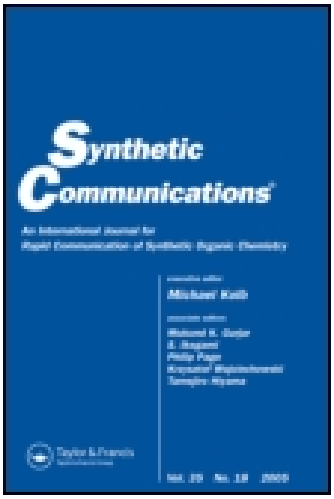

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Simple and Efficient Method for the Protection of Hydroxyl Groups as 4-Methoxybenzyl Ethers

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SIMPLE AND EFFICIENT METHOD FOR THE PROTECTION OF HYDROXYL GROUPS AS 4-METHOXYBENZYL ETHERS

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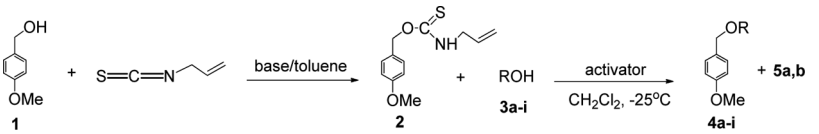
GRAPHICAL ABSTRACT



Abstract *PMB ethers of alcohols are obtained in good yields and under mild conditions using the 4-methoxybenzyl N-allyl thiocarbamate and N-bromosuccinimide (NBS)/TfOH as the catalyst. The present method is very fast, simple, and efficient.*

Keywords 4-Methoxybenzyl alcohol; 4-methoxybenzyl N-allyl thiocarbamate; 4-methoxybenzyl (PMB) ether; 4-methoxybenzyl protection; synthesis of ethers

INTRODUCTION

The synthesis of complex molecules (e.g., natural products) is still a challenge despite tremendous progress in organic synthesis in recent decades.[1] Most multistep syntheses still require numerous protection and deprotection procedures. In response to the increasing complexity of the molecular structures synthesized, a large number of protecting groups have been developed, as well as methods for their introduction and their deprotection.[2–4] Nevertheless, new and more selective protecting groups are still required[5–10] while milder and more selective conditions are actively pursued.[11–14] A desirable protecting group should satisfy the following main criteria: The formation of the installed protecting group must render inert an otherwise reactive site during a synthetic sequence aimed at affecting other regions of the molecular system, the removal (cleavage) of the protecting group must occur easily and under mild conditions at the appropriate point in the synthetic scheme, and, in addition, orthogonal reactivity with other common protecting groups is especially valuable for highly functionalized systems.

The benzyl groups, such as 4-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMB), and others, have been used extensively as protecting groups in carbohydrate

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chemistry.[15] Benzyl ethers are frequently used as protecting groups indispensable to the process of obtaining oligosaccharides.[16,17] Benzylated sugars are among the most popular glycosyl donors. For example, benzyl-protected glycosyl donors are "armed" relative to acylated analogues.[17–19] Deprotection of the corresponding benzyl ethers may be readily accomplished under mild oxidative conditions with, for example, ceric ammonium sulfate (CAN) in acetonitrile[20] or with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dichloromethane.[21]

Traditionally, preparation of arylmethyl ethers from alcohols is accomplished by Williamson ether synthesis protocol under basic conditions, which involves treating the substrate with benzyl halide and a strong base, such as potassium hydroxide.[22,23] Typical benzylation reactions are thus limited to substrates that tolerate basic conditions. Benzylation in the synthesis of selectively protected sugars can be problematic and the selective protection of polyol systems (e.g., carbohydrates) can also be complicated by base-catalyzed migration of esters and silyl ethers. Benzyl trichloroacetamidate, readily obtained from trichloroacetonitrile and benzyl alcohol,[24–28] has been used to prepare benzylated carbohydrate derivatives. The reaction is carried out in the presence of Brønsted acids such as *para*-toluenesulfonic acid, triflic acid, Lewis acids such as BF_3 etherate, $TrBF_4$, TMSOTf, $Sn(OTf)_2$, $TrClO_4$, and $La(OTf)_3$ in a nonpolar solvent such as tetra- or di-chloromethane and cyclohexane.[2–4] The disadvantage of the methods described lies in the application of heavy-metal salts, which are biologically active and thus prohibited in the biological and medical experiments.

