Tetrahedron 67 (2011) 5750–5761

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

1-Methyl 1′-cyclopropylmethyl (MCPM) as an anomeric protecting group

Siu Hong Yu, Dennis M. Whitfield *

National Research Council, Institute for Biological Sciences, 100 Sussex Drive, Ottawa, ON, Canada K1A 0R6

ARTICLE INFO

Article history:
Received 21 April 2011
Received in revised form 30 May 2011
Accepted 31 May 2011
Available online 13 June 2011

Keywords:
Protecting group
Glycolipid
Glycopeptide
Oligosaccharide

ABSTRACT

A pragmatic approach for preparing glycoconjugates of complex oligosaccharides is to prepare the oligosaccharide as a building block with most of its protecting groups exchanged to protecting groups whose cleavage and other manipulations are highly compatible with the functional groups of complex aglycones. For such an approach the reducing end sugar of the building bloc must be protected with a cleavable protecting group during the oligosaccharide synthesis. We demonstrate that the acid labile 1-methyl 1′-cyclopropylmethyl (MCPM) can be effectively used for this purpose. A trisaccharide glycolipid and a disaccharide glycoamino acid are prepared. The absolute chirality of the MCPM in one key acceptor is determined by a combination of NMR NOE measurements, DFT molecular modeling and Noyori catalyst catalyzed asymmetric reduction.

1. Introduction

In order to meet the increasing demand for oligosaccharides and their related glycoconjugates it is often advantageous to prepare oligosaccharide building blocks that can be subsequently converted into oligosaccharide donors.[1] Such donors can be reacted with an array of aglycones. Since the aglycones in many glycoconjugates are often expensive or sensitive to the reagents used in functional group manipulations it is often practical to minimize functional group transformations post glycosylation.[2] Our research group is involved in the preparation of various glycoconjugates including glycolipids and glycopeptides. For example, we recently synthesized a series of Man(α1→2)$_n$Man(α1→O)Arch (n=0–4) where Arch is a glycerol derived diether lipid from the domain *archaea* named archaeol. Immunological experiments showed that the trisaccharide and tetrasaccharides were the most active giving both major histocompatibility complex type I and type II activation. The initial studies were done by sequential glycosylations with donor **1**,[4] see Fig. 1. Thus, the relatively expensive archaeol lipid had to be carried through multiple glycosylation, deprotection steps followed by overall deprotection. We reasoned that synthesizing a trisaccharide donor with only *O*-acetyl groups could be more efficient due to minimizing the steps with the lipid. Since this trisaccharide is frequently found in cell surface oligosaccharides a number of syntheses of similar oligosaccharide donors have been reported.[5] Consequently, a mannose derivative that could be chain extended at O-2 and subsequently converted into an anomeric leaving group such as trichloroacetimidate, was needed.

For another synthetic project we wanted to make the disaccharide GlcNAc(β1→2)Man α-linked to Serine in sufficient quantities to be made into a glycopeptide that could be used to study enzyme specificities. A few syntheses of similar building blocks have been reported.[6] Such glycopeptides are found in the glycoprotein α-dystroglycan and defects in the related glycosyltransferases are correlated with a variety of neuromuscular disease states.[7] Thus, we needed a temporary anomeric protecting group that is stable to hydrogenation conditions. Although the 2-trimethylsilylethanol group[8] likely would work we reasoned that the 1-methyl 1′-cyclopropylmethyl (MCPM) protecting group that was introduced by us could be an attractive alternative. It is an acid

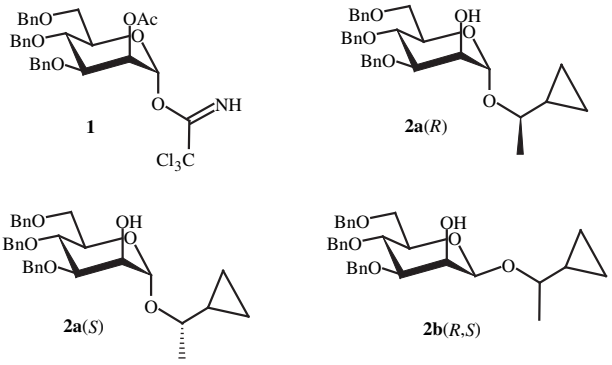


Fig. 1. Structures of donor **1** and target 2-OH glycosides **2a**(*R*,*S*) and **2b**(*R*,*S*).

* Corresponding author. Tel.: +1 613 993 5265; fax: +1 613 952 9092; e-mail address: dennis.whitfield@nrc-cnrc.gc.ca (D.M. Whitfield).

