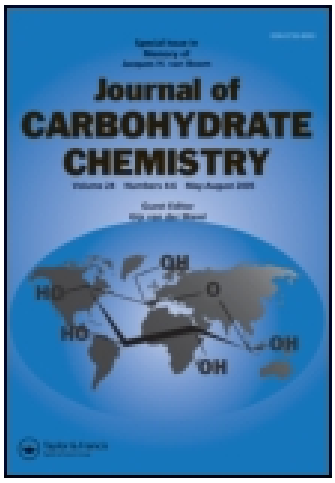

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DE-O-BENZYLATION OF STERICALLY HINDERED BENZYL ETHERS

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DE-*O*-BENZYLATION OF STERICALLY HINDERED BENZYL ETHERS[1]

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ABSTRACT

Sterically hindered benzyl ethers that cannot be removed by hydrogenolysis with a variety of catalysts are removed readily by the reaction with *N*-bromosuccinimide and light in the presence of aqueous calcium carbonate, a reaction developed by Binkley and Hehemann. It was found that these conditions are compatible with the presence of phthalimides and glycosyl sulfides and fluorides, in addition to the groups previously shown to be inert.

INTRODUCTION

Benzyl ethers are probably the most commonly used protecting groups for alcohols. The normal technique for deprotection is hydrogenolysis, either catalytic or by transfer of hydrogen.[2–6] Palladium on charcoal is the most commonly used catalyst but some benzyl groups resist hydrogenolysis with this catalyst and other catalysts, such as Pearlman's catalyst ($Pd(OH)_2$), are often tried. Many other methods have been utilized, such as dissolving metal reductions,[7–9] various oxidative methods which convert benzyl ethers to benzoyl esters,[10–15] or cleavage with Lewis acids. However, few of these alternative methods are compatible with esters and/or thioglycosides or other sensitive functional groups.

The method discovered by Binkley and Hehemann,[16] which uses light-catalysed α-bromination of benzyl ethers in the presence of aqueous base, has only been

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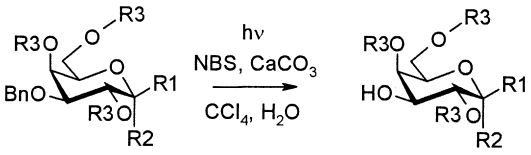

a **b**

1 R1 = SPh, R2 = R3 = H
2 R1 = SPh, R2 = H, R3 = Piv
3 R1 = H, R2 = F, R3 = Piv
4 R1 = $O(CH_2)_5CO_2Et$, R2 = H, R3 = Piv
5 R1 = SPh, R2 = H, R3 = Ac
6 R1 = $O(CH_2)_5CO_2Et$, R2 = H, R3 = Ac

Scheme 1.

used preparatively three times in the ten years since the initial publication.[17–19] We now report that this method is very effective for the removal of hindered benzyl ethers and also note that it is compatible with many sensitive functional groups, such as thioglycosides and glycosyl fluorides.

RESULTS AND DISCUSSION

A key part of a synthetic sequence required the removal of a benzyl group on an oxygen atom flanked by two pivaloyloxy groups, that is, the benzyl group in compound **2a** in Scheme 1. Despite repeated attempts, this benzyl group could not be removed by hydrogenolysis at 4 atm using a variety of catalysts, including Pd/C, $Pd(OH)_2$ and $Pd(OAc)_2$. Because most alternatives were not compatible with ester protecting groups, we tried photochemical α-bromination,[16,20] and this method proved to be very effective.

Scheme 1 shows the de-*O*-benzylation of some substituted 3-*O*-benzyl-D-galactopyranoside derivatives. Removal of the *O*-benzyl groups proceeds in short times under mild conditions in excellent yields as summarized in the Table. The conditions of Binkley and Hehemann were used,[16] that is, irradiation with a 375 W white light lamp of a vigorously magnetically stirred two-phase system consisting

Table 1. Reaction Times and Yields in de-*O*-benzylation Reactions

Substrate	Reaction Time (min)	Yield (%)
2a	15	95
3a	15	87
4a	15	95
5a	30	76
6a	45	83
7a	15	72

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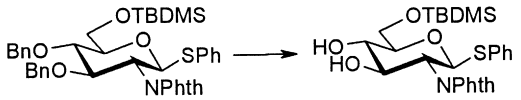

7a 7b

Scheme 2.

of the compound and *N*-bromosuccinimide in carbon tetrachloride and aqueous calcium carbonate. It was necessary to purge the reaction mixtures thoroughly with nitrogen before irradiation to avoid the conversion of the benzyl ethers to benzoate esters, a process which has been noted as being a difficulty with this reaction.[18] Recrystallization of the *N*-bromosuccinimide resulted in improved yields. The inexpensive 375 W lamps, usually called heat lamps, were originally used by Binkley and Hehemann[16,17] and are available in speciality lighting stores. The reactions were monitored by TLC and stopped when the substrate had been consumed. Reaction times for the benzyl ether to disappear completely ranged from 15 to 45 min.

Scheme 2 shows the application of the reaction to a di-*O*-benzyl derivative.

As can be seen from the Table, this procedure is remarkably effective for the de-*O*-benzylation of sterically hindered benzyl ethers. Moreover, a number of protecting groups and reactive glycosidic groups that had not been studied by previous workers were shown to be unaffected; these include glycosyl thiophenyl groups and fluorides, and phthalimide protecting groups.

