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Graphical Abstract

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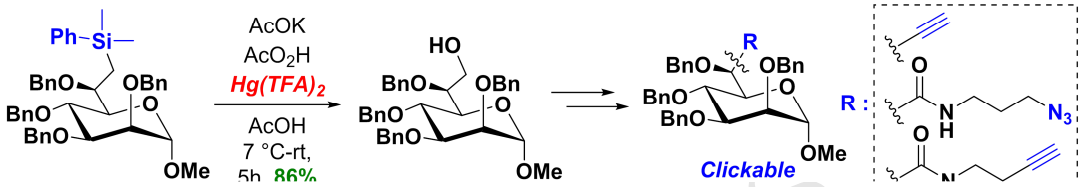


Multigram-scale Synthesis of L,D-heptoside Using a Fleming-Tamao Oxidation promoted by Mercuric Trifluoroacetate

Tianlei Li,[a] Abdellatif Tikad,[a] Maxime Durka,[a] Weidong Pan,[b] and Stéphane P. Vincent,[a,]*

[a] *Department of Chemistry, University of Namur, Rue de Bruxelles 61, 5000 Namur, Belgium.*

[b] *The Key Laboratory of Chemistry for Natural Products of Guizhou Province and Chinese Academy of Sciences 202, Sha-chong South Road, Guiyang 550002, P. R. China.*

Keywords: Heptose, Fleming-Tamao oxiadation, Homologation, Grignard addition, Lipopolysaccharide.

Abstract: An efficient multigram-scale synthesis of methyl 2,3,4,6-tetra-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranoside from methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside is reported. It involves a sequence of Swern oxidation, Grignard addition and Fleming-Tamao reactions. The resulting scaffold was used as a precursor to design a small library of clickable L-heptosides. This study shows that the use of mercuric bistrifluoroacetate is required both to accelerate and to cleanly perform the Fleming-Tamao oxidation, without side-reactions.

Introduction

The preparation of ‘‘higher-carbon sugars’’ such as heptoses has been investigated for more than a century. L,D-heptosides (L-*glycero*-D-*manno*-heptopyranosides) are found in important bacterial glycolipids such as lipopolysaccharide (LPS) but they are not commercially available. The biological relevance of this carbohydrate is illustrated by the fact that its biosynthesis is targeted for the development of novel antibacterial agents. Indeed, Gram-negative bacteria lacking the heptose units display the deep rough phenotype[1] and show a reduction in outer membrane protein content, an increased sensitivity towards detergents or hydrophobic antibiotics and are much more susceptible to phagocytosis by macrophages.[2] Molecules **1**-**3** represented in Figure 1 are typical examples of L,D-heptosides designed to inhibit heptosyl processing enzymes : **1** is a conformational probe,[3] **2** a donor substrate

* Corresponding author. Tel.: +32 (0) 81724521; fax: +32 (0) 81724517; e-mail: stephane.vincent@unamur.be

analogue of bacterial heptosyl transferase WaaC[4] and glycofullerenes **3** was shown to inhibit WaaC in a multivalent manner.[5]

Synthetic LPS fragments containing heptosides have also been used to develop synthetic vaccines or diagnostic tools.[6] Such an approach may aid the design of a protective immunization against many pathogenic gram negative bacteria.[7]