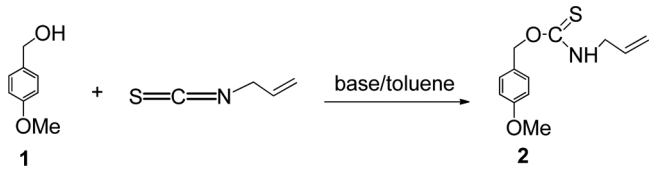
We report here a new method for the protection of alcohols and sugars as the corresponding 4-methoxybenzyl ethers by means of the reaction with a new alkylation reagent PMB N-allyl thiocarbamate (**2**).

RESULTS AND DISCUSSION

In the course of our program toward the synthesis of complex glycosides, we have developed a simple method for activation of anomeric hydroxyl group.[29] We have already reported the synthesis of O-glycosyl thiocarbamates and evaluated them in stereoselective glycosylation. Study of the reaction mechanism leads to the conclusion that the crucial step is activation of thiocarbamate in reaction with an electrophile and the formation of a carbonium ion following nucleophilic substitution at the anomeric carbon atom. Taking this into account, one can expect that the electrophilic activation of benzyl thiocarbamates should lead to a relatively stable benzyl carbonium ion. Our experience with O-glycosyl N-allyl thiocarbamates, which are easily activated, efficient glycosylating reagents for various unstable substrates,[29] encouraged us to try PMB N-allyl thiocarbamate (**2**) as an alkylating agent for alcohols. The preparation of this reagent is relatively simple. The synthesis of **2** is illustrated in Scheme 1.

The PMB alcohol (**1**) can react with N-allyl isothiocyanate under basic conditions to give the PMB N-allyl thiocarbamate (**2**). First, several reaction conditions were examined in the reaction of 4-methoxybenzyl alcohol (**1**) and N-allyl isothiocyanate with various bases. The results are summarized in Table 1.

Potassium carbonate (K_2CO_3) and *N,N*-di-isopropylethylamine (DIPEA) appeared to be too weak as bases for this type of reaction. However, the phosphazene base (BEMP)



Scheme 1. Preparation of PMB N-allyl thiocarbamate.

was too strong and observed in a large number of by-products in these reactions. The optimal method for receiving methoxybenzyl N-allyl thiocarbamate (**2**) as donor protective groups is from the reaction of the corresponding methoxybenzyl alcohol (**1**) with N-allyl isothiocyanate in the presence of a strong nonnucleophilic base, 1,8-diazobicyclo[5.4.0]undec-7-en (DBU), in the microwave. Using a microwave reactor considerably shortened the reaction time, reduced formation of by-products, and significantly improved performance in comparison with the reaction carried out under standard conditions. Thus, the starting materials, 4-methoxybenzyl alcohol (**1**) and N-allyl isothiocyanate were irradiated at 2 W at 50 °C for 1 h in toluene, in the presence of a catalytic amount of DBU and 4 Å micronized molecular sieves (Scheme 1). The method produced the desired product (**2**) at a 90% yield, following purification using column chromatography. This compound is stable and can be stored on laboratory bench tops without degradation for several months.

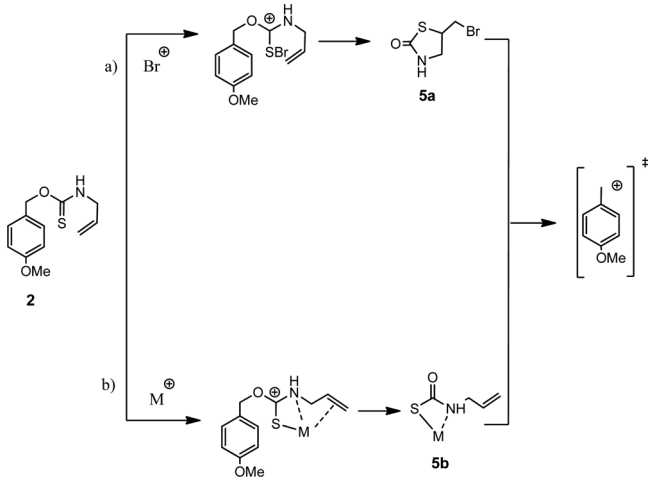
Development and Analysis of the Optimal Benzylation Protocol

