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Synthesis of a β-glycoside functionalized GΛC motif for self-assembly into rosette nanotubes with predefined length

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ABSTRACT

Progress toward the synthesis of guanine–cytosine (GΛC) oligonucleotides for the spontaneous self-assembly of rosette nanotubes (RNTs) with predefined length is described. Highlighted is the synthesis of the β-glycoside functionalized GΛC base along with a new nitrogen protecting group strategy that is compatible with Boc and Bn groups.

1. Introduction

GΛC base **1** (Fig. 1) is a self-complementary guanine–cytosine hybrid molecule that was shown to self-assemble[1,2] in aqueous or organic solvents into six-membered supermacrocycles maintained by 18-hydrogen bonds. These assemblies further organize into linear stacks (termed rosette nanotubes, RNTs) with a central channel running the length of the stack. In principle, any functional group R covalently linked to the GΛC base **1** ends up being expressed on the outer surface of the RNTs, thereby providing a 'built-in' strategy to alter the RNTs' chemical and physical properties and ultimately their applications.

While we have reported several strategies to functionalize the GΛC motif,[1a–d] they either relied on early functionalization via S_NAr, reductive amination or on Suzuki cross-coupling late in the synthetic scheme. Herein our aim was to develop a strategy that would allow us to streamline the synthesis of RNTs with predefined length by taking advantage of the automated DNA synthesis methodology. A convergent approach illustrated in Scheme 1 was proposed, whereby the free amide nitrogen atom of intermediate **5** would be directly alkylated with the desired electrophile[3] to provide **6**. Conversion to the corresponding phosphoramidite **7**[4] followed by oligomerization using automated DNA synthesis,[5] then global deprotection, would furnish the corresponding GΛC oligomers. The latter are anticipated to undergo spontaneous self-assembly in water to generate discrete tubular architectures whose length is pre-determined by the length of the GΛC base oligomer.

2. Results and discussion

The studies commenced by investigating the protecting group strategies that would allow us to readily access the free amide **5** for the ensuing glycosylation reaction. We initially attempted a selective de-allylation reaction of an N-allylated GΛC base precursor **4** (PG = Allyl), the synthesis of which we have reported previously.[1] Despite using many different conditions, standard protocols such as Rh-catalyzed isomerization[6] and Pd-catalyzed π-allyl methodologies[7] were unproductive in this deprotection reaction.

An alternative protecting group, trimethysilylethane ($TMSCH_2CH_2$–) was next explored since its removal is known to be carried out under mild conditions (fluoride induced fragmentation).[8] Furthermore, initial attempts at the S_NAr reaction between 2,4,6-trichloropyrimidine-5-carbaldehyde (**2**) and TMS-ethylamine proceeded in good yield (Scheme 2). Overall, compound **12** was synthesized from pyrimidine **2** in nine-steps in 82% average stepwise yield (18% overall). Unfortunately, treatment of **12** with fluoride sources such as TBAF, $Et_3N{\cdot}3HF$, $C_6H_5N{\cdot}HF$, CsF and KF under a variety of reaction conditions failed to unmask the amide. Basic (e.g., *n*BuLi) and acidic deprotection conditions (e.g., 4 N HCl in dioxane at 45 °C, 4 h) were also unsuccessful. The latter acidic conditions did remove the Bn and the Boc groups however, to provide GΛC base **13** in 80% yield (Scheme 2).

Given the unusual stability of the silyl derivative **12**, we decided to develop a fragmentation strategy that would yield the desired compound according to Scheme 3. We reasoned that the fragmentation could be triggered thermally via the cyclic transition state **22** (Path 1), or promoted with a primary or secondary amine (Path 2). In the latter case, imine **17** obtained from aldehyde **16** could

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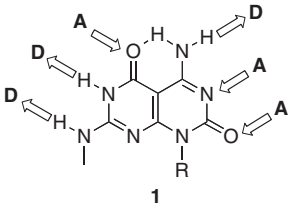
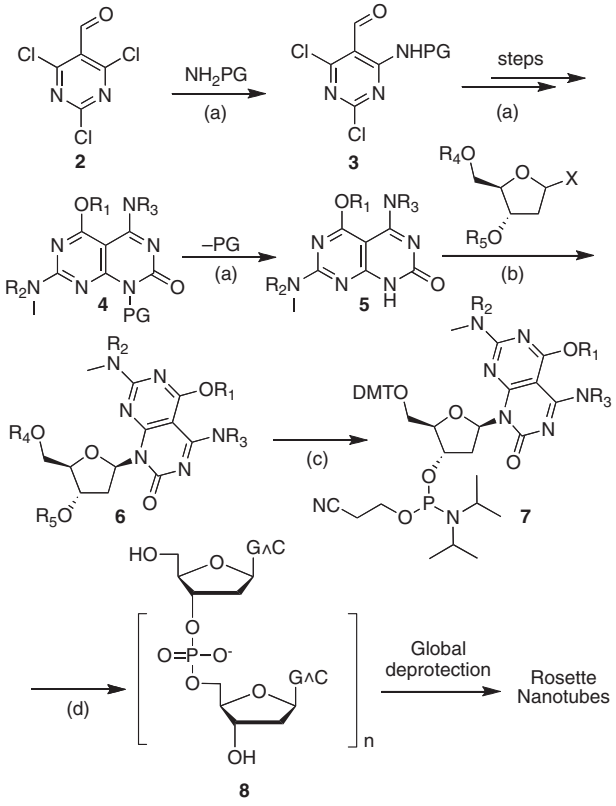
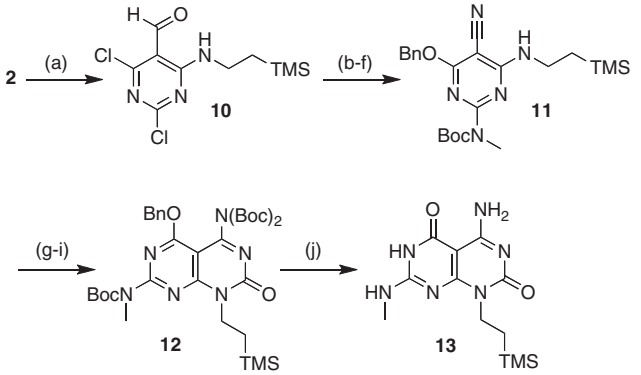