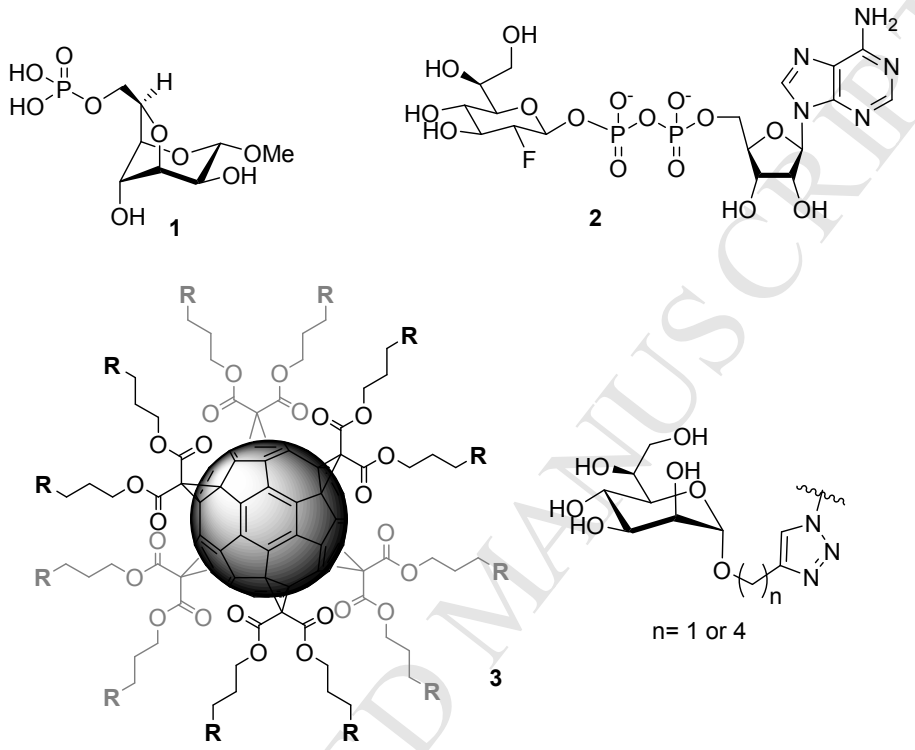
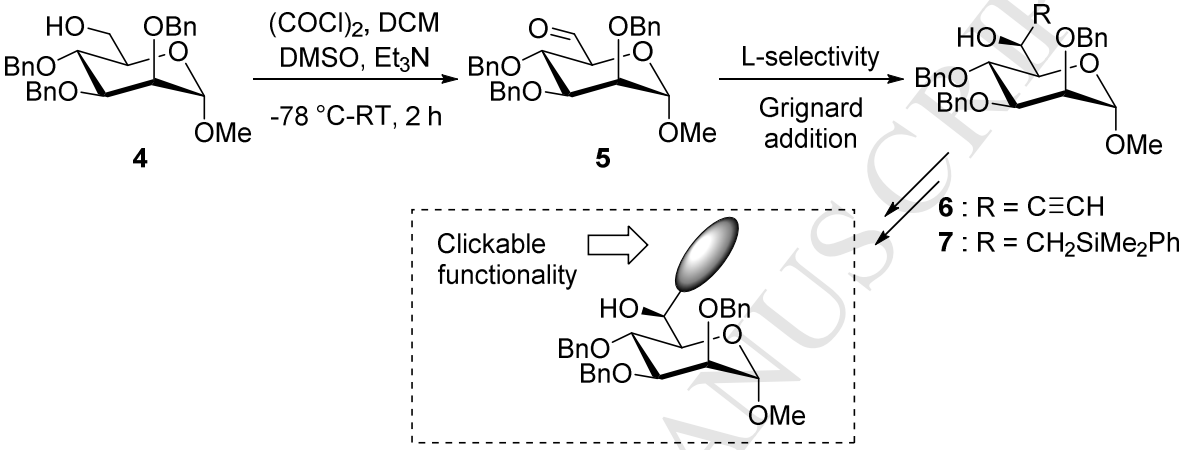


Figure 1 Typical L,D-heptosides designed as inhibitors of heptosyl processing enzymes.

Due to their biological interests, heptosides and their glycomimetics have attracted the attention of synthetic chemists. Among other methods (see our recent review[8]), the one carbon homologation via a Grignard approach from an aldehyde generated at C-6 of D-mannopyranosides usually affords heptose derivatives in good yields and high stereoselectivity in favor of the L-*glycero*-isomers (Scheme 1).[9] It must be stressed that alkoxy-methyl Grignard reagents easily decompose and high yields of reactions depend strongly on the quality of the chloromethyl ethers used. Alternately, α-silylmethyl Grignard reagents are stable under standard conditions and exhibited the highest L-selectivity especially when they are hindered.[10] In addition, organosilanes have broad application in total synthesis and are used as "masked hydroxy groups" thanks to the Fleming-Tamao oxidation.[11]

In the late 1980's, a convenient diastereoselective hydroxymethylation of a suitably protected

pyranoside was developed by van Boom and collaborators. [9e, 10, 12] As an example, treatment of perbenzylated α-D-*manno*-hexodialdo-1,5-pyranoside **4** with the Grignard reagent generated from dimethylphenylsilylmethyl chloride gave diastereoselectively the silane **7**. Cleavage of the carbon-silicon bond in **7** by a Fleming-Tamao oxidation, in the presence of peracetic acid and potassium bromide, afforded the diol displaying the L-configuration at C-6.[12c]



Scheme 1 L,D-Heptose synthesis via a Grignard homologation.