Having synthesized thiocarbamate, we turned our attention to the evaluation of their alkylating properties. At a low temperature (−25 °C), the PMB thiocarbamate (**2**) is freely soluble in chlorinated solvents (dichloromethane, chloroform, dichloroethane), in ethereal solvents (THF and ether), and in aromatic hydrocarbons

Table 1. Results from optimization of reaction conditions for preparation of PMB thiocarbamate

Entry	Base	Temp./conditions	Time	Yield[b] (%)
1	K_2CO_3	rt to 50 °C	8 h	—
2		50 °C,)))	4 h	7
3		50 °C, mw	1 h	—
4	DIPEA	rt to 50 °C	8 h	6
5		50 °C,)))	4 h	6
6		50 °C, mw	1 h	7
7	BEMP	rt to 50 °C	1 h	45[c]
8		50 °C,)))	1 h	50[c]
9		50 °C, mw	15 min	55[c]
10	DBU	rt to 50 °C	6 h	65
11		50 °C,)))	3 h	78
12[a]		50 °C, mw	1 h	94

[a]The method at 50 °C in the reactor microwaves was chosen.
[b]Isolated yield of pure product.
[c]In this method a lot of regrouping product was created.



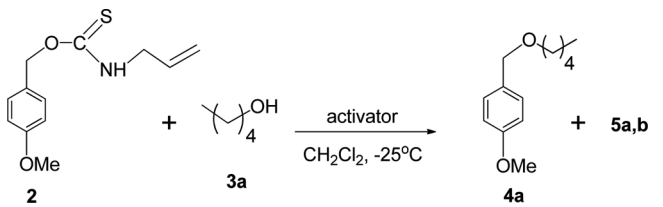
Scheme 2. Activation pathways for thiocarbamate alkylation.

(toluene). Owing to its ability to dissolve, the initial screening of reaction conditions was conducted in dichloromethane (DCM).

Considering the multifunctional character of the leaving group, we anticipated that these could be activated via a number of conceptually different modes. Considering the multifunctional character of O-alkyl-thiocarbamoyl moiety, we have developed activation pathways for their use in alkylation reactions (Scheme 2).

In the first approach (a), a "soft" electrophilic promoter such as a bromonium ion targets the "soft" sulfur of thiocarbamoyl or adds to the double bond (pathway a). The driving force is the formation of the stable heterocycle. In the second approach (b), a metal-salt-based activator (AgOTf or CuOTf) can complex to both sulfur and nitrogen and bring about benzylic activation. Thus, a heavy-metal-salt-based promoter system would complex sulfur and nitrogen, improving the leaving group ability by producing a partial positive charge on sulfur. Alternatively, a thiophilic or electrophilic reagent would act via the a or b pathway. With this consideration in mind, and to evaluate the benzylating properties of PMB thiocarbamate, (**2**) was coupled with n-pentanol in the presence of molecular sieves (MS) in nonpolar solvents (Scheme 3). The results are summarized in Table 2.

Good yields were obtained with thiophilic salts, such as silver or cuprous triflate. Positive results were also observed using a precursor of the halonium ion. NBS and NIS in chemical synthesis are known sources of bromonium and iodonium



Scheme 3. General scheme for optimization of preparation of PMB ether of n-pentanol.

Table 2. Results from optimization of reaction conditions for preparation of PMB ethers of alcohols managed on n-pentanol

Entry	Catalyst	Temp.	Time	Yield[a] (%)
1	$Br_2/LiClO_4/NaHCO_3$	–25 °C	5 min	50
2	AgOTf		1 h	62
3	CuOTf		30 min	63
4	NIS/TfOH/Et_4NTf		15 min	34
5	NBS/TfOH/Et_4NTf		10 min	83

[a]Isolated yield of pure product.