EXPERIMENTAL

General Methods. ^{1}H and ^{13}C NMR spectra were run at 300 K on Bruker AC-250 or AMX-400 NMR instruments operating at 250.13 and 62.9 MHz, and 400.16 and 100 MHz, respectively. The samples were made up in concentrations between 10 and 15 mM in chloroform-*d* unless otherwise specified. Chemical shifts are given in parts per million (ppm)(+/−0.01 ppm) relative to TMS (tetramethylsilane) in the case of ^{1}H NMR spectra, and to the central line of chloroform-*d* (δ 77.23) for the ^{13}C NMR spectra. Spectral assignments were made by first-order analysis and COSY and HETCOR experiments. Mass spectra were measured on a CEC 21-110B mass spectrometer using electron ionization (70.0 eV). The probe and source temperature was 143°C. Pyridine was dried by refluxing over calcium hydride before distillation. Dichloromethane was first dried with calcium chloride, then refluxed over calcium hydride for one hour, fractionally distilled and stored over molecular sieves (4 Å). *N*,*N*-Dimethylformamide was stored over activated molecular sieves (4 Å) for 72 h before distillation under reduced pressure from freshly activated molecular sieves (4 Å). Toluene was stored over calcium hydride for 3 h then distilled onto activated molecular sieves (4 Å). Benzyl chloride was dried with $MgSO_4$, refluxed over calcium hydride and then fractionally distilled under reduced pressure, collecting the middle fraction and then storing over calcium hydride. *N*-Bromosuccinimide was recrystallized from water then dried for 12 h at room temperature under vacuum (1 torr). Thin-layer chromatography

(TLC) was performed on 0.25 mm thick Whatman G/UV silica gel on aluminum plates. Components were visualized by spraying with a 2% ceric sulfate solution in 1 M H_2SO_4 followed by heating on a hot plate until discolouration occurred. Flash chromatography was performed on silica gel TLC standard grade (230–400 mesh) with mixed solvents of ethyl acetate: hexanes at volume ratios indicated. Irradiation was performed with a Phillips 375 W reflector lamp.

Phenyl 3-*O*-Benzyl-1-thio-β-D-galactopyranoside (1a). Phenyl 1-thio-β-D-galactopyranoside[21] (20.13 g, 0.0740 mol) and dibutyltin oxide (19.57 g, 0.0786 mol, 1 equiv) were refluxed for 12 h in toluene (500 mL) with azeotropic removal of water. The solvent was removed and the residue was dried at 0.1 torr for 1 h. Cesium fluoride (16.60 g, 0.109 mol, 1.45 equiv) was added followed by a solution of distilled benzyl bromide (15.82 g, 0.0925 mol, 1.0 equiv) in *N*,*N*-dimethylformamide (300 mL) and the reaction mixture was stirred until TLC (eluant, 4:1 ethyl acetate: acetone) indicated that the starting material had been completely consumed (3.5 h). Distilled water (2 mL) was added, the solvent evaporated and the residue was dissolved in ethanol and filtered through celite. The filtrate was reconcentrated to a dark brown syrup that was purified by flash chromatography using 1:1 ethyl acetate: hexanes as eluant. Crystallization (ethyl acetate) produced fine white needles (15.9 g, 60 %): mp 156–160°C, lit[22] 161–163°C; $[\alpha]_D$ −8.4° (*c* 2.0, methanol), lit[22] $[\alpha]_D$ −8.5°; ^{1}H NMR (acetone-d_6): δ 3.36 (dd, 1H, $J_{3,4}$ = 3.36 Hz, $J_{2,3}$ = 9.16 Hz, H-3), 3.64 (td, 1H, $J_{4,5}$ = 0.92 Hz, $J_{5,6}$ = $J_{5,6'}$ = 5.95 Hz, H -5), 3.76 (s, 1H, OH-4), 3.77 (d, 2H, $J_{5,6}$ = 5.80 Hz, H-6,6′), 3.84 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.5 Hz, H-2), 4.22 (td, 1H, $J_{4,5}$ = 1.0 Hz, $J_{3,4}$ = 3.35 Hz, H-4), 4.42, 4.40 (2s, 2H, OH-2 and OH-3), 4.67 (d, 1H, $J_{1,2}$ = 9.77 Hz, H-1), 4.69, 4.79 (2d, 2H, J = −12.2 Hz, OCH_2Ph), 7.22–7.60 (m, 10H, CH_2Ph, SPh); ^{13}C NMR (acetone-d_6): δ 61.8 (C-6), 66.4 (C-4), 69.3 (C-2), 71.6 (*C*H_2Ph) , 79.6 (C-5), 83.4 (C-3), 88.9 (C-1), 127.2–131.6 (Ph, SPh).

