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SYNTHESIS AND APPLICATIONS OF A FLUOROUS THP PROTECTIVE GROUP

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Abstract: A recyclable fluorous labeled THP protecting group has been developed that allows for simple purification of small molecules by liquid-liquid extraction with FC-72/MeCN, and of larger or more polar molecules by solid phase extraction with fluorous reverse phase silica gel. In addition, we report a new glycosylation method which uses the Cp_2ZrCl_2-$AgClO_4$ reagent system to activate an anomeric sulfoxide.

The use of organic reactants and reagents attached to highly fluorinated tags (fluorous synthesis) is rapidly developing into a viable alternative to traditionally solid phase oriented combinatorial synthesis.[1] This technique exploits the ability of a highly fluorinated compound to partition predominantly into the fluorocarbon phase in a liquid-liquid extraction between an organic and a fluorinated solvent. Organic substrates are readily rendered "fluorous" by attachment of an appropriately fluorinated phase label.[1] Subsequent solution phase reactions may be performed on the substrate and purification of the resultant products is readily accomplished via extraction of the product with a perfluorinated solvent or by filtration through perfluorinated SiO_2. To date, the fluorous phase label mainly used in fluorous synthesis has been silane **1**.[1,2] **1** is attached to alcohol-bearing substrates using standard conditions, and can be cleaved with fluoride; however, it cannot be readily recycled. In addition, the powerful electron withdrawing effect of three fluorous chains makes the silyl ether rather labile towards nucleophiles and polar reaction conditions.

$$(C_{10}F_{21}CH_2CH_2)_3SiBr\ (\mathbf{1}) \quad + \quad ROH \xrightarrow{\text{imidazole}} (C_{10}F_{21}CH_2CH_2)_3SiOR$$

Our aim was to develop a series of complementary fluorous phase labels that are stable to basic and nucleophilic reaction conditions and become readily recyclable after cleavage. A fluorous-labeled tetrahydropyranyl (THP^F) ether seemed a logical choice due to the excellent stability of this group.[3] Initially, we prepared a perfluoroalkyl-substituted dihydropyran which could be installed on any hydroxy-bearing substrate via acid catalysis in the same way a standard THP protection is performed. Dihydropyran **4** was synthesized in one step from perfluorooctyl iodide (**3**) and dihydropyran (**2**) in 46% yield (Scheme 1).[4] However, treatment of alcohols with an excess of **4** using a variety of acids, solvents, and temperatures failed to give any of the desired acetal **5**. This was the first manifestation in our work of the powerful electron withdrawing effect of the perfluoroalkyl chain, presumably the cause of the loss of reactivity of the vinyl ether.

Our second route involved glycosylation methodology. Glycosyl fluorides have been effectively activated by the Cp_2ZrCl_2-$AgClO_4$ reagent system.[5] Glycosyl iodide **6** was accessible in one step from perfluorooctyl iodide (**3**) with excess dihydropyran and stoichiometric $Na_2S_2O_4/NaHCO_3$ under phase transfer conditions in 64% yield.[6] Unfortunately, this reaction was often irreproducible, and was typically plagued by formation of hemiacetal **7**. Use of catalytic Raney Nickel in refluxing THF gave **6** more reliably but in 32-38% yield.[7] Addition of a slight excess of **6** to a solution of one equivalent of Cp_2ZrCl_2, two equivalents of $AgClO_4$, and one equivalent of an alcohol gave good yields of fluorous THP labeled products **8**, presumably via an intermediate