For instance, this strategy was used to synthesize a trisaccharide from the inner core region of *Nesseria meningitidis* LPS,[12a] and ADP-heptopyranose derivatives.[13] However, during our own synthetic investigations, several problems were encountered during the Fleming-Tamao oxidative cleavage of the C-Si bond. Several by-products such as the Peterson elimination product appeared under the usual conditions, sometimes in substantial amount. Using this procedure, we observed that the yields were very dependent on the scale of the reaction, and generally were lower on a large scale.

Here we describe the large scale synthesis of L-*glycero*-D-*manno*-heptosides **13** designed as a precursor to generate clickable L-heptoside derivatives displaying an azido or an alkyne group. Our procedure involves the van Boom's sequence: a Grignard addition followed by a Fleming-Tamao oxidation catalyzed by mercury trifluoroacetate. The targeted molecules have been designed to generate libraries of heptose glycomimetics as ligands or inhibitors of heptose processing enzymes and heptose binding lectins.

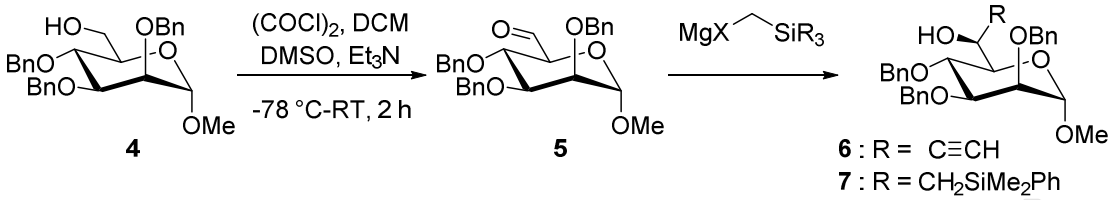
Results and Discussion

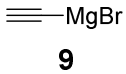
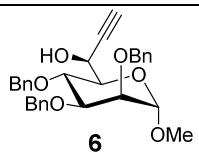
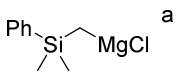
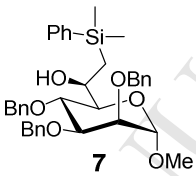
As mentioned above, we privileged, for this study, the van Boom's strategy[9e, 10a, 12a, 12c] depicted in Scheme 1. This sequence employs (phenyldimethylsilyl)-methylmagnesium chloride **8** (Table 1, entry 2) as a very convenient reagent for the one-carbon elongation. Ethynylmagnesium bromide **9** (entry 3) was also used as nucleophilic Grignard reagent to construct the alkyne heptoses which could directly serve as potentially clickable building block. The organomagnesium **8** was freshly prepared following the procedure detailed in the supporting informations, while ethynylmagnesium bromide **9** is commercially available. Alcohol **4** was prepared following literature's procedures.[14]

The synthesis begins with a Swern oxidation of primary alcohols **4** to afford the corresponding aldehyde **5**. We observed that it is important to assess the purity of aldehyde **5** by ^{1}H NMR is required before engaging it into the next step. Moreover, aldehyde **5** is unstable and decomposes during silica gel chromatography. For this reason, the vacuum-dried crude aldehyde was directly engaged without further purification. In addition, when the temperature is higher than -60 °C during the Swern oxidation, a significant amount of side-products was observed, which dramatically decreased the yield.

