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A New, Lipophilic *p*-Alkoxybenzyl Ether Protecting Group and Its Use in the Synthesis of a Disaccharide

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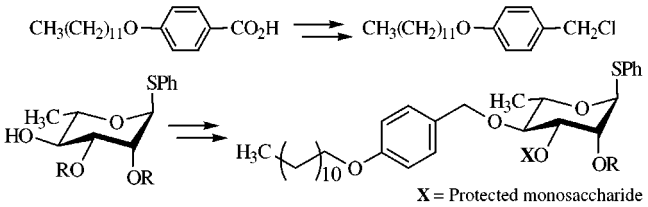
ABSTRACT



In contrast to major advances in the chemical synthesis of oligosaccharides, the methods of purification of the intermediates are essentially the same as they were decades ago. Here, the synthesis of *p*-(dodecyloxy)benzyl chloride is described and it is demonstrated that the new *p*-(dodecyloxy)benzyl ether protecting group can render a protected disaccharide sufficiently lipophilic for selective adsorption on C_{18} silica, thus sidestepping the expensive silica gel chromatography traditionally used for the isolation of protected oligosaccharides.

Despite major advances in the chemical synthesis of oligosaccharides,[1] for example the development of efficient, stereocontrolled glycosylation methods and versatile protecting group schemes, synthesis of higher-membered oligosaccharides remains a challenge in part because of the difficulty of product isolation. In contrast to the chemical advances, the methods of purification of oligosaccharide intermediates are essentially the same as they were decades ago. Silica gel chromatography, the only general method available for this purpose, requires a great deal of ingenuity on the part of the practitioners, especially in the case of higher-membered oligosaccharides. Solid-phase chemistry, while successful in the synthesis of peptides and nucleotides, has not solved this problem so far and its advantages over liquid-phase oligosaccharide synthesis have yet to be demonstrated by way of direct comparison.[2] As the alternative, soluble polymer-supported methods have also been suggested.[3] To facilitate product isolation in enzymatic glycosylations, the use of a lipophilic aglycon as a phase tag has been proposed by Sweeley, who employed Sep Pak C_{18} cartridges that contain dimethyloctadecylsilyl-bonded silica, to separate the phase-tag-bearing product from the more polar, nontagged precursors and reagents.[4] A related solid-phase extraction protocol employs the hydrophobic 8-(*p*-methoxyphenoxy)-octyl moiety as the aglycon.[5] A recently proposed approach uses a fluorous benzyl protecting group that renders oligosaccharide intermediates containing this group soluble in a fluorinated solvent while insoluble in other organic solvents or water, thus permitting, in principle, product isolation in a single extraction step.[6]

In this communication initial results are reported toward a new strategy to oligosaccharide synthesis that relies on lipophilic protecting groups. Our method preserves the advantages of solution-phase glycosylations and sidesteps

(1) For a recent review on oligosaccharide synthesis, see: Kanie, O.; Ogawa, T.; Ito, Y. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 952.

(2) For a recent review on the synthesis of oligosaccharides on solid support and related methods, see: Osborn, H. M. I.; Khan, T. H. *Tetrahedron* **1999**, *55*, 1807.

(3) Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. *J. Am. Chem. Soc.* **1991**, *113*, 5095.

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(6) Curran, D. P.; Ferritto, R.; Hua, Y. *Tetrahedron Lett.* **1998**, *39*, 4937.

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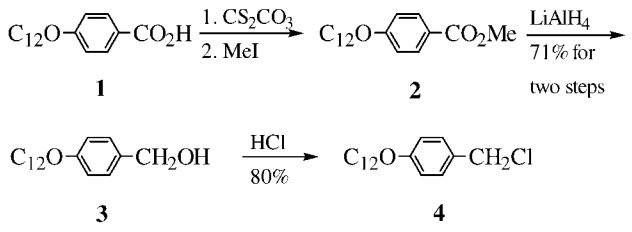
most of the difficulties associated with conventional silica gel chromatography. The objective of the experiments described herein is to demonstrate the feasibility of the proposed approach for efficient product isolation.

The synthesis of the new lipophilic *p*-alkoxybenzyl chloride **4** is outlined in Scheme 1.[7] Reaction of the commercially available *p*-(dodecyloxy)benzoic acid (**1**) with Cs_2CO_3 followed by MeI afforded the methyl ester **2**. Reduction of **2** with $LiAlH_4$ under the usual conditions provided the alcohol **3** as a solid material. Chlorination of compound **3** using HCl yielded the chloride **4**, which was isolated as a crystalline product from methyl alcohol. Compound **4** showed no sign of decomposition at 0 °C after several weeks.

