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Report

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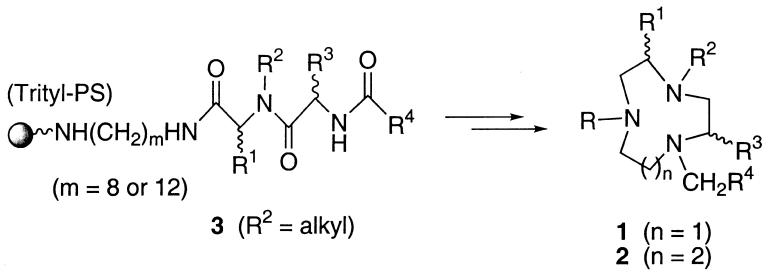

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General Solid-Phase Approach to the Synthesis of Chiral Triazacycloalkane Ligands with Stereogenic Backbone Substituents

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Macrocyclic polyamines generate continuous interest because of their biological properties and their importance in coordination chemistry.[1] In particular, triazacycloalkanes such as derivatives of 1,4,7-triazacyclononane (tacn) constitute a sought-after class of tridentate ligands for coordinating various cations including transition metals (Figure 1). Triazacyclononane complexes with manganese have been used as effective catalysts for alkene epoxidation,[2] while complexes with other metals (mainly with copper and zinc) and manganese have been designed as sensors,[3] as active site mimetics of redox metalloenzymes such as catalase and superoxide dismutase,[4] and as cleaving agents for phosphate esters[5] including DNA[6] and RNA.[7]

Although the elaboration of simple triazacycloalkanes by varying the exocyclic, pendent nitrogen substituents can be accomplished using well-established methods,[8] the synthesis of chiral derivatives with substituents on the stereotopic backbone carbons is considerably more difficult to envisage. Recently, Kim and co-workers have reported a solution-phase approach based on the use of chiral aziridines as building blocks.[9] However, a general solid-phase route to chiral triazacycloalkanes has remained elusive despite their enormous potential in combinatorial asymmetric catalysis and medicinal chemistry. Herein, we describe our preliminary efforts to develop a general solid-phase approach to the synthesis of "chiral-backbone" triazacyclononanes **1** and triazacyclodecanes **2** (Figure 1). This modular approach is potentially amenable to the elaboration of parallel libraries of chiral triazacycloalkane ligands embodying as many as four sites of diversity (R^1-R^4) including two stereogenic centers.

We envisaged that resin-bound acyclic precursors **4** could be accessed from our solid-phase peptide reduction protocol involving the use of borane followed by a mild oxidative workup with iodine in buffered organic media (Scheme 1).[10] These intermediates, which feature a central tertiary amine center ($R^2 \neq H$) flanked by two secondary amines located two carbons away, would be derived from the reduction of acylated dipeptides **3** containing an *N*-alkylamino acid as the first residue. The reduction process is essentially epimerization-free[10] and would thus provide optically pure material. Ring formation via alkylation and cyclization of the secondary amines with the bis(triflate)s of 1,2-ethanediol and 1,3-propanediol would afford the respective triazacyclononanes **1** and triazacyclodecanes **2** after cleavage from the resin.[9a]

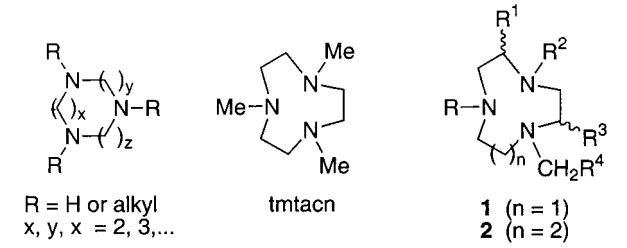
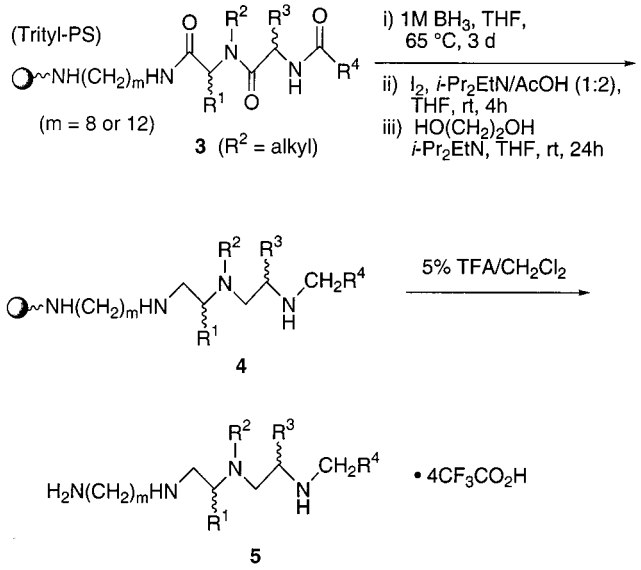


Figure 1. Generic structure of triazacycloalkanes, trimethyltriazacyclononane (tmtacn), and the chiral triazacyclononanes (**1**) and triazacyclodecanes (**2**) reported herein.

