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Preparation of a Fluorous Benzyl Protecting Group and Its Use in a Fluorous Synthesis Approach to a Disaccharide

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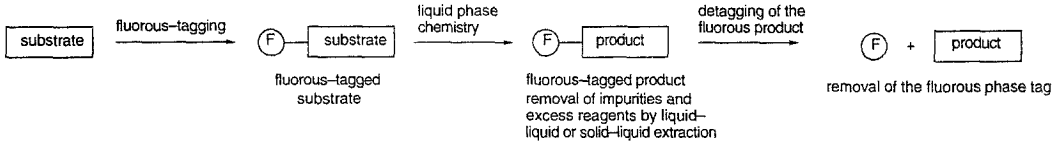
Summary: *Benzylation of glucal with a fluorous benzyl group provided a fluorous tribenzyl glucal derivative which was coupled with excess diacetone galactose to make a fluorous disaccharide. These experiments break ground for a fluorous approach to oligosaccharide synthesis.* © 1998 Elsevier Science Ltd. All rights reserved.

We have recently introduced the concept of "fluorous synthesis" as a fundamental strategic alternative to traditional small molecule synthesis and solid phase synthesis.[1,2] As shown pictorially in Figure 1, an organic substrate is tagged with a group "F" containing enough fluorines to render the resulting molecule fluorous with respect to simple fluorous–organic phase separation techniques like liquid–liquid or solid–liquid extraction.[1d] At the end of a reaction or sequence of reactions, tagged molecules can be readily separated from untagged organic molecules as well as water-soluble, volatile, and insoluble additives or products by simple workup techniques. Fluorous synthesis is one of a number of emerging techniques that provide for separation at a strategy level.[3]

Figure 1. A Cartoon of Fluorous Synthesis



In principle, fluorous synthesis techniques have the facile purification features that have made solid phase synthesis so popular, but they retain many of the advantages of traditional small molecule synthesis.[4] In practice, there are a number of issues that need to be better understood to aid in the broader application of fluorous synthesis. Among these are the availability of fluorous tagging groups, the number of fluorines that are needed to render organic molecules fluorous, and the general effectiveness with which fluorous substrates react in organic transformations. We are addressing these issues on a number of fronts, and we report herein our preliminary efforts directed towards fluorous oligosaccharide synthesis. We introduce a fluorous version of the popular benzyl protecting group[5] and use this to make a fluorous glucal derivative, which is then processed to a disaccharide. Among the interesting features of the sequence are a "reverse fluorous" tin hydride reduction, the use of a supported metal catalyst to conduct a reductive debenyzlation in a fluorinated solvent, and the recovery and recycle of the fluorous benzyl group.

The synthesis of the new fluorous benzyl protecting reagent **3** is outlined in eq 1. Reaction of *p*-tolyl magnesium bromide with readily available tris(perfluorohexylethyl)silyl bromide **1** in THF ether provided aryl silane **2** in 95% yield after purification by FC-72[6]–acetonitrile extraction. Bromination of **2** under standard conditions (NBS, CCl_4, AIBN) provided the benzyl bromide **3** in 75% yield after flash chromatography (which removed a small amount of unreacted **2**).

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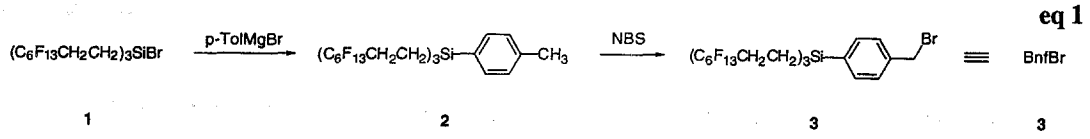
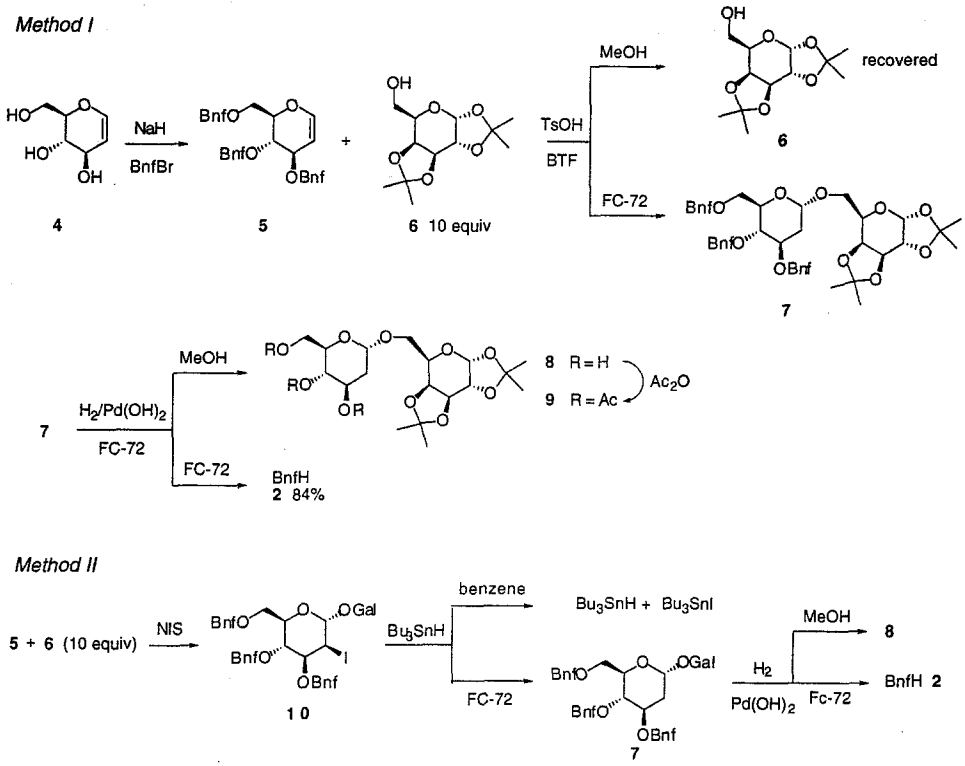


