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N-Cyanomethyl-β-chloro amines: chiral building blocks for the synthesis of azacrown ethers

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Abstract—(1*R*,2*S*)-Ephedrine and norephedrine derived *N*-cyanomethyl-β-chloro amines react with tri-, tetra- and penta-ethylene glycol to stereoselectively give the corresponding amino ethers. Further transformation into chiral monoaza 12-, 15- and 18-crown-4, -5 and -6 ethers was realized in three steps and good overall yields by: (i) mesylation, (ii) deprotection of the *N*-cyanomethyl group and (iii) intramolecular alkylation. Binding affinities of these azacrown ethers for alkali cations was studied by FAB-MS.

Chiral cryptands have recently found a growing number of applications in many fields such as enantioselective catalysis,[1] selective transport of enantiomers[2] and enantiomeric differentiation.[3] Enantiopure β-amino alcohols being among the most widely used members of the chiral pool,[4] one would expect their incorporation in many azamacrocycles. Surprisingly, a careful examination of the literature shows that they have only been scarcely used for the preparation of azacrownethers in which they systematically act either as *N*,*N*-bis nucleophiles, which lead to a chiral azamacrocycle bearing the chirality outside the ring or as *N*,*O*-bis nucleophile, that gives access to macrocycles possessing the chirality within the ring (Fig. 1).[5]

We recently reported that amino alcohols-derived *N*-cyanomethyl-β-chloroamines act as efficient, easy to use and readily available building blocks for the synthesis of chiral amino ethers or diamines by their simple reaction with alcohols and amines, a reaction that was shown to proceed via an aziridinium intermediate.[6] In this letter, we report the use of these chiral synthons for the efficient preparation of azacrown ethers. This strategy is completely different from those reported in the sense that the amino alcohol now acts as both an electrophilic and nucleophilic partner. This results in a highly efficient formation of the macrocycle with no modification of the absolute and relative configuration of the starting amino alcohol. Importantly, this procedure allows for

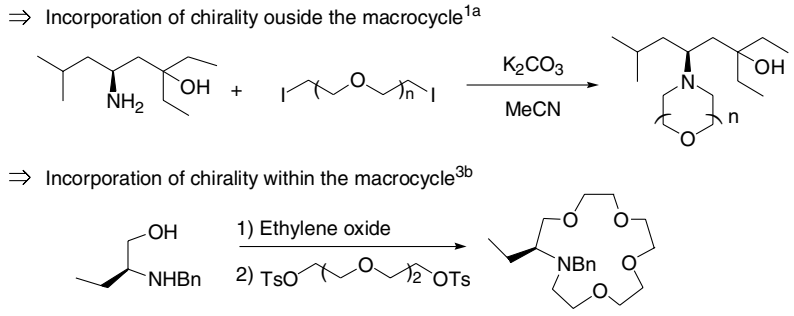

Figure 1. Use of chiral amino alcohols as bis-nucleophiles in azacrown synthesis: the possibilities.

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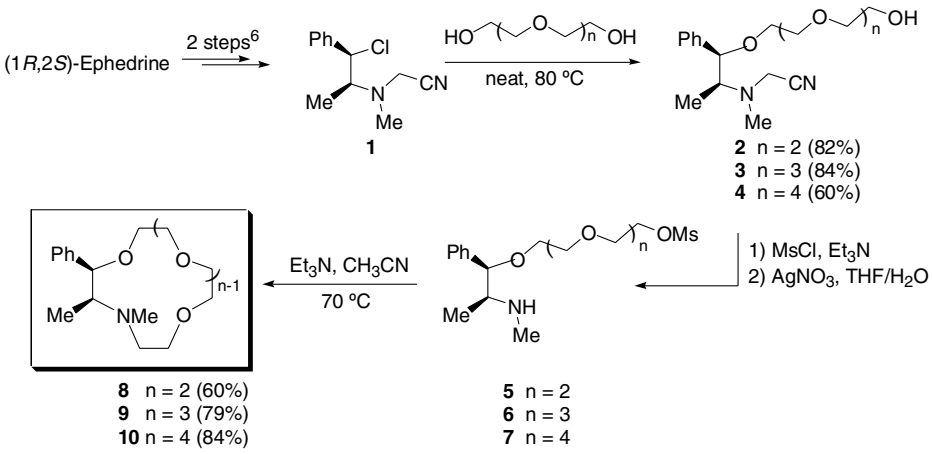


