} are tolerated.

The aim of developing a polymer-supported methodology in order to increase the practicality of DCLs has been achieved. Scale-up of the reactions and exploitation via continuous flow systems are two possible applications of highly efficient polymer-supported templates. Separation of libraries after the equilibrating synthetic step is another potential application.

Experimental Section

Materials: All reagents and solvents were used as received from the suppliers, except dry tetrahydrofuran and dry dichloromethane which were obtained from a solvent purification system (SPS 400, Innovative Technologies) using alumina as drying agent, acetonitrile was distilled over CaH_2, 2,2′-azo-bis(isobutyronitrile) was recrystallised from acetone, styrene, divinylbenzene (DVB-80) and vinylbenzyl chloride (mixture of *m*- and *p*-isomers, gift from DOW Chem. Co) were passed though a silica column to remove radical inhibitors.

Analytical methods

NMR: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer at 300 K. In all spectra the residual solvent signal was used as a reference. HETCOR and COSY correlation spectra were used to assign proton and carbon signals of the products. All the NMR data is presented in the Supporting Information.

FTIR: ATR-FTIR spectra were obtained on a Perkin-Elmer 1600 Series FTIR Spectrometer, using a diamond compression cell, recording transmission spectra with a resolution of 4 cm^{-1} and a series of 16 scans. Due to the high number of absorption bands, assignment of specific functional groups are summarised in a table in the Supporting Information.

Mass spectrometry: MS data was obtained from the EPSRC National Mass Spectrometry Service centre at the University of Wales, Swansea.

Accurate mass measurements were recorded on a Finnigan MAT 900 XLT high resolution double focussing spectrometer with tandem ion trap.

Elemental microanalysis: All data were obtained from the microanalysis laboratory at Strathclyde University. Conversion data and calculations[82] are presented in the Supporting Information.

C,H,N Analysis: C, H, N are simultaneously determined in a Perkin Elmer 2400 analyser. The sample, wrapped in tin foil, is combusted at 1800 °C in pure oxygen. The combustion products are catalysed and interferences removed before being swept into the detector zone where each element is separated and eluted as CO_2, H_2O and NO_2. The signals are converted to a percentage of the elements.

Halogens (except F) analysis: The sample was combusted in an O_2 flask containing H_2O_2 and KOH as absorbent. After 30 minutes the flask was washed down with distilled water. The flask was cooled to room temperature. Absolute alcohol was then added, the solution acidified to bromophenol blue and titrated with a mercuric nitrate solution using diphenylcarbazone as indicator.

Porosimetry measurements: The porous morphology of each resin was quantified by N_2 sorption porosimetry using a Micromeritics ASAP 2000 gas adsorption instrument. The data was manipulated using the software supplied with the instrument.

Optical rotation: All optical rotation values were obtained on a Perkin Elmer Polarimeter 341, using a Na/Hal lamp set at 589 nm, with a sample cell kept at 20 °C.

Solvent-uptake tests on resins: Solvent uptake data for each resin using swelling and non-swelling solvents were determined gravimetrically and expressed as g of solvent per g of dry resin, using a sinter stick and centrifugation (3 min at 3000 rpm) to remove excess solvent.[51,83] Resins were contacted with each solvent for 3 h to allow equilibrium to be attained prior to centrifugation. The resin (0.2–0.3 g) was weighed into a glass sinter stick and 5 mL of solvent was added so as to swell the beads. The tube was sealed, left to stand for 3 h and was then placed in the centrifuge at 3000 rpm for 3 min in order to remove any excess solvent. Finally, the tube containing the swollen resin was immediately weighed and from this value the weight of solvent absorbed per gram of resin was obtained. Additional data is presented in the Supporting Information.

Optical microscopy: Optical microscopy photographs were obtained in transmission mode on a Reichert Polyvar 2 MET microscope.