0040-4020/$ – see front matter
doi:10.1016/j.tet.2011.05.133

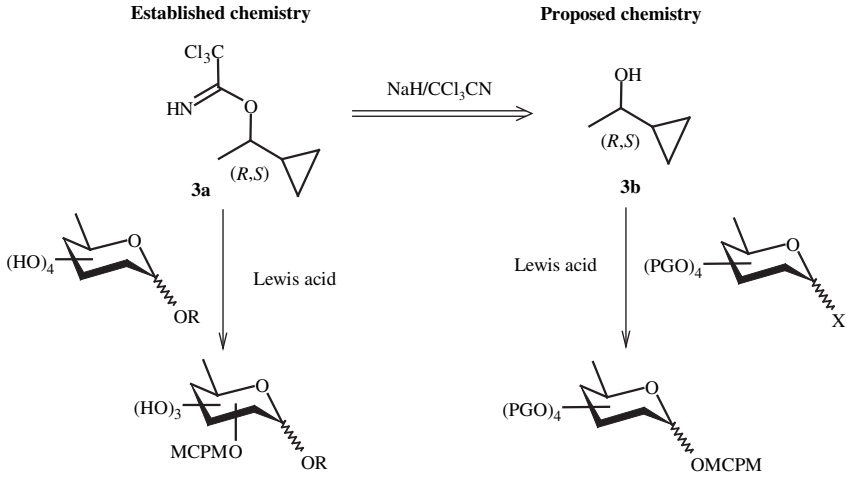
cleavable protecting group orthogonal to many common protecting groups.[9] As well, since it is an ether and relatively small it can be considered an activating protecting group. Its use as an anomeric protecting group was not tested in the previous study. Combining these two synthetic objectives led to a desire to synthesize the anomerically protected 2-OH free glycoside **2ab**, see Fig. 1. The expectation was that the anomeric MCPM group would allow both for functional group transformations and activate the adjacent hydroxyl for glycosylation due to its electron donating potential.[9]

In a previous study, the MCPM group was introduced as an electrophile via trichloroacetimidate **3a**, see Scheme 1.[9] Mild Lewis acids like silver triflate and boron trifluoride etherate were used as activators. Attachment to the anomeric position by glycosylation chemistry requires that alcohol **3b**, which is the synthetic precursor to **3a**, act as a nucleophile. Previous reports from our group with an electronically similar alcohol namely **4** had shown that glycosylation chemistry led to styrene **5** as the major by-product, see Scheme 2.[10] We reasoned that styrene **5** was generated by elimination from the corresponding resonance-stabilized carbenium ion derived from **4**. Since the MCPM is cleaved by Lewis acids or Bronstead acids in the presence of nucleophiles, glycosylation with alcohol **3b** was previously deemed difficult and had never been explored. In addition, we have determined that the MCPM is stable to 5% TFA in CH_2Cl_2 but partly labile to 7.5% and completely labile to 10% TFA, which contrasts with methoxybenzyl protecting group, which is labile to 5% TFA in CH_2Cl_2.[9]

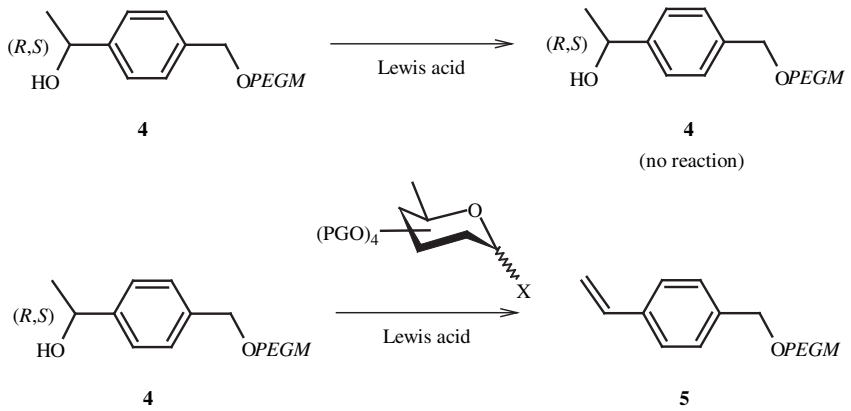
2. Results and discussion

To implement this strategy we reacted well known donor **1** with the commercially available racemic alcohol 1-methyl 1′-cyclopropylmethanol under standard glycosylation conditions with triethylsilyl trifluoromethanesulfonate to yield an inseparable α/β (85/15) of the (*R*/*S*)-MCPM glycosides **6a** and **6b**, respectively, see Scheme 3. The yield was only 65% possibly reflecting the anticipated reactivity difficulties but still sufficient to continue the synthesis. The acetates in **6a** and **6b** were readily removed under Zemplen conditions to give the desired acceptor mixture **2ab**. This mixture could be glycosylated with donor **1** to **7ab**, deacetylated to **8ab**, glycosylated again with donor **1** to trisaccharide **9ab**. All transformations proceeded smoothly indicating the stability of the anomeric MCPM group to glycosylation conditions. Since the MCPM group is orthogonal to most hydrogenation conditions the *O*-benzyl groups were removed at this stage by standard Pd catalyzed hydrogenation. Subsequent acetylation led to peracetyl trisaccharides **10ab** in 50% yield for two steps. Then the MCPM group was cleaved with 10% TFA in CH_2Cl_2 to yield the α/β-hemiacetal **11ab**, which was readily transformed into known α/β-trichloracetimodyl donor **12ab**.[11]

The lipid archaeol could then be glycosylated with the promoter silver trifluormethanesulfonate (AgOTf)[12] to give in 61% isolated yield pure α-glycoside **13a** after separation from traces of β-glycoside **13b** by careful silica gel chromatography. After Zemplen



Scheme 1. Switching of reactivity to introduce the MCPM group from the established electrophilic route to a nucleophilic route.



Scheme 2. Glycosylation dependent elimination reaction of an alcohol (**4**) that can form a resonance-stabilized carbenium ion.