# AN EFFICIENT PREPARATION OF 3-PERFLUOROOCTY-1-CHLOROMETHOXYPROPANE AND APPLICATION OF THE FLUOROUS MOMCL IN TAGGING HYDROXYL AND AMINE GROUPS

by

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Submitted to the Graduate Faculty of

Arts and Science in partial fulfillment

of the requirements for the degree of

Master in Science.

University of Pittsburgh

2006

UNIVERSITY OF PITTSBURGH

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# AN EFFICIENT PREPARATION OF 3-PERFLUOROOCTY-1-CHLOROMETHOXYPROPANE AND APPLICATION OF THE FLUOROUS MOMCL IN TAGGING HYDROXYL AND AMINE GROUPS

Claude Afona Ogoe, M.S.

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A fluorous version of MOMCl: Perfluorooctyl-1-propoxy methyl chloride has been synthesized and the procedure for the preparation of the γ-perfluorooctylpropoxy-methyl chloride was amenable to a 10 g scale synthesis. Tagging of both primary and secondary alcohols were achieved in good to excellent yield. Successful detagging was achieved in most cases by employing $ZnBr_2$ and butanethiol or by using CSA. Competition studies on both the classical MOMCl and the fluorous MOMCl reagents indicate that the reactivities of both reagents are similar and substrates bearing the fluorous MOM ether or the standard MOM ether have a similar lability to Brønsted acid conditions. Tagging of a heterocyclic aromatic amine was successfully performed and the aminal was obtained in good yield.

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

## LIST OF SCHEMES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| **BOM** | Benzyloxymethyl |
| **$^{F}$Cbz-OSu** | Fluorous Carbobenzyloxy-O-Succinimidoyl |
| **CSA** | Camphor Sulfonic Acid |
| **DCM** | Dichloromethane |
| **FBC** | Fluorous Biphase Chemistry |
| **FMS** | Fluorous Mixture Synthesis |
| **FSPE** | Fluorous Solid Phase Extraction |
| **MEM** | Methoxy ethoxy methyl |
| **MOM** | Methoxymethyl |
| **$^{F}$MOM** | Fluorous Methoxymethyl |
| **$^{F}$PMB** | Fluorous *para*-Methoxybenzyl |
| **PMBM** | *para*-Methoxybenzyloxymethyl |
| **$^{F}$PMP** | *para*-Methoxyphenyl |
| **SEM** | Trimethylsilylethoxymethyl |
| **TBAB** | Tetrabutylammonium bromide |
| **TBAI** | Tetrabutylammonium iodide |
| **TBDPS** | *tert*-butyldiphenylsilyl |
| **TBS** | *tert*-butyldimethyllsilyl |

| | |
|---|---|
| **THF** | Tetrahydrofuran |
| **THP** | Tetrahydropyran |
| **$^{F}$TIPS** | Fluorous Triisopropylsilyl |
| **TMSBr** | Trimethylsilyl bromide |
| **TMSCl** | Trimethylsilyl chloride |
| **TMSI** | Trimethylsilyl iodide |
| **TMSOTf** | Trimethylsilyl trifluoromethane sulfonate |

## PREFACE

I am grateful to Professor Dennis Curran for letting me join the Curran group and for all the assistance he gave me and the chemistry he taught me. I benefited immensely from the knowledge he shared with me. I will also like to thank Professors Wipf and Floreancig for accepting to be on my committee and for helpful discussions.

I also will like to thank members of the Curran group for helping provide a conducive atmosphere for doing research and for all the non chemistry experience we shared together.

Finally I will like to thank the NMR and mass spec facilities group for their assistance and the chemistry department staff for all the help they gave me.

## ACKNOWLEDGEMENTS

To my family; the Murphrees; the Lombardis; the Giebells; the O'Boyles and the Grassos. I am deeply grateful for your support all these years.

# 1.0 INTRODUCTION

The seminal paper published in 1994,[1a] by Horváth and Rábai, in which they discuss the ability of highly fluorinated molecules to selectively partition into perfluorinated solvents as a separation technique[1] marks the beginning of the vibrant and rapidly growing field of fluorous chemistry. Indeed, fluorous chemistry is carving an important niche in oligonucleotide,[2] oligosaccharide[3] and peptide[4] synthesis and purification, supercritical fluid chemistry,[5] as well as in biology.[6] In the paper, Horváth and Rábai introduced Fluorous Biphase Chemistry (FBC). The first demonstration of FBC involved selectively partitioning an organic hydroformylation product into the organic phase and the florinated catalyst into the fluorous phase after the hydroformylation reaction. The fluorous phase containing the fluorinated catalyst was recycled and used in more hydroformylation reactions.

Despite the important position that FBC occupies in fluorous chemistry, its general utility was limited by the use of catalysts that were heavily fluorinated and the use of a combination of an organic and perfluorocarbon solvents which were only miscible at high temperatures.[1a] This limited synthetic protocols employing this separation and recycling strategy to using highly fluorinated substrates or reagents and high temperatures. Thus this technique was not suitable for reactions that were sensitive to elevated temperatures and/or were solvent dependent.