Phenyl 3-*O*-Benzyl-2,4,6-tri-*O*-pivaloyl-1-thio-β-D-galactopyranoside (2a). Compound **1a** (7.19 g, 0.0199 mol) was dissolved in dry pyridine (50 mL) and pivaloyl chloride (8.81 g, 9.0 mL, 0.0731 mol, 3.7 equiv) was added dropwise. The reaction was stirred at a bath temperature of 75°C for 12 h. The reaction mixture was poured into ice water (150 mL) that was then extracted with dichloromethane (150 mL). The organic layer was washed with 1 M hydrochloric acid (3 × 150 mL), saturated sodium hydrogen carbonate solutions (3 × 150 mL), and water (2 × 150 mL), then dried, and concentrated. The residue was applied to a flash chromatography column and eluted with ethyl acetate:hexanes 1:4. The title compound was obtained as colorless crystals (10.356 g, 0.0168 mol, 85 %), recrystallized from methanol-water: mp 101–2°C; $[\alpha]_D$ +21.3° (*c* 2.0, dichloromethane); ^{1}H NMR: δ 1.14, 1.21, 1.22 (3s, 3 × 9H, 3 C(CH_3)$_3$), 3.64 (dd, 1H, $J_{3,4}$ = 3.3 Hz, $J_{2,3}$ = 9.3 Hz, H-3), 3.93 (br t, 1H, $J_{5,6}$ = $J_{5,6'}$ = 6.7 Hz, H-5), 4.16 (m, 2H, H-6,6′), 4.36, 4.67 (2d, 2H, J= −11.29 Hz, OCH_2Ph), 4.68 (d, 1H, $J_{1,2}$ = 10.07 Hz, H-1), 5.16 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.8 Hz, H-2), 5.54 (br d, 1H, $J_{3,4}$ = 3.21 Hz, H-4), 7.2–7.6 (m, 10H, CH_2Ph, SPh); ^{13}C NMR: δ 26.8, 26.9, 27.0 (3

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C(CH_3)$_3$, 38.3,38.5, 38.8 (3 C(CH_3)$_3$), 62.0 (C-6), 65.5 (C-4), 67.9 (C-2), 71.2 (CH_2Ph), 74.6 (C-5), 78.2 (C-3),86.1 (C-1), 127.4, 127.8, 127.9, 132.2, 132.8, 137.0 (Ph, SPh), 176.4, 177.2, 177.8 (3 OCO).

Anal. Calcd for $C_{34}H_{46}O_8S$: C, 66.42; H, 7.54; S, 5.22. Found: C, 66.57; H, 7.52; S, 5.68.

3-*O*-Benzyl-2,4,6-tri-*O*-pivaloyl-α-D-galactopyranosyl Fluoride (3a). Compound **2a** (0.5215 g, 0.848 mmol) was dissolved in dry dichloromethane (20 mL) and cooled with a calcium chloride ice bath that maintained the temperature at 0°C. Diethylaminosulfur trifluoride (0.155 mL, 1.27 mmol) was added dropwise to the stirred solution followed by *N*-bromosuccinimide (NBS) (0.196 g, 1.10 mmol). After 40 min, the reaction mixture was poured into a saturated solution of sodium hydrogen carbonate (50 mL). The aqueous mixture was extracted with ether (4 × 25 mL) and the combined extracts were dried ($MgSO_4$) and concentrated. The residue purified by flash chromatography on silica gel (eluant, ethyl acetate: hexanes 1:5) to give the title compound (R_f, 0.94) as pure colorless crystals (0.3675 g, 88%) that were recrystallized from ether-hexanes: mp 103–104°C; $[\alpha]_D$ +73.0° (*c* 0.9, dichloromethane); ^{1}H NMR: δ 1.21 (s, 3 × 9H, 3 C(CH_3)$_3$), 3.99 (dd, 1H, $J_{3,4}$ = 3.20 Hz, $J_{2,3}$ = 10.20 Hz, H-3), 4.13 (d, 2H, H-6,6′), 4.34 (br t, 1H, $J_{5,6}$ = $J_{5,6'}$ = 6.71 Hz, H-5), 4.46, 4.71 (2d, 2H, J= 11.14 Hz, OCH_2Ph), 5.16 (ddd, 1H, $J_{1,2}$ = 2.59 Hz, $J_{2,3}$ =10.22 Hz, $J_{2,F}$ = 24.72 Hz, H-2), 5.64 (br d, 1 H, $J_{3,4}$ = 2.51 Hz, H-4), 5.64, 5.86 (2d, 1H, $J_{1,2}$ = 2.59, $J_{1,F}$ = 53.86 Hz, H-1), 7.2–7.6 (m, 5H, CH_2Ph); ^{13}C NMR: δ 27.21, 27.24, 27.34 (3 C(CH_3)$_3$, 39.0, 39.3 (3 C(CH_3)$_3$), 61.6 (C-6), 66.0 (C-4), 69.4 (d, $^2J_{C,F}$ = 24.0 Hz, C-2), 69.4 (C-5), 71.9 (CH_2Ph), 73.0 (C-3), 104.7 (d, $^1J_{C,F}$ = 226.7 Hz, C-1), 127.2, 127.5, 127.8, 128.3, 129.1, 137.3 (Ph), 177.3, 177.9, 177.9 (3 OCO); ^{19}F NMR: δ −150.52 (dd, $J_{H1,F}$ = 53.4 Hz, $J_{H2,F}$ = 25.1 Hz,F); EIMS *m/z*: 524 (1.0%, M^+), 489 (0.5%, M^+ - HF -CH_3), 439 (57%, M^+ - *t*-BuC=O).

