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# Methylsulfonylethoxycarbonyl (Msc) and fluorous propylsulfonylethoxycarbonyl (FPsc) as hydroxy-protecting groups in carbohydrate chemistry

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ABSTRACT

The methylsulfonylethoxycarbonyl (Msc) group is presented as a non-lipophilic, base-labile, participating protecting group for carbohydrate alcohols. It can be introduced using Msc–Cl and pyridine and is readily cleaved via β-elimination under mild basic conditions. Its fluorous counterpart, the perfluorooctyl propylsulfonylethoxycarbonyl (FPsc) group, is used in a 'light fluorous' trisaccharide synthesis sequence.



The development of new protecting groups is important in synthetic organic chemistry.[1] In the field of carbohydrate chemistry, protecting groups occupy a central position and an effective protecting group strategy is at the heart of every complex oligosaccharide synthesis.[2] New protecting groups in carbohydrate chemistry improve the efficiency with which oligosaccharides can be assembled.[3] In this respect, fluorous-protecting groups have attracted considerable attention.[4] Installment of a 'light' fluorous group in a molecule allows for easy separation from non-fluorous compounds using fluorous silica gel chromatography, in a so-called fluorous solid phase extraction (FSPE) process.[5] A variety of fluorinated protecting groups have been reported to date, including fluorous analogues of benzyl[6] and benzyloxycarbonyl,[7] *tert*-butyl[8] and *tert*-butyloxycarbonyl,[9] pentenyl,[10] trityl,[11] benzylidene,[12] and various acyl[13] and silyl-based[14] groups. We recently introduced the fluorous methylsulfonylethoxycarbonyl (FMsc, **2**, Fig. 1)[15] group as an amine-protecting group in peptide chemistry. The FMsc-group was used as a purification tag for a peptide assembled using Fmoc-based solid phase peptide synthesis. After purification of the peptide using fluorous HPLC (FHPLC), in which the fluorinated product was separated from non-fluorous deletion sequences, the FMsc group was removed using mild basic conditions. We report here on the use of Msc (**1**, Fig. 1) and its fluorous counterpart, perfluorooctyl propylsulfonylethoxycarbonyl (FPsc, **3**, Fig. 1) as hydroxy-protecting groups in carbohydrate chemistry.

Although Tesser's methylsulfonylethoxycarbonyl (Msc)[16] group is popular for the protection of amino groups, and the methylsulfonylethyl ester has been used to mask carboxylic acids,[17] the related sulfonylethoxycarbonate functionality has not been employed very often for the protection of alcohols.[18,19] We reasoned that Msc could be a favorable alternative to 9-fluorenylmethyl carbonate (Fmoc), which is becoming increasingly popular in carbohydrate chemistry.[20,21] It was expected that the Msc group could be cleaved under similarly mild conditions as those used for Fmoc deprotection, but that it would be sterically less demanding and less lipophilic than bulky Fmoc. In addition, fluorous analogues of Msc can be readily prepared.[22]

As a first objective, we investigated the installation and cleavage of the Msc group on a range of carbohydrate building blocks. As depicted in Table 1, the Msc group is introduced readily using methylsulfonylethoxycarbonyl chloride (Msc–Cl) and pyridine in $CH_2Cl_2$, to both primary and secondary hydroxy functions in the presence of various other functionalities (Table 1, entries 1–6). It can also be introduced selectively to the primary position of a partially protected pyranoside (Table 1, entry 7) by reaction at −20 °C. Several basic cleavage conditions were examined to remove the Msc group from glucofuranose **9** as summarized in Table 2. The use of a catalytic amount of sodium methoxide (NaOMe, 0.1 equiv) in methanol required 18 h to completely remove the Msc group (Table 2, entry 1). Tetrabutylammonium fluoride (TBAF, 0.1 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.1 equiv) on the other hand cleaved the Msc group within 30 min (Table 2, entries 2 and 3). β-Elimination using 30 equiv of triethylamine proceeded slowly and complete deprotection took 20 h (Table 2, entry 4). Cleavage of the Msc group from galacturonic acid lactone **10**[23] was accomplished with DBU without compromising the integrity of the labile lactone ring to afford the deprotected alcohol in 97% yield (Table 2, entry 5). Having established conditions for both installation and cleavage of the Msc group, we next investigated its orthogonality with the levulinoyl (Lev) ester. To this end alcohol **11** was levulinoylated to provide fully protected glucoside **12** (Scheme 1). The levulinoyl group can be cleaved from this