In addressing the challenge of making fluorous chemistry general and more cost-effective, Curran and coworkers introduced light fluorous chemistry.[7] Light fluorous chemistry combines the ability to perform reactions on perfluorinated substrates or reagents using existing conditions for their non-fluorous counterparts with the powerful ability to facilitate separation and purification with less effort. Successful application of light fluorous chemistry employs separation on fluorinated silica gel. This new separation technique is known as fluorous solid phase extraction (FSPE).[8] As a result, the need to have lots of fluorines on substrates or reagents was rendered unnecessary due to improved fluorophilicity of the fluorinated substrates and reagents when partitioning from non-fluorous compounds is performed on fluorous silica gel. Fluorophilicity is defined as the affinity of fluorinated molecules, compounds or materials for perfluorinated media under a given set of conditions.[9] The introduction of FSPE spawned another method which is a subset in light fluorous chemistry: Fluorous Mixture Synthesis (FMS).[10]

FMS is a solution phase mixture synthesis technique to access analogues of a compound. Conceptually, FMS (Figure 1) involves tagging a number of substrates ($S^1$-$S^n$) with a series of homologous fluorous tags ($F^1$-$F^n$). The tagged substrates ($F^1$-$S^1$…$F^n$-$S^n$) are mixed to obtain $M^S$. The initial mixture is carried through a series of synthetic steps to afford intermediate mixture $M^I$. Diversification begins with splitting the mixture $M^I$ into equal amounts of x available building blocks. The new set of x mixtures are then reacted with a similar number of building blocks. Each mixture is carried though a series of transformations. Further diversification can be introduced via more splitting and transformations involving a new set of building blocks. The final sets of mixtures ($M_1^E$-$M_X^E$) are demixed to obtain individual final molecules that are

detagged to release the desired compounds ($P_1^1$-$P_X^n$). The homologous tags serve as a coding device for the substrates so that identification of the products from each starting substrates ($S^1$-$S^n$) after FMS is rendered facile. Indeed FMS provides the homogeneity needed for optimal reaction kinetics, ready analysis of reactions as well as intermediates, efficient separation of the components of a product mixture as well as the ability to obtain relatively large quantities of compounds.

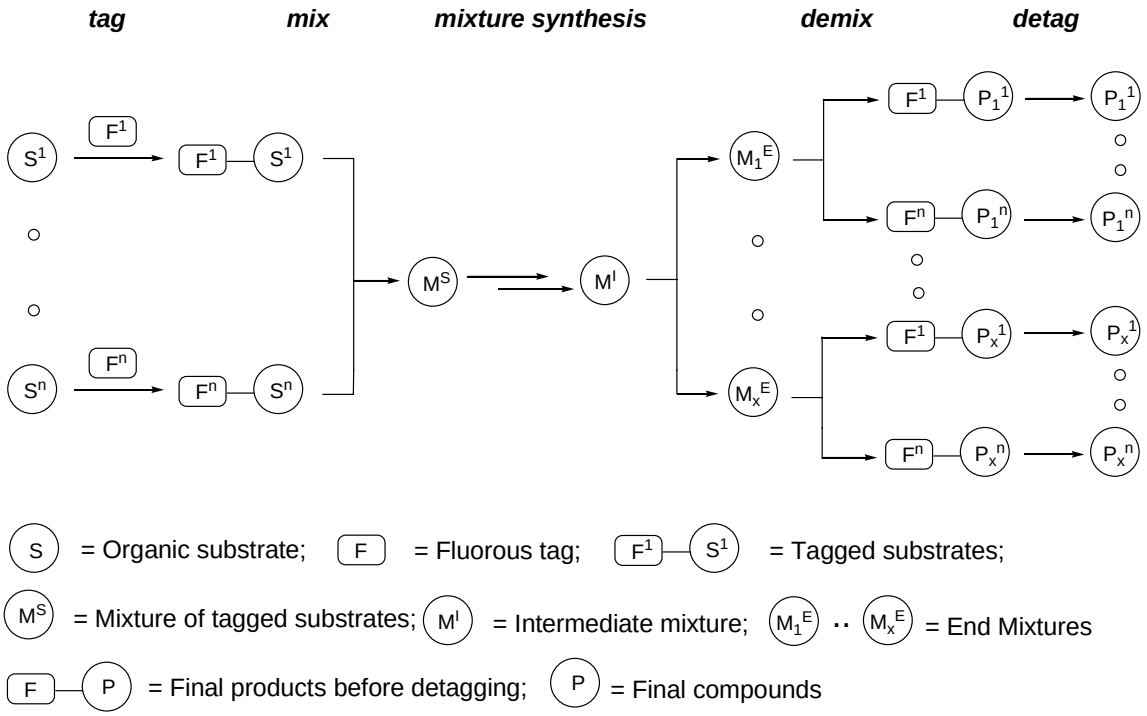



**Figure 1: Schematic illustration of the FMS concept.**

Critical to the success of fluorous chemistry has been the ability to render organic compounds fluorous. This is often done by protecting common functionalities like the hydroxyl, amino, carbonyl and carboxyl groups[11] on starting materials with fluorous variants of protecting

groups. Fluorous protecting groups are also sometimes called fluorous tags or fluorous phase labels. These labels are designed to resemble traditional protecting reagents but with perfluoroalkyl or perfluoroalkoxy chains. As a result, two birds are killed with a stone: a functional group is masked and the fluorines aid the compound's partition coefficient into fluorous media. The realization of the full potential of light fluorous synthesis depends on quantity as well as variety of fluorous reagents in the fluorous reagent pool.