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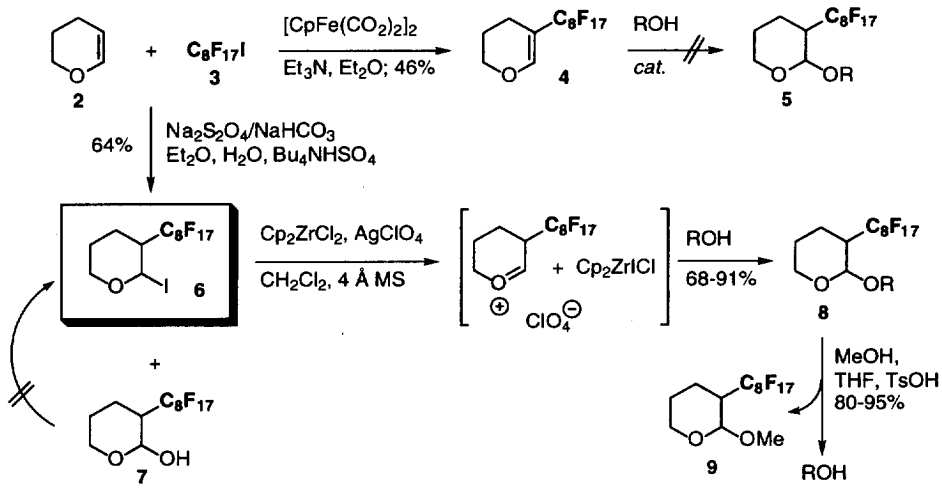
highly reactive oxonium species. Deprotection via transacetalization with methanol and catalytic TsOH proceeded to give the free alcohol in 80-95% yield, as well as the transacetalization product **9**. However, in spite of numerous attempts, we were unable to recycle methyl THP ether **9** to iodopyran **6**. Application of trimethylsilyl iodide (TMSI) and several of its *in situ* prepared variants[8] led in all cases to the undesired elimination product **4** as the primary product.

Scheme 1.



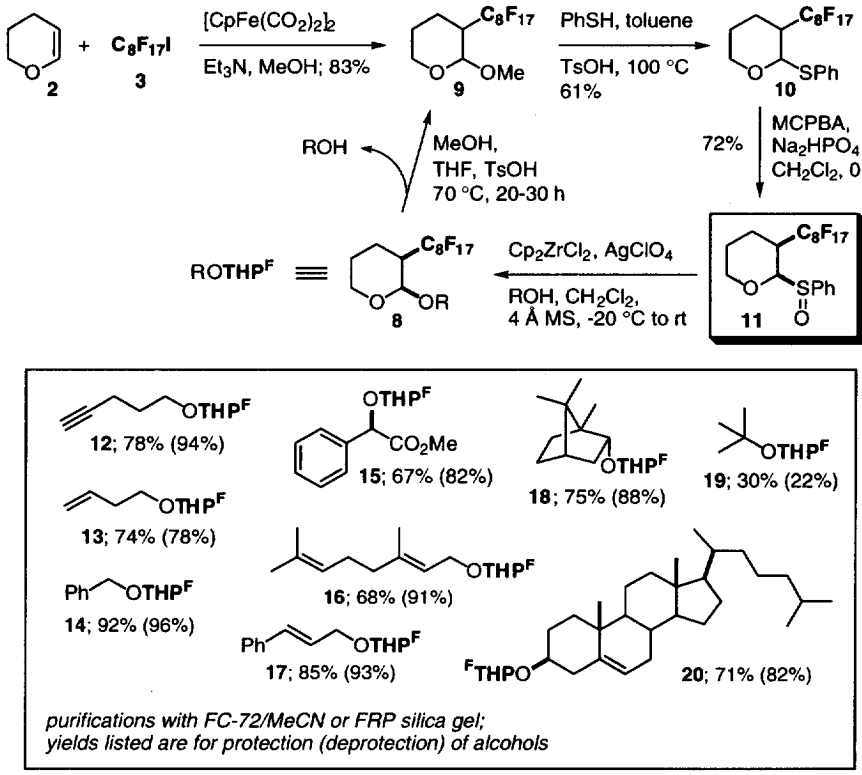
The sulfoxide method has proven to be a mild and effective means for constructing glycosidic linkages.[9] Application of this technique to our system began with the direct synthesis of methyl THP ether **9** (Scheme 2). Treatment of a methanolic solution of **3** and 5 mol% $[CpFe(CO)_2]_2$ with 1.5 equiv of dihydropyran and 1.1 equiv of Et_3N at room temperature gave **9** in 83% yield. Conversion of **9** to the phenylthioacetal **10** was first accomplished using Nicolaou's method[10] (5 equiv $PhSSiMe_3$, 1.2 equiv Me_3SiOTf) to give **10** in 60% yield. Alternatively, heating **10** in a 1:1 mixture of PhSH and toluene at 100 °C with 1 equiv of TsOH gave **10** in 61% yield. Oxidation of sulfide **10** with a Na_2HPO_4-buffered solution of MCPBA in dichloromethane at 0 °C provided sulfoxide **11** as a 1.5:1 mixture of anomers in 72% yield. Subsequent conversion utilized the major, more reactive *cis*-isomer. *Trans*-**11** could be recycled to a 1:1 mixture of anomers in PhSH/dioxane (1:1) at 95 °C in the presence of a catalytic amount of $HgSO_4$.