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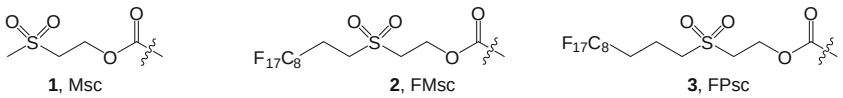
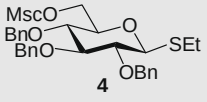
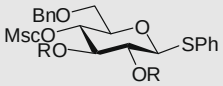
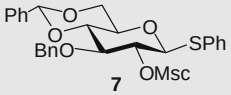
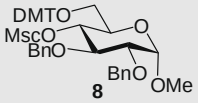
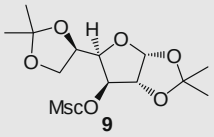
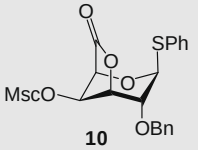
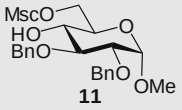



**Figure 1.** The Msc, FMsc, and FPsc protecting groups.

**Table 1**
Installation of Msc on carbohydrate hydroxy groups[a]

| Entry | Product | Temperature | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 |  **4** | 0 °C–rt | 3 | 98 |
| 2 |  **5** R = Bn **6** R = Bz | 0 °C–rt | 5 | **5** (R = Bn) 78 **6** (R = Bz) 76 |
| 3 |  **7** | 0 °C–rt | 4 | 79 |
| 4 |  **8** | 0 °C–rt | 4 | 79 |
| 5 |  **9** | 0 °C–rt | 3 | 95 |
| 6 |  **10** | 0 °C–rt | 3 | 88 |
| 7 |  **11** | −20 °C to rt | 5 | 90 |

[a] Msc–Cl (2 equiv), pyridine (3 equiv), $CH_2Cl_2$ (0.2 M).

**Table 2**
Cleavage of the Msc group

| Entry | Substrate | Conditions | Quantity (equiv) | Time | Yield (%) |
|---|---|---|---|---|---|
| 1 | **9** | NaOMe, MeOH | 0.1 | 18 h | 100 |
| 2 | **9** | TBAF, THF | 0.1 | 30 min | 100 |
| 3 | **9** | DBU, DMF | 0.1 | 25 min | 100 |
| 4 | **9** | $Et_3N$, DCM | 30 | 20 h | 100 |
| 5 | **10** | DBU, DMF | 0.1 | 1 min | 97 |

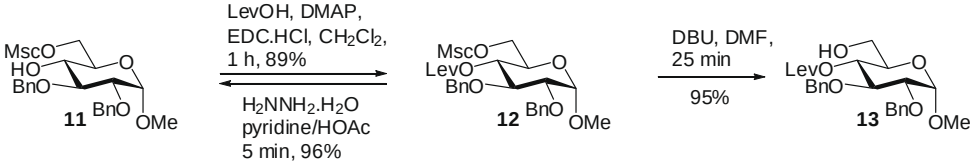
pyranoside without affecting the Msc-carbonate using hydrazine hydrate in a mixture of pyridine and acetic acid. Alternatively, cleavage of the Msc group using a catalytic amount of DBU provided primary alcohol **13** almost quantitatively, showing that the Msc and Lev groups are fully orthogonal.[24,25]

We next investigated the applicability of Msc-protected carbohydrates in a set of glycosylation reactions (Scheme 2). In the first example, the Msc-protected thioglucoside **6** was condensed with methyl glucoside **14** in the presence of *N*-iodosuccinimide (NIS) and a catalytic amount of trimethylsilyl triflate (TMSOTf) to provide disaccharide **15** in 63% yield. The Msc group could be selectively removed from this disaccharide leaving all the benzoyl functionalities untouched. A second glycosylation employed thioglucose **7**, with the Msc group at C2–OH, which was coupled to acceptor **14**. The β-linked dimer **17** was obtained in 74% yield, showing that the methylsulfonylethoxy carbonyl group provided efficient anchimeric assistance in the glycosylation reaction. When this glycosylation was carried out using diphenylsulfoxide ($Ph_2SO$) in combination with trifluoromethanesulfonic anhydride ($Tf_2O$)[26] in the presence of excess tri-*tert*-butylpyrimidine (TTBP),[27] disaccharide **17** was isolated in similar yield (67%). Use of a catalytic amount of DBU, quantitatively liberated the C2′-hydroxy group in **17** to afford **18**. The Msc group was also well tolerated when present in an acceptor building block as shown in the glycosylations in which the perbenzoylated *S*-phenyl glucoside **19** was coupled to primary alcohol **20** and secondary alcohol **11**, respectively. Disaccharides **21** and **22** were isolated in 70% and 64% yields, respectively.