Recent investigations in our group are aimed at exploring the potential of synthesizing naturally occurring molecules with intriguing biological activity and their analogues via FMS.[10] As the scope of the synthetic methods that we envisage to be applied to FMS gets broader, it becomes imperative that more fluorous protecting groups are made available. These fluorous tags should be easy to prepare (to enable easy access to homologous analogues), made in large quantities, impervious to many reaction conditions, attached and removed under mild conditions and recycled. Among the fluorous tagging reagents that have been used in FMS at present are $^{F}$TIPS,[10a,c] $^{F}$PMB,[12] $^{F}$PMP,[10f,g] and $^{F}$Cbz-OSu.[13] (Figure 2)

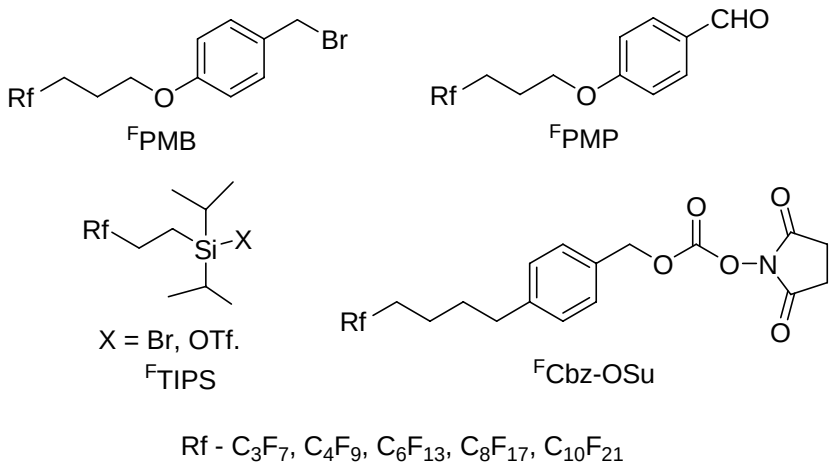
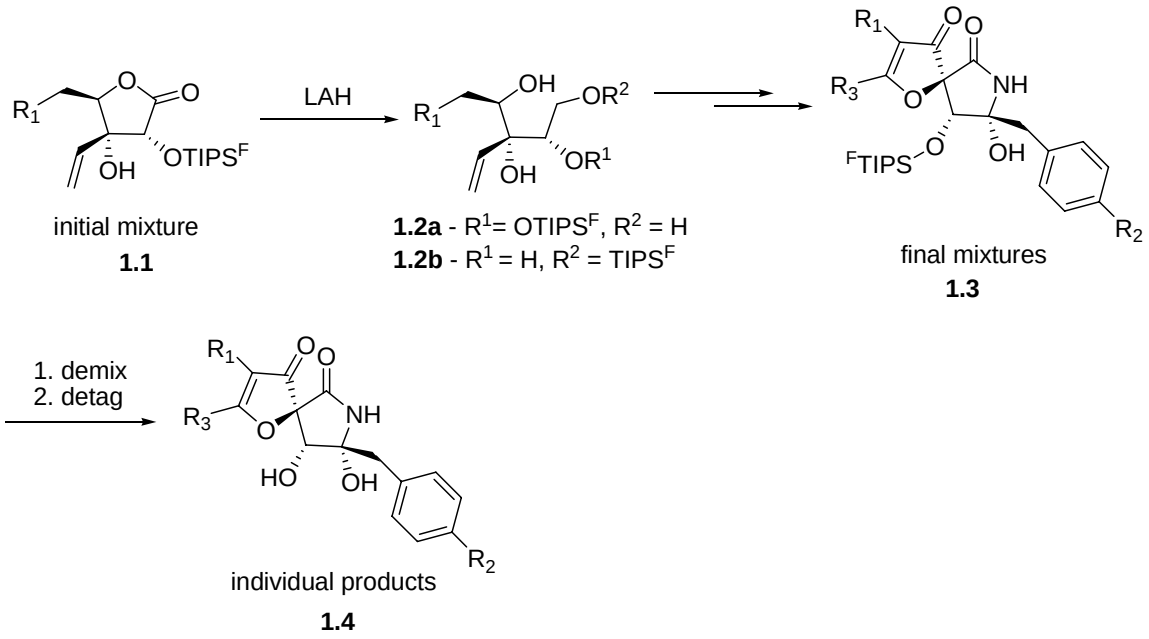



**Figure 2: Structures of fluorous tags used in FMS.**

The $^{F}$TIPS ether has been successfully applied in the syntheses of a 560 mappicine analogues,[5c] both enantiomers of pyridovericin,[15a] diastereomers of passifloricin,[15b] stereoisomers of dictyostatin[15c] and four diastereomers of lagunapyrone.[15d] $^{F}$PMB tagging strategy was chosen for the syntheses of (+)-murisolin and 15 stereoisomers,[5e] truncated analogues of discodermolide [5d] as well as all the 16 stereoisomers of the pine sawfly sex pheromone.[5f,g] Thus, utilization of FMS continues as we strive at unearthing its full potential.

We have recently been investigating the synthesis of (–)-azaspirene, an angiogenesis inhibitor, and analogues of it via a mix/split FMS approach. The initial plan had an $^{F}$TIPS on a hydroxyl group that would be unveiled in the final step after demixing to provide the desired products. (Scheme 1) A significant amount of the synthetic steps to the tagged final mixtures of azaspirene and analogues involved strongly basic protocols and there was considerable concern as to the stability of the fluorous silyl tag in the aforementioned conditions. A reductive ring opening on the ethyl analogue of lactone **1.1** using LAH in THF resulted in product **1.2b** instead