Then, aldehyde **5** was reacted with the above-mentioned Grignard reagents to obtain the homologated glycosides **6** and **7** in 89 and 82% yields, respectively (Table 1, entries 1-2). The L-stereoselectivity of these additions is in agreement with the Cram chelate model,[15] in which the pyranose ring oxygen *O*-5 and the exocyclic oxygen of the aldehyde are assumed to chelate the magnesium cation. The silylated Grignard reagent **8** provided the highest stereoselectivity (L/D = 15:1) compared to ethylnylmagnesium bromide **9** (Table 1, entries 1-2). In order to scale up the synthesis of homologated glycosides **6** and **7** and to improve the yield, it was necessary to control the addition rate of the solution of aldehyde **2** and the reaction temperature. This protocol could be scaled up from 100 mg scale to 20 g with reproducible yields (Table 1, entries 3-4).

Table 1. Homologation of methyl mannoside **4** by Swern oxidation followed by Grignard addition.



Entry	Amount of Alcohol **4**	Grignard reagent	Product	Time	Yield (%)[b]	Ratio (L/D)
1	1.6 g	 **9**	 **6**	12 h	82	9:1
2	4.0 g	 **8**[a]	 **7**	15 h	89	15:1
3	10.0 g	**8**	**7**	15 h	90	15:1
4	20.0 g	**8**	**7**	20 h	85	15:1

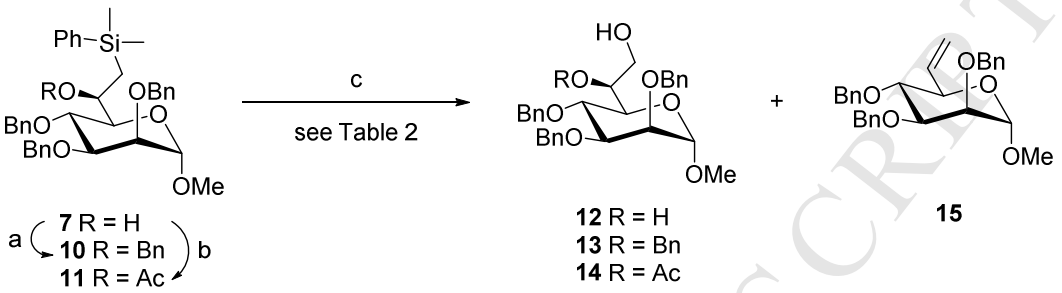
[a] Grignard reagent **8** was freshly prepared; [b] Isolated yields in pure L-heptoside.

Optimization of the Fleming-Tamao reaction

In order to generate the L-heptosides, the cleavage of the C-Si bond by the Fleming-Tamao oxidation was then investigated. In particular, the effect of the C-6 protecting group on this oxidative cleavage was also investigated. To do so, the hydroxyl group at C-6 position of the silane **7** was protected under classical conditions as a benzyl ether **10** and an acetyl ester **11** in excellent yields. As shown in Table 2, the first experiments were carried out using silane **10** as a starting material under standard conditions[10b, 12a-c, 16] in the presence of KBr (1.5 equiv.), AcOK (10 equiv.), AcO_2H (30 equiv.) in AcOH (0.4 M) (Table 2, entry 1). After 2 hours, analysis of the crude ^1H NMR spectrum showed that silane **7** had not completely disappeared and that the desired product **13** had been formed in 44% yield along with 46% of alkene **15** as a side product (Table 2, entry 1). Increasing the reaction time to 5 hours was required for the reaction to go to completion but it did not improve the yield because the Peterson elimination became predominant (Table 2, entry 2). Interestingly, Ley *et al.* described, for the total synthesis of Azadirachtin, that the use of mercuric salts could accelerate the oxidation of dimethylphenylsilanes.[17] Inspired by these impressive results, we

employed $Hg(OAc)_2$, instead of KBr, under the previous conditions. Rewardingly, this protocol modification prevented the side-products formation and the desired L-heptoside **13** was isolated in 90% after 15 hours (Table 2, entry 3). Excellent results were also obtained with $Hg(TFA)_2$ which significantly decreased the reaction time to 2 hours (Table 2, entry 4).

Table 2. Optimization of the Fleming-Tamao oxidation.