Scheme 1



The acylated dipeptide precursors **3** were synthesized on tritylpolystyrene resin (1% DVB, 1.3 mmol/g) as described previously.[10] The very hindered aminotrityl anchor site on the diamine spacer is not expected to react with the bis(triflate) reagents. In addition, to avoid competitive attack at the anchor site in the second cyclative alkylation, long diaminoalkyl spacers with 8 and 12 methylenes were employed. We have previously shown that the reduction of triamides containing a central tertiary amide tends to give putative aminoborane intermediates after the oxidative workup.[10] These robust intermediates require further treatment for quantitative boron extrusion in order to afford the free oligoamine. Toward this end, the use of ethylene glycol under basic conditions is advised as part of the workup following the oxidative step. Alternatively, the use of Houghten's reduction protocol ($BH_3/B(OMe)_3/B(OH)_3$ mixture followed by piperidine treatment)[11] precluded the use of ethylene glycol and provided material of comparable purity. To ascertain the identity and high homogeneity of the resin-bound cyclization precursors, samples of resin **4** were cleaved with dilute trifluoroacetic acid and the resulting tetraamine tetrakis(trifluoroacetate) salts **5** were analyzed by NMR and HPLC (Scheme 1). The cyclization of resin-bound triamines **4** by slow addition of freshly prepared 1,2-

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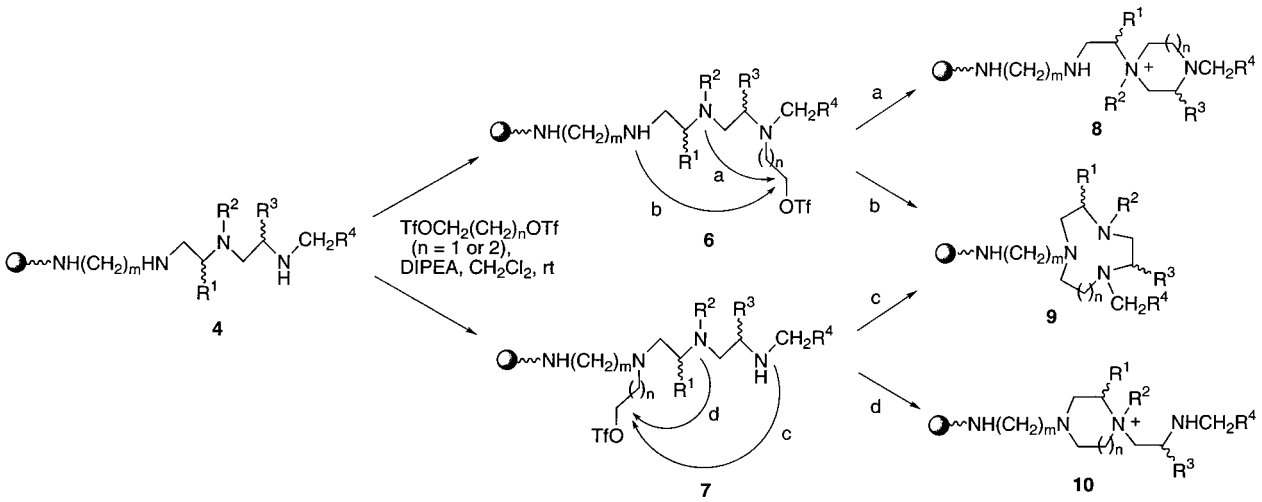
Scheme 2