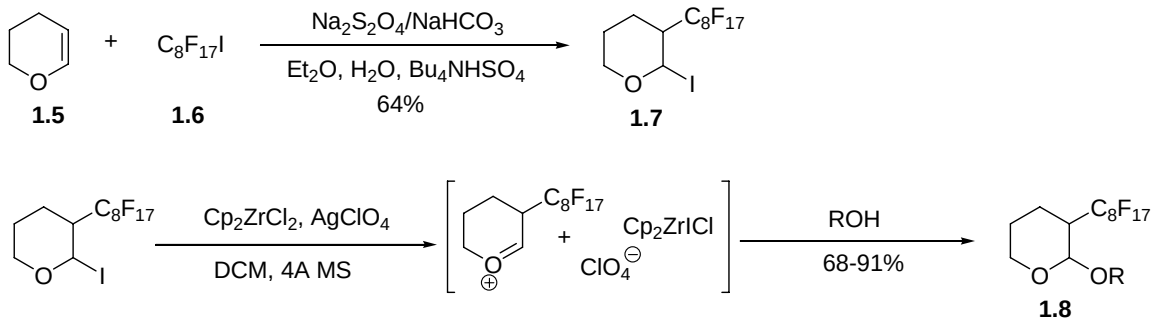
of the anticipated triol **1.2a**. This was due to silyl group migration[16] of the $^{F}$TIPS from the secondary alcohol to primary one during the reaction. As a result, using a fluorous variant of an acetal protecting groups seemed attractive. This owing to the remarkable stability of acetals to strongly basic and nucleophilic conditions and in some cases mild acidic conditions.




**Scheme 1: Strategy for FMS of azaspirene and analogues using $^{F}$TIPS tag**

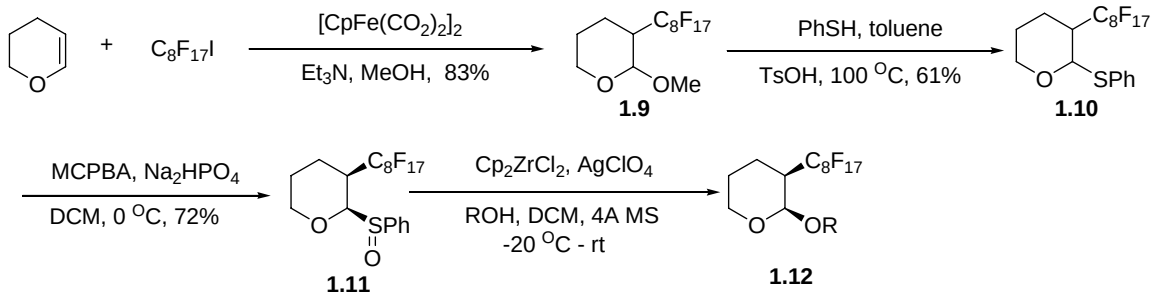
Fluorous acetals to protect alcohols were initially introduced by Wipf and coworkers. The first foray by the Wipf group resulted in the preparation of two fluorous THP reagents: the iodopyran **1.7** and pyranyl phenyl sulfoxide **1.11**.[17] The iodopyran **1.7** was obtained from perfluorooctyl iodide **1.6** and dihydropyran **1.5** with either using $Na_2S_2O_4/NaHCO_3$ or catalytic Raney Nickel. Even though the yield obtained using $Na_2S_2O_4/NaHCO_3$ was better, 64% as compared to 32-38% for Raney Nickel, they switched to using Raney Nickel because that protocol was more reliable. The hydroxyl compounds were tagged with the iodopyran **1.7** that

was activated by a $Cp_2ZrCl_2$-$AgClO_4$ reagent system (Scheme 2). The hydroxyl groups were unveiled via transacetalization with methanol in THF catalyzed by TsOH. Attempts to recycle the methylpyranyl ether after releasing the alcohol went without success. Thus they synthesized and utilized sulfoxide **1.11** as the glycosidic donor for tagging the alcohol bearing substrates.



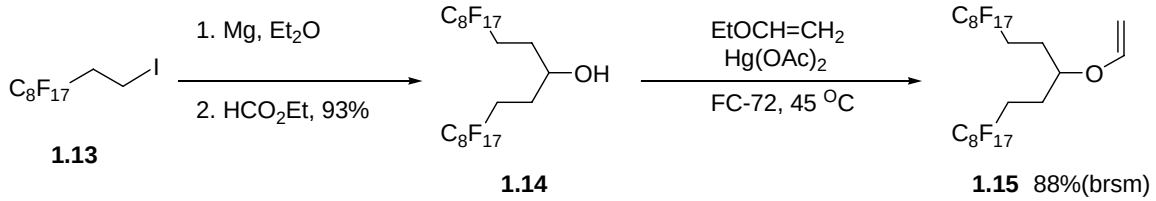

**Scheme 2: Synthesis of fluorous iodo pyran 1.7 and its use in tagging alcohols.**

The sulfoxide **1.11** and its anomer (not shown) were prepared as seen in Scheme 3. The more reactive cis version of the phenylsulfinyl pyran **1.11**, obtained from oxidation of the sulfide that was formed via either refluxing fluorous methyl THP ether **1.9** in 1:1 PhSH/toluene or $PhSSiMe_3$ in the presence of TMSOTf,[17] was added to a mixture of $Cp_2ZrCl_2$,$AgClO_4$ and the alcohols to form the THP ethers. (Scheme 3) Delabelling of **1.12** was achieved in a similar transacetalization fashion described for the iodopyran protocol. Conversion of the methyl pyranyl ether **1.9** to the sulfoxide had already been established, thus this solved the goal of recycling the tagging reagent.