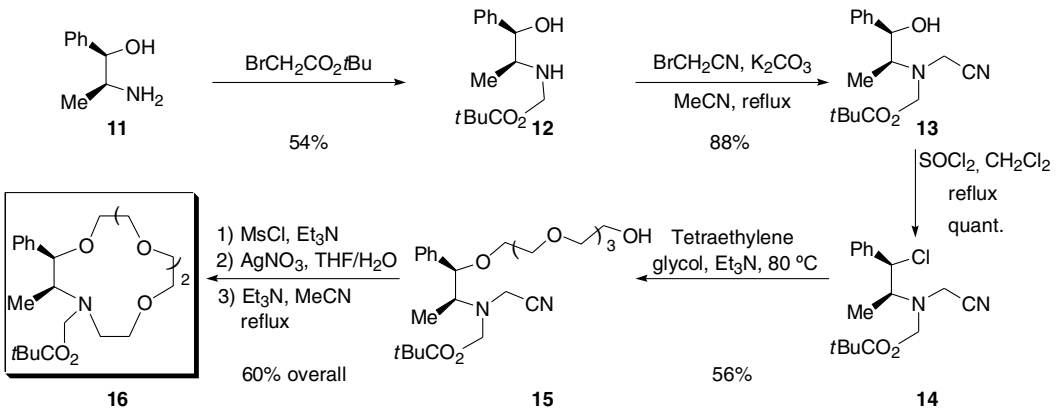
Scheme 1. Ephedrine-derived azacrown ethers.

the use of highly substituted aminoalcohols which would typically act as poor nucleophiles. Using this protocol, ephedrin-derived aminoalcohols, which are inexpensive and available in both enantiomeric forms, can therefore be incorporated in the macro- cyclic core of azacrown ethers.

The first step of our synthesis consists in the neat reaction of **1** with tri-, tetra- or penta-ethylene glycol at 80 °C: in fair to good yields, the corresponding ethers **2**–**4** were obtained with retention of configuration at the reacting centre.[7] Activation of the primary alcohol as a mesylate was then followed by deprotection of the *N*-cyanomethyl protecting group using silver nitrate in a H_2O/THF solvent mixture. Intramolecular alkylation was finally initiated by treating the crude amine with triethylamine in acetonitrile at 80 °C: to our delight, the desired azamacrocycles **8**–**10** were obtained in good overall yields (Scheme 1).[8]

Key features of these syntheses are their straightforwardness and their easy scale up. Interestingly, the yield of the cyclization increases with the size of the ring formed during the process. Moreover, the dilution did not have a pronounced effect on this cyclization since tri- and tetra-ethylene glycols were used as solvents in the first step (typically 20 mL/g) and the more expensive penta-ethylene glycol was used only in twofold molar excess (2 mL/1.5 g) without a severe drop of the yield; if the cyclization step was quite sluggish (typically 5 days), it did not require high dilution to avoid side reactions.