DCL experiments

Analytical HPLC: Solvents used to make up solutions for DCL experiments and as eluents for HPLC analysis were: $CHCl_3$, MeOH 215, TFA and CH_3CN 230 all Romil SpS (Super Purity Solvent); DMSO Alfa Caesar 99+ %. H_2O was obtained from a Millipore purification system. The HPLC system used was an Agilent 1100 Series equipped with multiwavelength detector (signal set at 290 nm, reference at 550 nm). The following columns and conditions were used (the column heater was set at 50 °C): For *p*PF: Nucleosil, C18-symmetry, 3 μm, 4.6×100 mm: 0–12 min 40:60 to 60:40 MeCN/H_2O 1 mL min^{-1}, 12–12.1 min to 80:20 MeCN/H_2O 2 mL min^{-1}, 12.1–14 min 80:20 MeCN/H_2O 2 mL min^{-1}. For *p*PV: Waters, C18 symmetry, 3.5 μm, 4.6×75 mm: 0–8 min 40:60 to 54:56 MeCN/H_2O 1 mL min^{-1}, 8–9 min to 80:20 MeCN/H_2O 2 mL min^{-1}.

LC-MS: The experiment was performed using an Agilent LC-MSD-Trap-XCT system. The LC is an Agilent 1100 series HPLC equipped with an online degasser, binary pump, autosampler, heated column compartment and diode array detector. MS was performed using an Agilent XCT ion trap MSD mass spectrometer.

Polymer synthesis

Poly(DVB-co-VBC), **MA-1**: For the preparation of the continuous phase, the suspension stabiliser PVOH [$M_W \approx 127\,000$, Mowiol 40–88] (7.5 g) was dissolved in water at ≈50 °C after which the NaCl (33 g) was added and duly dissolved. The volume was brought to 1 L to give a 0.75% PVOH and 3.3% NaCl solution. 580 mL of this solution was then added to the 1 L parallel-sided, jacketed glass baffled reactor, fitted with a condenser, double impeller and mechanical stirrer. The volume ratio of organic phase to aqueous phase was chosen to be 1:20. The monomer phase was prepared simply by adding the monomers DVB (75%, 11.25 g, 10.28 mL) and VBC (25%, 3.75 g, 4.03 mL), AIBN (1% w/w with respect to (wrt) co-monomers, 0.15 g), and toluene (1:1 volume ratio relative to co-monomers, 14.31 mL, 12.378 g) as porogen into a small conical flask where they were stirred, and dissolved, under nitrogen. Finally the organic phase was added to the reactor, containing the continuous phase, and the stirrer started. Nitrogen gas was bubbled through the oil in water dispersion, but the needle was removed before starting the reaction. The suspension polymerisation was carried out under a nitrogen atmosphere. The temperature of reaction was set at 80 °C and the reaction allowed to proceed for 6 h. A stirrer speed of 500 rpm was used. After the reaction the aqueous solution was decanted off, the resin or beads from the suspension were then washed with water several times, then with methanol and acetone to remove any NaCl and PVOH. Where amorphous polymer fragments were observed on the bead surface under the optical microscope, these were removed by repetitive sonication–washing steps. The beads were then cleaned overnight using a Soxhlet extraction apparatus, with acetone as solvent. Finally they were dried overnight in a 40 °C vacuum oven. Yield: 12.73 g (81%) elemental analysis calcd (%) for: C 86.76, H 7.84, Cl 4.88, N 0; found: C 86.76, H 7.84, Cl 4.88, N 0.

Poly(Sty-co-DVB-co-VBC), **MA-2**: The same experimental procedure was used as for **MA-1**, but with different monomer feed: DVB (75%, 11.25 g, 12.31 mL), VBC (10%, 1.5 g, 1.40 mL) and styrene (15%, 2.25 g, 2.48 mL), AIBN (1% w/w wrt co-monomers, 0.15 g) and toluene (1:1 vol ratio wrt co-monomers, 16.18 mL, 13.996 g) as porogen. Yield: 13.55 g (90%). elemental analysis calcd (%) for: C 89.52, H 7.73, Cl 1.81, N 0; found: C 89.52, H 7.73, Cl 1.81, N 0.

Poly(DVB-co-VBC), **GT-1**: The same procedure was used as described above for **MA-1**, but the compositions of organic and aqueous phase were different. The aqueous phase was made by adding prepared solutions of PVOH [$M_W = 115\,000$ g mol^{-1}] (14 g in 700 mL H_2O) and boric acid (6 g in 175 mL). The PVOH was first dissolved in 90 °C hot water, the water topped up to 700 mL after cooling down, and only then the boric acid solution was added. 600 mL of the aqueous phase was used in the suspension polymerisation, the volume ratio of organic phase to aqueous phase was chosen to be ≈1:20. The organic phase consisted of: DVB (2.5%, 0.75 g, 0.82 mL), VBC (25%, 7.5 g, 6.98 mL), and styrene (72.5%, 21.75 g, 23.93 mL), AIBN (1% w/w wrt co-monomers, 0.3 g). Yield: 12.34 g (41%). elemental analysis calcd (%) for: C 84.77, H 7.20, Cl 5.77, N 0; found: C 84.77, H 7.20, Cl 5.77, N 0.

