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A recyclable heavy fluorous tag carrying an allyl alcohol pendant group: design and evaluation toward applications in synthetic carbohydrate chemistry

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ABSTRACT

Toward applications in synthetic carbohydrate chemistry, we converted our previous acid-resistant heavy fluorous tag [$(Rf)_3C{-}CH_2{-}OH$, **1**] to allyl alcohol derivatives [$(Rf)_3C{-}CH_2{-}O{-}(CH_2)_n{-}CH{=}CH{-}CH_2{-}OH$, **3** ($n$=1) or **4** ($n$=3)] by means of olefin cross metathesis. They were then subjected to β-glycosylation reactions by using a series of glycosyl donors, including glycosyl bromide and trichloroacetimidates. The terminal OH group in **3** and **4** was found to be β-glycosylated in moderate yield when 2,3,4,6-tetra-O-benzoyl-D-galactosyl trichloroacetimidate was used as the glycosyl donor. Upon a detachment reaction using $Pd(PPh_3)_4$, the initial heavy fluorous tag **1** was recovered in high yield (>90%) together with 1-hydroxy sugar, indicating that not only the allyl ether linkage in the glycosides but also the internal di-alkyl ether linkage in **4** be cleaved by the action of the Pd-catalyst enabling long-range olefin transmigration. Potential utility was demonstrated by using the tetra-O-benzoyl-β-D-galactosylated derivative of **3** in a series of deprotection, protection and glycosylation reactions, which were conductible in high yields without using chromatographic purification process. These findings prompt us to propose a general scheme in which the acid-resistant heavy fluorous compound **1** is applied as a recyclable tag in synthetic carbohydrate chemistry.

1. Introduction

Recent chemical techniques for fluorous liquid–liquid extraction (F-LLE) and fluorous-tagging synthesis are based on a unique physicochemical property of highly fluorinated (heavy fluorous) compounds: they can be selectively partitioned into fluorous solvents and thus can be easily separated from non-fluorous compounds.[1,2] Their potential utility has been examined in a wide range of chemistry, including catalytic chemistry, combinatorial chemistry, and green chemistry.[3] Our group has demonstrated the utility of the heavy fluorous-tagging method in synthetic carbohydrate chemistry, including for the chemical synthesis of cell-surface oligosaccharide chains and the design and development of new heavy fluorous tags for carbohydrate molecules.[4–15] Recently, we reported an acid-resistant heavy fluorous tag **1** and its derivatives **2** (**2a** and **2b**) (Fig. 1).[16] The chemical backbone of these tags was highly stable under acidic conditions and also tolerated various chemical reactions. For example, when the ether derivative **2a** is treated with BBr_3, a bromide derivative **2b** can be derived quantitatively without affecting the inner ether linkage vicinal to the heavy fluorous chains.

Here, we converted the acid-resistant tag **1** to allyl alcohol derivatives **3** and **4** (Fig. 1), expecting that the terminal OH group would be suited not only to O-glycosylation but also to detachment owing to the functionality of the allyl alcohol being used in solid phase synthesis.[17–19] In this paper, we report the synthesis of **3** and **4** starting from **1** by using an olefin cross metathesis.[20–22] The derived allyl alcohols were subjected to O-glycosylation under various conditions and then to a release reaction at sugar moiety using a palladium catalyst.[23,24] We report herein also an unexpected result: upon treatment of O-glycosides of **3** and **4** with $Pd(PPh_3)_4$, both the terminal O-glycosidic linkage and the inner ether one even in the alkyl chain **4** could be cleaved to afford a 1:1

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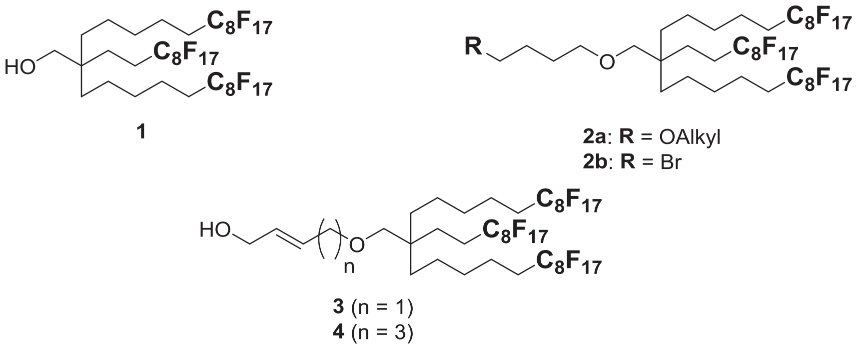