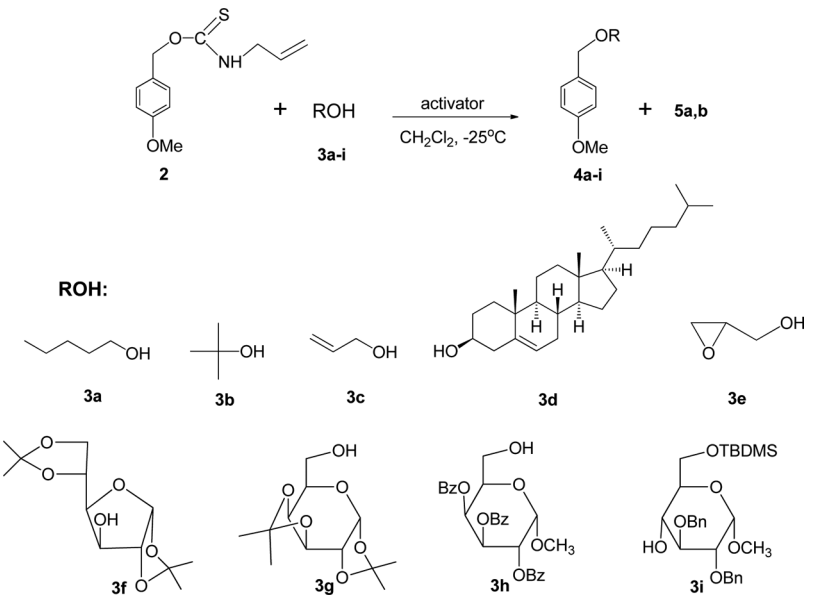
ions, respectively. Both are frequently used together with different additives to increase yields and stereoselectivity. Moreover, NBS and NIS are inexpensive and commercially available reagents. Conditions for the reaction of PMB protection were established using methylene chloride and a temperature of −25 °C. PMB N-allylthiocarbamate (**2**) was used in double excess to alcohol (**3a**) to direct the reaction toward the formation of an asymmetrical ether. Trifluoromethanesulfonate acid (TfOH) served as an additive activating electrophile, whose amount was constantly adjusted with respect to NBS or NIS, comprising 0.1 of its quantity. An anion of strong acid (Et_4NTf) was added to stabilize the carbonium ion, whereas anhydrous conditions were maintained by the presence of 4 Å micronized molecular sieves. As a result, while the reaction of n-pentanol with PMB N-allyl thiocarbamate in the presence of NBS gave 83% of the desired product (**4a**) within 10 min, the reaction activated by NIS gave only 34% within 15 min.

Another approach involved activation of the PMB group donor with the aid of Br_2, which is characterized by the ability of exceptionally rapid addition to the double bond of the allyl group. The application of bromine necessitates the introduction of an acceptor (salt) for evolved hydrogen bromide. Thus, reaction was carried out in CH_2Cl_2 at a temperature of −25 °C, in the presence of $NaHCO_3$ as HBr acceptor. As expected, the reaction was completed within 5 min, but the yield was rather poor, only 50%. Differences in the promoting activity of NBS, NIS, and Br_2 are clearly shown in Table 2.

In addition to the desired benzyl ether, a by-product was observed in the crude product mixture: 1,3-thiazolone (**5**) (Scheme 2). 1,3-Thiazolone was identified as an expected by-product of the benzylation reactions using **2**. It is freely water soluble and easily removed by aqueous extraction.

The mechanistic course of alkylation reaction using **2** undoubtedly falls along the continuum between the S_{N1} and S_{N2} pathways (Scheme 2). Although we have not performed detailed kinetic studies, formation of thiazolone **5** appears to be more consistent with an S_{N1} mechanism. Addition of a bromonium ion to an allylic double bond is expected to produce a halonium intermediate followed by alkylation of the thiocarbonyl group. The formation of a stable heterocycle is the driving force of alkylation. Activation of **2** provides a highly electrophilic species that is quickly trapped by the alcohol.

Having established the preferred reaction conditions, PMB protection of n-pentyl alcohol was performed to demonstrate the versatility of the present chemical route. Scheme 4 illustrates the benzylation reactions of various alcohols



Scheme 4. PMB protection of representative alcohols.

and sugars containing one unprotected hydroxyl group under our preferred conditions. Primary (**3a**), secondary (**3d**), and tertiary (**3b**) alcohols reacted with PMB N-allyl thiocarbamate to give corresponding ethers in good yields (Table 3). Similarly, good yields were obtained in the case of allyl alcohol (**3c**) and epoxy alcohol–glycidol (**3e**). Reactions were carried out in DCM as a solvent, with a double excess of **2** as the PMB donor. In each case examined, the reaction was complete in approximately 10 min, as monitored by thin-layer chromatography (TLC). The structure of these products was confirmed by ^{1}H NMR and ^{13}C NMR analysis and compared with published reports.

