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Synthesis of morpholino nucleosides starting from enantiopure glycidol†

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The synthesis of modified morpholino monomers was performed in a few steps through the condensation between 6-hydroxymethyl-morpholine acetal and nucleobases under Lewis acid conditions. The key common precursor of the targets – 6-hydroxymethyl-morpholine acetal – is easily synthesised *via* oxirane ring opening of optically pure glycidol using *N*-nosyl aminoacetaldehyde as a nucleophile, followed by an *O*-benzoylation/ring-closure tandem reaction sequence. Using readily available building blocks, this strategy allows access to diversified optically pure morpholino monomers in good yields and anomeric ratios.

Introduction

During the past few decades, the development of "oligonucleotide therapies" has been revealed as a crucial strategy for the treatment of mutagenic diseases, leading to repercussions throughout the synthetic planning in drug discovery. Synthetic oligonucleotides regulate gene expression by interacting selectively with the RNA target. As a consequence, the transfer of genetic information and, in turn, the production of degenerate proteins are blocked.[1] Depending on the modes of action, different synthetic oligos were realized.[2] Among these analogues, the antisense[3] oligos phosphorodiamidate morpholinos (PMOs) have gained substantial interest, offering realistic prospects for the treatment of diseases involved in gene expression.[4] The synthesis of the monomers was disclosed by the Summerton research group in 1997 (Fig. 1, path a).[5] Following this procedure, several modifications were realised on the morpholino subunit to enhance or modify the PMO properties. Modifications have been realised at the phosphoramidate linkage,[6] either dendrimers or peptides rich in arginine residues at the terminal 3′-nitrogen atom were introduced.[7] In this way, two PMO drugs have been approved for the treatment of Duchenne muscular dystrophy.[8] Modifications at the nucleobase level have also been explored by functionalization of the canonical morpholino monomer.[9]

Beyond the interest in the oligonucleotide field, 2,6-substituted morpholines are widely embedded in compounds with a range of biological activities.[10] For example, this class of heterocycles has found wide application in peptide synthesis,[11] and has been used as HIV protease inhibitors,[12] antimicrobial agents,[13] or therapeutics in obesity and diabetes,[14] tumors,[15] sexual dysfunction,[16] and pain experience.[17] Therefore, various synthetic strategies have been reported in the literature to access the 2,6-substituted morpholine skeleton.[18] To the best of our knowledge any of them describes the direct morpholine functionalization with a nucleic base.

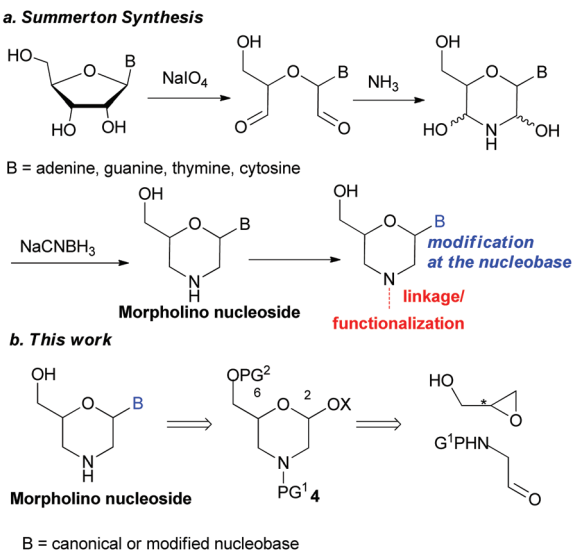

Fig. 1 Chemical structures of the morpholino unit and functionalization sites.

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On these bases and given our ongoing interest in the synthesis of functionalised nitrogen containing heterocycles,[19] here we reported our efforts toward the development of a synthetic protocol for nucleobase-modified morpholino monomers (Fig. 1, path b). The key step of the process involves the condensation of **4**, which is the common precursor of target nucleoside analogues, with model nucleic bases as nucleophiles under Lewis acid-catalysed glycosylation reaction conditions. The proposed strategy gives access to optically pure compounds whose stereochemistry is strictly related to the geometry of the starting epoxide sources.