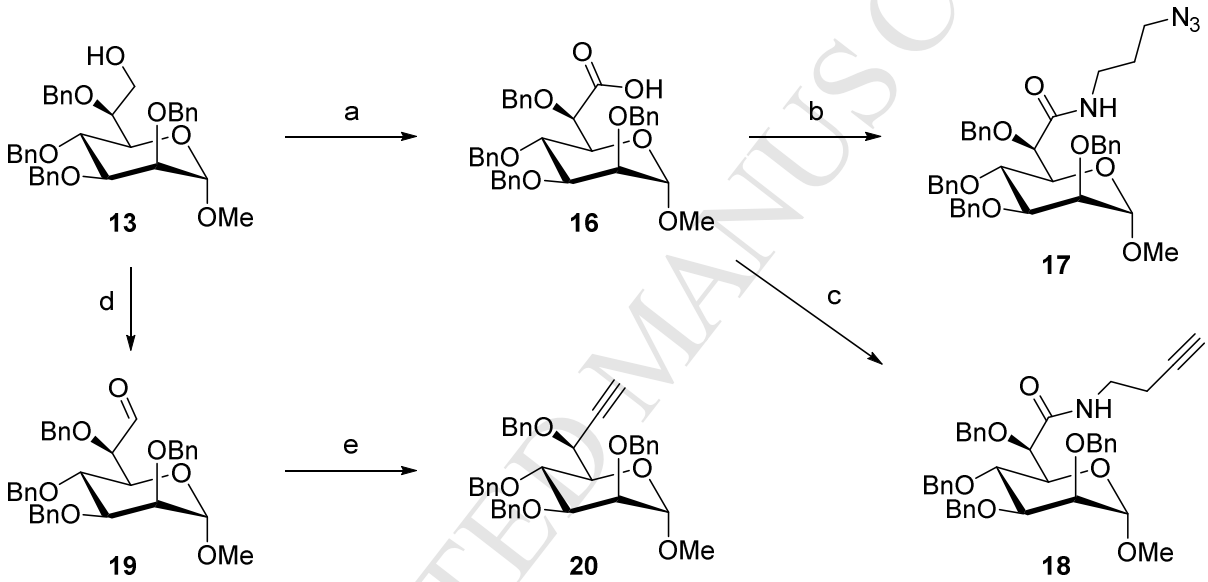
entry	starting material (mass (g))	additive	time (h)	product (yield (%))		
				7, **10** or**11**	**12-14**	**15**
1[d]	**10** (0.1)	KBr	2	**7** (10)	**13** (44)	46
2[d]	**10** (0.1)	KBr	5	-	**13** (44)	56
3[e]	**10** (0.1)	$Hg(OAc)_2$	15	-	**13** (90)	-
4[e]	**10** (0.1)	$Hg(OCOCF_3)_2$	2	-	**13** (90)	-
5[e]	**7** (0.1)	$Hg(OCOCF_3)_2$	4	-	**12** (85)	-
6[e]	**11** (0.1)	$Hg(OCOCF_3)_2$	5	-	**14** (78)	-
7[e]	**10** (0.5)	$Hg(OCOCF_3)_2$	2	-	**13** (89)	-
8[e]	**7** (0.5)	$Hg(OCOCF_3)_2$	5	-	**12** (66)	-
9[e]	**11** (0.5)	$Hg(OCOCF_3)_2$	7	-	**14** (71)	-
10[e]	**10** (5)	$Hg(OCOCF_3)_2$	4	-	**13** (92)	-
11[e]	**10** (10)	$Hg(OCOCF_3)_2$	5	-	**13** (90)	-
12[e]	**10** (15)	$Hg(OCOCF_3)_2$	5	-	**13** (86)	-

Reagents and conditions: (a) BnBr, NaH, DMF, 0 °C-r.t., 15h, 92%; (b) Ac_2O, DMAP, pyridine, 0 °C-r.t., 12h, 95%; (c) All reactions were carried out in the presence of: AcOK (10 equiv.), AcO_2H (30 equiv.), AcOH (0.4 M), additives: [KBr (1.5 equiv.), $Hg(OAc)_2$ (2.5 equiv.) and $Hg(OCOCF_3)_2$ (2.5 equiv)], at 7 °C for 30 min, then warmed at room temperature.