The tolerance of this protocol for sensitive functionality will be determined in due course, but for an initial data point we tested our benzylation reaction in the presence of a primary silyl ether (**3i**). The desired benzyl ether was obtained in excellent yields, and the silyl ether was recovered unchanged. It was observed that

Table 3. Data from PMB protection of representative alcohols

Entry	Substrate	Isolated yield (%)
1	**3a**	83
2	**3b**	80
3	**3c**	70
4	**3d**	80
5	**3e**	72
6	**3f**	78
7	**3g**	81
8	**3h**	85
9	**3i**	84

conventional acetal (**3f, 3g**) and acyl (**3h**) protecting groups are stable under the proposed conditions.

In summary, the reaction of alcohols with **2** in the presence of NBS and catalytic amounts of triflic acid rapidly affords the corresponding PMB ethers in good yields. The short reaction time, low catalyst loading, along with ease of handling and tolerance of protective groups render this an effective method for the preparation of PMB ethers.

CONCLUSION

Stimulated by an increasing need for selective protection strategies, this synthesis has provided a convenient route to obtaining PMB derivatives of alcohols and sugars. A mild protection method, preserving the integrity of both alkaline- and acid-labile protective groups, was developed. In summary, the PMB derivative of N-allyl thiocarbamate upon treatment with N-bromosuccinimide (NBS), in the presence of a catalytic amount of trifluoromethanesulfonic acid (TfOH), a carbocation-stabilizing salt (Et_4NTf), and 4 Å molecular sieves, transfers the PMB group to a free hydroxyl of alcohol or sugar.

EXPERIMENTAL

Proton magnetic resonance spectra were recorded with a Varian 300-MHz spectrometer for solutions in $CDCl_3$. Chemical shifts are reported in (δ) ppm relative to the tetramethylsilane (TMS) peak at $\delta = 0.0$ ppm (^{1}H spectra). Mass spectra were recorded on an electrospray ionization (ESI) mass spectrometer, ABSciex System 4000 QTRAP, at positive and negative modes of ionization. TLC was performed on precoated plates of silica gel $60F_{254}$ (Merck), using hexane/ethyl acetate (3:1 v/v) or toluene/ethyl acetate (8:1 v/v), and the spots were visualized by spraying with sulfuric acid and palladium chloride. Chromatographic purification was performed on silica gel 60 (Merck), 0.063–0.2 mm. All solutions were concentrated under diminished pressure at 40 °C. Organic solutions were dried over anhydrous $MgSO_4$.

Synthesis 4-Methoxybenzyl N-Allyl Thiocarbamate (2)

4-Methoxybenzyl N-allyl thiocarbamate (**2**) was prepared according to procedure of alcohol thiocarbamate preparation in a microwave reactor. A solution of corresponding alcohol (138 mg, 1 mmol) in toluene was stirred at room temperature for 20 min in the presence of 4 Å micronized molecular sieves (10 mg). Suitable base (Table 4) and N-allylisothiocyanate (0.39 ml, 4 mmol) were added and subsequently reaction mixture was exposed to microware irradiation (2 W) for 1 h at a temperature of 50 °C. Reaction progress was monitored by TLC (toluene/EtOAc 8/1). Afterward, the reaction mixture was filtered, washed with brine (2×3 ml), and dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by column chromatography on silica gel, eluting with EtOAc/hexane (1/18). Fractions containing the product were combined, and solvent was removed to afford corresponding alcohol N-allyl thiocarbamate.

Table 4. Suitable base using to synthesis of alcohol N-allyl thiocarbamate

Entry	Base	Equivalent (mmol)
1	K_2CO_3	1.5
2	iPr_2NEt	1
3	BEMP	0.01
4	DBU	0.15

4-Methoxybenzyl N-Allyl Thiocarbamate (2)

Yield: 94%; yellow oil; 7.29–7.33 (2H, m, *o*-Ph), 6.87–6.91 (2H, m, *m*-Ph), 6.40 (1H, br.s, NH), 5.80–5.91 (1H, 2dt, J 10.2 Hz, J 17.1 Hz, J 5.8 Hz $^{1'}CH_2^{2'}CH^{3'}CH_2$), 5.45 (2H, ps, CH_2Ph), 5.15–5.20 (2H, m, $^{1'}CH_2^{2'}CH^{3'}CH_2$), 4.17–4.21 (2H, tt, J 5.8 Hz, J 3.05 Hz, J 1.52 Hz, $^{1'}CH_2^{2'}CH^{3'}CH_2$), 3.80 (3H, s, PhOMe); d_C (100.6 MHz, $CDCl_3$) 190.12, 159.60, 132.48, 130.18, 128.66, 117.43, 113.80, 71.82, 55.17, 47.54; HRMS (ESI-MS): calcd for $C_{12}H_{15}NO_2S$: 260.0721 $[M + Na]^+$; found: 260.0709 (as a supplement material).

