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New insight on 2-naphthylmethyl (NAP) ether as a protecting group in carbohydrate synthesis: a divergent approach towards a high-mannose type oligosaccharide library†‡

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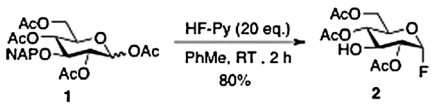
A new method for selective cleavage of 2-naphthylmethyl (NAP) ether utilizing 10–20 molar excess of HF/pyridine in toluene was revealed and strategically applied to a divergent approach towards generation of a high-mannose type oligosaccharide library.

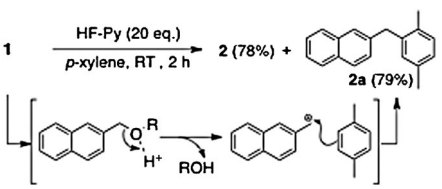
The emergence of glycobiology as a major research field demands the rapid access of structurally defined oligosaccharides.[1] Chemical synthesis of complex carbohydrates and glycoconjugates relies on novel glycosylating agents, but also robust protecting group chemistry that can be strategically applied to differentiate a collection of hydroxyl and amino groups during and at the end of the synthetic processes.[2] Thus, there is a continuous need for inventing novel and reliable protective groups for oligosaccharide synthesis.[3] 2-Naphthylmethyl (NAP) ether has recently emerged as a new type of protecting group for hydroxyl functionality.[4] NAP ether retains the ease of installation as benzyl ether and can be readily cleaved under either oxidative or hydrogenolytic conditions.[4,5] The acid-stable nature of NAP ether, in comparison with analogously oxidant-labile *p*-methoxylbenzyl (PMB) ether, popularized its application as a temporary hydroxyl protecting group in complex natural product and carbohydrate syntheses.[6]

During our recent effort to develop new chemical and enzymatic glycosylation methods, we discovered that 3-*O*-NAP ether in glucose tetraacetate **1** was cleanly removed by the treatment of HF/pyridine (Olah's reagent) in toluene with simultaneous generation of glucosyl fluoride **2** in good yield (eqn (1)). We captured this serendipitous discovery and herein report the details of selective cleavage of NAP ether using gentle the acidic condition that involves 10–20 molar excess of HF/Py in toluene in the context of carbohydrate synthesis. We further demonstrated the versatility of this new approach in an effort to generate a high-mannose type oligosaccharide library.



(1)

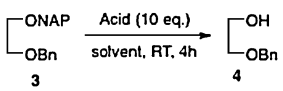
The stoichiometry of HF/Py required to cleave NAP ether in compound **1** was readily optimized to be 10–20 molar equivalents to afford **2** in 2–4 hours at room temperature. Mechanistically, we postulated the generation of a NAP cation (eqn (2)) upon the acidic activation of NAP ether, which can be subsequently trapped by the solvent. This hypothesis was supported by the clean isolation of adduct **2a** where the NAP cation was trapped when using *p*-xylene as a solvent (eqn (2)).



(2)

With this mechanistic support in hand, we used compound **3** to investigate whether other solvent and/or acid combinations might be more suitable for the cleavage of NAP ether (Table 1). Strong Lewis acids such as TMSOTf or $BF_3{\cdot}Et_2O$ were not effective under identical conditions, nor TFA and HF/H_2O. When employing HF/Py as the acid, neither

Table 1 Screening acids and solvents for selective cleavage of NAP ether in the presence of benzyl ether



Entry	Acid	Solvent	Conversion (%)
1	HF–Py	Toluene	100
2	HF–Py	CH_2Cl_2	ND
3	HF–Py	THF	ND
4	TMSOTf	Toluene	<5
5	$BF_3{\cdot}OEt_2$	Toluene	<5
6	TFA	Toluene	NR
7	HF/H_2O	Toluene	NR

ND = not determined, NR = no reaction.

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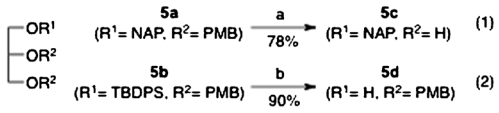


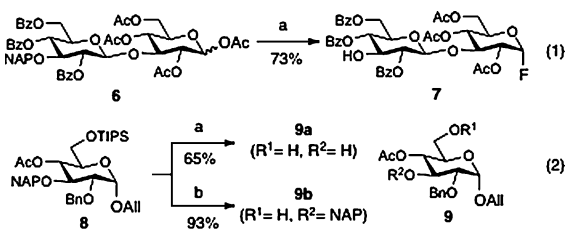
Scheme 1 Selective differentiation of NAP, PMB and silyl ethers using amine-buffered HF/Py. (a) HF–Py (20 eq.), Et_3N (3 eq.), toluene, rt, 12 h; (b) HF–Py (40 eq.), pyridine, rt, 24 h.

dichloromethane nor THF is suitable as a solvent, even in the presence of a cation scavenger such as anisole, suggesting that HF/Py exhibits maximal efficiency in toluene that serves as a non-Lewis-basic cation scavenger.[7]

Recognizing that the acidity of HF/Py in toluene is essential for the cleavage of NAP ether, we envisioned that buffering HF/Py with a suitable amine base should allow for efficient differentiation of NAP ether from more acid-labile PMB ether and/or fluoride-sensitive silyl ether, thus making HF/Py a versatile reagent for selective or tandem removal of single or multiple protecting groups in a complex molecule. This approach was validated using NAP, PMB and/or *tert*-butyldiphenylsilyl (TBDPS) protected glycerols (Scheme 1). Selective removal of PMB ether in **5a** in the presence of NAP ether was readily achieved by buffering HF/Py in toluene with triethylamine (Scheme 1, eqn (1)), while selective removal of TBDPS ether in **5b** was effective with HF/Py in pyridine where PMB ether remains intact (Scheme 1, eqn (2)).