**Scheme 3: Tagging of alcohols via phenylsulfinyl pyran.**

Later, a heavily fluorinated vinyl ether tag **1.15**[14a] (Scheme 4) was prepared by the same group. Labelling the alcohols proceeded using 3 equiv of **1.15** with 5 mol% CSA in diethyl ether for primary alcohols or THF at 65 ºC for secondary and tertiary hydroxyl groups. Deprotections were achieved via tranacetalization in diethyl ether with methanol and 5 mol% CSA. The protocol was used to facilitate purification of a mixture of intermediates via a 'catch and release' form of scavenging in the Wipf's group synthesis of curacin analogues.[14b]




**Scheme 4: Synthesis of the fluorous vinyl ether tag 1.15.**

The use of fluorous acetals that are different from the aforementioned ones include the use of fluorous *p*-methoxy phenyl acetal ($^{F}$PMP) to protect a 1,3-diol[5f,g] and diols with either one

or two perfluorinated alky chains to mask aldehydes and ketones.[19] The successful synthesis and utility the aforementioned fluorous acetals demonstrated the stability of such compounds.

We were attracted to the idea of using the $^{F}$THP ether in our synthesis; however, it is known that the classical THP group does not afford a highly stereoselective adduct via effective participation in a 1,2 chelation controlled addition of nucleophiles to carbonyl compounds bearing an alpha stereogenic center.[20] The just mentioned transformation was one of the key steps in the azaspirene project. We were also interested in making the tagging reagents with minimal synthetic manipulations as homologous analogues would be required for FMS.

The use of alkoxymethyl ethers as protecting groups for alcohols features prominently in organic synthesis.[21] The principal members of this set of protecting groups are: methoxymethyl ether (MOM),[22] methoxyethoxymethyl ether (MEM),[23] benzyloxymethyl ether (BOM),[24] *p*-methoxybenzyloxymethyl ether (PMBM),[25] and trimethylsilylethoxymethyl ether (SEM)[26] (Figure 2). Indeed a number of the alkoxymethyl ethers are orthogonal to each other and can be used strategically in multistep organic syntheses. For example, SEM, BOM and PMBM ethers are cleaved using a fluoride source, hydrogenolysis and oxidation respectively. The alkoxymethyl ethers also vary in their degree of lability to Brønsted acids with MOM ether being the most robust.[18a]

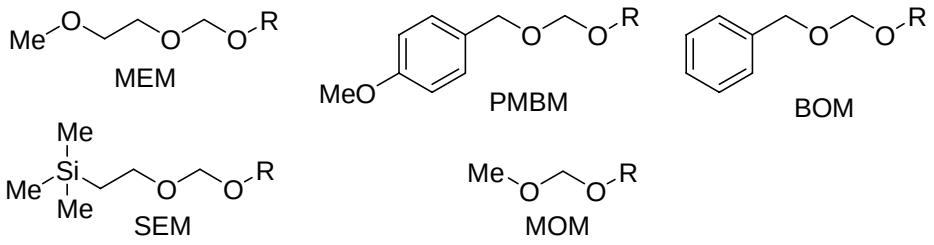


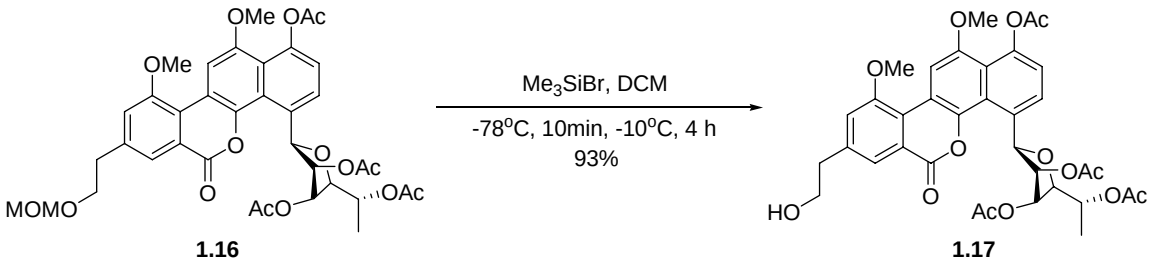

**Figure 3 Principal members of the alkoxymethyl ether family.**

MOM ethers withstand hydride reduction, Grignard and other organometallic reactions, hydrogenation and even mild Brønsted acidic conditions. The MOM ethers are known to participate in chelation controlled nucleophilic addition to carbonyls with high levels of stereoselectivity.[20] Methoxymethyl ethers are also effective in the protection of amines as N,O acetals.[21a] The absence of a stereogenic center in MOM ether protecting reagents reduces the difficulty in $^{1}$H NMR analysis of protected chiral alcohols.

We envisioned that perfluoroalkoxymethyl chloride could be obtained in a one step reaction. Just like the other fluorous tags, we expect that deprotection conditions for the new tag would be similar to the classical MOM ether. Even though some conditions (such as 3-6N HCl/MeOH or TFA in DCM) to excise MOM ethers seem harsh, there are a significant amount of mild Lewis acid conditions developed to detach the MOM group.[21] The most prevalent are the silyl and boron lewis acids.

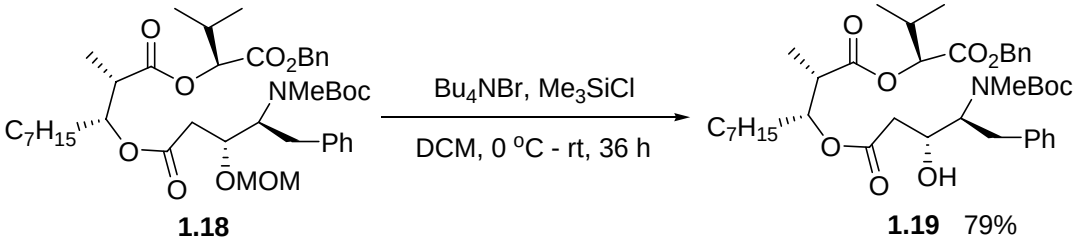
The silyl Lewis acids used are trimethylsilyl bromide (TMSBr) and trimethylsilyl iodide (TMSI). TMSBr is either used as obtained commercially or generated in-situ from TMSCl and TBAB as TMSBr decomposes slowly to form bromine. TMSI is also generated in-situ from