ethanediol bis(triflate) (Scheme 2, $n = 1$) afforded the desired triazacyclononanes **1** after acidolytic cleavage of **9** from the resin (5% CF_3CO_2H/CH_2Cl_2). As opposed to reported examples on the corresponding solution-phase approach,[9a] we found no evidence for interchain cross-alkylation in these cyclization reactions. This interesting observation, which may be explained by partial site isolation of the individual triamine chains on the polymer support, highlights a major benefit of the solid-supported approach. The crude material cleaved off the resin, however, was accompanied by variable amounts of the isomeric quaternized piperazines originating from **8**/**10**. Apparently, from the two possible monoalkylated intermediates **6** and **7**, quaternization of the central amine to form a six-membered ring competes with the attack of a less hindered secondary amine to form a rather unfavored nine-membered medium ring (**9**) via pathways b and c. Irrespective of the presence of potential epimers at the quaternary piperazinium nitrogen, it appears that one of two possible quaternized side products **8** and **10** forms preferentially from the corresponding cyclization pathways a and d. We tentatively assign it to be **10** because it would result from the first alkylation intermediate **7** originating from attack of TfO-$(CH_2)_2$OTf at the least hindered secondary amine of **4**. After cleavage from the resin, the undesired piperazinium product can be eliminated from the mixture by semipreparative HPLC to afford triazacyclononanes **1** in a high level of purity.[12] Unambiguous evidence for distinguishing supported compounds **9** and **10** came from chemical control experiments. As exemplified for **1b** in Scheme 3, acetylation of the resin mixture **9b**/**10b** prior to the cleavage step led to a crude mixture containing monoacetylayed piperazinium derivative **12b** and intact triazacyclononane **1b**.[13] The two products are easily distinguishable by comparing their retention times and peak mass with those observed for the non-acetylated mixture **1b**/**11b** by HPLC−ES-MS (see Supporting Information). To demonstrate the generality of this approach, four chiral triazacyclononane derivatives **1a**−**1d** were synthesized and purified, including two compounds (**1a** and **1b**) embodying a reduced proline residue (see Table 1 and Figure 2). In fact, according to HPLC−UV analysis of the crude material, the latter residue led to higher proportions of the desired product compared to the N-methylated phenylalanine, which provided about equimolar amounts of the undesired piperazinium

Scheme 3

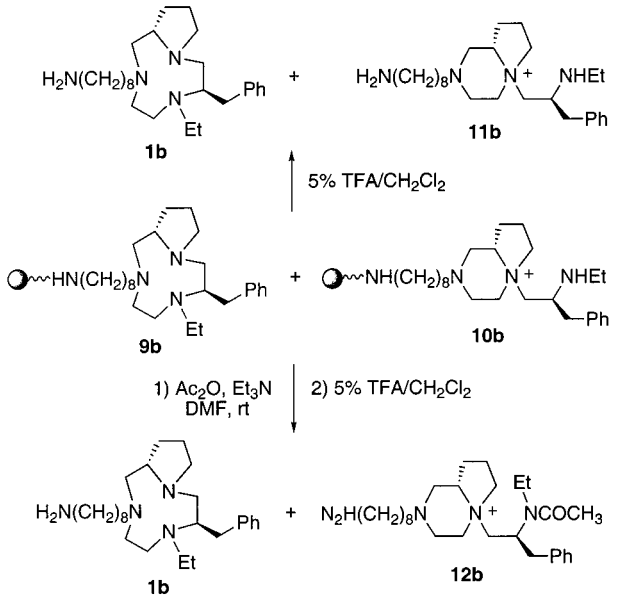


Table 1. Preparation of Chiral Triazacycloalkanes **1** and **2** (Structures Shown in Figure 2)[a]

entry	spacer (*m*)	AA1	AA2	*n*	product	yield[b] (%)	ratio[c]
1	12	L-Pro	D-Phe	2	**1a**	61	3:1
2	8	L-Pro	D-Phe	2	**1b**	70	2.5:1
3	8	L-NMePhe	D-Phe	2	**1c**	72	1:1
4	8	L-NMePhe	L-Ala	2	**1d**	73	1:1.4
5	8	L-NMePhe	D-Phe	3	**2a**	88	>10:1
6	8	L-NMeLeu	D-Leu	3	**2b**	72	7:2
7	8	L-Pro	D-Phe	3	**2c**	85	9:1

[a] Reactions were conducted according to Schemes 1 and 2. See Supporting Information section for detailed conditions. [b] Nonoptimized weight yields of crude products isolated as tetrakis(trifluoroacetate) salts directly after cleavage from the resin. [c] Ratio of triazacycloalkane product (**1** or **2**) to quaternary ammonium byproduct estimated by HPLC analysis (both ES-MS and UV at 210 and 250 nm).