Poly(Sty-co-DVB-co-VBC), **GT-2**: The same experimental procedure was used as for **GT-1**, but with different monomer feed: DVB (2.5%, 0.75 g, 0.82 mL), VBC (10%, 3 g, 2.79 mL) and styrene (87.5%, 26.25 g, 28.88 mL), AIBN (1% w/w wrt co-monomers, 0.3 g). Yield: 12.29 g (41%). elemental analysis calcd (%) for: C 90.43, H 7.29, Cl 2.00, N 0; found: C 90.43, H 7.29, Cl 2.00, N 0.

Poly(Sty-co-DVB-co-3.6), **ML-1 3.6**: Compound **3.6** (80.0 mg, 16.7%), DVB (9.6 mg, 2%), styrene (389.4 mg, 81.3%) and AIBN (4.8 mg, 1% wrt co-monomers) were weighed into a 10 mL Kimax culture tube. The reagent bottle and contents were purged with N_2 for 20 minutes prior to being sealed for polymerisation. Cooling to 0 °C during the deoxygenation was necessary to reduce loss of volatile compounds due to evaporation. The polymerisation reaction was left for 24 h at 80 °C. After cooling down, the monolith could be recovered by swelling it in DCM and cutting it into smaller particles with a spatula. Alternatively the glass tube could be broken for the product recovery. Grinding up the monolith still has to be performed in its swollen gel-phase, in order to avoid large amounts of product being lost using the usual techniques of dry state grinding. The recovered particles were washed with DCM and acetone to remove any soluble material, e.g., remaining monomer or low molecular weight polymer, before being cleaned overnight using a Soxhlet extraction apparatus, with acetone as solvent. Finally they were dried overnight in a 40 °C vacuum oven. Yield: 0.42 g (83%). elemental analysis calcd (%) for: C 88.34, H 7.50, N 0.93; found: C 88.34, H 7.50, N 0.93.

Precursor synthesis

(3*R*,4S,8S,9*R*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}-6′-methoxycinchonan (1.2): To a solution of quinine **1.1** (8 g, 24.66 mmol, 324.42 g mol^{-1}) in DMF (40 mL) was added triethylamine (17.2 mL, 123.3 mmol, 101.19 g mol^{-1}, 0.726 g mL^{-1}), *tert*-butydimethylsilyl chloride (5.58 g,

36.99 mmol, 150.728 g mol^{-1}) and dimethylaminopyridine (0.301 g, 2.47 mmol, 10 mol% in quinine, 122.17 g mol^{-1}). The suspension was allowed to stir for 12 h at room temperature. The reaction was worked up by adding 50 mL toluene and washing with saturated aqueous $NaHCO_3$ (2x50 mL). The organic phase was dried over anhydrous magnesium sulfate and evaporated. The remaining brownish oil was purified by flash chromatography (silica gel, ethyl acetate/MeOH 9:1 (10% triethylamine)) to remove the excess of reagent and traces of DMAP. Yield: 10.49 g (97%) of a slightly orange syrup. R_f (ethyl acetate/MeOH/Et_3N 9:1:1) = 0.66; HRMS: m/z: calcd for $C_{26}H_{38}N_2O_2Si$: 439.2775; found: 439.2779 $[M+H]^+$.