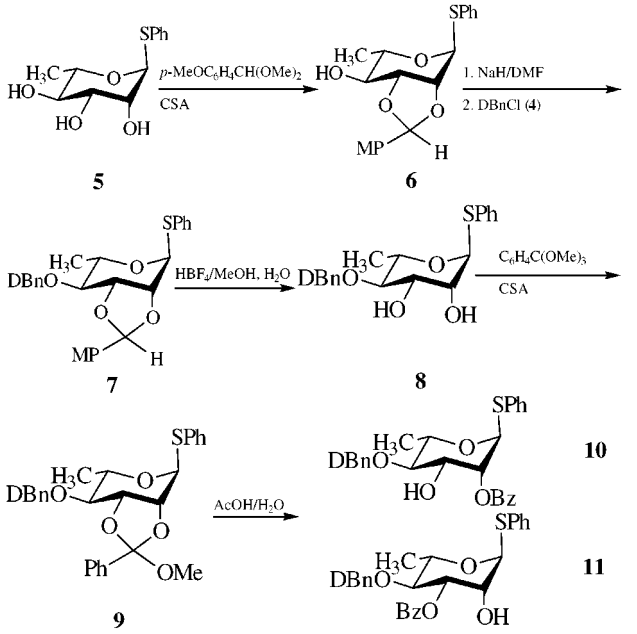
Scheme 1



C_{12} = n-dodecyl

In a representative test, the new *p*-(dodecyloxy)benzyl chloride (**4**; DBnCl) was condensed with the thiorhamnoside **6** obtained from the triol[8] **5** by treatment with *p*-methoxybenzaldehyde dimethylacetal/CSA (Scheme 2). The etherification followed the established method for benzyl ether formation using NaH in DMF to convert the alcohol to its sodium salt and proceeded to completion with only a small excess of **4**. The resulting *p*-(dodecyloxy)benzyl ether **7** was treated with aqueous HBF_4 to remove the acetal protection without affecting the DBn ether, whose acid sensitivity is similar to that of the well-known *p*-methoxybenzyl ether.[9] The diol **8** so formed was converted to the benzoate **10** using a standard protocol involving cyclic ortho ester formation at HO-2 and -3 with trimethyl orthobenzoate/CSA (→**9**) followed by mild, acetic acid hydrolysis.[10] The lipophilic compound **10** was purified by solid-phase extraction using a Waters Preparative C_{18} 125 Å column made in 80% aqueous MeOH. This solvent completely eluted the impurities. Compound **10** was eluted with MeCN. Because of the formation of an isomeric benzoate (**11**) that coeluted from the C_{18} adsorbent with **10** as expected, the final purification was done on a silica gel column to afford **10** in an overall yield of 52% for five steps (from **5**).

Scheme 2



Overall yield of **10** from **5**: 52%.

MP = *p*-methoxyphenyl DBn = *p*-dodecyloxybenzyl
Bz = benzoyl

The use of the lipophilic protecting group-tagged acceptor in the synthesis of a disaccharide is shown in Scheme 3. Thus, the rhamnosyl donor[11] **12** (2 equiv) was combined with the lipophilic acceptor **10** under AgOTf activation using standard conditions (DTBMP, 4 Å molecular sieves, CH_2Cl_2, −60 to −10 °C). TLC analysis of the reaction mixture showed complete conversion of **10** within 30 min, thus

(7) **Procedure for the Synthesis of Compound 4.** To a solution of 4-(*n*-dodecyloxy)benzoic acid (20 g, 65.2 mmol) in hot MeOH (300 mL) was added Cs_2CO_3 (12.0, 36.8 mmol) in 10:1 MeOH−H_2O (110 mL). After dissolution of the solids the solution was concentrated. To the residue were added DMF (100 mL) and MeI (30 mL) at 25 °C. After 1 h, the solution was concentrated. The residue was equilibrated between $CHCl_3$ and H_2O, and the organic layer was dried (Na_2SO_4) and concentrated. A solution of the solid so obtained in dry THF (100 mL) was treated with $LiAlH_4$ (3.5 g): then the mixture was stirred under reflux for 1 h. The usual workup afforded a solid that was recrystallized from EtOAc. The mixture was kept at 0 °C for 1 day before filtration to give **3** (13.5 g, 71% for three steps) as a white crystalline solid: mp 68−69 °C; ^{1}H NMR ($CDCl_3$) δ 7.27 (d, 2 H, J = 8.6 Hz), 6.88 (d, 2 H, J = 8.6 Hz), 4.61 (s, 2 H), 3.95 (t, 2 H, 6.5 Hz), 1.78 (m, 2 H), 1.62 (s, 1 H), 1.55−1.20 (m, 18 H), 0.88 (t, 3 H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 128.6, 114.5, 68.0, 65.1, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 26.0, 22.7, 14.1. Dry HCl gas was bubbled through a solution of **3** (16.5 g) in toluene (100 mL) at 25 °C for 6 h; then the solution was kept at 0 °C for 24 h. The solution was concentrated. The crystalline residue was triturated in MeOH at 0 °C. Filtration afforded **4** (14.0 g, 80%): mp 38−40 °C; ^{1}H NMR ($CDCl_3$) δ 7.27 (d, 2 H, J = 8.7 Hz), 6.86 (d, 2 H, J = 8.7 Hz), 4.56 (s, 2 H), 3.95 (t, 2 H, 6.5 Hz), 1.77 (m, 2 H), 1.6−1.2 (m, 18 H), 0.88 (t, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 114.7, 68.1, 46.4, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 26.0, 22.7, 14.1.

