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A Facile, One-Step Conversion of 6-*O*-Trityl and 6-*O*-TBDMS Monosaccharides into the Corresponding Formate Esters

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A convenient method has been developed for a facile and high-yield conversion of 6-*O*-*tert*-butyldimethylsilyl and 6-*O*-trityl protected monosaccharides to their formate esters, which may serve as useful intermediates for the replacement of the primary hydroxyl group of sugars by other functional groups.

Keywords Formate ester, Formic acid, Trityl, *tert*-Butyldimethylsilyl, *O*-branched chain reactions

INTRODUCTION

Multiple use of protecting groups is a critical part of many synthetic schemes that involve carbohydrate, nucleoside, and natural product chemistry. Trityl and silyl ethers, including the *tert*-butyldimethylsilyl group (TBDMS), have

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become popular protecting groups for hydroxyl functions during complex multistep syntheses, especially when orthogonal protection/deprotection steps are required.^[1,2] These ethers display a unique set of properties, ranging from their easy introduction to their good stability under a wide range of conditions and possible one-step deprotection.^[1,2] Nevertheless, if performed on multifunctional or sensitive molecules, one-step *O*-trityl and *O*-TBDMS deprotection may be problematic.^[3,4] Alternatively, innovative two-step procedures interconverting trityl and TBDMS ethers to a different kind of protected ether followed by its smooth hydrolysis could also be of interest.

O-Formylation could be the method of choice for protecting an alcoholic group in a complex synthetic sequence because it can be selectively introduced to primary hydroxyl groups^[5] and deformylation can be effected selectively in the presence of other ester-protecting groups.^[6,7] Further, if the alcoholic group is planned to be oxidized, the formylated alcoholic group need not be deprotected and direct oxidation under Oppenauer conditions can be realized.^[8,9] In some steroidal transformations formylation has been found to be superior to acetylation.^[8] Formate esters also serve as useful synthetic reagents and intermediates, and specifically for *O*-branched chain extension reactions through Wittig type olefinations.^[10–14] Despite these uses and considerable potential, the formyl-protecting group has been rather overlooked.

Various one-step formylation methods have been reported over the years, using formylation agents such as formyl fluoride, formic acetic anhydride,^[15] 2-(*N*-methyl-*N*-formylamino)pyridine, dimethylchloromethyl-ammonium chloride, *N*-formylbenzotriazole,^[16] and *N,N*-dimethylformamide,^[17] among many others.^[18] However, there are serious limitations for the preparation of formate esters due to the hard experimental conditions, the use of uncommon reagents, and formation of undesirable or toxic byproducts. Recently the one-step conversion of silyl ethers into the corresponding formates has been reported using $\text{PPh}_3/\text{CBr}_4$ in $\text{HCOOEt}/\text{H}_2\text{O}$ ^[19] or POCl_3/DMF .^[20–23]