We next wanted to further test our reaction sequence and to determine whether another functionalized/functionalizable group could be introduced on the nitrogen atom without affecting its overall efficiency or not. Therefore, (1*R*,2*S*)-norephedrine **11** was selectively monoalkylated with *t*-butylbromoacetate ($BrCH_2CO_2$-*t*-Bu, DBU, toluene, rt), which was followed by introduction of the *N*-cyanomethyl protecting group by alkylation with bromoacetonitrile. The resulting amino alcohol **13** was chlorinated to give **14** with retention of configuration as previously demonstrated for related substrates,[9] which was next reacted with tetra-ethylene glycol. Using the conditions described above, ether **15** was isolated in only 33% yield, which was attributed to a partial cleavage of the *t*-butyl ester by the hydrochloric acid released during the process. Addition of triethylamine thus allowed to limit this side reaction, improving the yield to 56%. Mesylation, deprotection and final ring-closure were next conducted using the



Scheme 2. Norephedrine-derived azacrown ethers: functionalized azacrown.

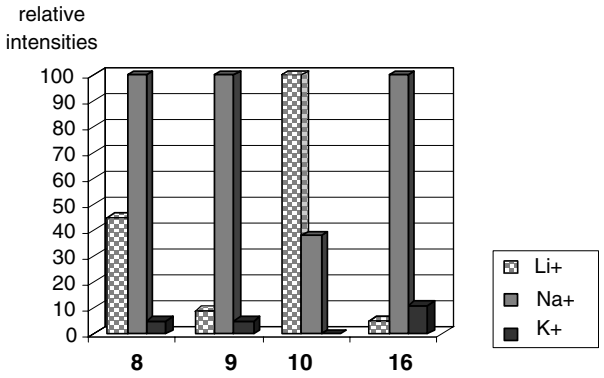


Figure 2. Relative binding affinities of macrocycles **8**–**10** and **16** for alkali cations. Conditions: macrocycle (10^{-5} M in acetonitrile/H_2O: 9/1) was complexed with equimolar amounts of LiCl, NaCl and KCl (10^{-7}, 2×10^{-7} and 10^{-6} M each in acetonitrile/H_2O: 9/1). Values reported in the graph are an average of the peak intensities for MS spectra recorded for these three concentrations.

conditions optimized for the ephedrine-derived substrates and gave the functionalized macrocycle **16**. The presence of the additional bulky *t*-butyl ester was found to slow down the rate of the cyclization reaction (10 days vs 5 days for the cyclization to **9**) but a fair 60% yield of **16** was still obtained (Scheme 2).

Binding abilities of macrocycles **8**–**10** and **16** for Li^+, Na^+ and K^+ cations were next determined using the FAB-MS competition technique. Data obtained with this technique are collected in Figure 2 where relative peak intensities of [macrocycle + metal]$^+$ ions reflect the relative cation binding affinities.[10]

Quite unexpectedly, increasing the ring size resulted in a higher affinity for the lithium cation (compare **8** and **10**). However, modifying the *N*-substituent did not affect a very good binding selectivity for the sodium cation (compare **9** and **16**).

Finally, NMR data of **8** displayed an unexpected feature: we found that the resolution of the ^{1}H NMR spectrum of **8** in $CDCl_3$ at rt was dependent on the concentration of the sample: while sharp well-resolved signals were recorded at *high* concentration (0.3 mol L^{-1}), the spectrum