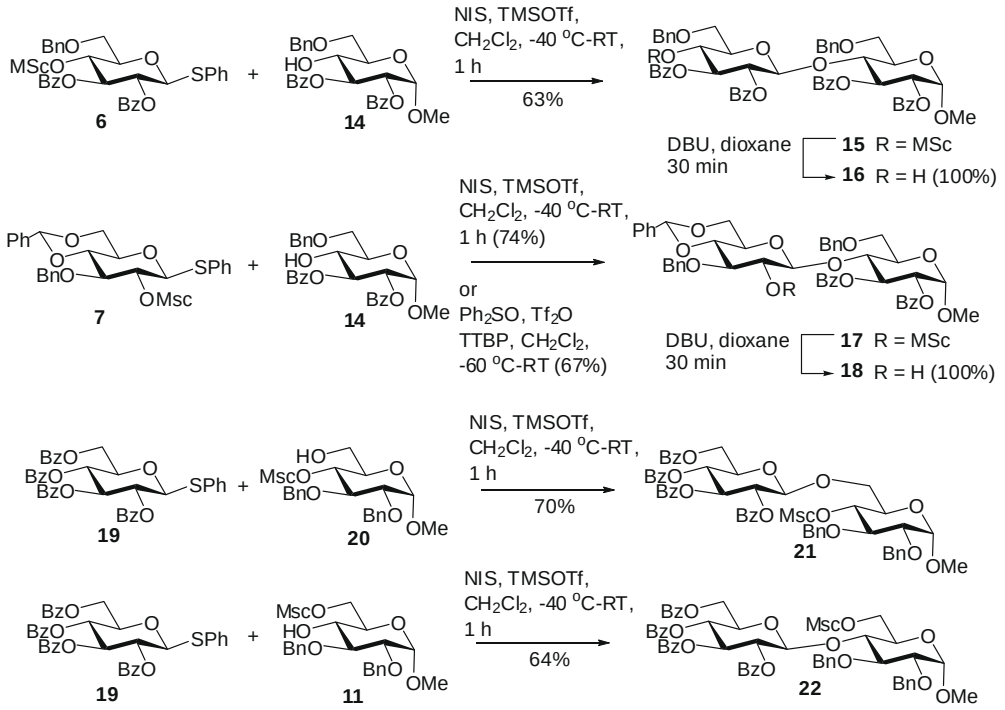
Having established conditions to install and remove the Msc group on carbohydrate alcohols and having studied their behavior under glycosylation conditions, we next focused our attention on the applicability of the fluorous Msc group (**2**, Fig. 1) in oligosaccharide synthesis. Although the FMsc group can be introduced to carbohydrate hydroxy functions under the above-mentioned conditions for the introduction of the Msc group, it soon became apparent that the resulting fluorous carbonate was rather labile. We judged this lability to be the result of the inductive electron-withdrawing effect of the perfluoro chain, which makes the FMsc carbonate very susceptible to β-elimination. Therefore, we decided to develop a new fluorous version of the Msc group, in which the perfluoro part is positioned further away from the sulfonyl group by adding an extra 'insulating' three methylene units, in the form of fluorous propylsulfonylethoxycarbonyl (FPsc, **3**, Fig. 1).

The synthesis of fluorous propylsulfonylethoxycarbonyl chloride (FPsc–Cl, **26**) started from commercially available 3-(perfluorooctyl)propyl iodide,[22] as depicted in Scheme 3. The primary iodide was substituted with mercaptoethanol in refluxing *tert*-butyl alcohol to give thioether **24**, which was oxidized to the corresponding sulfone **25**. Treatment of **25** with phosgene in THF transformed the primary alcohol into the chlorocarbonate **26** (FPsc–Cl).

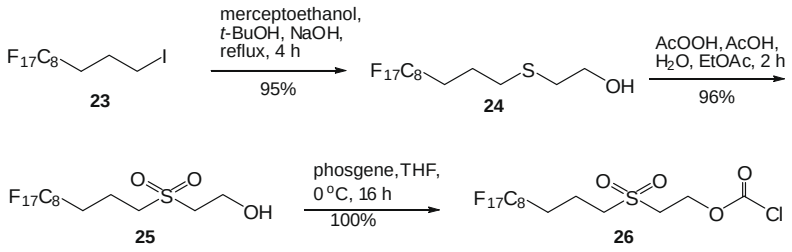
The FPsc group was utilized in the assembly of trisaccharide **33** starting with the selective introduction of the fluorous propylsulf-