Anal. Calcd for $C_{28}H_{41}O_8F$: C, 64.10; H, 7.88. Found: C, 64.22; H, 7.71.

Ethyl 6-(3-*O*-Benzyl-2,4,6-tri-*O*-pivaloyl-β-D-galactopyranosyloxy)hexanoate (4a). Compound **2a** (0.81 g, 1.317 mmol) was dissolved in dry dichloromethane (40 mL) under nitrogen in a glove bag and ethyl 6-hydroxyhexanoate (0.428 mL, 2.635 mmol) was added, followed by *N*-iodosuccinimide (0.341 g, 1.515 mmol), silver triflate (0.677 g, 2.635 mmol), and powdered 4Å molecular sieves. The reaction vessel was then stoppered with a rubber septum and covered with aluminum foil. After 3 h, the mixture was filtered over celite and the filtrate was washed with saturated sodium hydrogen carbonate solutions (3 × 30 mL) and water (3 × 30 mL). The organic layer was dried and concentrated to a residue that was applied to a flash chromatography column. Elution with ethyl acetate: hexanes 1:5 gave the title compound (R_f, 0.43) as a colorless syrup (0.739 g, 84.4%): $[\alpha]_D$ +18.0° (*c* 3.7, chloroform); ^{1}H NMR: δ 1.17, 1.20, 1.21 (3s, 3 × 9H, 3 C(CH_3)$_3$), 1.24 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 1.29–1.41 (complex m, 2H, OCH_2CH_2CH_2), 1.5–1.7 (complex m, 4H, OCH_2CH_2CH_2CH_2), 2.28 (t, 2H, J = 7.3 Hz, OCOCH_2), 3.42 (complex m, 1H, one OCH_2CH_2), 3.58 (dd, 1H, $J_{3,4}$ = 3.4 Hz, $J_{2,3}$ = 9.9 Hz,

H-3), 3.78–3.89 (complex m, 2H, one OCH_2CH_2, H-5), 4.05–4.22 (complex m, 4H, OCH_2CH_3, H-6,6′), 4.40 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 4.37, 4.68 (2d, 2H, J = −11.3 Hz, OCH_2Ph), 5.13 (dd, 1H, $J_{1,2}$ = 8.2 Hz, $J_{2,3}$ = 10.1 Hz, H-2), 5.50 (br d, 1H, $J_{3,4}$ = 2.8 Hz, H-4), 7.2–7.4 (m, 5H, Ph); ^{13}C NMR: δ 14.4 (OCH_2CH_3), 24.8 ($CH_2CH_2CO_2Et$), 25.7 ($OCH_2CH_2CH_2$), 27.1–27.7 (9 $C(CH_3)_3$), 29.4 (OCH_2CH_2), 34.3 (CH_2CO_2Et), 38.9, 38.9, 39.2 (3 $COC(CH_3)_3$), 60.4, (OCH_2CH_3), 61.9 (C-6), 65.6 (C-4), 69.6 (OCH_2CH_2), 70.3 (C-2), 71.1 (C-5), 71.6 (CH_2Ph), 77.5 (C-3), 101.6 (C-1), 127.7, 127.8, 128.3, 128.3, 137.5 (Ph), 173.8 ($COCH_2$), 176.9, 177.7, 178.1 ($COC(CH_3)_3$),; EIMS *m/z*: 664 (not observed, M^+), 505 (2.4%, M^+ - $O(CH_2)_5CO_2Et$); HRMS for $C_{28}H_{41}O_8$: Calcd 505.2801. Found: 505.2806.

Phenyl 3-*O*-Benzyl-2,4,6-tri-*O*-acetyl-1-thio-β-D-galactopyranoside (5a). Acetic anhydride (470 mL) was added slowly to a stirred solution of compound **1a** (15.67 g, 0.04353 mol) in pyridine (470 mL) at 0°C and the solution was left for 12 h, then poured into an ice-cold saturated solution of sodium hydrogen carbonate (900 mL). The resulting mixture was extracted with dichloromethane (3 × 500 mL) and the combined extracts were washed with 0.8 M hydrochloric acid (3 × 250 mL), dried and concentrated to a dark yellow solid (25.69 g). Recrystallization (ethyl acetate: hexanes 1:3) yielded the title compound as colourless needles (19.05 g, 90.2%): $[\alpha]_D$ 63.4° (*c* 3.07, chloroform); mp 100–101°C; ^{1}H NMR δ: 2.06, 2.08, 2.16 (3s, 3 × 3H, 3 $COCH_3$), 3.57 (dd, 1H, $J_{3,4}$ = 3.36 Hz, $J_{2,3}$ = 9.46 Hz, H-3), 3.83 (td, 1H, $J_{4,5}$ = 1.7 Hz, $J_{5,6}$ = $J_{5,6'}$ = 6.26 Hz, H -5), 4.17 (d, 2H, $J_{5,6}$ = 6.41 Hz, H-6,6′), 4.62 (d, 1H, $J_{1,2}$ = 10.07 Hz, H-1), 4.40, 4.68 (2d, 2H, J = −12.26 Hz, OCH_2Ph), 5.16 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.8 Hz, H-2), 5.54 (dd, 1H, $J_{4,5}$ = 1.07 Hz, $J_{3,4}$ = 3.36 Hz, H-4), 7.23–7.55 (m, 10H, CH_2Ph,SPh); ^{13}C NMR δ: 20.8,20.8,21.0 (3 $COCH_3$), 62.3 (C-6), 66.0 (C-4), 68.8 (C-2), 71.3 (CH_2Ph), 74.7 (C-5), 77.6 (C-3), 86.6 (C-1), 127.9, 127.8, 128.4, 128.8, 132.3, 133.0, 137.3 (Ph, SPh), 169.4, 170.4, 170.5 (CO); EIMS *m/z*: 488 (not observed, M^+), 379 (60.6%, M^+ - SPh); HRMS for $C_{19}H_{23}O_8$: Calcd 379.1393. Found: 379.1377.