2-[((3*R*,4*S*,8*S*,9*R*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}-6′-methoxy-10,11-dihydrocinchonan-11-yl)sulfanyl]ethanol (1.3): To **1.2** (3 g, 6.839 mmol, 438.68 g mol^{-1}) was added under nitrogen atmosphere a solution of 2-mercaptoethanol (3.84 mL, 54.71 mmol, 78.13 g mol^{-1}, 1.114 g mL^{-1}) and AIBN (0.2246 g, 1.3677 mmol, 20 mol% in 1.3, 164.21 g mol^{-1}) in $CHCl_3$ (15 mL). The mixture was refluxed for 48 h. The light yellow solution was cooled to room temperature and extracted with HCl (2 N, 2×50 mL). The separated aqueous layers were extracted with diethyl ether and then treated with NaOH pellets until the solution became basic. This was then extracted with $CHCl_3$ (3×50 mL) and the organic layers were combined and concentrated at reduced pressure. The remaining brownish oil was purified by flash chromatography (silica gel, ethyl acetate/MeOH 9:1 (10% triethylamine)) to remove the excess starting material. Yield: 2.73 g (77%) of a slightly yellow syrup. R_f (ethyl acetate/MeOH/Et_3N 9:1:1) = 0.53; HR-MS: m/z: calcd for $C_{28}H_{44}N_2O_3S$: 517.2914; found: 517.2915 $[M+H]^+$.

2-{[(3*R*,4*S*,8*S*,9*R*)-9-Hydroxy-6′-methoxy-10,11-dihydrocinchonan-11-yl]-sulfanyl}ethanol (1.4): To a solution of **1.3** (356.7 mg, 0.6902 mmol, 516.81 g mol^{-1}) in THF (5 mL) was added TBAF (2.1 mL, 2.1 mmol, 1 M). Once this had stirred for 3 h, ethyl acetate was added to the solution which was then washed with brine (4×0 mL) and dried over Mg_2SO_4. The ethyl acetate was then removed under vacuum and the resulting oil purified by flash chromatography (silica gel, ethyl acetate/MeOH 9:1→8:2 (10% triethylamine)). Yield: 72 mg (26%) of a slightly yellow powder. R_f (ethyl acetate/MeOH/Et_3N 8:2:1) = 0.35; HR-MS: m/z: calcd for $C_{22}H_{30}N_2O_3S$: 403.2050; found 403.2050 $[M+H]^+$.

(3*R*,4*S*,8*S*,9*R*)-9-{[*tert*-butyl(dimethyl)silyl]oxy}cinchonan-6′-ol (1.5): The vacuum dried **1.2** (2 g, 4.56 mmol, 438.68 g mol^{-1}) was put under nitrogen using vacuum/nitrogen cycles in a 50 mL three-necked round-bottomed flask equipped with septum, condenser, nitrogen inlet, and bubbler. L-Selectride in 1 M THF (13.68 mL, 13.68 mmol) was added under nitrogen flow. After all starting material was dissolved, the solution was heated at reflux for 48 h under nitrogen atmosphere. The reaction mixture was cooled to 0 °C with an ice bath, diluted with diethyl ether (50 mL) and very slowly quenched with H_2O. The ethereal solution was then extracted with saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate and evaporated. The yellowish oil was purified by flash chromatography (silica gel, ethyl acetate/MeOH 9:1 (10% triethylamine)) to remove leftover starting material and traces of other side products. Yield: 1.38 g (71%) of a slightly yellow solid. R_f (ethyl acetate/MeOH/Et_3N 9:1:1) = 0.55; HRMS: m/z: calcd for $C_{25}H_{36}N_2O_2Si$: 425.2619; found 425.2622 $[M+H]^+$.

2-{2-[((3*R*,4*S*,8*S*,9*R*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}cinchonan-6′-yl)-oxy]ethoxy}ethanol (1.6): Cinchonan-6′-ol **1.5** (1.5 g, 3.53 mmol, 424.65 g mol^{-1}), K_2CO_3 (2.44 g, 17.66 mmol, 138.21 g mol^{-1}) and a spatula tip of NaI were put under nitrogen. Dry CH_3CN (10 mL) was then added and the suspension was allowed to stir at room temperature for half an hour. 2-(2-Chloroethoxy)ethanol (0.41 mL, 3.88 mmol, 124.57 g mol^{-1}, 1.18 g mL^{-1}) was added before the suspension was heated at reflux under a nitrogen atmosphere for four days. After cooling to room temperature, the suspension was diluted with CH_3CN (10 mL) and filtered through celite. The CH_3CN was evaporated under vacuum, the product dissolved in CH_2Cl_2 and washed with saturated hydrogen carbonate. The organic phase was then dried using Mg_2SO_4 and evaporated. The brown solid was purified by flash chromatography (silica gel, ethyl acetate/MeOH 10:0→9:1 (10% triethylamine)) to remove leftover starting material and other side products. Yield: 0.95 g (54%) of a slightly yellow viscous syrup. R_f (ethyl acetate/MeOH/Et_3N 8:2:1) = 0.73; $[\alpha]_D^{20}$ $[\alpha]_D^{20}$ = −9.39 (c = 0.20 g mL^{-1} in CH_2Cl_2); HRMS: m/z: calcd for $C_{29}H_{44}N_2O_4Si$: 513.3143; found: 513.3145 $[M+H]^+$.