Results and discussion

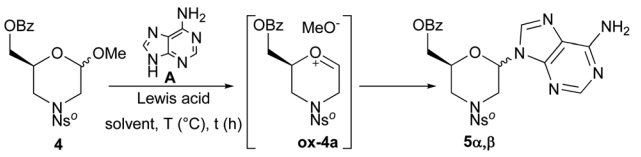
The protocol for the synthesis of morpholinos begins with the nucleophilic ring-opening of optically pure (*R*)-glycidol using *N*-nosyl 2,2-dimethoxyethanamine (**1**). The *ortho*-nosyl (Ns^o) protective group was selected for its easy cleavage under mild reaction conditions. This reaction was carried out under solid–liquid phase transfer catalysis (SL-PTC) conditions (Scheme 1, step a), which did not affect the carbon stereocenter[20] and the corresponding enantiopure tertiary amide **2** was isolated in very good yield. The key intermediate **4** was then prepared through a tandem protecting/ring-closing sequence by reacting equimolar amounts of diol **2**, benzoyl chloride and pyridine (Scheme 1, step b).[21] Benzoylation of the primary hydroxy function generated the intermediate **3** that, through *in situ* cyclization promoted by pyridinium chloride, finally gave the desired acetal **4** in 92% yield. The ring-closing reaction to **4** formed a glycosyl-like hemiacetal bond, with the consequent formation of the anomeric C-2 carbon atom (25 : 75-α/β anomeric ratio), which is the reactive site for the nucleobase attack to the morpholine ring.

To study the nucleobase insertion reaction conditions, **4** was coupled with adenine (**A**) (Table 1). Preliminary runs, in the presence of $SnCl_4$, evidenced that the use of MeCN as a solvent and the addition of a Lewis acid at 0 °C followed by the raising of the reaction temperature to 25 °C are the essential requisites for the reaction progress (entry 1). Under these conditions, **5α** was isolated as the major anomer (47%) together with **5β** (22%). This 68 : 32-α/β ratio remained the same when pure **4α** or **4β** anomer was made to react instead of using the **4α,β** mixture. Since the anomeric configuration of **4** does not influence the product stereochemistry, we suppose that the reaction most likely proceeds *via* an intermediate oxocarbenium ion **ox-4a**. Moreover, since *N*-glycosylation of monosaccharides, except in the case of 2-deoxysugar,[22] provided complete β-selectivity,[23] we can assume that the ratio of the **5α/5β** mixture depends on the absence of coordinating substituents at the C-3 position of **4**. Further experiments indicated that the use of a higher or lower reaction temperature was detrimental (entries 2 and 3).

Using DMF, CH_2Cl_2, or *p*-xylene as the solvent instead of -MeCN (entries 4–6), a complex reaction mixture was formed. In the presence of softer Lewis acids (such as indium trichloride, ytterbium chloride, zirconium tetrachloride or titanium isopropoxide), morpholine **4** was recovered unchanged (entries 7–10), while titanium tetrachloride furnished a mixture of anomers **5α,β** (entry 11). Conversely, using trimethylsilyl (trifluoromethane)sulfonate (TMSOTf, entry 12), together with a good overall yield, a reversed **5α/5β** ratio was found, **5β** being the major anomer.

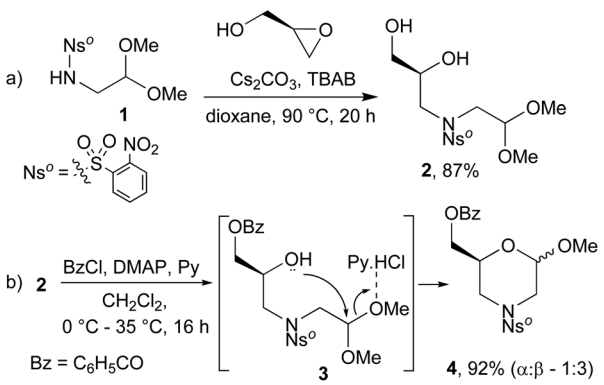
To evaluate the scope of this procedure, the best reaction conditions using TMSOTf were applied to the condensation of acetal **4** with modified nucleobases 6-chloropurine (**CHP**, Fig. 2), silylated hypoxanthine (**HPX**), 2,6-diaminopurine (**Z**), and silylated 5-fluorouracil (**5-FU**). To our delight, nucleobases **NB**-H (Scheme 2) gave the corresponding *N*,*O*-protected monomers **6–9** in good yields with the prevalence of the β-anomer. The condensation of **4** with the adenine derivatives, **CHP** and