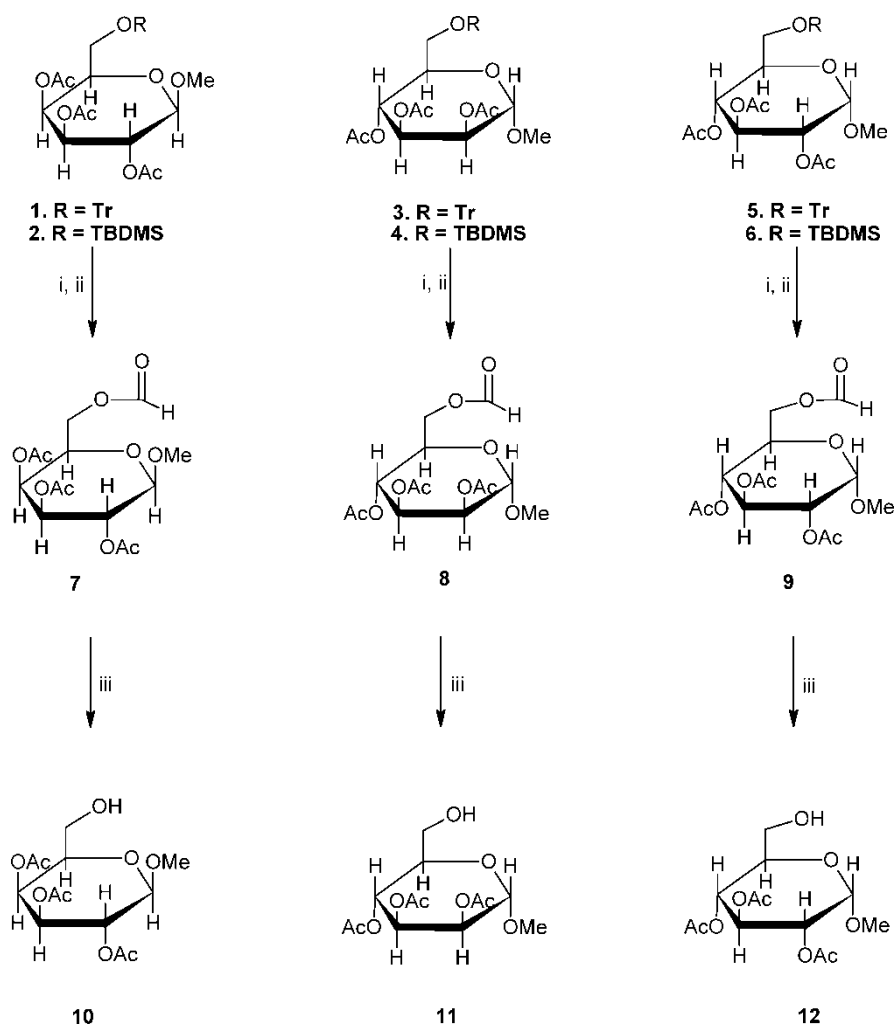
In this work a new highly efficient, simple, and low-cost method for such conversion is described and its mechanism is tentatively proposed. Thus, 6-*O*-TBDMS and 6-*O*-trityl monosaccharides were converted into the corresponding formate esters. Besides, the potential usefulness of such transformation for subsequent *O*-branched chain extension is exemplified.

RESULTS AND DISCUSSION

Methyl β -D-galactopyranoside, methyl α -D-mannopyranoside, and methyl α -D-glucopyranoside were tritylated or silylated and then acetylated, one pot, to give in over 85% yield trityl derivatives **1**, **3**, and **5**, and silyl derivatives **2**, **4**, and **6**, respectively. Treatment of the trityl derivatives **1**, **3**, and **5** with a 1/1 mixture of concentrated formic acid/diethyl ether at reflux temperature for

30 min afforded formate esters **7** (86%), **8** (90%), and **9** (87%), respectively (Sch. 1). Likewise, the same compounds were obtained in over 80% yield upon reaction for 60 min in a 1.5/1 formic acid/diethyl ether mixture of silyl derivatives **2**, **4**, and **6**, respectively.

These results were confirmed by ^1H NMR spectroscopy, which indicated a singlet at around 8 ppm corresponding to the formate proton and a deshielding of the protons at position 6 by an average of 0.40 ppm as commonly observed for such transformation.^[23] Moreover, when products **7–9** were deformylated under conventional conditions,^[6] the corresponding 2,3,4-tri-*O*-acetylated



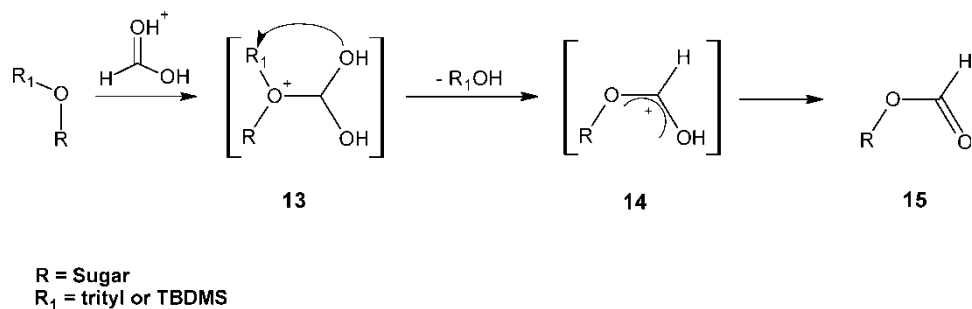
Scheme 1: Reagents and conditions: i. (R = Tr) HCOOH /diethyl ether (1/1), reflux, 30 min; ii. (R = TBDMS) HCOOH /diethyl ether (1.5/1), 60 min; iii. MeOH, 3 days, 25°C.

derivatives **10**^[24] (92%), **11**^[25] (96%), and **12**^[26] (94%) were isolated, respectively. The overall good yields of **10–12** thus obtained ascertained that no acetyl migration had occurred. It is interesting to note that the four-step transformation of the methyl glycosides provides the tri-*O*-acetylated products in higher yield (68% to 77%) than the more familiar three-step route (37% to 62%),^[24–26] reinforcing the potential of the described methodology.