(3*R*,4*S*,8*R*,9*S*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}-6′-methoxycinchonan (2.2): Compound **2.2** was prepared according to the same procedure as compound **1.2**, using quinidine **2.1** (16 g, 49.32 mmol, 324.42 g mol^{-1}) in DMF (75 mL), triethylamine (34.4 mL, 246.59 mmol, 101.19 g mol^{-1}, 0.726 g mL^{-1}), *tert*-butyldimethylsilyl chloride (11.15 g, 73.98 mmol, 150.728 g mol^{-1}) and dimethylaminopyridine (0.6025 g, 4.932 mmol, 10 mol% in quinidine, 122.17 g mol^{-1}). Yield: 21 g (97%) of a slightly orange honey-like product. R_f (ethyl acetate/MeOH/Et_3N 9:1:1) = 0.68; HRMS: m/z: calcd for $C_{26}H_{38}N_2O_2Si$: 439.2775; found 439.2778 $[M+H]^+$.

(3*R*,4*S*,8*R*,9*S*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}cinchonan-6′-ol (2.3): Compound **2.3** was prepared according to the same procedure as compound **1.5**, using **2.2** (20 g, 45.59 mmol, 438.68 g mol^{-1}) and L-Selectride in 1 M THF (136.77 mL, 136.77 mmol). Yield: 13.75 g (71%) of a slightly yellow solid. R_f (ethyl acetate/MeOH/Et_3N 9:1:1) = 0.55; HRMS: m/z: calcd for $C_{25}H_{36}N_2O_2Si$: 425.2619; found 425.2623 $[M+H]^+$.

2-{2-[((3*R*,4*S*,8*R*,9*S*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}cinchonan-6′-yl)-oxy]ethoxy}ethanol (2.4): Compound **2.4** was prepared according to the same procedure as compound **1.6**, using **2.3** (13 g, 30.61 mmol, 424.65 g mol^{-1}), K_2CO_3 (21.16 g, 153.07 mmol, 138.21 g mol^{-1}), a spatula tip of NaI, dry CH_3CN (80 mL), and 2-(2-chloroethoxy)ethanol (4.19 mL, 33.67 mmol, 124.57 g mol^{-1}, 1.18 g mL^{-1}). Yield: 8.79 g (56%) of a slightly yellow viscous syrup. R_f (ethyl acetate/MeOH/Et_3N 8:2:1) = 0.73; $[\alpha]_D^{20}$ = +9.39 (c = 0.20 g mL^{-1} in CH_2Cl_2); HRMS: m/z: calcd for $C_{29}H_{44}N_2O_4Si$: 513.3149; found 513.3150 $[M+H]^+$.

2-(2-{[(3*R*,4*S*,8*R*,9*S*)-9-Hydroxycinchonan-6′-yl]oxy}ethoxy)ethanol (2.5): To a solution of **2.4** (500 mg, 0.9751 mmol, 512.76 g mol^{-1}) in THF (3 mL) was added a tetrabutylammonium fluoride solution in THF (2.93 mL, 2.93 mmol, 1 M). Once this had stirred for 12 h, ethyl acetate was added to the solution which was then washed with brine (4x30 mL) and dried over a lot of Mg_2SO_4 to remove most of the remaining tetrabutylammonium salt. The ethyl acetate was then removed under vacuum and the resulting oil purified by flash chromatography (silica gel, ethyl acetate/MeOH 9:1→8:2 (10% triethylamine)). Yield: 185 mg (48%) of a white powder. R_f (ethyl acetate/MeOH/Et_3N 8:2:1) = 0.43; HRMS: m/z: calcd for $C_{23}H_{31}N_2O_4$: 399.2284; found 399.2290 $[M+H]^+$.

