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High-yield synthesis of pyrrolidinyl PNA monomers

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ABSTRACT

Two monomers for the syntheses of conformationally restricted peptide nucleic acids were synthesized through a simple procedure, involving an asymmetric 1,3-dipolar cycloaddition chemistry as a key step, from common starting materials in 3 and 5 steps, and 58.8% and 30.5% overall yields, respectively.
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The discovery of the remarkable biological profiles of peptide nucleic acids (PNA) in 1991 by Nielsen and co-workers[1] has led to the preparation of several types of conformationally restricted cyclic congeners in which an additional bond is introduced into the aminoethyl glycine backbone.[2] From the several possibilities for constraining the conformation of PNA by including pyrrolidine rings into their backbone,[3] the constrained structure *pyr*-PNA **2** (Fig. 1), firstly reported by Nielsen and co-workers[4] in 2001, has two stereogenic centers in the monomeric unit of the PNA molecule so, up to 4 different diastereomers could be prepared.

In their original paper,[4] Nielsen and co-workers prepared both (3*R*,5*R*) and (3*S*,5*R*) monomers **4** in 13 and 15-step sequences and 2.53% and 2.29% overall yields (Scheme 1), respectively, starting from **3** (prepared from pyroglutamic acid in five steps and 49% yield). Compounds **4** were used for preparing the corresponding conformationally restricted PNA and it was found that *pyr*-PNA **2** derived from (3*S*,5*R*) isomer had the highest affinity toward RNA, recognizing both RNA and PNA better than DNA.[4]

Since the Nielsen's report no other synthetic approaches have been communicated to obtain compounds **4** in a more efficient way. In this context, we have recently reported[5] the synthesis of isoxazolidinyl nucleosides as building blocks for PNA analogues through a strategy based on asymmetric nitrone 1,3-dipolar cycloaddition reactions. The same strategy has also been applied in our laboratories for the synthesis of pyroglutamic acid derivatives[6] thus demonstrating the synthetic utility of nitrone chemistry for the construction of pyrrolidines.[7]

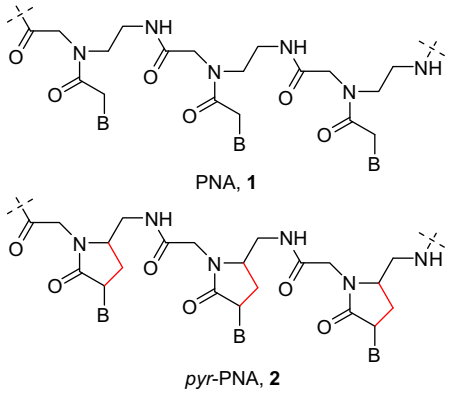

Figure 1. PNA and conformationally restricted analogue *pyr*-PNA.

In this Letter we wish to report a direct asymmetric entry to compounds **4** through an enantioselective 1,3-dipolar cycloaddition between an easily accessible nitrone **A** and a chiral acrylate **B** (Scheme 2). DFT calculations have also been carried out in order to rationalize the stereochemical outcome of the reaction.

Nitrone **8** was generated in situ from commercially available aldehyde **5** and hydroxylamine **6**. Compound **6** was obtained in

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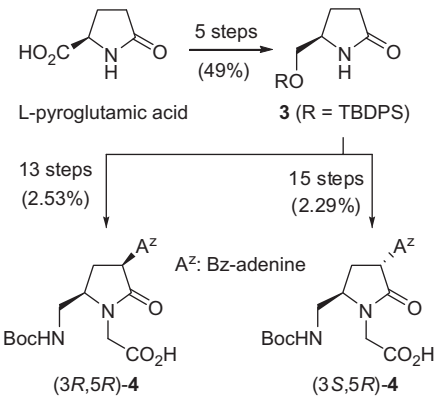
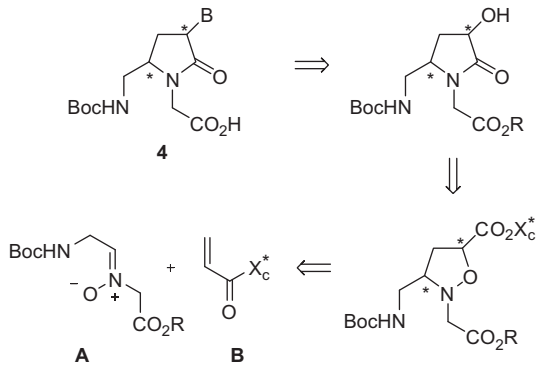


Scheme 1. Synthesis of *pyr*-PNA monomers by Nielsen and co-workers.[4]



Scheme 2. Retrosynthetic analysis for *pyr*-PNA monomers **4**.