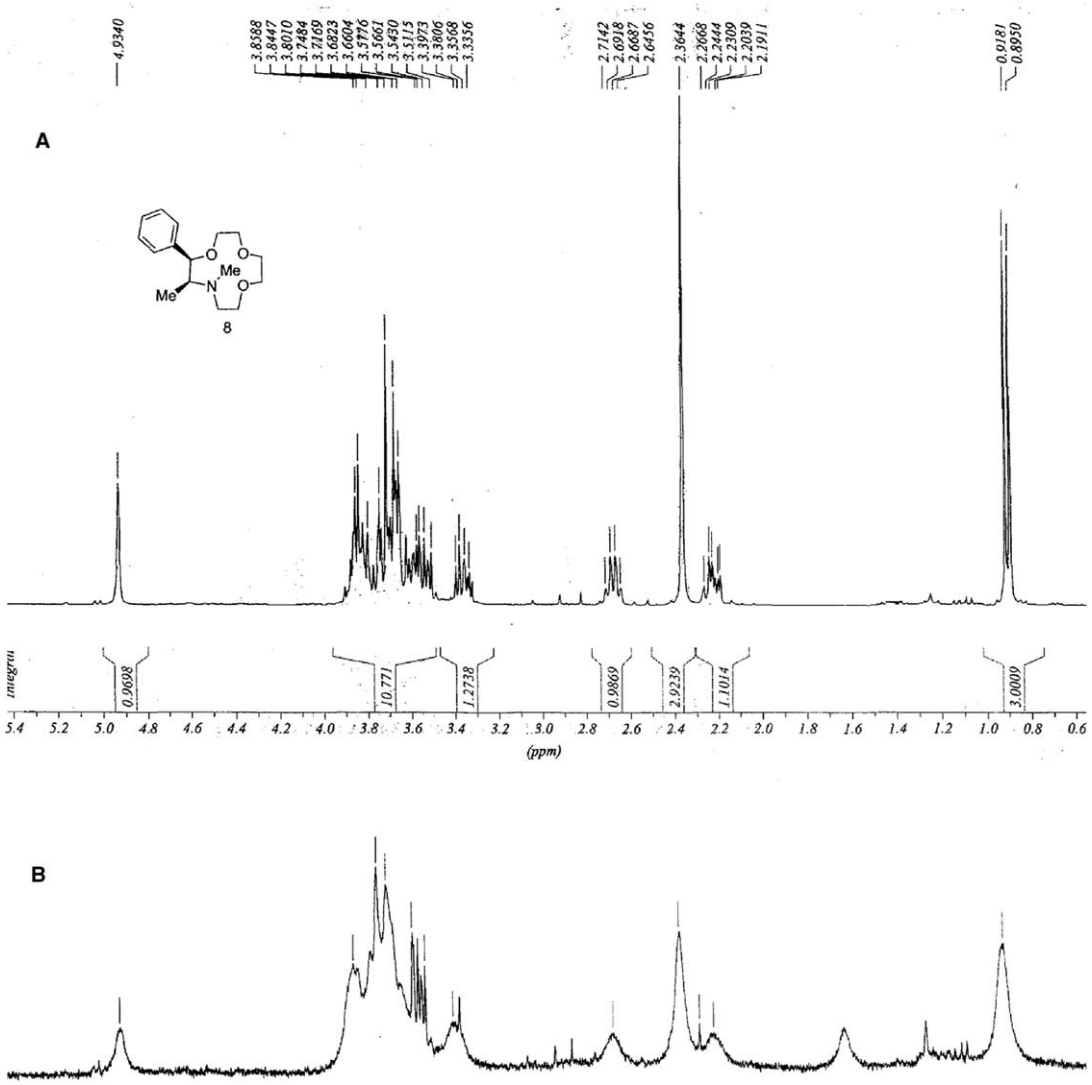


Figure 3. ^{1}H NMR of **8** in $CDCl_3$ at rt. (A): $C = 0.3$ mol L^{-1}. (B): $C = 1.410^{-2}$ mol L^{-1}.

showed broadened resonances at *low* concentration (Fig. 3). This unusual observation suggests the occurrence of a slow conformational exchange of the macrocycle whose rate is dependent on the concentration. The well-resolved spectrum at high concentration might be due to a freezing of this conformational exchange that could result from a supramolecular organization of the macrocycles due to intermolecular π-stacking interactions between phenyl substituents. Resolution of the ^{1}H NMR spectrum recorded at a low concentration was also restored by addition of NaI or of 1 equiv of mandelic acid.

In conclusion, we have described a new strategy for the synthesis of monoazamacrocycles of various sizes from β-amino alcohols. Since amines were also shown to react efficiently with *N*-cyanomethyl-β-chloro amines, this strategy may be extended to prepare other classes of polyazamacrocycles. The evaluation of these compounds for enantiomeric differentiation is currently under study.