(3*R*,4*S*,8*R*,9*S*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}-6′-methoxy-10,11-dihydrocinchonan (3.2): Compound **3.2** was prepared according to the same procedure as compound **1.2**, using 10,11-dihydroquinidine **3.1** (10.5 g, 32.17 mmol, 326.44 g mol^{-1}) in DMF (50 mL), triethylamine (22.6 mL, 160.83 mmol, 101.19 g mol^{-1}, 0.726 g mL^{-1}), *tert*-butyldimethylsilyl chloride (7.27 g, 48.25 mmol, 150.73 g mol^{-1}), dimethylaminopyridine (0.393 g, 3.217 mmol, 10 mol% in dihydroquinidine, 122.17 g mol^{-1}). Yield: 12.56 g (89%) of a slightly orange syrup. R_f (ethyl acetate/MeOH/Et_3N 9:1:1) = 0.79; HRMS: m/z: calcd for $C_{26}H_{40}N_2O_2Si$: 441.2932; found: 441.2931 $[M+H]^+$.

(3*R*,4*S*,8*R*,9*S*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}-10,11-dihydrocinchonan-6′-ol (3.3): Compound **3.3** was prepared according to the same procedure as compound **1.5**, using **3.2** (11.92 g, 27.04 mmol, 440.69 g mol^{-1}) and L-Selectride in THF (81.1 mL, 81.1 mmol, 1 M). Yield: 8.68 g (75%) of a slightly yellow solid. R_f (ethyl acetate/MeOH/Et_3N 9:1:1) = 0.50; HRMS: m/z: calcd for $C_{25}H_{38}N_2O_2Si$: 427.2775; found 427.2771 $[M+H]^+$.

2-{2-[((3*R*,4*S*,8*R*,9*S*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}-10,11-dihydrocinchonan-6′-yl)oxy]ethoxy}ethanol (3.4): Compound **3.4** was prepared according to the same procedure as compound **1.6**, using **3.3** (8.06 g, 18.91 mmol, 426.67 g mol^{-1}), K_2CO_3 (13.05 g, 94.54 mmol, 138.21 g mol^{-1}), dry CH_3CN (120 mL) and 2-(2-chloroethoxy)ethanol (2.19 mL, 20.78 mmol, 124.57 g mol^{-1}, 1.18 g mL^{-1}). Yield: 5.51 g (62%) of a slightly orange syrup. R_f (ethyl acetate/MeOH/Et_3N 9:1:1) = 0.55; $[\alpha]_D^{20}$ = +13.30 (c = 0.20 g mL^{-1} in CH_2Cl_2); HRMS: m/z: calcd for $C_{29}H_{46}N_2O_4Si$: 515.3000; found 515.3302 $[M+H]^+$.

2-{2-[((3*R*,4*S*,8*R*,9*S*)-9-{[*tert*-butyl(dimethyl)silyl]oxy}-10,11-dihydrocinchonan-6′-yl)oxy]ethoxy}ethyl 2-methylacrylate (3.5): A solution of **3.4** (3.5 g, 6.80 mmol, 514.77 g mol^{-1}) in dry THF (40 mL) was cooled to 0 °C under N_2. Triethylamine (9.56 mL, 67.99 mmol, 101.19 g mol^{-1},

0.726 g mL^{-1}), dimethylaminopyridine (83.1 mg, 0.680 mmol, 10 mol% in **3.4**, 122.17 g mol^{-1}) and methacroyl chloride (3.32 mL, 33.40 mmol, 104.54 g mol^{-1}, 1.07 g mL^{-1}) were added and the reaction mixture stirred at 0°C for 30 min, followed by room temperature overnight. The reaction was worked up by quenching excessive acid chloride with a saturated $NaHCO_3$ solution (10 mL), following by addition of toluene (100 mL) and washing with saturated $NaHCO_3$ (2×50 mL). The organic phase was dried over anhydrous magnesium sulfate and evaporated. The remaining brownish oil was purified by flash chromatography (silica gel, ethyl acetate/MeOH 10:0→9:1 (10% triethylamine)). Yield: 3.04 g (77%) of an off-white powder. R_f (ethyl acetate/MeOH/Et_3N 9:1:1) = 0.65; HRMS: *m/z*: calcd for $C_{33}H_{50}N_2O_5Si$: 583.3562; found 583.3556 $[M+H]^+$.

