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Synthesis of an Asymmetrically Substituted AZA Crown Ether as Metal and Amino Acid Binding Site in DNA Conjugates

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ABSTRACT

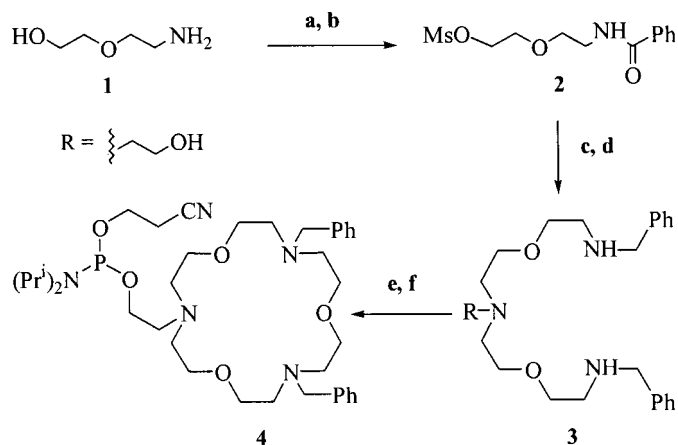
Crown ether **4** as a receptor core for protonated primary amines such as amino acids has been synthesized and incorporated into oligodeoxynucleotides as dangling ends.

Key Words: Aza crown ether; Amino acid binding.

A very limited number of binding sites for organic molecules have been incorporated into oligonucleotides. Functionalised crown ethers have special interest in terms of host-guest chemistry.^[1] Their selectivity for metal cations of different sizes and complexation of organic molecules such as amines and amino acids is a starting point for promising applications. It is noteworthy that especially triaza crown ethers show a remarkable affinity for protonated primary amines.^[2]

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Scheme 1. a) $(\text{PhCO})_2\text{O}$, EtOH, reflux, 90%; b) MsCl, pyridine, 80%; c) RNH_2 , NEt_3 , MeCN, 70%; d) LiAlH_4 , THF, 90%; e) $\text{TsO}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OTs}$, Na_2CO_3 , MeCN, 50%; f) $\text{NC}(\text{CH}_2)_2\text{OP}(\text{Cl})\text{N}(\text{iPr})_2$, $(\text{iPr})_2\text{NEt}$, CH_2Cl_2 , 50%.

We here report synthesis of an appropriately modified triaza crown ether compatible with automated synthesis using the phosphoramidite approach. Commercially available **1** was treated with benzoic anhydride and subsequently mesylated to give building block **2**. Treatment of **2** with 2-aminoethanol afforded a diamide. Reduction of the diamide led to the triamine **3** suitable for subsequent macrocyclization reaction.^[3] Accordingly, treatment of the triamine **3** with diethylene glycol ditosylate led to a macrocycle which was subsequently converted into the phosphoramidite **4** (Sch. 1).

Compound **4** was successfully incorporated (monomer **X**) into two complementary 9-mer sequences [5'-d(XCGT ATA GTG) and 3'-d(XG^{Me}C^LA T^LAT^L CAC, ^{Me}C^L and T^L are LNA monomers). Data on the complexation behaviour with amines and T_m values will be reported in due course.

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