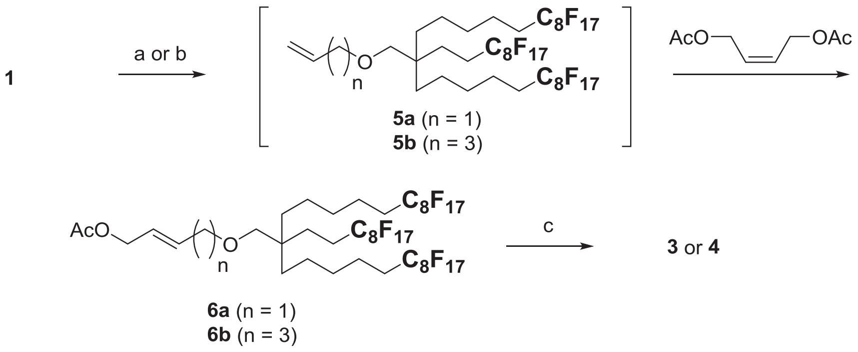
Fig. 1. Acid-resistant heavy fluorous tag **1** and its derivatives **2**–**4**.

mixture of **1** (or its O-acetate derivative) and 1-hydroxy sugar. We wish to demonstrate the potential utility of **1** and its allyl alcohol derivatives **3** and **4** in synthetic carbohydrate chemistry.

2. Results and discussions

2.1. Synthesis of allyl alcohol derivatives 3 and 4

The allyl alcohols **3** and **4** were synthesized by using an established chemical route as summarized in Scheme 1. Synthesis of **3** was started with the Williamson ether formation of **1** by using allyl bromide in a manner as we our previously reported,[16] while that of **4** was done with 5-bromo-1-pentene to afford an alkenyl ether **5b**. Next, an olefin cross metathesis reaction was conducted between **5** and a *cis*-2-butene-1,4-diol derivative[25] by using a Hoveyda–-Grubbs 2nd generation catalyst[26] to afford mixtures of allyloxy acetates **6** together with their (*Z*)-isomers (*E*/*Z*=11/1 from **5a** and *E*/*Z*=8/1 from **5b**, respectively), and the *E*-isomers of **6a** and **6b** were isolated by chromatography on silica gel using a mixture of *n*-hexane and EtOAc (30:1) as eluting solvents. After deacetylation with sodium methoxide in a mixture of MeOH and HFE7100, the target compounds **3** and **4** were obtained. Here, it may be worthy of notifying that all of the heavy fluorous products in Scheme 1 could be purified easily with an F-LLE methodology owing to the presence of the three heavy fluorous alkyl chains extending symmetrically from the quaternary carbon.



Scheme 1. Conversion of **1** to allyl alcohol derivatives **3** and **4**.

Reagents and conditions: (a) (i) for **5a**: allyl bromide, NaH, 15-crown-5, THF, rt, 16 h; (ii) Hoveyda–Grubbs 2nd generation catalyst, Et_2O, reflux, 18 h, 76%, (2 steps); (b) (i) for **5b**: 5-bromo-1-pentene, NaH, NaI, 15-crown-5, THF, rt, 23 h, 45%; (ii) Hoveyda–-Grubbs 2nd generation catalyst, Et_2O, reflux, 24 h, 87%; (c) NaOMe, MeOH, HFE7100, rt; 17 h, 92% for **3** or 3 h, 98% for **4**.

2.2. Attachment and detachment of carbohydrate derivative on the heavy fluorous tag

In the case of the allyl alcohol **4**, an O-glycosylation reaction was examined carefully by using tetra-O-acetyl or tetra-O-benzoyl-D-galactopyranosyl donors (Table 1) carrying a series of leaving groups at the anomeric carbon, namely β-O-acetate, α-bromide, β-*S*-Mbp (2-methyl-5-*tert*-butylphenylthio),[27] and α,β-O-trichloroacetimidate.[28] The molar ratio of the donor was set at a three times excess of the acceptor **4**, and the promoter was changed according to the type of leaving group. When tetra-O-acetyl derivatives were used as donors, the O-acetyl derivative of **4** was derived as a major product regardless of the leaving group used. For example, our objective, *i.e.* O-glycosylated derivative **7**, could be obtained in 34% yield together with the 1-O-acetylated byproduct (58%) when a 1-trichloroacetimidyl donor was employed (Entry 4 in Table 1). The undesired transacylation reaction seemed to occur through orthoester formation at the donor 1,2-position and may be pronounced under fluorous solvent conditions (HFE7100). The side reaction was eliminated to a considerable extent when 2,3,4,6-tetra-O-benzoyl-D-galactopyranosyl trichloroacetimidate was employed as glycosyl donor, by which β-galactopyranoside **8** was obtained in 62% yield (Entry 5 in Table 1) together with a O-benzoylated tag (ca. 30% yield). The two products could be separated quite easily from the other non-fluorous sugar derivatives by the F-LLE technology. Moreover, the targeted product **8** could be isolated from the side *trans*-acylation product by chromatography on silica gel using a mixture of *n*-hexane and EtOAc (10:1) as eluting solvents.

When the optimized reaction conditions were adapted to the 1,2-*trans*-glycosylaion on another tag **3**, a β-galactosylated product **9** was obtained successfully (70% isolate yield) (Scheme 2). The bi-allyl tag **3** was found to possess a similar or even higher activity as