Attempted glycosylation of alcohols with **11** using the standard Tf_2O/2,6-di-*tert*-butyl-4-methyl pyridine reagent system gave low yields of **8** contaminated with large amounts of elimination product **4**. In contrast, treatment of a 1:2:1 mixture of Cp_2ZrCl_2, $AgClO_4$, and alcohol at –20 °C with 1.5-2.5 equivalents of **11** provided after 8-10 h the desired fluorous THP labeled ethers **12-20** (ROTHP^F) in good yields for 1° and 2° alcohols. In addition, deprotection of THP^F-ethers **12-20** and recycling of the protective group was accomplished by a transacetalization reaction using 25 mol% TsOH in MeOH:THF (2:1) at 70 °C for 20-30 h to give good yields of recovered alcohols and **9**.[11]

Purification of most THP^F-ethers was accomplished simply by dissolving the crude product in MeCN and extracting 5 times with FC-72.[12] Concentration of the fluorous extracts yielded the fluorous product, which contained small amounts of **4**, as well as trace amounts of unreacted sulfoxide **11**. After this extraction, only minor amounts of the fluorous product remained in the MeCN

layer. The crude deprotection mixture, treated with the same MeCN/FC-72 extraction procedure, gave the fluorous methyl-THP ether **9** in the FC-72 extracts, while the deprotected alcohol was found in the organic layer. As the organic mass or the polarity of a fluorous THP-labeled substrate becomes larger, however, simple liquid-liquid extraction becomes inefficient. Solid phase extraction by filtration through fluorous reverse-phase (FRP) silica gel was found to be effective for these cases.[13] The rather polar **11** is almost insoluble in FC-72. This is advantageous in terms of separation of excess **11** during extractive purification of **THP^F**-labeled alcohols, but also suggests a sufficiently polar moiety on the substrate to be protected may overpower the fluorous nature of the protected product. Fluorous THP-labeled cholesterol and methyl mandelate could not be fully extracted from MeCN with multiple (15) FC-72 extractions. Loading of the crude product onto a MeCN-wetted FRP-SiO_2 column, washing first with MeCN to elute organic components, then with FC-72 to elute the fluorous labeled compounds, conveniently allowed total separation of **15** and **20** from organic side products.[14]

Scheme 2.



In conclusion, we have developed a recyclable fluorous labeled THP protecting group which allows for simple purification of small molecules by liquid-liquid extraction with FC-72/MeCN, and of larger or more polar molecules by solid phase extraction with fluorous reverse phase silica gel. In addition, we have developed a new glycosylation method which uses the Cp_2ZrCl_2-$AgClO_4$ reagent system to activate an anomeric sulfoxide. Work is underway to further improve upon and apply this fluorous THP phase label to combinatorial synthesis.