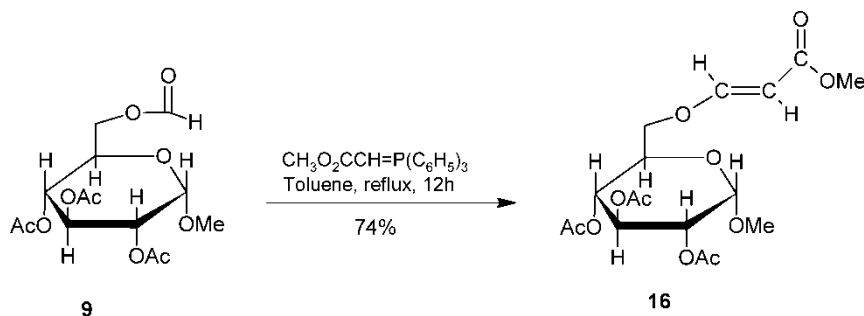
Of note, when the formylation reaction was attempted on compounds **1** to **6** at rt for 7 and 15 min, the detritylated and desilylated derivatives (**10–12**), respectively, were mainly obtained.^[27] The reaction mechanism probably involves the oxonium cation formed by the self-dissociation of formic acid in nonaqueous media. Addition of the formic oxonium cation to the trityl or TBDMS ether gave the intermediate **13**. Elimination of *TrOH* or *TBDMSOH* affords the corresponding formate **15** via the intermediate **14** (Sch. 2). It is hypothesized that the elimination step is fast at high temperature, but slow at room temperature, and hydrolysis of intermediate **13** will occur during the aqueous work-up.

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-formyl- α -D-glucopyranoside (**9**) was treated with carbomethoxymethylene triphenylphosphorane in toluene to afford, in a Wittig-type reaction,^[10–14] the methyl acrylate derivative **16** (Sch. 3). ¹H NMR data for this compound (*J* = 12,7 Hz) confirmed the presence of the *E* isomer only.

In conclusion, the reported procedure describes a one-step formylation of primary 6-*O*-TBDMS and 6-*O*-trityl monosaccharides into their corresponding formate esters. The method provides several advantages, including operational simplicity, mild reaction conditions, low cost of the reagents, and high yields of the formylated products. Formates can serve as intermediates for the replacement of the primary hydroxyl group of sugars by other functional groups such as aldehydes^[28] and vinyl ethers.^[14] In particular, their conversion to Wittig-Horner products may allow the introduction of additional diversity based on the choice of the Wittig-Horner reagent. Thus, formates and their Wittig-Horner products could be very useful intermediates for coupling of



Scheme 2



Scheme 3

carbohydrates to biologically important molecules as well as important key precursors to oligosaccharide or glycoconjugate mimics.^[29–36]

EXPERIMENTAL

Melting points were recorded in a Mel-Temp apparatus and are uncorrected. TLC was performed on Silica Gel (240–400 mesh, Merck). NMR spectra were recorded at rt with a Bruker 250-MHz spectrometer in CDCl_3 with internal TMS. Mass spectra were obtained with a Micromass Platform LC (ESI-MS).

Methyl 2,3,4-tri-O-acetyl-6-O-trityl- β -D-galactopyranoside (1). A solution of methyl β -D-galactopyranoside (1 g, 5.1 mmol) and trityl chloride (1.55 g, 5.4 mmol) in pyridine (5 mL) was heated for 3 h at 100°C , and then kept overnight at rt. To the solution, acetic anhydride (4 mL, 42.4 mmol) was added, and the mixture was kept for 24 h at rt. It was then poured into ice water, and the solid was filtered off, washed with water, and dried. The product was recrystallized from ether-petroleum ether to give **1** (2.49 g, 86%). NMR spectra were identical to those described.^[24] m.p. $139\text{--}141^\circ\text{C}$, lit.^[24] m.p. 138°C .

Methyl 2,3,4-tri-O-acetyl-6-O-trityl- α -D-mannopyranoside (3). Compound **3** was prepared from methyl α -D-mannopyranoside as for **1** in 89% yield, and crystallized from ethanol. NMR spectra were identical to those described.^[25] m.p. $99\text{--}101^\circ\text{C}$, lit.^[25] m.p. $97\text{--}98^\circ\text{C}$.