Table 1 Lewis acid activation of **4**: study of the reaction conditions[a]



Entry	Lewis acid	Solvent	*t* (h)	**5** (%)	[α : β]
1	$SnCl_4$	MeCN	2	69	[68 : 32]
2	$SnCl_4$	MeCN[b]	24	—	
3	$SnCl_4$	MeCN[c]	24	16	
4	$SnCl_4$	DMF	24	<5	
5	$SnCl_4$	*p*-Xylene	24	<5	
6	$SnCl_4$	CH_2Cl_2	24	<5	
7	$InCl_3$	MeCN	24	—	
8	$YbCl_3$	MeCN	24	—	
9	$ZrCl_4$	MeCN	24	—	
10	$Ti(OiPr)_4$	MeCN	24	—	
11	$TiCl_4$	MeCN	4	70	[60 : 40]
12	TMSOTf	MeCN	4	73	[30 : 70]

[a] Reaction conditions: **4** (0.5 mmol), **A** (1.0 mmol), Lewis acid (1.5 mmol), solvent (1.0 mL). 0 °C to 25 °C, after Lewis acid addition. [b] Addition of the Lewis acid and reaction temperature: −20 °C. [c] Addition of the Lewis acid at 25 °C.



Scheme 1 Synthesis of the key precursor (**4**) of morpholino nucleosides. Reaction conditions: (a) **1** (2.2 mmol), (*R*)-glycidol (2.0 mmol), dioxane (4.0 mL), Cs_2CO_3 (0.2 mmol), TBAB (0.2 mmol); (b) **2** (1.0 mmol), BzCl (1.1 mmol), Py (1.0 mmol), DMAP (0.1 mmol), CH_2Cl_2 (3.0 mL).

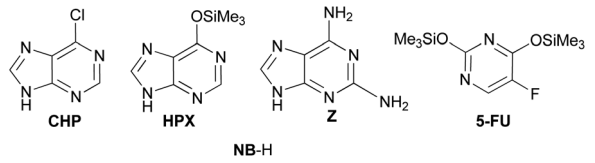
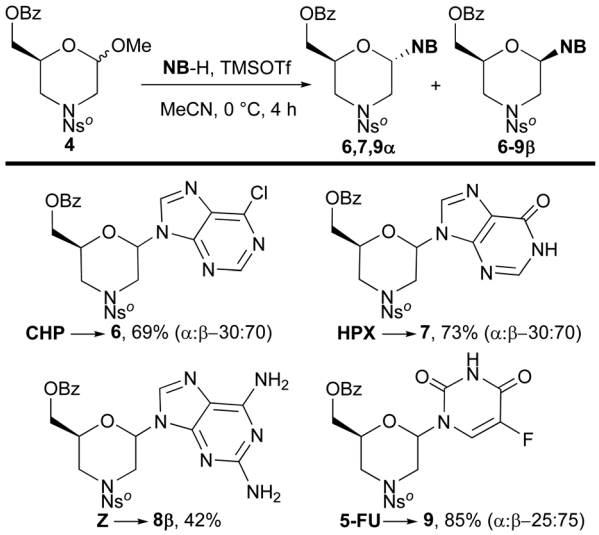
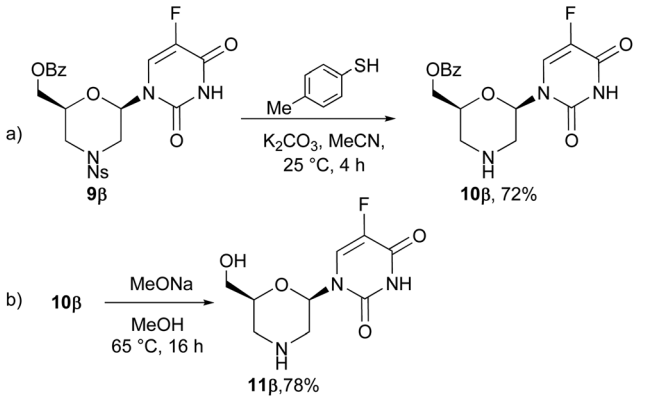