**Scheme 1.** Orthogonality of the Msc and Lev groups.

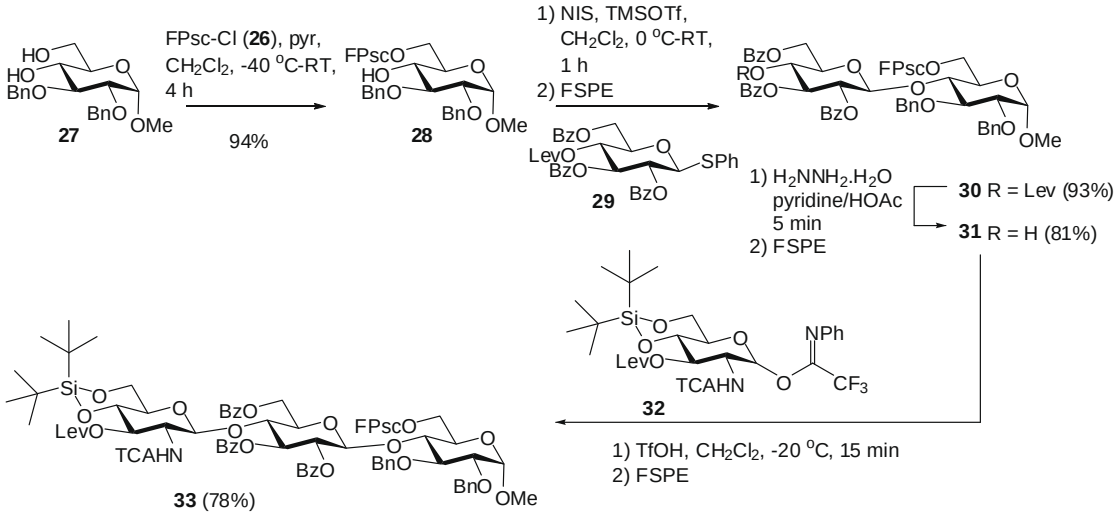



**Scheme 2.** Glycosylation reactions of Msc-containing carbohydrate building blocks.




**Scheme 3.** Synthesis of FPsc–Cl.

onylethoxycarbonate to diol **27** (see Scheme 4).[28] The primary alcohol was selectively acylated using 1 equiv of FPsc–Cl **26** at low temperature to give the acceptor glycoside **28** in 94% yield. This monosaccharide was then treated with an excess of donor **29** (2.6 equiv), bearing a levulinoyl group at C4–OH. TLC analysis showed formation of the desired disaccharide along with the formation of several donor-derived side-products. The disaccharide was purified by FSPE using a gradient of acetonitrile in water (50–100%) to provide the fluorous product **30** in excellent yield. Delevulinoylation of **30** did not affect the FPsc group and alcohol




**Scheme 4.** Oligosaccharide synthesis using the FPsc group.

**31** was obtained uneventfully. Next, the disaccharide **31** was elongated using an excess of (*N*-phenyl)trifluoroacetimidate glucosamine **32**[29] (3 equiv) and a catalytic amount of TfOH at −20 °C. After FSPE, trisaccharide **33** was isolated in 78% yield.[30]

In conclusion, we have reported on the successful introduction of the methylsulfonylethoxycarbonyl (Msc) group as a non-lipophilic alcohol-protecting group in oligosaccharide synthesis. The Msc carbonate can be introduced using standard conditions for the formation of carbonates and can be cleaved using mild basic conditions under which commonly used ester-protecting groups are stable. The Msc group was shown to be fully orthogonal with the levulinoyl group. The carbonate is completely stable to Lewis acidic glycosylation conditions and provides anchimeric assistance when situated at the C2–OH of a glycosyl donor. The fluorous version of Msc proved to be very labile when used as an alcohol-protecting group, and thus the fluorous propylsulfonylethoxycarbonyl (FPsc) group was developed. This fluorous carbonate was used successfully in the assembly of a trisaccharide.

## Acknowledgments

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## Supplementary data

Supplementary data (Detailed experimental procedures and analytical data for all new compounds) associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.146.

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21. During introduction and cleavage of the Fmoc group, dibenzofulvene polymers can be formed which can complicate purification.
22. Fluorous Fmoc–Cl is commercially available from Fluorous Techonologies Inc. for $95/mmol. 3-(Perfluorooctyl)propyl iodide (**22**, Scheme 3) used for the synthesis of fluorous propylsulfonylethoxycarbonyl chloride (FPsc-Cl, **25**) is available from Fluorous Techonologies Inc. for $15/mmol. See http://www.fluorous.com.
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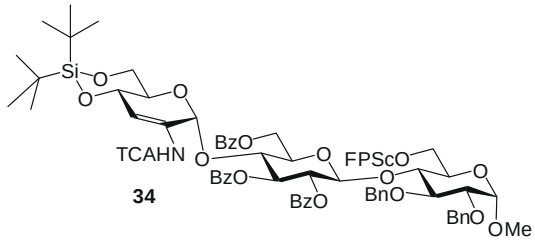
30. When this glycosylation was run at 0 °C a fluorous side-product was formed, which was separated from fluorous trimer **32** by silica gel column chromatography and was determined to be the dehydroglucosamine-coupled product **34**. Formation of this product can be explained by β-elimination of the imidate group of donor **31**, followed by a Ferrier glycosylation on the resulting glycal. Although formation of this kind of side-product is uncommon, it has been reported before.[31]




**34**

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