Under these optimized conditions, the Fleming-Tamao oxidation was also performed starting from **7, 10** and **11**. The results reported in entries 4-9 indicate that protecting groups at C-6 does influence the C-Si bond oxidative cleavage. Indeed, lower yields and longer

reaction times were observed either when an acetate was used as a protecting group instead of a benzyl ether or when the alcohol was not protected (entries 5-10).

Multigram syntheses of L-heptoside **13** were realized starting from 5 to 15 g of **7**. The yields were always reproducible, demonstrating that **10** is the best starting material for this reaction (entries 10-12). In addition, molecule **13** could serve as a central L-heptose scaffold for the construction of L-heptose glycomimetics. The functionalization at the 7-position was chosen based on the fact that the 3D-structure of heptosyltransferase WaaC in complex with the fluorinated analogue **2** (Figure 1) shows that WaaC does not interact with the 7-position of the heptose donor substrate.[2e,4a]



Scheme 2. Synthesis of clickable heptosides using **13** as a central precursor. Reagents and conditions: (a) TEMPO, $PhI(OAc)_2$, CH_2Cl_2/H_2O, 0 °C-r.t., overnight, 68%; (b) 3-azidopropylamine, HBTU, DIPEA, THF, r.t., 12 h, 62%; (c) But-3-yn-1-amine, HBTU, DIPEA, THF, r.t., 12 h, 82%; (d) Dess-Marin Periodinane, CH_2Cl_2, r.t., 4 h; (e) Dimethyl (1-diazo-2-oxopropyl) phosphonate, K_2CO_3, MeOH, 0 °C-r.t., 5 h, 60% over two steps.

In order to synthesize clickable heptose analogues, we then tried to install different clickable functional groups at the heptose 7-position. The heptoside **13** was used as a central scaffold to generate three clickable derivatives which displayed an azido-group or an alkyne at C-7 position with different spacers (Scheme 2). For the synthesis of heptosides **17** and **18** bearing a propyl linker, the primary alcohol **13** was oxidized by TEMPO[18] to give the carboxylic acid **16** which was reacted with primary amines under peptide coupling conditions to afford clickable heptosides **17** and **18** in 62% and 82% yields, respectively (Scheme 2). In parallel, alkyne-glycosides **6** and **20** were prepared by two complementary methods: the first

one, described in Table 1, was based on the addition of ethynylmagnesium bromide to aldehyde **5** giving access to alkyne **6** as a 9:1 diastereomeric L/D mixture. The second one was performed from alcohol **13** in 60% yield over two steps after a Dess-Martin periodinane oxidation followed by a Seyferth-Gilbert reaction.

In conclusion, the efficient access to 2,3,4,6-tetra-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranoside **13** from primary alcohol **4** was realized through a van Boom's sequence consisting in a Swern oxidation immediately followed by a Grignard addition and a Fleming-Tamao oxidation. The latter step was optimized and it was found that the use of mercuric trifluoroacetate instead of sodium bromide was a key parameter to efficiently and reproducibly obtain the desired heptosides, whatever the scale. Moreover, L-heptoside **13** was exploited as a precursor to generate clickable L-heptoside derivatives bearing an azido or an alkyne group. These clickable molecules can now be exploited to generate libraries of potential inhibitors of heptosyl processing enzymes and heptose-binding lectins.

Acknowledgments

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Supplementary Material

Detailed experimental procedures and NMR spectra for all new compounds are available in the supplementary material.

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Professor Stéphane VINCENT
University of Namur

Director of the
Laboratory of Bio-Organic Chemistry

Rue de Bruxelles, 61
B-5000 Namur, Belgique
Tél : +32 (0)81 72 45 21
Fax : +32 (0)81 72 45 17
Stephane.Vincent@unamur.be

Highlights

manuscript entitled "*Multigram-scale Synthesis of L-heptoside Using a Fleming-Tamao Oxidation Catalyzed by Mercuric Trifluoroacetate*".

- Heptosides are important bacterial carbohydrates associated with key cellular functions.
- Heptosides are involved in the pathogenicity and the virulence of some important infectious agents.
- Multi-gram scale synthesis of L,D-mannoheptose, a key component of Lipopolysaccharide
- Clickable heptosides as interesting molecular tools for generating libraries of heptose mimetics.
- Heptose glycomimetics