Anal. Calcd for $C_{25}H_{28}O_8S$: C, 61.46; H, 5.78. Found: C, 61.50; H, 5.62.

Ethyl 6-(2,4,6-Tri-*O*-acetyl-3-*O*-benzyl-β-D-galactopyranosyloxy)hexanoate (6a). Compound **5a** (21.28 g, 0.0441 mol) was dissolved in distilled, dry dichloromethane (200 mL) containing activated 3Å powdered molecular sieves in a 2 necked round bottomed flask wrapped in aluminum foil. Ethyl 6-hydroxyhexanoate (14.78 g, 15.0 mL, 0.09222 mol, 2.0 equiv) was added, followed by *N*-iodosuccinimide (11.46 g, 0.0511 mol, 1.15 equiv), and then a solution of silver triflate (12.76 g, 0.04966 mol, 1.10 equiv) in 100 mL of dry toluene. The reaction mixture was stirred at room temperature under a stream of N_2 (g) until starting material was consumed (1.5 h). The reaction mixture was filtered through celite, and the filtrate was washed with saturated sodium hydrogen carbonate solutions (2 × 250 mL), followed by water (2 × 250 mL). The combined aqueous layers were washed with dichloromethane (2 × 250 mL). The organic fractions were combined, dried and concentrated to a dark yellowish residue. Flash chromatography

on silica gel using 1:2 ethyl acetate: hexanes as eluant gave the title compound as a syrup (4.58 g, 19.5%): $[\alpha]_D$ +36.6° (*c* 4.18, chloroform); ^{1}H NMR 1.24 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 1.29–1.41 (complex m, 2H, $OCH_2CH_2CH_2$), 1.5–1.7 (complex m, 4H, $OCH_2CH_2CH_2CH_2$), 2.02, 2.06, 2.13 (3s, 3 × 3H, 3 $COCH_3$), 2.27 (t, 2H, J = 7.3 Hz, $OCOCH_2$), 3.45 (complex m, 1H, one OCH_2CH_2), 3.54(dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{2,3}$ = 9.9 Hz, H-3), 3.79 (t, 1H, $J_{5,6} = J_{5,6'}$ = 6.76 Hz, H-5), 3.82–3.94 (m, 1H, one OCH_2CH_2), 4.11 (q, 2H, J = 7.0 Hz, OCH_2CH_3), 4.17 (AB part of ABX, 2H, H-6,6′), 4.35 (d, 1H, $J_{1,2}$ = 8.2 Hz, H-1), 4.40, 4.69 (2d, 2H, J = −12.2 Hz, OCH_2Ph), 5.11 (dd, 1H, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 10.0 Hz, H-2), 5.51 (br d, 1H, $J_{3,4}$ = 3.4 Hz, H-4), 7.2–7.4 (m, 5H, Ph); ^{13}C NMR δ: 14.3 (OCH_2CH_3), 20.7, 20.8, 20.8 (3 $COCH_3$), 24.6 ($CH_2CH_2CO_2Et$), 25.4 ($OCH_2CH_2CH_2$), 29.1 (OCH_2CH_2), 34.2 (CH_2CO_2Et), 60.3 (OCH_2CH_3), 62.0 (C-6), 65.9 (C-4), 69.6 (OCH_2CH_2), 70.5 (C-2), 70.9 (C-5), 71.3 (OCH_2Ph), 76.6 (C-3), 101.4 (C-1), 127.8, 127.9, 128.4, 137.6 (Ph), 169.4, 170.5, 170.6 ($COCH_3$), 173.6 ($COCH_2$); EIMS *m/z*: 538 (not observed, M^+), 379 (11.6%, M^+ - $O(CH_2)_5CO_2Et$); HRMS for $C_{19}H_{23}O_8$: Calcd 379.1393. Found: 379.1369.