We further examined the suitability of HF/Py-mediated NAP ether cleavage in complex carbohydrate building block preparations (Scheme 2). As shown with di- and mono-glucosides **6** and **8**, this approach worked very well with allyl, benzyl ethers and esters. It is noteworthy to mention that in both occasions, the glycosidic linkages remained intact, while anhydrous HF, a known agent that can cleave benzyl ether,[8] would simultaneously cleave any glycosidic linkage.[9]

To fully explore the versatility of HF/Py-mediated deprotection of NAP, PMB and silyl ethers, we set out to use it for a strategic assembly of a high-mannose type (HMT) oligosaccharide library. HMT oligosaccharide is the major component of eukaryotic glycoprotein.[10] Moreover, its presence in HIV-1 glycoprotein gp120 rendered it a viable antigen for HIV vaccine development.[11] Structurally, HMT oligosaccharide has three oligomannoside branches, stemming from a core dimannoside (Fig. 1). Previous syntheses including those by the groups of Ito,[12] Wong,[13] Danishefsky[14] and Seeberger[15] relied on either a co-block or a linear assembly strategy that limits the number of possible oligomannosides generated. We envisioned that a dimannoside building block



Scheme 2 Functional group compatibility of HF/Py-mediated NAP ether cleavage. (a) HF–Py (20 eq.), toluene, rt, 2 h; (b) HF–Py (40 eq.), pyridine, rt, 24 h.

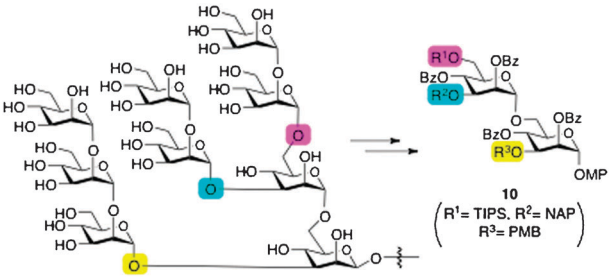
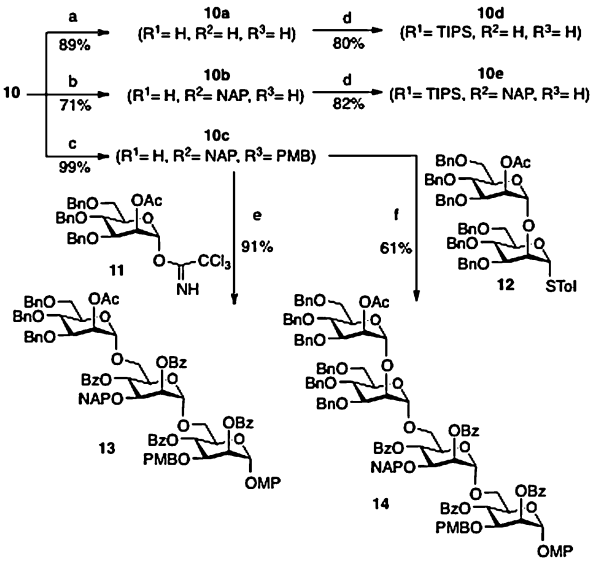


Fig. 1 Structure of HMT oligosaccharide and a retrosynthetic approach from the differentially protected core dimannoside **10**.

10 with three hydroxyl groups at each branch point, masked with triisopropylsilyl (TIPS), NAP and PMB groups, should allow for the facile generation of five mono-, di-, and tri-hydroxyl unmasked dimannosides using the HF/Py-mediated deblocking protocols developed here.

Sequential exposure of **10** with HF/Py in toluene, Et_3N-supplemented toluene and pyridine led to dimannosides **10a**, **10b** and **10c** in excellent yields with a varied degree of hydroxyls unmasked (Scheme 3), while leaving all glycosidic linkages and reducing-end *p*-methoxylphenol (MP) group intact. The TIPS group was readily installed to the primary hydroxyls in **10a** and **10b** to further give **10d** and **10e**. Thus, five dimannosides (**10a–e**) are ready for further diversification with mannosylations. Exemplary glycosylation of **10c** with mannosyl imidate **11** and dimannosyl thioglycoside **12** afforded tri- and tetra-mannoside **13** and **14** in excellent yields. The details of the library synthesis and its application in addressing glycobiology problems will be reported in due course.

In summary, we have disclosed an unprecedented strategy that utilizes 10–20 molar excess of HF/Py in toluene for



Scheme 3 Divergent approach towards an HMT oligosaccharide library using HF/Py-mediated selective removal of NAP, PMB and silyl ethers in dimmanoside **10**. (a) HF–Py (20 eq.), toluene, rt, 2 h; (b) HF–Py (20 eq.), Et_3N (3 eq.), toluene, rt, 12 h; (c) HF–Py (40 eq.), pyridine, rt, 24 h; (d) TIPSCl, Imid, CH_2Cl_2, rt, 16 h; (e) $TBSOTf_{(cat.)}$, CH_2Cl_2, 0 °C, 20 min; (f) NIS, $TMSOTf_{(cat.)}$, CH_2Cl_2, 0 °C, 45 min.

selective removal of NAP ether in the context of complex carbohydrate synthesis. With proper buffering, HF/Py is shown to be a versatile reagent for selective differentiation of NAP, PMB and silyl ethers, as exemplified in a straightforward generation of five dimannoside structures for a divergent HMT oligosaccharide library synthesis. The unique reactivity of NAP ether towards acids, as shown here, is expected to have this protecting group strategy find more applications in complex molecule synthesis. Exploring the NAP group as well as related analogues in complex carbohydrate assembly is currently undergoing in our laboratory.

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