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

REFERENCES

1. (a) Nicolaou, K. C.; Sorensen, E. J. In *Classics in Total Synthesis*; Wiley-VCH: Weinheim, 1996; (b) Nicolaou, K. C.; Snyder, S. A. In *Classics in Total Synthesis II*; Wiley-VCH: Weinheim, 2003; (c) Nicolaou, K. C.; Chen, J. S. *Classics in Total Synthesis III*; Wiley-VCH: Weinheim, 2010.
2. Kocienski, P. J. In *Protecting Groups*, 3rd ed.; Thieme: New York, 2004; pp. 241–269.
3. Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp. 5–15 and 120–135.
4. Blanc, A.; Bochet, C. G. In *CRC Handbook of Organic Photochemistry and Photobiology*, 3rd ed.; Taylor & Francis: New York, 2012; pp. 73–93.
5. Hibino, H.; Nishiuchi, Y. *Org. Lett.* **2012**, *7*, 1926.
6. Muranaka, K.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2011**, *76*, 9278.
7. Liang, H.; Hu, L.; Corey, E. *J. Org. Lett.* **2011**, *13*, 4120.
8. Bröhmer, M. C.; Mundinger, S.; Bräse, S.; Bannwarth, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 6175.
9. Bikard, Y.; Weibel, J.-M.; Sirlin, C.; Dupuis, L.; Loeffler, J. P.; Pale, P. *Tetrahedron Lett.* **2007**, *48*, 8895.

10. Bikard, Y.; Mezaache, R.; Weibel, J.-M.; Benkouider, A.; Sirlin, C.; Pale, P. *Tetrahedron* **2008**, *64*, 10224.
11. Lazar, L.; Janossy, L.; Csavas, M.; Herczeg, M.; Bordas, A.; Antus, S. *Arkivoc* **2012**, *5*, 312.
12. Blanc, A.; Bochet, C. G. *Org. Lett.* **2007**, *9*, 2649.
13. Mezaache, R.; Dembele, Y. A.; Bikard, Y.; Weibel, J.-M.; Blanc, A.; Pale, P. *Tetrahedron Lett.* **2009**, *50*, 7322.
14. Specklin, S.; Gallier, F.; Mezaache, R.; Harkat, H.; Dembele, Y. A.; Weibel, J.-M.; Blanc, A.; Pale, P. *Tetrahedron Lett.* **2011**, *52*, 5820.
15. McCloskey, C. M. *Adv. Carbohydr. Chem.* **1957**, *12*, 137.
16. Hanessian, S. In *Preparative Carbohydrate Chemistry*; Marcel Dekker: New York, 1997; pp. 413–466.
17. Levy, D. E.; Fügedi, P. In *The Organic Chemistry of Sugars*; Taylor & Francis: Boca Raton, FL, 2006; chapter 5.
18. Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583.
19. Paulsen, H.; Richter, A.; Sinnwell, V.; Stenzel, W. *Carbohydr. Res.* **1978**, *64*, 339.
20. Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291.
21. Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3651.
22. Glaudemans, C. P. J.; Fletcher Jr., H. G. *Methods Carbohydr. Chem.* **1972**, *6*, 373.
23. Brimacombe, J. S. *Methods Carbohydr. Chem.* **1972**, *6*, 376.
24. Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.
25. Wessel, H. P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.
26. Eckenberg, P.; Groth, U.; Huhn, T.; Richter, N.; Schmeck, C. *Tetrahedron* **1993**, *49*, 1619.
27. Okada, Y.; Ohtsu, M.; Bando, M.; Yamada, H. *Chem. Lett.* **2007**, *36*, 992–993.
28. Aoki, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1255.
29. Kasprzycka, A.; Szeja, W.; Grynkiewicz, G. *Carbohydrate Res.* **2005**, *340*, 2443.