Phenyl 6-*O*-*tert*-Butyldimethylsilyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (7b). *Tert*-butyldimethylsilyl chloride (0.903 g, 5.99 mmol) in dry pyridine (15 mL) was added dropwise (3 mL / 20 min) via a syringe pipet to a stirred solution of phenyl 2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside[23] (2.004 g, 4.99 mmol) in dry pyridine (30 mL). The reaction mixture was stirred 12 h, then poured into water (200 mL). The mixture was extracted with diethyl ether (5 × 40 mL). The combined extracts were dried ($MgSO_4$), concentrated, and the residue purified by flash chromatography on silica gel (eluant ethyl acetate: hexanes 2:1) to give the title compound (R_f, 0.66) as a colorless syrup (1.402 g, 70.0%), crystallized from ethanol-water to give very fine colorless needles: mp 68–70°C; $[\alpha]_D$ +26.1° (*c* 2.1, dichloromethane); ^{1}H NMR δ 0.11 (d, 2 × 3H, $Si(CH_3)_2$), 0.91 (d, 9H,$SiC(CH_3)_3$, 3.55–3.65 (br m, 2H, H-4, H-5), 3.88, 3.97 (AB part of ABX pattern, 2H, $J_{6,6'}$ = −10.5 Hz, $J_{5,6}$ = 5.1 Hz, $J_{5,6'}$ = 4.5 Hz, H-6,6′), 4.18 (t, 1H, $J_{1,2} = J_{2,3}$ =10.38 Hz, H-2), 4.35 (dd, 1H, $J_{2,3}$ = 10.24 Hz, $J_{3,4}$ = 7.94 Hz, H-3), 5.60 (d, 1H, $J_{1,2}$ = 10.23 Hz, H-1), 7.2–7.6 (4m, 9H, SPh, Phth): ^{13}C NMR: δ −5.4 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 55.2 (C2), 64.7 (C6), 72.7, 74.3, 78.0 (C3, C4, C5), 83.6 (C1), 127.8, 128,9, 131.6, 132.3, 134.2 (SPh, Phth), 210.6 (2 CO, Phth). EIMS *m/z*: 515(M^+, not observed, 406 (10 %, M - SPh), 388 (72 %, 406 - H_2O).

Anal. Calcd for $C_{26}H_{33}NO_6SSi.H_2O$: C, 58.51; H, 6.61; N, 2.62. Found: C, 58.69; H, 6.54; N, 2.55.

Phenyl 6-*O*-*tert*-Butyldimethylsilyl-2-phthalimido-3,4-di-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (7a). Compound **7b** (0.100 g, 0.194 mmol) was dissolved in dry benzyl chloride (10 mL, 71.8 mmol). Sodium hydride (60% in mineral oil, 0.017 g, 0.423 mmol) was then added and the reaction was allowed to proceed under nitrogen at 70°C for 12 h. The reaction mixture was then poured into water (20 mL) and extracted with dichloromethane (3 × 30 mL). The com-

bined organic extracts were dried ($MgSO_4$), concentrated, and the residue purified by flash chromatography on silica gel (eluant ethyl acetate: hexanes 1:2) to give the title compound (R_f, 0.65) as a colorless syrup (0.068 g, 50 %): $[\alpha]_D$ +22.3° (*c* 0.9, dichloromethane); ^{1}H NMR: δ 0.11 (d, 2 × 3H, Si(C*H*$_3$)$_2$), 0.91 (d, 9H, SiC(C*H*$_3$)$_3$), 3.52 (broad dt, 1H, $J_{4,5}$ = 10.38, $J_{5,6}$ = $J_{5,6'}$ = 2.59 Hz, H-5), 3.78 (broad t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 8.54 Hz, H-4), 3.92 (broad s, 2H, H-6,6′), 5.16 (t,1H, $J_{1,2}$ = $J_{2,3}$ =10.22 Hz, H-2) 4.35 (t, 1H, $J_{3,4}$ = $J_{2,3}$ = 8.85 Hz, H-3), 4.43, 4.78 (2d, 2H, J= 12.05 Hz, OC*H*$_2$Ph), 4.77, 4.86 (2d, 2H, J = 10.99 Hz, OC*H*$_2$Ph), 5.51 (d, 1H, $J_{1,2}$ = 10.23 Hz, H-1), 7.2–7.6 (4m, 19H, 2CH$_2$*Ph,* S*Ph*, *Npth*): ^{13}C NMR: δ −4.9 (SiC(*C*H$_3$)$_3$) 26.0 (SiC(*C*H$_3$)$_3$), 29.7 (Si*C*(CH$_3$)$_3$), 54.9 (C2), 61.5 (C3), 62.1 (C6), 72.1, 75.0 (2 O*C*H$_2$Ph), 79.0 (C4), 80.2 (C5), 83.1 (C1), 127.4, 127.8, 128.0, 128.4, 128.5, 128.8, 132.7, (2 CH$_2$*Ph,* S*Ph*, *Npth*), 138.2, 138.4(2 *C*O, *Npth*).