eq 1

Among the many possible ways to make disaccharides, we chose a glycal route because glycals have become very popular intermediates in both solution and solid phase carbohydrate synthesis[7] and because glycals are fairly sensitive (especially to acid) and they should provide a representative test of the fluorous methodology. The synthesis of the known galactosyl glucose derivative **9** is shown in Scheme 1.

Scheme 1



Reaction of D-glucal **4** with sodium hydride in DMF[8] followed by addition of 4 equiv of benzyl bromide **3** (abbreviated as BnfBr) in BTF[9] and 10% tetrabutylammonium iodide provided the crude tribenzyl glucal derivative **5** after three-phase (water, CH_2Cl_2, FC-72) extraction to remove organic and inorganic materials. This was separated from the excess benzylating reagent and other impurities by standard silica gel chromatography. Pure tribenzyl glucal **5** was isolated in 51% yield. To date, we have tried several other benzylation procedures, but none has yet proved superior to this standard one. Although the chromatographic purification is not necessarily desirable, it nonetheless illustrates a potential advantage over solid phase synthesis: when reaction products are not deemed sufficiently pure, they can be purified by standard techniques. During the chromatography, the fluorous groups function as chromatographic tags rendering the desired product very non-polar with respect to impurities.[4b,c]

The fluorous glucal **5** was then coupled with diacetone galactose **6** under two standard sets of conditions to make 2-deoxydisaccharides.[7c] In the first method, treatment of a BTF[9] solution of **5** and 10 equiv of diacetone galactose **6** with a catalytic amount of pTSA[10] followed by standard three-phase extraction provided reasonably pure fluorous disaccharide **7** in 85% yield upon evaporation of the fluorous phase. This disaccharide was not contaminated by the unreacted diacetone galactose **6**, which was recovered in excellent purity from the organic phase. Thus, the method allows for recovery of both the desired product and the excess organic component, which can be reused in a subsequent coupling. For characterization purposes, one of the coupling reactions was purified by flash chromatography over silica gel to provide pure **7** in 69% yield.

The fluorous disaccharide **7** was then debenzylated by catalytic hydrogenation with $Pd(OH)_2$ and H_2 (50 psi) in FC-72. Procedures with insoluble catalysts are not usually considered for solid phase synthesis, but the success of this reaction suggests that a range of standard supported metal reactions might be applicable to fluorous synthesis. After filtration and three-phase extraction, the product **8** in the organic phase was directly subjected to acylation and then flash chromatographic purification to provide the known disaccharide **9**[11] in 45% overall yield from the fluorous glucal **5**. Evaporation of the fluorous phase provided the expected fluorous tolyl silane **2** in 84 % yield. This was routinely rebrominated to regenerate the fluorous tagging reagent **3**. Analysis of the crude disaccharide **9** by ^1H NMR spectroscopy showed that it contained a small amount (5-10%) of acetyl diacetone galactose, which apparently originated from cleavage during the hydrogenation.[12]

For comparison, the whole reaction sequence was repeated with standard benzyl groups (not shown). As expected the normal benzylation occurred in much higher yield (95%) than the fluorous benzylation (51%), but the rest of the steps were roughly comparable and **9** was isolated in 52% overall yield for the sequence of coupling, debenzylation, and acetylation. In the coupling of the benzyl glucal, only 2 equiv of galactose **6** was used, and chromatography was required to separate the disaccharide from excess galactose.