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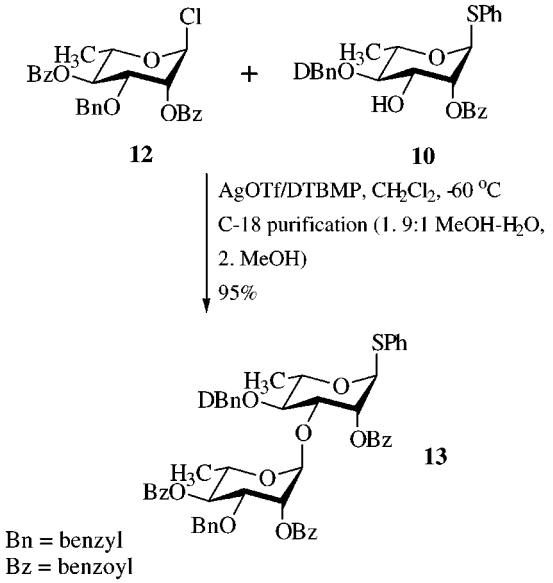
(13) NMR data for **13**: ^{1}H ($CDCl_3$), δ (selected) 5.66 (dd, 1 H), 5.63 (dd, 1 H), 5.57 (d, 1 H, J = 1.5 Hz), 5.38 (t, 1 H, J = 9.7 Hz), 5.32 (d, 1 H, J = 1.8 Hz), 4.81 and 4.61 (2 d, 2 H, J = 10.4 Hz), 4.52 and 4.36 (2 d, 2 H, J = 12.5 Hz), 1.75 (m, 2 H), 1.36 and 1.20 (2 d, 2 × 3 H, $J \approx$ 6.2 Hz), 0.88 (t, 3 H); ^{13}C ($CDCl_3$), δ 165.6, 165.5, 159.0, 137.5−128.5, 114.5, 99.7 ($J_{H-1,C-1}$ = 172 Hz), 85.6 ($J_{H-1,C-1}$ = 168 Hz), 80.0, 77.5, 75.4, 74.5, 74.0, 72.8, 71.1, 69.3, 69.1, 68.0, 67.6, 31.9, 29.6−29.2, 26.0, 22.7, 18.0, 17.5, 14.1.

Scheme 3



indicating that the large DBn protecting group does not create a "steric mismatch" situation.[12] After the usual processing, the reaction mixture was applied to a column of Waters Preparative C_{18} 125 Å adsorbent made in 80% aqueous MeOH. Elution with 9:1 MeOH−H_2O removed the side products. Subsequent elution with MeOH afforded the lipophilic group-tagged **13** in >95% purity, as estimated by integration of selected ^{1}H NMR signals,[13] thus verifying our initial assumption that one hydrophobic DBn tag may, indeed, be sufficient for selective adsorption of a disaccharide onto the C_{18} silica.

In conclusion, we have developed a new protecting group and demonstrated its utility in the synthesis and rapid isolation of a disaccharide, thus avoiding the conventional silica gel chromatographic purification. The new technique combines the advantages of liquid-phase oligosaccharide synthesis with the simplicity of product isolation of solid-phase methods. An advantage of our protocol over the solid-phase techniques is that it also allows separation of isomers of the tagged material by silica gel chromatography if necessary. The importance of this preliminary work is that it provides a generally applicable and easily available lipophilic tagging device. The new *p*-alkoxybenzyl group may be used not only for the protection of hydroxyl groups as demonstrated in this exploratory work but also for the masking of carboxyl and amino functionalities. As found here, one lipophilic group provides sufficient hydrophobicity to disaccharide **13** that allowed its isolation by using a simple adsorption/washing sequence through a C_{18} silica column. Considering the high price of silica gel and organic solvents, sidestepping the conventional silica gel chromatographic separation may make chemical synthesis of oligosaccharides less expensive. In this context it is also noted that the C_{18} material can be recycled many times without appreciable loss of capacity. Current work is aimed at exploring the utility of other ether- and ester-type protecting groups in the chemical synthesis of higher-membered oligosaccharides, with particular attention to the size and number of such groups that may be required for efficient separation.

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