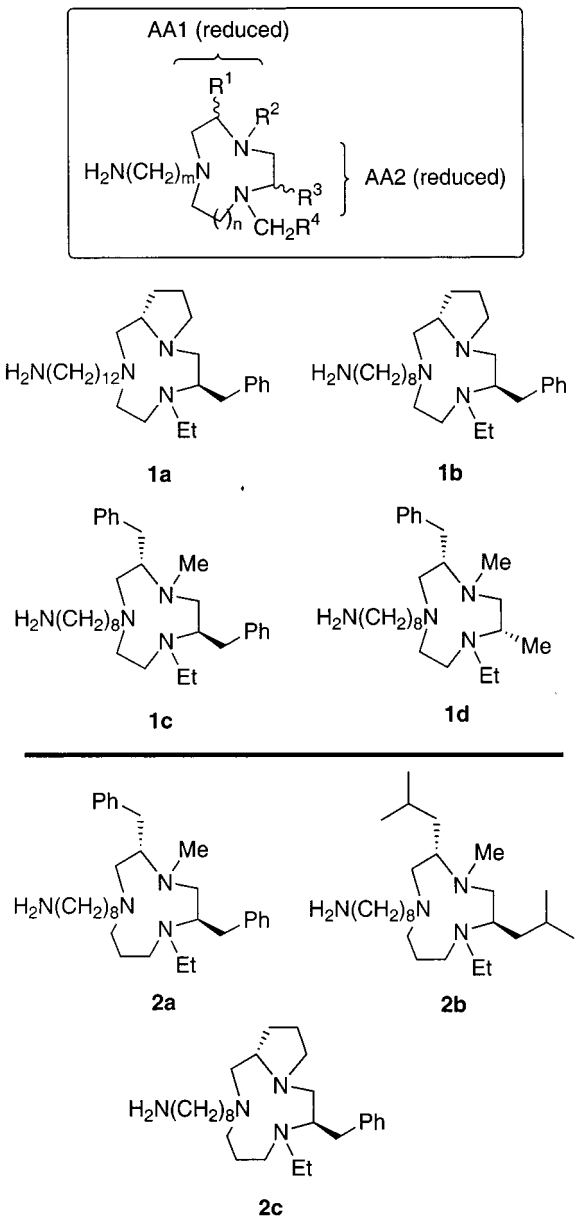


Figure 2. Chemical structures of chiral triazacyclononanes **1a**−**1d** and triazacyclodecanes **2a**−**2c** (see Table 1 for more details).

product (see Table 1). Although the R^4 position constitutes another potentially diversifiable site, for simplification purposes only, acetyl (R^4 = Me in Schemes 1 and 2) was used as the peptide end-group in all cases reported herein.

In contrast with the triazacyclononanes **1**, the formation of triazacyclodecane products **2** by using 1,3-propanediol bis(triflate) as the tethering agent led to crude products of higher purity containing only little of the cyclic seven-membered quaternary ammonium byproducts (Table 1, entries 5−7). In this system, competition between seven-membered and 10-membered ring formation clearly favored the latter (Scheme 2, $n = 2$). All reported chiral triazamacrocycles **1** and **2** shown in Figure 2 were purified by semipreparative HPLC and characterized as tetrakis(trifluoroacetate) salts by NMR and MS. Although the isolated yields after purification were low (in the 15−25% range overall from dipeptides **3**), in part due to a conservative selection of chromatography fractions, the final products showed a high level of homogeneity (>90−95%) as monitored by HPLC under both ES-MS and UV detection. If required for further applications, the primary amine at the resin anchor site can be neutralized as an amide cap. This was demonstrated by the acetylation of crude triazacyclodecane **2b**, followed by purification of the resulting amide that was obtained in >95% homogeneity (Figure 3).

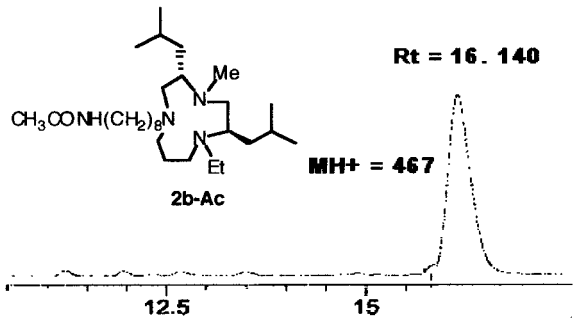


Figure 3. HPLC−ES−MS chromatogram of purified acetylated derivative **2b-Ac** (see Supporting Information for detailed conditions).

In summary, we have described an efficient and general solid-phase synthetic route to "chiral-backbone" triazacycloalkane ligands from simple end-acylated dipeptides. Whereas the triazacyclodecane ligands (**2**) are generally obtained in high crude purity after cleavage from the support, the lower homologues triazacyclononanes (**1**) required careful purification to eliminate the quaternary piperazinium side product. The latter are formed by competitive cyclization onto the central tertiary amine of the acyclic precursors. Although a more efficient access to the triazacyclononanes may be desirable, this solid-phase approach is nonetheless suitable toward the preparation of parallel libraries of highly diverse, chiral triazacycloalkane ligands.

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Supporting Information Available. General experimental section with characterization data (NMR, MS) and spectral reproductions for all triazacycloalkanes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Control experiments with tmtacn have confirmed that the ring's tertiary amines are not acylated under these conditions.

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