Acknowledgements

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8. **Representative experimental procedures**: *General procedure for the reaction of N-cyanomethyl-β-chloroamines with alcohols*. A solution of the chloride (1 mmol) in the required alcohol (10 mL) was heated for 1 h at 80 °C. The reaction mixture was next diluted with water (30 mL) and diethyl ether (50 mL) and basified with a saturated aqueous solution of $NaHCO_3$. Aqueous layer was extracted with ether, combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was finally purified by flash column chromatography (silica gel, elution: ether followed ether/methanol: 5/95).
(1S,2R)-{[2-(2-{2-[2-(2-Hydroxyethoxy)-ethoxy]-ethoxy}-ethoxy)-1-methyl-2-phenylethyl]-methylamino}-acetonitrile **3**. Yield: 84%; $[\alpha]_D^{20}$ −35 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (d, $J = 6.9$ Hz, 3H), 2.54 (s, 3H), 2.82 (qd, $J = 6.9$ and 3.0 Hz, 1H), 2.98 (br s, 1H), 3.47–3.82 (m, 18H), 4.59 (d, $J = 3.0$ Hz, 1H), 7.25–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 8.9, 40.0, 41.8, 61.7, 64.0, 68.3, 70.4, 70.5, 70.6, 70.8, 72.6, 72.8, 83.4, 117.5, 126.8, 127.4, 128.3, 140.2; MS (CI, NH_3): 381, 354, 97.
General procedure for the mesylation. To a solution of the alcohol (1 mmol) and triethylamine (280 μL, 2 mmol) in dichloromethane (10 mL) was added methanesulfonylchloride (175 μL, 1.5 mmol) dropwise at 0 °C. The reaction mixture was warmed to rt, stirred for 1 h, and quenched by addition of water. Aqueous layer was extracted with dichloromethane, combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude mesylate derivatives which were used in the next step without further purification.
General procedure for the deprotection/cyclization step. To a solution of mesylate (0.623 mmol) in THF (5 mL) was added a solution of silver(I)nitrate (136 mg, 0.8 mmol) in water (1 mL). Upon addition, a brownish precipitate was immediately formed and the suspension was stirred in the dark at rt for 5 h. Crude reaction mixture was then filtered through a plug of Celite®, which was thoroughly washed with DCM and then with methanol to avoid loss of product. Filtrate was concentrated under reduced pressure to give crude N-deprotected compound as a nitrate salt. This residue was dissolved in acetonitrile (20 mL), and triethylamine (175 μL, 1.25 mmol) was added. The solution was heated at 70 °C for 5 days (or until consumption of starting material), cooled to rt, filtered through a plug of Celite®, which was again thoroughly washed with DCM and then with methanol to avoid loss of product. Filtrate was concentrated under reduced pressure and the residue was treated with water and with 2 M aqueous NaOH solution. Aqueous layer was extracted with ether (3 × 20 mL), combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was finally purified by flash column chromatography (silica gel, elution: ether then ether/30% NH_4OH: 98/2, then ether/30% NH_4OH/ethanol: 93/2/5) to give the desired macrocycle.
(11R,12S)-12,13-Dimethyl-11-phenyl-1,4,7,10-tetraoxa-13-aza-cyclopentadecane **9**. Yield: 79%; $[\alpha]_D^{20}$ −525 (*c* 0.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, $J = 7.0$ Hz, 3H), 2.40 (s, 3H), 2.63–2.76 (m, 2H), 3.21–

3.30 (m, 1H), 3.46–3.77 (m, 14H), 4.71 (d, $J = 1.5$ Hz, 1H), 7.25–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 7.1, 42.3, 51.2, 65.6, 68.5, 70.45, 70.49, 70.52, 70.62, 70.9, 71.0, 84.1, 126.6, 126.9, 128.2, 141.6; MS (CI, NH_3): 324.

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