TMSCl and NaI. In the gilvocarcin synthesis[27] TMSBr was employed in cleaving MOM ether in the presence of methyl ethers as well as acetates. (Scheme 5)



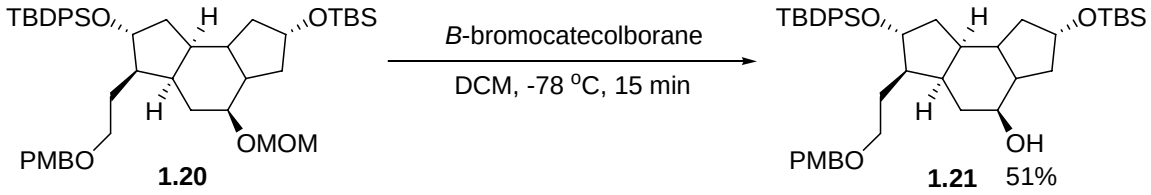

**Scheme 5: MOM ether deprotection in nogalamycin synthesis using TMSBr.**

TMSBr was generated in-situ for MOM ether deprotection during the synthesis of hapalosin[28] (Scheme 6). Attendant problems with the use of halosilanes in MOM ether deprotection are that functionalities like the acetonides, TBS ethers, THP ethers and trityl ethers are often cleaved as well.[21a]



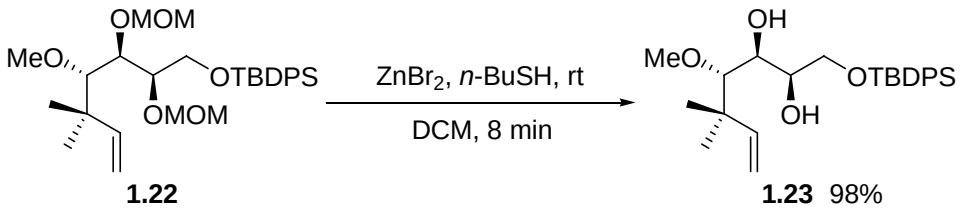

**Scheme 6: Utility of TMSBr obtained in-situ for MOM ether deprotection.**

The use of haloboranes in MOM ether deprotection is widespread. The boranes vary from very electron poor species such as $BF_3{\cdot}OEt_2$ that Corey and coworkers used in MOM ether removal in the synthesis of ginkolide A.[29] to electron rich species. On placing electron donating groups on boranes, the reactivity of such species is attenuated. This way more functional groups are tolerated. For example in the spinosyn synthesis,[30] the Paquette group utilized bromocatecolborane to unveil the secondary alcohol masked as a MOM ether in the presence of a primary PMB and secondary TBS and TBDPS ether groups. (Scheme 7).




**Scheme 7: Electron rich haloborane in selective MOM ether cleavage.**

Another Lewis acid that has been reported to be useful in MOM ether cleavage is $MgBr_2$.[34] Better yields are obtained when a nucleophile such as butanethiol is used. However, it seems that this protocol has not enjoyed much use. The Rawal group recently reported a mild and facile deblocking of two hydroxyl groups in methoxymethyl ether form **1.22** by using $ZnBr_2$ with butanethiol for nucleophilic assistance to obtain **1.23** in a remarkable 98% yield in 8 min [31] (Scheme 8). They reported that unmasking the alcohols in the absence of butanethiol gave a messy looking reaction.




**1.22** **1.23** 98%

**Scheme 8: Deprotection of MOM ether using $ZnBr_2$, and n-BuSH.**

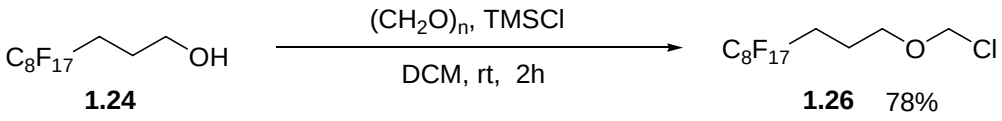
With the information gleaned thus far, we set out to prepare 3-perfluorooctyl-1-chloromethoxypropane for $^{F}$MOM ether formation, to obtain conditions for efficient tagging of primary and secondary hydroxyl functions, to detag employing mild conditions and prepare a fluorous N,O acetal.

## 1.1 RESULTS AND DISCUSSION

### 1.1.1 Preparation of Perfluorooctyl-1-propoxymethyl chloride 1.26.

The design for the perfluoroalkoxymethyl chloride took into consideration the powerful electron withdrawing effects of perfluoroalkyl group on functionalities that are adjacent to it.[32] Thus we wanted to have spacers to attenuate the electron withdrawing effect. We chose the all carbon spacer to separate the perfluoroalkyl moiety from the oxygen atom to get as close as possible to the reactivity to the classical MOM ether. We also hoped that the nucleophilicity of the alcohol will not be significantly diminished in the synthesis of the 3-perfluorooctyl-1-chloromethoxypropane.