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11. All new compounds, including **12-20**, were obtained in pure form and fully characterized. ***Cis*-11**: Mp 66-69 °C; IR (KBr) 3063, 2919, 2853, 1664, 1603, 1445, 1199 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00-7.90 (m, 2 H), 7.70-7.55 (m, 3 H), 4.87 (d, 1 H, J = 4.3 Hz), 4.50 (dt, 1 H, J = 11.5, 3.4 Hz), 3.72-3.66 (m, 1 H), 3.17-3.00 (m, 1 H), 2.64-2.56 (m, 1 H), 2.05-1.75 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 136.5, 134.3, 129.3, 128.9, 125.0-105.0 (m, 8 C), 85.6, 63.3, 32.4 (t, 1 C, J = 20.1 Hz), 19.9, 17.5; MS (CI) *m/z* (rel. intensity) 629 ([M+H]$^+$).

    General Procedure for Glycosylation. A mixture of 200 mg of powdered molecular sieves (4Å), zirconocene dichloride (139 mg, 0.48 mmol), silver perchlorate (200 mg, 0.96 mmol), and 5 mL of CH_2Cl_2 was stirred at rt for 10 min. Benzyl alcohol (49.0 μL, 0.47 mmol) was added to the yellow solution, and the temperature was lowered to -20 °C. A solution of ***cis*-11** (446 mg, 0.71 mmol) in 10 mL of CH_2Cl_2 was added, and the reaction mixture was allowed to warm gradually to room temperature. After 10 h, the solution was filtered through a pad of SiO_2. After rinsing with CH_2Cl_2, the filtrate was concentrated and the residue partitioned between 4 mL of MeCN and 15 mL of FC-72. The MeCN layer was washed with 4 additional 10-15 mL portions of FC-72. ^1H NMR of the combined fluorous extracts showed the desired product **14** as well as elimination product **4** in a 5.3:1 ratio. ^1H NMR of the MeCN layer showed primarily excess sulfoxide **11**. Chromatography of the FC-72 extract on SiO_2 (hexanes/Et_2O, 97:3) provided pure **14** (264 mg, 0.43 mmol, 92%) as a colorless solid (7.4:1 ratio of diastereomers): Mp 36-37 °C; IR (KBr) 3037, 2966, 2879, 1501, 1450, 1358, 1209, 1147 cm^{-1}; Major diastereomer: ^1H NMR δ ($CDCl_3$) 7.37-7.29 (m, 5 H), 4.99 (d, 1 H, J = 3.5 Hz), 4.80 (d, 1 H, J = 11.6 Hz), 4.54 (d, 1 H, J = 11.7 Hz), 3.97-3.90 (m, 1 H), 3.63 (dt, 1 H, J = 11.3, 5.0 Hz), 2.60-2.40 (m, 1 H), 2.20-2.09 (m, 1 H), 1.90-1.80 (m, 2 H), 1.60-1.50 (m, 1 H); ^{13}C NMR δ ($CDCl_3$) 137.4, 128.5, 128.0, 125.0-105.0 (m, 8 C), 95.2, 69.6, 61.0, 41.3 (t, 1 C, J = 19.5 Hz), 21.9, 18.7, 17.4; HRMS (EI) calculated for $C_{20}H_{15}O_2F_{17}$ 610.0801, found 610.0803.

    General Procedure for Deprotection. A solution of **14** (112 mg, 0.18 mmol) and p-toluenesulfonic acid (9 mg, 0.05 mmol) in 2 mL of MeOH and 2 mL of THF was heated at 70 °C for 24 h. The reaction mixture was diluted with Et_2O and washed with a saturated $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), concentrated, and partitioned between 2 mL of MeCN and 8 mL of FC-72. The MeCN layer was washed with three 8 mL portions of FC-72. ^1H NMR analysis of the combined FC-72 extracts showed **9** (82 mg, 0.15 mmol, 84%) with a trace amount of **4**. ^1H NMR analysis of the MeCN layer showed pure benzyl alcohol (19.0 mg, 0.176 mmol, 96%).
12. FC-72 is a fluorocarbon solvent commercially available (3M) which consists of perfluorohexane (C_6F_{14}) isomers (bp 56 °C, price: $389/gallon).
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$$\text{Silica-OH} \xrightarrow[\text{imidazole, toluene}]{\text{ClSi(Me)}_2\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13}} \underset{\textit{FRP silica gel}}{\text{Silica-OSi(Me)}_2\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13}}$$

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