Methyl 2,3,4-tri-O-acetyl-6-O-trityl- α -D-glucopyranoside (5). Compound **5** was prepared from methyl α -D-glucopyranoside as for **1** in 89% yield, and crystallized from ethanol. NMR spectra were identical to those described.^[26] m.p. $134\text{--}136^\circ\text{C}$, lit.^[26] m.p. $132\text{--}135^\circ\text{C}$.

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl- β -D-galactopyranoside (2). A solution of methyl β -D-galactopyranoside (1 g, 5.1 mmol) and TBDMS chloride (1 g, 6.6 mmol) in pyridine (10 mL) was stirred for 1 h at 0–5°C, and then kept overnight at rt. To the solution, acetic anhydride (4 mL, 42.4 mmol) was added, and the mixture was kept for 24 h at rt. Then MeOH (4 mL) was added and the solvent was removed under reduced pressure. Column chromatography (EtOAc/hexane 1/9) of the residue gave compound **2** (2.62 g, 98%). R_f 0.44 (EtOAc/hexane 1/9); ^1H NMR (CDCl_3 , 250 MHz) δ 5.44 (d, 1H, $J = 3.4$ Hz, H-4), 5.15 (dd, 1H, $J = 10.4$ Hz, $J = 7.9$ Hz, H-2), 5.01 (dd, 1H, $J = 3.4$ Hz, $J = 10.4$ Hz, H-3), 4.36 (d, 1H, $J = 7.9$ Hz, H-1), 3.70 (m, 2H, H-6), 3.61 (m, 1H, H-5), 3.47 (s, 3H, OMe), 2.09, 2.02, 1.94 (3s, 9H, 3Ac) ppm; ESI-MS (m/z): Found 435.85 ($M + \text{H}^+$). Anal. Calcd. for $\text{C}_{19}\text{H}_{34}\text{O}_9\text{Si}$: C, 52.52; H, 7.89. Found C, 52.36; H, 7.52.

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl- α -D-mannopyranoside (4). Compound **4** was prepared from methyl α -D-mannopyranoside as for **2** (87%). R_f 0.40 (EtOAc/hexane 1/9); ^1H NMR (CDCl_3 , 250 MHz), δ 5.32 (dd, 1H, $J = 3.2$ Hz, $J = 10.0$ Hz, H-3), 5.23 (t, 1H, $J = 10.0$ Hz, H-4), 5.18 (dd, 1H, $J = 1.7$ Hz, $J = 3.2$ Hz, H-2), 4.67 (d, 1H, $J = 1.7$ Hz, H-1), 3.69 (m, 2H, H-6), 3.62 (m, 1H, H-5), 3.40 (s, 3H, OMe), 2.10, 2.08, 2.01 (3s, 9H, 3Ac) ppm; ESI-MS (m/z): Found 435.85 ($M + \text{H}^+$). Anal. Calcd. for $\text{C}_{19}\text{H}_{34}\text{O}_9\text{Si}$: C, 52.52; H, 7.89. Found C, 52.86; H, 7.44.

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl- α -D-glucopyranoside (6). Compound **6** was prepared from methyl α -D-glucopyranoside as for **2** (86%). R_f 0.45 (EtOAc/hexane 1/9); NMR spectra were identical to those already described.^[22]

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-formyl- β -D-galactopyranoside (7). a) From 1: A solution of **1** (0.5 g, 0.89 mmol) was dissolved in a 1/1 mixture of HCOOH /diethyl ether (16 mL). The mixture was refluxed for 30 min and diluted with diethyl ether, neutralized with solid hydrogen carbonate, washed successively with brine and water, dried over magnesium sulfate, and concentrated. Column chromatography (EtOAc/hexane 3/7) of the residue gave compound **7** (0.27 g, 86%). R_f 0.40 (EtOAc/hexane 4/6).

b) From 2: A solution of **2** (0.5 g, 1.15 mmol) was dissolved in a 1,5/1 mixture of HCOOH /diethyl ether (22 mL). The mixture was refluxed for 60 min and diluted with diethyl ether, neutralized with solid hydrogen carbonate, washed successively with brine and water, dried over magnesium sulfate, and concentrated. Column chromatography (EtOAc/hexane 2/8) of the residue gave compound **7** (0.33 g, 83%). ^1H NMR (CDCl_3 , 250 MHz) δ 8.03 (s, 1H, HCOO), 5.41 (d, 1H, $J = 2.9$ Hz, H-4), 5.23 (dd, 1H, $J = 10.8$ Hz,

$J = 7.9$ Hz, H-2), 5.02 (dd, 1H, $J = 2.9$ Hz, $J = 10.8$ Hz, H-3), 4.29 (d, 1H, $J = 7.8$ Hz, H-1), 4.16 (m, 2H, H-6), 3.85 (m, 1H, H-5), 3.41 (s, 3H, OMe), 2.08, 2.04, 2.01 (3s, 9H, 3Ac) ppm; ESI-MS (m/z): Found 349.62 ($M + H^+$). Anal. Calcd. for $C_{14}H_{20}O_{10}$: C, 48.28; H, 5.79. Found C, 48.36; H, 5.82.