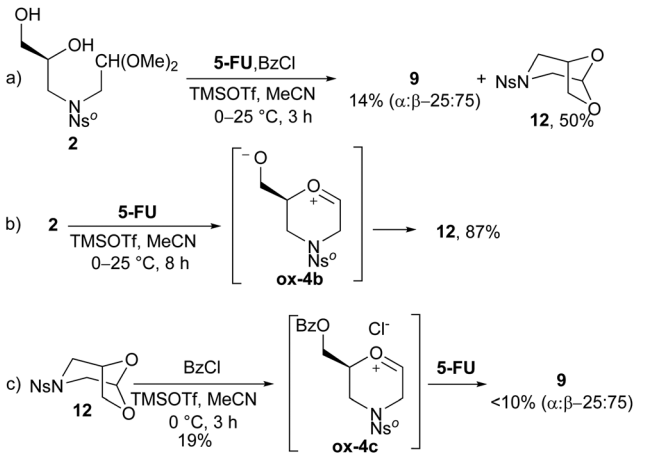
Fig. 2 Nucleobase **NB**-H employed in the synthesis of morpholinos.



Scheme 2 Scope of the reaction: synthesis of protected morpholino derivatives **6–9**. Reaction conditions: **4** (0.5 mmol), **NB**-H (1.0 mmol), TMSOTf (1.5 mmol), MeCN (1.0 mL).



Scheme 3 *N*- and *O*-deprotection of the 5-fluorouridine analogue **9β**. Reaction conditions: (a) **9β** (0.3 mmol), 4-methylbenzenethiol (0.4 mmol), K_2CO_3 (1.0 mmol), MeCN (3.0 mL); (b) **10β** (0.23 mmol), MeONa (0.5 mmol), MeCN (1.0 mmol), MeOH (2.0 mL).



Scheme 4 Reactivity of diol **2**. Reaction conditions: (a) **2** (0.5 mmol), **5-FU** (1.0 mmol), BzCl (0.7 mmol), TMSOTf (1.5 mmol), MeCN (2.0 mL); (b) **2** (0.5 mmol), **5-FU** (4.0 mmol), TMSOTf (1.5 mmol), MeCN (2.0 mL); (c) **12** (0. mmol), **5-FU** (1.5 mmol), BzCl (0.7 mmol), TMSOTf (1.5 mmol), MeCN (2.0 mL).

silylated **HPX**, gave analogous results to that obtained with adenine itself, and the corresponding analogues **6** and **7** were isolated in 69% and 73% yield, respectively, in a 30 : 70-α/β anomeric ratio. In particular, the reaction conditions promoted the silylether cleavage in **HPX** providing the corresponding *O*-deprotected analogues **7**. The reaction on **Z** furnished the corresponding nucleoside **8β** in 42% yield. It is worth noting that **8α** has not been isolated, even though the NMR spectra of the crude showed a set of signals consistent with this anomer. Finally, the reaction of silylated **5-FU** gave both better yield and selectivity of the corresponding *O*,*O*-deprotected products **9** (85% yield; 25 : 75-α/β anomeric ratio).

To investigate the chemoselective *N*- and *O*-deprotection reactions of these compounds, **9β** was chosen as a model.

Firstly, the *N*-(2-nitrobenzene)sulfonyl group was efficiently removed by reaction with *p*-thiocresol and the corresponding morpholine **10β** was isolated in good yields (Scheme 3, step a). In the next step, the benzoate function was removed from **10β** by trans-esterification with sodium methoxide in refluxing methanol, and the corresponding 5-fluorouridine analogue **11β** was isolated in good yields (Scheme 3, step b).