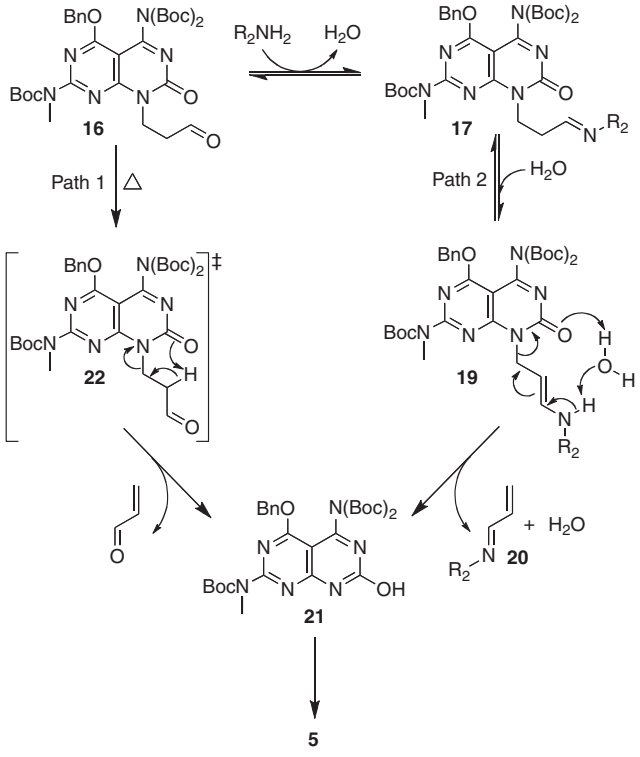
Figure 1. GΛC motif. 'D' and 'A' refer to hydrogen bond donors and acceptors, respectively.



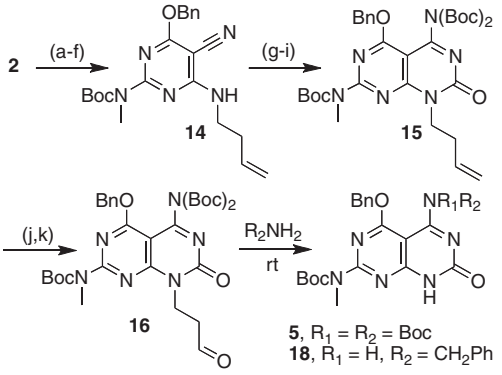
Scheme 1. Reagents and conditions: (a) according to the synthetic strategy detailed in this paper; (b) the ribose moiety would be prepared and coupled to the GΛC base according to previously reported procedures;[3] (c) according to reported procedures;[4] (d) automated DNA synthesis.[5]



Scheme 2. Reagents and conditions: (a) trimethylsilylethylamine hydrochloride,[9] DIPEA, CH_2Cl_2, 60%; (b) $MeNH_2$, THF, 88%; (c) BnOH, NaH, THF, 77%; (d) $(Boc)_2O$, DMAP, Et_3N, THF, 94%; (e) $NH_2OH{\cdot}HCl$, pyridine; (f) TFAA, Et_3N, THF, 79%, two-steps; (g) *N*-(chlorocarbonyl) isocyanate, CH_2Cl_2, 78%; (h) 7 N NH_3 in MeOH, 97%; (i) $(Boc)_2O$, DMAP, Et_3N, THF, 79%; (j) 4 N HCl in dioxane, 80%.



Scheme 3. Proposed mechanism for the deprotection of **16**.



Scheme 4. Reagents and conditions: (a) but-3-en-1-amine, CH_2Cl_2, quant.; (b) $MeNH_2$, 4 h, 92%; (c) BnOH, NaH, THF, 74%; (d) $(Boc)_2O$, DMAP, Et_3N, THF, 98%; (e) $NH_2OH{\cdot}HCl$, $KHCO_3$, MeOH, 53%; (f) TFAA, Et_3N, THF, 70%; (g) *N*-(chlorocarbonyl) isocyanate, Et_3N, CH_2Cl_2; (h) 7 N NH_3 in MeOH, 95%, two-steps; (i) $(Boc)_2O$, DMAP, Et_3N, THF, 62%; (j) OsO_4, NMO, acetone/H_2O, 77%; (k) $NaIO_4$, CH_2Cl_2/H_2O, 89%.

tautomerize to the corresponding intermediate enamine **19**, which can then eliminate imine **20** to furnish the target compound **5** (tautomer of **21**). To test this strategy compound **16** was synthesized in 12-steps according to Scheme 4 and then treated with a variety of amines (Table 1).

While the thermal fragmentation gave several unidentified byproducts along with target compound **5**, activation with primary amines gave **5** in good yields as shown in Table 1. Secondary amines such as diethylamine were unproductive and only starting material was recovered after 24 h. Aromatic amines such as aniline were also ineffective, giving a mixture of products. Interestingly, performing the reaction for longer periods of time (>36 h) or heating (>40 °C) with 0.25–2.0 equiv of benzylamine led to a decline in the yield caused by the formation of the substituted product **18** (Scheme 4).