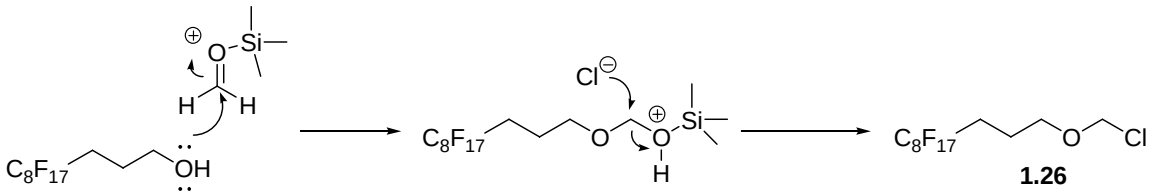
With the need to synthesize homologues in mind, γ-perfluorooctyl-1-propanol[33] seemed the suitable choice. It belonged to the class of the γ-perfluoroalkylpropanols which can be used to prepare the analogues for FMS.[34] Perfluorooctyl-1-propoxymethylchloride was prepared by adding 4 equiv of anhydrous TMSCl dropwise to a suspension of the perfluorooctyl-1-propanol and paraformaldehyde in anhydrous DCM at rt. The reaction mixture was allowed to stir for 2 h after the suspension cleared.[35a] (Scheme 9)




**Scheme 9: Synthesis of Perfluorooctyl-1-propoxy methyl chloride 1.26.**

Vacuum distillaton at 2 torr provided a colorless distillate. The boiling point recorded was 69-73 ºC. We estimated the density of the distillate by pre-weighing a syringe wetted with the $^{F}$MOMCl distillate. Then the syringe was filled with 50μL of the distillate and then the weight of the filled syringe was taken. This was repeated three times. The estimated density, 1.63 g/mL, is the average for the three densities obtained from each measurement. Large scale preparation of the fluorous MOMCl was feasible. Starting from 10.0 g (20.9 mmol) of the perfluorooctyl-1-propanol, we isolated 8.56 g (16.3 mmol of the distillate. This corresponds to 78% yield. The residue still had an unquantified amount of the product as evidenced by $^{1}$H NMR spectrum.

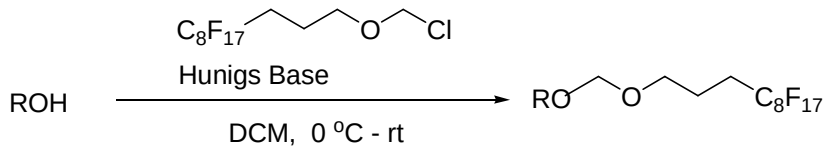
The proposed mechanism for preparing compound **1.26** is illustrated in Scheme 10




**Scheme 10: Proposed mechanism for the formation of the $^{F}$MOMCl reagent.**

### 1.1.2 Tagging of substrates bearing hydroxyl functional groups.

We selected protecting the hydroxyl functional groups using Hünigs base and the perfluorooctyl-1-propoxymethyl chloride protocol. This condition was mild and the most general method used for the classical MOM ether protection of alcohols.[21]

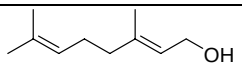
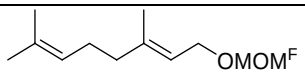
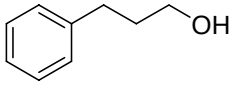
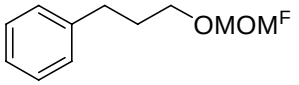
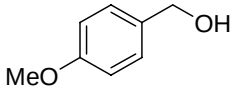
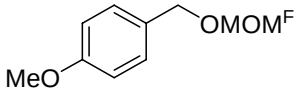
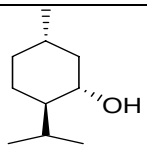
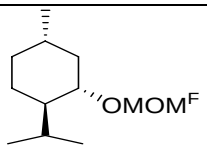
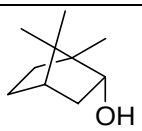
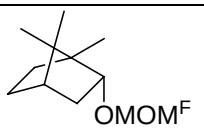
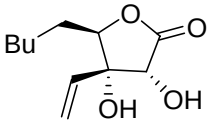
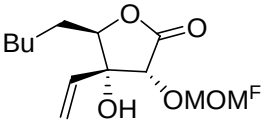
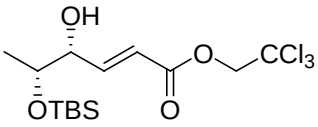
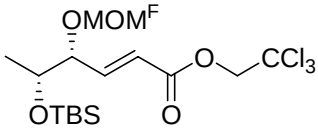



**Scheme 11: General procedure for tagging alcohols.**

The general procedure that was used to tag the alcohols (Scheme 11) was as follows: A solution of geraniol (88. 9 µL, 0.5 mmol) in DCM (2.0 mL) was cooled to 0 ºC after which diisopropylethylamine (0.26 mL, 0.5 mmol), was added. A 0.5 mL solution of the $^{F}$MOMCl (0.17 mL, 0.55 mmol) in DCM was added to the mixture at 0 ºC warmed to rt and stirred for 4 h. Quenching the reaction with sat. aqeous $NaHCO_3$, extracting with DCM and removing the solvent under reduced pressure gave the crude product that was purified by column

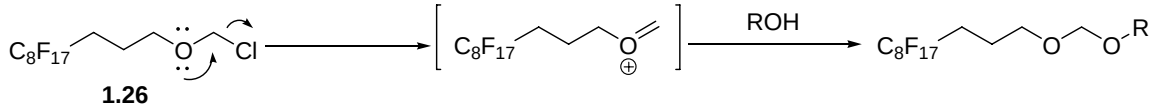
chromatography to give (0.32 g, 100%) of the tagged geraniol (Table 1: Entry 1). 3-Phenyl-1-propanol was also tagged in a 100% yield (Table 1: Entry 2). *p*-Methoxybenzyl alcohol is another primary alcohol that was tagged to afford the adduct in 83% yield.(Table 1: Entry 3) Secondary alcohols were also tagged using the same protocol. For example (+)-menthol was labeled in 91% yield (Table 1: Entry 4). The tagged endo-borneol was obtained in 83% yield.(Table 1: Entry 5). We also investigated a selective protection of the secondary alcohol in the presence of a tertiary one. Thus we selected the lactone, which was one of the substrates used in our FMS studies. The latone was tagged in 69% (Table 1: Entry 6). Only the secondary alcohol was protected. The TBS alcohol (Table 1: Entry 7) was also tagged in a low yield of 44% when 1.1 equiv of $^{F}$MOMCl was used. However, the $^{F}$MOM ether was obtained in 81% albeit under relatively forcing conditions: 2 equiv of $^{F}$MOMCl, 1 equiv of TBAI and at 50 ºC in DCE.