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-formyl- α -D-mannopyranoside (8). Compound **8** was prepared from **3** (and **4**) as for **7**. Column chromatography (EtOAc/hexane 3/7) of the residue gave compound **8** (90% from **3** and 84% from **4**). ^1H NMR (CDCl_3 , 250 MHz) δ 8.06 (s, 1H, HCOO), 5.33 (dd, 1H, $J = 3.1$ Hz, $J = 9.9$ Hz, H-3), 5.33 (t, 1H, $J = 9.9$ Hz, H-4), 5.20 (dd, 1H, $J = 1.9$ Hz, $J = 3.1$ Hz, H-2), 4.72 (d, 1H, $J = 1.9$ Hz, H-1), 4.29 (m, 2H, H-6), 3.95 (m, 1H, H-5), 3.42 (s, 3H, OMe), 2.14, 2.10, 2.09 (3s, 9H, 3Ac) ppm; ESI-MS (m/z): Found 349.74 ($M + H^+$). Anal. Calcd. for $C_{14}H_{20}O_{10}$: C, 48.28; H, 5.79. Found C, 48.25; H, 5.75.

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-formyl- α -D-glucopyranoside (9). Compound **9** was prepared from **5** (or **6**) as for **7**. Column chromatography (EtOAc/hexane 3/7) of the residue gave compound **9**. The product was crystallized from EtOAc-hexane (87% from **5** and 84% from **6**). m.p. 89–91°C. ^1H NMR (CDCl_3 , 250 MHz) δ 8.08 (s, 1H, HCOO), 5.50 (t, 1H, $J = 10.0$ Hz, H-3), 5.05 (t, 1H, $J = 10.0$ Hz, H-4), 4.95 (d, 1H, $J = 3.6$ Hz, H-1), 4.90 (dd, 1H, $J = 3.6$ Hz, $J = 10$ Hz, H-2), 4.29 (m, 2H, H-6), 4.04 (m, 1H, H-5), 3.43 (s, 3H, OMe), 2.08, 2.04, 2.01 (3s, 9H, 3Ac) ppm; ESI-MS (m/z): Found 349.62 ($M + H^+$). Anal. Calcd. for $C_{14}H_{20}O_{10}$: C, 48.28; H, 5.79. Found C, 48.34; H, 5.77.

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-(methyl (2E) acrylate)- α -D-glucopyranoside (16). A solution of methyl 2,3,4-tri-*O*-acetyl-6-*O*-formyl- α -D-glucopyranoside (0.2 g, 0.57 mmol) and carbomethoxymethylene triphenylphosphorane (0.38 g, 1.14 mmol) in toluene (10 mL) was refluxed for 12 h and concentrated. Column chromatography (EtOAc/hexane 2/8) of the residue gave compound **16** (0.17 g, 74%). R_f 0.40 (EtOAc/hexane 4/6). The product was crystallized from EtOAc-hexane. m.p. 101–102°C. ^1H NMR (CDCl_3 , 250 MHz) δ 7.55 (d, 1H, $J = 12.7$ Hz, H'-3 acrylate), 5.48 (t, 1H, $J = 9.8$ Hz, H-3), 5.23 (d, 1H, $J = 12.7$ Hz, H'-2 acrylate), 5.02 (d, 1H, $J = 9.8$ Hz, H-4), 4.95 (d, 1H, $J = 3.6$ Hz, H-1), 4.87 (dd, 1H, 3.6 Hz, $J = 9.8$ Hz, H-2), 4.25 (m, 2H, H-6), 4.01 (m, 1H, H-5), 3.70 (s, 3H, COOMe acrylate), 3.41 (s, 3H, OMe), 2.07, 2.02, 1.99 (3s, 9H, 3Ac) ppm; ESI-MS (m/z): Found 405.49 ($M + H^+$). Anal. Calcd. for $C_{17}H_{24}O_{11}$: C, 50.49; H, 5.99. Found C, 50.44; H, 5.88.

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