General Method for De-*O*-benzylation: Phenyl 2,4,6-Tri-*O*-pivaloyl-1-thio-β-D-galactopyranoside (2b). Compound **2a** (0.100 g, 0.16 mmol) was dissolved in carbon tetrachloride (10 mL) and water (5 mL). NBS (2.5 equiv, 0.049 g, 0.276 mmol) was then added, followed by calcium carbonate (4.4 equiv, 0.072 g, 0.716 mmol). The solution was then purged with nitrogen for one hour. Using a 375 W incandescent light, the reaction mixture was irradiated for 15 min while being monitored by TLC. The mixture was then poured into water (25 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and the residue was purified by flash chromatography on silica gel using ethyl acetate: hexanes 1:5 as eluant, to give the title compound (0.081 g, 95%) as a colorless syrup (R_f, 0.23). The product was crystallized from hexane to give fine colorless needles: mp 105–106°C; $[\alpha]_D$ −5.0° (*c* 1.2, chloroform); ^{1}H NMR: δ 1.27, 1.20 (2s, 3 × 9H, 3 C(C*H*$_3$)$_3$), 3.91 (m, 2H, H-3, H5), 4.12 (m, 2H, H-6,6′), 4.70 (d, 1H, $J_{1,2}$ = 10.07 Hz, H-1), 4.92 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.76 Hz, H-2), 5.32 (br dd, 1H, $J_{3,4}$ = 3.35 Hz, $J_{4,5}$ = 0.9, H-4), 7.2–7.6 (m, 5H, SPh); ^{13}C NMR: δ 27.1 (3 C(*C*H$_3$)$_3$), 38.7, 38.9, 39.2 (3 *C*(CH$_3$)$_3$), 62.1 (C-6), 69.5 (C-4), 70.2 (C-2), 73.0, 74.9 (C-3, C-5), 8.6 (C-1), 128.3, 128.9, 131.9, 133.2, (SPh), 178.0, 178.1, 178.6 (3 OCO); EIMS *m/z*: 524 (0.1%, M^+), 509(0.1%, M-Me), 415(100%, M-SPh); HRMS for $C_{27}H_{40}O_8S$: Calcd 524.2444. Found: 524.2437.

2,4,6-Tri-*O*-pivaloyl-β-D-galactopyranosyl Fluoride (3b). Compound **3a** (0.229 g, 0.56 mmol) was reacted as outlined for compound **2a** to give the title compound (0.187 g, 87%) as a colorless syrup: R_f, 0.50 (ethyl acetate: hexanes 1:5); $[\alpha]_D$ +52.5° (*c* 3.9, dichloromethane); ^{1}H NMR: δ 1.20, 1.28, 1.29 (3s, 3 × 9H, 3 C(C*H*$_3$)$_3$), 4.11 (d, 2H, H-6,6′), 4.28 (dd, 1H, $J_{3,4}$ = 3.36 Hz, $J_{2,3}$ = 10.37 Hz, H-3), 4.37 (br t, 1H, $J_{5,6}$ = $J_{5,6'}$ = 6.72 Hz, H-5), 4.98 (ddd, 1H, $J_{1,2}$ = 2.60 Hz, $J_{2,3}$ =10.38 Hz, $J_{2,F}$ = 24.42 Hz, H-2), 5.44 (br d, 1 H, $J_{3,4}$ = 3.36 Hz, H-4), 5.63, 5.84 (2d, 1H, $J_{1,2}$ = 2.89, $J_{1,F}$ = 53.86 Hz, H-1); ^{13}C NMR: δ 27.1, 27.2, 27.4 (3 C(*C*H$_3$)$_3$), 38.9, 39.2, 39.5 (3 *C*(CH$_3$)$_3$), 61.4 (C-6), 67.0 (C-3), 69.5 (2C, C-4, C-5), 70.5 (d, $^2J_{C,F}$ = 23.8 Hz, C-2), 104.8 (d, $^1J_{C,F}$ = 227.7 Hz, C-1),178.1, 178.4, 178.9 (3 OCO); EIMS *m/z*: 434 (not observed, M^+), 414 (7.6%, M^+ - HF), 399

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(1.5%, M^+ - HF - CH_3), 333 (2.8 %, M^+ - OCO*t*Bu); HRMS for $C_{21}H_{34}O_8$: Calcd 414.2253. Found: 414.2245.

Ethyl 6-(2,4,6-Tri-*O*-pivaloyl-β-D-galactopyranosyloxy)hexanoate (4b). Compound **4a** (0.068 g, 0.10 mmol) was reacted as outlined for compound **2a** to give the title compound (0.057 g, 95%) as a colorless syrup: $[\alpha]_D$ +3.2° (*c* 6.1, dichloromethane); ^{1}H NMR: β 1.20, 1.22, 1.27 (3s, 3 × 9H, 3 C(CH_3)$_3$), 1.25 (t, 3H, J = 6.8 Hz, OCH$_2$CH_3), 1.29–1.41 (complex m, 2H, OCH$_2$CH$_2$CH_2), 1.5–1.8 (complex m, 4H,OCH_2CH$_2$CH$_2$CH_2), 2.30 (t, 2H, J = 7.3 Hz, OCOCH_2), 3.41–3.50 (complex m, 1H, one OCH_2CH$_2$), 3.80–3.92 (m, 3H, one OCH_2CH$_2$, H-3, H-5), 4.10 (q, 2H, J = 7.0 Hz, OCH_2CH$_3$), 4.12 (AB part of ABX, 2H, H-6,6′), 4.46 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 4.90 (dd, 1H, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 10.1 Hz, H-2),, 5.30 (br d, 1H, $J_{3,4}$ = 3.5 Hz, H-4); ^{13}C NMR: δ 14.3 (OCH$_2$*C*H$_3$), 21.1 (*C*H$_2$CH$_2$COOEt), 24.7 (OCH$_2$CH$_2$*C*H$_2$), 25.6 (OCH$_2$*C*H$_2$),27.2–27.3 (9 C(*C*H$_3$)$_3$) 29.4 (*C*H$_2$COOEt), 39.8, 39.0, 39.4 (3 *C*(CH$_3$)$_3$) 60.3 (O*C*H$_2$CH$_3$), 61.9 (C-6), 69.4, 69.7 (C-4, OCH$_2$*C*H$_2$), 71.1, 72.1 (C-3, C-5), 72.9 (C-2), 101.1 (C-1), 173.7 (*C*OCH$_2$), 178.0, 178.2, 179.2 (*C*OC(CH$_3$)$_3$); EIMS *m/z*: 574 (not observed, M^+), 415 (5.3%, M^+ - O(CH$_2$)$_5$CO$_2$Et); HRMS for $C_{21}H_{35}O_8$: Calcd 415.2332. Found: 415.2333.