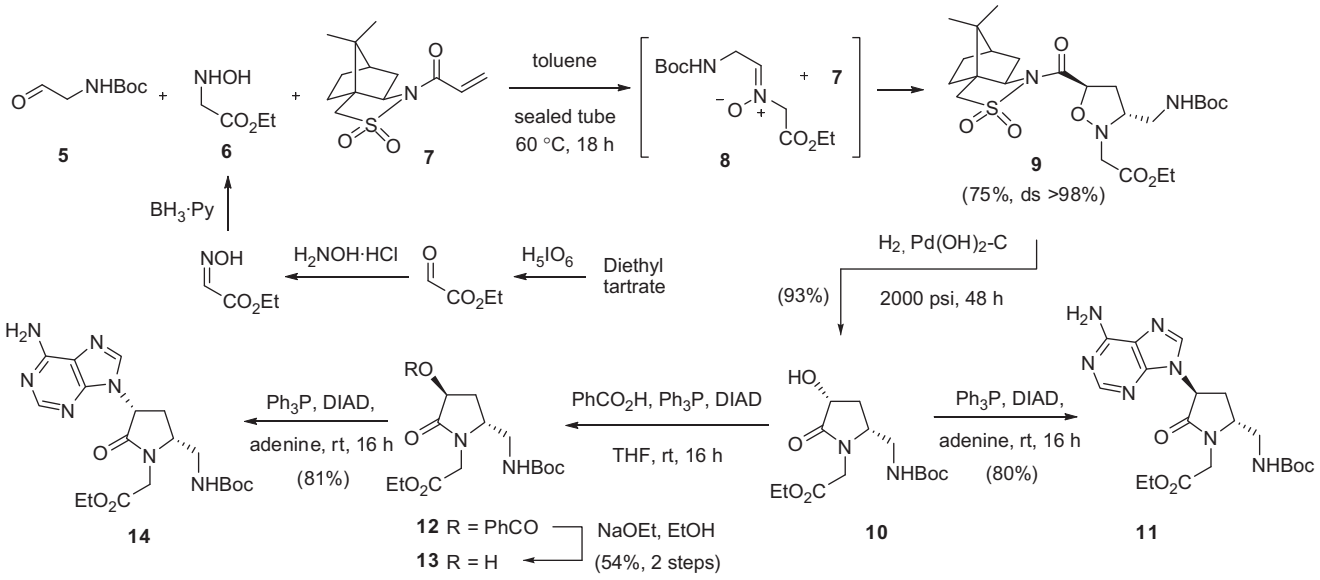
three steps from diethyltartrate by sequential treatment with periodic acid[8] to form ethyl-2-oxoacetate, hydroxylamine hydrochloride, and further reduction of the resulting oxime with borane in pyridine.[9] Based on the previous results from our[10] and other[11] laboratories we chose *N*-acryloyl-(2*R*)-bornane-10,2-sultam **7** as the dipolarophile. The reaction between the three reagents **5**, **6,** and **7** in a sealed tube using toluene as a solvent afforded after 18 h at 60 °C compound **9** in 76% yield[12] (Scheme 3) and complete regio-(3,5), diastereo-(*trans*), and enantioselectivities (3*S*,5*R*). Indeed, after column chromatography of the reaction mixture only one isomer could be detected by NMR. The reduction (N–O cleavage) of compound **9** was first attempted with Zn in acetic acid, a procedure successfully used in our laboratory for promoting the transformation of 5-carboxy isoxazolidines into 3-hydroxy-2-pyrrolidines.[13] However, under typical reaction conditions (THF, 60 °C, 5 h) a low yield (20%) was obtained. Fortunately, the catalytic hydrogenation of **9** using $Pd(OH)_2$–C (Pearlman's catalyst) at 2000 psi for 48 h[14] took place in high yield to provide pyrrolidin-2-one **10**.[15] The last step consisting of the introduction of the base moiety (adenine) into the pyrrolidine ring was carried out under Mitsunobu conditions (PPh_3, DIAD, CH_3CN) with the free heterocyclic base. After 16 h at rt compound (3*S*,5*R*)-**11** was obtained in 80% yield (3 steps, 58.8% overall yield).[16]

In order to obtain the (3*R*,5*R*) isomer compound **10** was subjected to a typical Mitsunobu reaction[17] to afford, after saponification (NaOEt, EtOH) of the intermediate benzoate **12** the pyrrolidin-2-one **13**.[18] Introduction of the base moiety as described for compound **11** furnished **14** in 81% yield. Globally, compound **14** has been obtained in 4 steps and 30.5% overall yield.[19]

The relative configuration of compounds **10–14** was ascertained by conventional NMR techniques including 1D NOE, 2D NOESY, COSY, and HMBC experiments. The absolute configuration and stereochemical integrity of compounds **10** and **13** were determined by preparing the corresponding Mosher esters.[20] Analysis of the 400 MHz NMR spectra of those esters showed the presence of only one diastereomer in each case, at the limit of detection indicating the enantiomeric purity >98%.

For a successful application of Kakisawa's rule[21] it is needed a comparison between the values corresponding to a pair of isomers having an opposite configuration. In consequence, we prepared the corresponding Mosher esters derived from (*R*)- and (*S*)-Mosher acids[22] (Scheme 4) and the ^1H NMR spectra of the pure esters were recorded to calculate the differences in the chemical shift.

According to Kakisawa's rule[21] the methylene group (H_{4a} and H_{4b}) is selectively shielded by the phenyl group when the two groups are located on the same plane containing H_3 and the carbonyl group (compounds **15a** and **16a**). By defining $\Delta\delta$ as indicated in Scheme 4 (δ_S and δ_R refers to chemical shifts of (*S*)- and (*R*)-MTPA esters, respectively) positive values would indicate a 3*R* configuration, whereas negative values indicate a 3*S* configuration. According to the values illustrated in Scheme 4 it was confirmed



Scheme 3. Synthesis of PNA monomers **11** and **14**.

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