To by-pass the *O*-protection/deprotection steps and to better understand the cyclization mechanism, the same runs were carried out (Scheme 4). Initially, one-pot *O*-protection/cyclization/**NB**-H nucleophilic attack was performed on diol **2** in the presence of BzCl and **5-FU** (path a), without adding a base (*i.e.* pyridine; Scheme 1, step b). Under these conditions, the target compound **9** was isolated in only 14% yield together with a large amount of bicyclic 1,3-dioxolane **12** (path a). A successive attempt at the tandem cyclization/**NB**-H coupling reaction under similar conditions, without benzoyl chloride (path b), gave **12** as the sole product. The hypothesized mechanism for the formation of **12** implicates the formation of a zwitterionic species **ox-4b** that, in turn, was evolved by intramolecular attack of the oxanion, the strongest nucleophile, on the carbocation. Besides, compound **12** resulted to be stable when made to react with a large excess (4.0 mol equiv.) of **5-FU**, whereas when BzCl was used together with **5-FU**, a small amount of **9** was formed (path c). The latter result proves that, under these conditions, an equilibrium between dioxolane **12** and the oxonium species **ox-4b** is effective. Actually, by

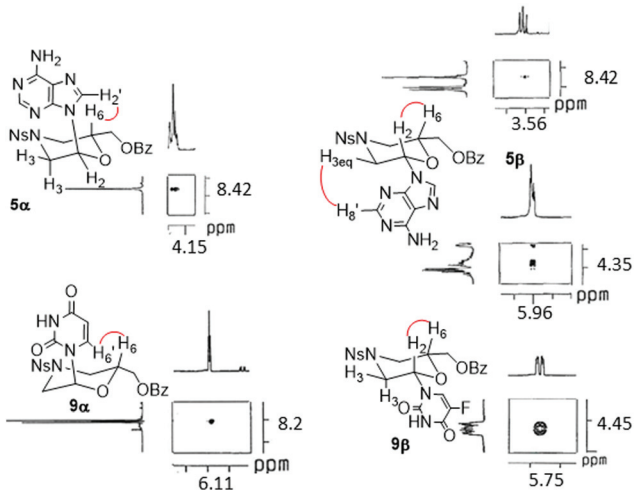


Fig. 3 Selected NOE correlations for morpholino **5–9**.

O-benzoylation of **ox-4b**, the oxonium chloride **ox-4c** forms and then it can evolve to **9**.

NMR experiments corroborate the stereochemistry assigned to protected morpholino anomers **5,6,7, and 9α** and **5–9β**. As shown for compounds **5α,β** and **9α,β** (Fig. 3), the NOESY analysis of the β-anomers showed H_2–H_6 spatial proximity indicating, in agreement with the *J* values, that the substituents on C_2 and C_6 are both equatorial. In fact, this interaction is absent in the α-anomers. Furthermore, in the **5α** anomer, the H'_2–H_6 correlation was found, revealing their proximity. On the other hand, derivative **5β** presented a weak H_{3eq}–H'_8 correlation. The NH_2 residue of purine residues in **5α,β** did not show spatial proximity to any other proton. As regard the pyrimidine derivative **9α**, a correlation between H_6–H'_6 occurs, while the nucleobase in **9β** did not reveal any spatial interaction.

Conclusions

In summary, we have described a rapid synthesis of morpholino monomers from readily available building blocks. The 2-methoxymorpholine **4** is the key intermediate for the direct installation of the nucleobase. The proposed methodology furnished the biologically relevant β-morpholino analogues as the major anomers, when (trimethyl)silyltriflate was used to promote the condensation reaction. Conversely, when $SnCl_4$ was used as a Lewis acid, the main reaction products were the α-anomers, which have never been synthesised before. Pseudo α- and β-morpholino nucleosides, having *R*-configuration on C_6, could be constructed using (*S*)-glycidol in the synthesis of **2**. Further work will also be done to study and extend the activation of morpholine **4** toward different nucleophiles.

Conflicts of interest

There are no conflicts to declare.

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