In the second method, fluorous glucal **5** was coupled with galactose **6** (10 equiv) by using NIS (8 equiv) in BTF at ambient temperature.[13] Three-phase extraction provided the iodide **10** in 92% crude yield, free from galactose and any succinimide products. Purification of the crude product of one reaction by chromatography gave **10** in 72% yield. Next, **10** was reductively deiodinated with tributyltin hydride, followed by two-phase extraction. The product **8** was isolated from the fluorous phase (81% yield after chromatography) and the tin residue was extracted into the organic phase. This is the reversal of our previous work on fluorous applications of tin hydride chemistry,[14] where the tin hydride is fluorous and the substrate is organic. Reductive debenzylation and acetylation as above then provided **9** in 41% overall yield from fluorous glucal **5**. For reference, an identical sequence with the standard benzyl group was conducted and this provided **9** in 55% overall yield. Once again, the crude organic product **9** was contaminated by small amounts (5-10%) of acetyl diacetone galactose.[12]

The significance of this preliminary work extends in a number of directions. First, the fluorous benzyl tagging reagent is expected to be a generally useful reagent for protection both in and beyond carbohydrate chemistry; however, improved yields for the benzylation step are still needed. With regard to rendering large organic substrates fluorous, previous work had focused on simply adding more fluorines to single group.[1] In areas like carbohydrate synthesis where multiple functional groups are needed, it appears to be easier to add more fluorines simply by adding more tagging groups. The disaccharides **8-10** are highly fluorous and show no tendency to partition into a organic phases like benzene, acetonitrile or methanol. The work also establishes the potential for heterogeneous reactions (like the catalytic hydrogenation) of fluorous substrates in fluorous

solvents and provides another potentially general method for separating products from tin residues (make the substrate fluorous instead of the tin.) In the long run, we envision that many other types of fluorous protecting groups can be introduced to complement the silyl groups that are now available[1] and the benzyl group that is introduced in this paper.

Several things also detract from this work at this early stage of development. While the liquid–liquid extractions do work well, the products of the reactions are not always as pure as desired due to side reactions. In this work, we sometimes used chromatography to obtain pure products, but for parallel synthesis applications, the crude products of these reactions might be of sufficient purity to move ahead. In addition, the relatively large numbers of fluorine (117) may render these tribenzylated molecules inconveniently large (MW ~3,700). For example, NMR spectra of the fluorous benzylated products had significantly broader lines than those of the normal benzyl products, and while we suspect that the galactose in the final samples of disaccharide **9** arises from the hydrogenation step,[12] the peaks in the NMR spectra of the fluorous products are sufficiently broad that we cannot completely rule out the possibility that a fluorous galactose impurity is harbored therein. A potential solution to these problems is emerging with the advent of the techniques of fluorous reverse phase chromatography and solid phase extraction.[1d,3b] We are now investigating methods to either reduce the number of fluorous groups or reduce the number of fluorines per group yet retain the simple separation features.

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References and Notes

1. a) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823. b) Studer, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 6681. c) Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 2917. d) Curran, D. P.; Hadida, S.; He, M. *J. Org. Chem.* **1997**, *62*, 6714.
2. a) Introduction to "fluorous biphasic catalysis", Horvath, I. T.; Rabai, J. *Science* **1994**, *266*, 72. b) Overview of recent progress in "fluorous biphasic catalysis": Cornils, B. *Angew. Chem. Int. Ed. Eng.* **1997**, *36*, 2057.
3. a) Curran, D. P. *Chemtracts—Org. Chem.* **1996**, *9*, 75. b) Curran, D. P. *Angew. Chem. Int. Ed. Eng.* **1998**, in press.
4. a) Some of these features are shared by polyethylene glycol (PEG) tagging methods. Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489. For a related strategy based on lipophilic tagging, see b) Palcic, M; Srivastava, O. P.; Hindsgaul, O. *Carb. Res.* **1987**, *59*, 315. c) Nilsson, V. J.; Fournier, E.; Hindsgaul, O. submitted for publication.
5. a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, 1991. b) Jarowicki, K.; Kocienski, P. *Contemporary Organic Synthesis* **1996**, *3*, 397.
6. FC-72 is a trademark of the 3M Corporation. It consists of isomers of C_6F_{14}, mostly perfluorohexane.
7. a) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. b) Boons, G. J. *Tetrahedron* **1996**, *52*, 1095. (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.
8. a) Kanai, K; Sakmoto, S.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Japan* **1987**, *60*, 1529. b) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrhedron Lett.* **1976**, *39*, 3535.
9. BTF is benzotrifluoride, $C_6H_5CF_3$, which is sold inexpensively under the name Oxsol-2000™ by Oxychem. Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450.
10. Tu, C. J.; Lednicer, D. *J. Org. Chem.* **1987**, *52*, 5624.
11. Sabesan, S.; Neira, S. *J. Org. Chem.* **1991**, *56*, 5468.
12. Extraction experiments showed that galactose **6** does not partition into FC-72, so this impurity cannot originate from residual **6** from the coupling which was not removed by extraction. Even chromatographically purified samples of the fluorous disaccharides provided **6**, suggesting that this is formed during the hydrogenation step. Further support for this came from a control hydrogenation with the standard (non-fluorous) tribenzyl disaccharide, which provide small amounts of diacetone galactose and 2-deoxyglucose (isolated as their peracetate derivatives). See: Urbanek, R. A.; Salaes, S. F.; Forsyth, C.. *J. Am. Chem. Soc.* **1998**, *120*, 2523.
13. Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696.
14. a) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531. b) Ryu, I.; Niguma, T.; Minakata, S.; Komatsu, M.; Hadida, S.; Curran, D. P. *Tetrahedron Lett.* **1997**, *38*, 7883.