Phenyl 2,4,6-Tri-*O*-acetyl-1-thio-β-D-galactopyranoside (5b). Compound **5a** (0.197 g, 0.404 mmol) was reacted as outlined for compound **2a** to give the title compound (0.122 g, 76%) as a colorless syrup, crystallized from hexanes: ethyl acetate to give fine colorless needles: mp 120–121°C; R_f 0.21 (ethyl acetate: hexanes 2:3); $[\alpha]_D$ +14.6° (*c* 1.0, chloroform); ^{1}H NMR: δ 2.05, 2.15, 2.73 (3s, 3 × 3H, 3 COCH_3), 3.89 (m, 2H, H-3, H-5), 4.13, 4.16 (AB part of ABX pattern, 2H, $J_{5,6}$ = 7.4 Hz, $J_{5,6'}$ = 5.5 Hz, $J_{6,6'}$ = −11.5 Hz, H-6,6′), 4.68 (d, 1H, $J_{1,2}$ = 9.92 Hz, H-1), 5.04 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.77 Hz, H-2), 5.36 (dd, 1 H, $J_{3,4}$ = 3.53 Hz, $J_{4,5}$ = 0.94 Hz, H-4), 7.20–8.10 (3m, 6H, SPh); ^{13}C NMR: δ 20.8, 21.2, 29.7 (3 CO*C*H$_3$), 62.4 (C-6), 70.1 (C-4), 70.8 (C-2), 72.1, 74.9 (C-5, C-3), 86.3 (d, C-1), 128.1, 129.0, 129.0, 130.2, 132.4, 132.4 (SPh), 171.2, 171.2, 178.5 (3 OCO); EIMS *m/z*: 398 (0.5%, M^+), 289 (100, M^+ - SPh); HRMS for $C_{18}H_{22}O_8S$: Calcd 398.1035. Found: 398.1054.

Ethyl 6-(2,4,6-Tri-*O*-acetyl-β-D-galactopyranosyloxy)hexanoate (6b). Compound **6a** (2.00 g, 3.43 mmol) was reacted as outlined for compound **2a** to give the title compound (1.26g, 83%) as a colorless syrup: $[\alpha]_D$ +7.7° (*c* 1.3, dichloromethane); ^{1}H NMR: δ 1.25 (t, 3H, J = 6.8 Hz, OCH$_2$CH_3), 1.29–1.41 (complex m, 2H, OCH$_2$CH$_2$CH_2), 1.5–1.8 (complex m, 4H, OCH$_2$CH_2CH$_2$CH_2), 2.02, 2.04, 2.13 (3s, 3 × 3H, 3 COCH_3), 2.29 (t, 2H, J = 7.3 Hz, OCOCH_2), 3.48 (X of ABXY, 1H, OCH_2CH$_2$), 3.79–3.93 (complex m, 3H, OCH_2′CH$_2$, H-3, H-5), 4.12 (q, 2H, J = 7.2 Hz, OCH_2CH$_3$),4.15 (AB part of ABX, 2H, H-6,6′), 4.41(d, 1H, $J_{1,2}$ = 7.9 Hz, H-1), 4.97 (dd, 1H, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 5.33 (br d, 1H, $J_{3,4}$ = $J_{4,5}$ = 3.2, H-4); ^{13}C NMR: δ 14.4 (OCH$_2$*C*H$_3$), 20.8, 20.9, 21.1 (3 CO*C*H$_3$), 24.7 (*C*H$_2$CH$_2$CO$_2$Et), 25.5 (OCH$_2$CH$_2$*C*H$_2$), 29.2 (OCH$_2$*C*H$_2$), 34.23

(CH_2CO_2Et), 60.4 (OCH_2CH_3), 62.1 (C-6), 69.9 (C-4, OCH_2CH_2), 71.0, 71.4 (C-3, C-5), 72.8 (C-2), 101.1 (C-1),170.7**,** 171.1, 171.1 ($COCH_3$), 173.6 ($COCH_2$); EIMS *m/z*: 448 (not observed, M^+), 403 (0.9%, M^+ - OEt), 289 (14.8%, M^+ - $O(CH_2)_5CO_2Et$); HRMS for $C_{18}H_{27}O_{10}$ and $C_{12}H_{17}O_8$: Calcd 403.1604 and 289.0923. Found: 403.1633 and 289.0987, respectively.

Phenyl 6-*O*-*tert*-Butyldimethylsilyl-2-deoxy-2-*N*-pthalimido-1-thio-β-D-glucopyranoside (7b). Compound **7a** (0.095 g, 0.137 mmol) was reacted as outlined for compound **2a** to give the title compound (0.51 g, 72.4%) as a colorless syrup, with R_f and spectral characteristics identical to **7b**, prepared above.

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