2-(2-{[(3*R*,4*S*,8*R*,9*S*)-9-Hydroxy-10,11-dihydrocinchonan-6′-yl]oxy}-ethoxy)ethyl 2-methylacrylate (3.6): Compound **3.6** was prepared according to the same procedure as compound **2.5**, using **3.5** (3.01 g, 5.17 mmol, 582.85 g mol^{-1}) in THF (15 mL) and a tetrabutylammonium fluoride solution in THF (15.5 mL, 15.5 mmol, 1 M). Yield: 1.51 g (62%) of a slightly yellow powder. R_f (ethyl acetate/MeOH/Et_3N 9:1:1) = 0.24; HRMS: *m/z*: calcd for $C_{27}H_{36}N_2O_5$: 469.2697; found 469.2701 $[M+H]^+$.

Template attachment to polymer resins and reactions on polymer supports

MA-X/GT-X 2.4 (Table 6): NaH (60%, suspension in oil) was dispersed under N_2 in THF (3 mL) using magnetic stirring in 10 mL microwave reactor vessels. The latter were employed simply as safe pressure vessels, but reactions were *not* subjected to microwave irradiation. After 10 min the NaH was allowed to settle down and the THF decanted. This washing step was repeated once so that most of the mineral oil on the NaH was removed. The magnetic stirrer was also taken out of the vessels.

THF (2.5 mL) and quinidine derivative **2.4** were added under N_2 and the vessels sealed. After 30 min at room temperature, the reaction was heated up to 50°C until no gas formation could be observed. The resin **MA-X** or **GT-X** was added under N_2 and the suspension heated up to 80°C in the closed reactor vessel for 72 h. For gel-type resins additional dry THF had to be added, only so much to cover the beads with a bit of an excess of solvent. After the reaction the beads turned from white opaque to a brownish colour. They were decanted and washed twice successively with 15 mL of each of the following solvents: THF, THF/H_2O (1:1), THF, acetone, MeOH, CH_2Cl_2. The product was finally cleaned by overnight Soxhlet extraction with acetone and afterwards dried in a 40°C vacuum oven. elemental analysis calcd (%) for: **MA-1 2.4A**: C 84.53, H 7.57, Cl 1.91, N 1.23; found: C 84.53, H 7.57, Cl 1.91, N 1.23; **MA-1 2.4B**: calcd for C 85.75, H 7.91, Cl 3.06, N 0.57; found: C 85.75, H 7.91, Cl 3.06, N 0.57; **MA-2 2.4**: calcd for C 89.25, H 7.36, Cl 0.95, N 0.48; found: C 89.25, H 7.36, Cl 0.95, N 0.48; **GT-1 2.4**: calcd for C 83.49, H 7.17, Cl 0, N 2.12; found: C 83.49, H 7.17, Cl 0, N 2.12; **GT-2 2.4**: calcd for C 88.42, H 7.59, Cl 0, N 1.01; found: C 88.42, H 7.59, Cl 0, N 1.01.

MA-X/GT-X 1.6 (Table 7): The same procedure was followed as described above using quinine **1.6**. elemental analysis calcd (%) for: **MA-1 1.6**: calcd for: C 85.23, H 8.02, Cl 2.53, N 1.03; found: C 85.23, H 8.02, Cl 2.53, N 1.03; **MA-2 1.6**: calcd for C 87.24, H 7.71, Cl 1.29, N 0.47; found: C 87.24, H 7.71, Cl 1.29, N 0.47; **GT-2 1.6**: calcd for: C 87.82, H 7.74, Cl 1.41, N 0.93; found: C 87.82, H 7.74, Cl 1.41, N 0.93.

Table 6. **MA-X/GT-X 2.4.**

	Template **2.4**		NaH in oil		**MA-X/GT-X**		
MA-1 2.4A	1.333 g	2.6 mmol	114.4 mg	2.860 mmol	1.0 g	1.30 mmol Cl	1.30 mmol Cl g^{-1}
MA-1 2.4B[a]	788 mg	1.537 mmol	67.9 mg	1.691 mmol	591.1 mg	0.768 mmol Cl	1.30 mmol Cl g^{-1}
MA-2 2.4	400 mg	0.780 mmol	34.3 mg	0.858 mmol	600.1 mg	0.390 mmol Cl	0.65 mmol Cl g^{-1}
GT-1 2.4	400 mg	0.780 mmol	34.3 mg	0.858 mmol	240.8 mg	0.390 mmol Cl	1.62 mmol Cl g^{-1}
GT-2 2.4	300 mg	0.586 mmol	25.8 mg	0.644 mmol	522.8 mg	0.293 mmol Cl	0.56 mmol Cl g^{-1}

[a] Reaction time was only 48 h.

Table 7. **MA-X/GT-X 1.6.** The same procedure was followed as described above using quinine **1.6**.

	Template **1.6**		NaH		**MA-X/GT-X**		
MA-1 1.6	300 mg	0.586 mmol	25.8 mg	0.644 mmol	225.2 mg	0.293 mmol Cl	1.30 mmol Cl g^{-1}
MA-2 1.6	300 mg	0.586 mmol	25.8 mg	0.644 mmol	574.1 mg	0.293 mmol Cl	0.51 mmol Cl g^{-1}
GT-2 1.6	573.8 mg	1.12 mmol	49.3 mg	1.232 mmol	1 g	0.56 mmol Cl	0.56 mmol Cl g^{-1}

Table 8.

		MA-X/GT-X 2.4	
MA-1 2.5A	1.076 g	0.473 mmol **2.4**	0.44 mmol **2.4** g^{-1}
MA-1 2.5B	660 mg	0.132 mmol **2.4**	0.20 mmol **2.4** g^{-1}
MA-2 2.5	567 mg	0.096 mmol **2.4**	0.17 mmol **2.4** g^{-1}
GT-1 2.5	305 mg	0.232 mmol **2.4**	0.76 mmol **2.4** g^{-1}
GT-2 2.5	586 mg	0.211 mmol **2.4**	0.36 mmol **2.4** g^{-1}
		MA-X/GT-X 1.6	
MA-1 1.7	210 mg	0.078 mmol **1.6**	0.37 mmol **1.6** g^{-1}
MA-2 1.7	537 mg	0.091 mmol **1.6**	0.17 mmol **1.6** g^{-1}
GT-2 1.7	1 g	0.33 mmol **1.6**	0.33 mmol **1.6** g^{-1}

MA-X/GT-X 2.5 and MA-X/GT-X 1.7 (Table 8): **MA-X/GT-X 2.4** or **MA-X/GT-X 1.6** were weighed into 8 mL glass vials and 5 mL TBAF in THF (1 M) added. The vials were then sealed and put on flatbed rollers for 24 h at room temperature. After the reaction the polymer resin was decanted and washed twice successively with 15 mL of each of the following solvents: THF, THF/H_2O (1:1), THF, acetone, MeOH, CH_2Cl_2. The product was finally cleaned by overnight Soxhlet extraction with acetone and afterwards dried in a 40°C vacuum oven. elemental analysis calcd (%) for: **MA-1 2.5A**: C 85.06, H 7.91, Cl 1.99, N 1.31; found: C 85.06, H 7.91, Cl 1.99, N 1.31; **MA-1 2.5B**: calcd for C 86.26, H 7.76, Cl 3.0, N 0.64; found: C 86.26, H 7.76, Cl 3.0, N 0.64; **MA-2 2.5**: calcd for C 89.19, H 7.61, Cl 1.29, N 0.50; found: C 89.19, H 7.61, Cl 1.29, N 0.50; **GT-1 2.5**: calcd for: C 83.56, H 7.37, Cl 0, N 2.15; found: C 83.56, H 7.37, Cl 0, N 2.15; **GT-2 2.5**: calcd for: C 88.66, H 7.46, Cl 0, N 0.98; found: C 88.66, H 7.46, Cl 0, N 0.98; **MA-1 1.7**: calcd for: C 85.90, H 7.63, Cl 2.49, N 0.96; found: C 85.90, H 7.63, Cl 2.49, N 0.96; **MA-2 1.7**: calcd for C 89.11, H 7.71, Cl 1.19, N 0.42; found: C 89.11, H 7.71, Cl 1.19, N 0.42; **GT-2 1.7**: calcd for C 88.00, H 6.87, Cl 2.91, N 0.91; found: C 88.00, H 6.87, Cl 2.91, N 0.91.

Acknowledgements

We are grateful to Dr. Ana Belenguer for valuable assistance with the HPLC analyses, the EPSRC National Mass Spectrometry Service Centre, Swansea, for mass measurements and to the EPSRC (P.B.) and the Royal Society (S.O.) for financial support.

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Received: February 21, 2008
Published online: August 27, 2008