**Table 1: Tagging and detagging of primary and secondary alcohols.**

| Entry | ROH | ROMOM$^F$ | Yield% (Tagging)[a] | Yield% (Detagging)[c] |
|---|---|---|---|---|
| 1 |  |  | 100 | 13(79)[d] |
| 2 |  |  | 100 | 89(85)[d] |
| 3 |  |  | 83 | 82 (decomp)[d] |
| 4 |  |  | 91 | 89(84)[d] |
| 5 |  |  | 83 | 91(90)[d] |
| 6 |  |  | 69[b] | 91(92)[d] |
| 7 |  |  | 81[e] | 91[f](17)[f] |

a - isolated yields for tagged alcohols b - isolated yields obtained by tagging substrate with 2 equiv of $^F$MOMCl c - yields for deprotection of $^F$MOM ethers. d - yields obtained for detagging with CSA e - isolated yield obtained by tagging substrate with 2 equiv of $^F$MOMCl and 1 equiv of TBAI at 50 ºC f - there was loss of the TBS group.

The mechanism for tagging the substrates was proposed to go through an oxocarbenium ion intermediate that is trapped by the alcohol to be masked. (Scheme 12)




**Scheme 12: Proposed mechanism for the labeling of alcohols.**

### 1.1.3 Detagging of substrates with the $^{F}$MOM ether labels.

The investigations into detagging the $^{F}$MOM ether compounds commenced with $ZnBr_2$ and butanethiol.[31] This choice was due to the remarkable results from the MOM ether deprotection using the same reagents from Rawal's group work. (Scheme 8). A typical procedure is as follows: A DCM solution of the tagged lactone was cooled to 0 ºC and 2 equiv of dry butanethiol was added to it. $ZnBr_2$, 3 equiv, was added to the reaction mixture at 0 ºC and the reaction was warmed up to rt. On completion of reaction, the product mixture was cooled back to 0 ºC, diluted with DCM and quenched with saturated aqueous $NaHCO_3$. The crude mixture was filtered through celite. The filtrate was dried, DCM was removed in vacuo and crude was purified by flash chromatography. The purity of the $ZnBr_2$ impacted the speed of the deprotection reactions. All the subtrates were deprotected in good yield with the exception geraniol. The tagged lactone and endo-borneol were both deprotected in 91% yield (Entry 5 and 6). The $^{F}$MOM group was removed from the (+)-menthol and 3-phenyl-1-propanol in 89% (Entry 4) and 89% (Entry 2) yield, respectively. The low yield (13%) observed for detagging of

the protected geraniol is perhaps due to the facile formation of stable allylic cation.[36] Cleavage of the $^{F}$MOM ether of trichloroethylester using $ZnBr_2$ and butanethiol was successful. However, there was also a loss of the TBS group in the process. Thus the diol was obtained in 91% yield.

Brønsted acids were also employed in the removal of the fluorous MOM group. We found out that 6M aqueous HCl in THF would not detag 3-phenyl-1-propoxymethyl methyl ether at rt. This was attributed to the hydrophobic nature of the perfluorinated compound. Employing CSA[37] seemed the most suitable. Preliminary attempts from 0.1 equiv of CSA to 0.5, 1.0 and 2.0 did not show significant detagging. Thus, a large excess (10 equiv) of CSA in 2:1 THF/MeOH was used in all the delabelling reactions. The protocol was: A solution of the tagged lactone substrate (0.12 g, 0.17 mmol) in 2:1 THF/MeOH (1.2 mL: 0.6 mL) solvent mixture was added CSA (0.40 g, 1.7 mmol). The reaction mixture was stirred at rt for 11 h. On complete cleavage, the product mixture was cooled to 0 ºC and the reaction mixture was quenched by careful addition of saturated aqueous $NaHCO_3$. The mixture was extracted with diethyl ether and upon removal of the solvent under reduced pressure, the crude was purified by flash chromatography to yield the lactone as a white solid (33.6 mg, 92%).

Using the same procedure, the tagged geraniol was deprotected in 79% yield (entry 1d). The 3-phenyl-1-propanol tagged substrate was detagged in 85% yield (Entry 2d). Deprotection of the tagged *p*-methoxybenzyl alcohol gave multiple spots (Entry 3d). The yields obtained for detagging the tagged (+)-menthol and endo-borneol are 84% (Entry 4d) and 90% (Entry 5d).

### 1.1.4 Estimation of Reactivity difference between $^{F}$MOMCl and MOMCl.

Based on the mechanism of the tagging procedure, there should be some reactivity difference between the $^{F}$MOMCl and MOMCl. This is owing to the potential influence of the perfluoroalkyl moiety. To estimate the likelihood of a reactivity difference, we conducted a competitive protection experiment where equal amounts of both the fluorous and standard MOMCl were introduced simultaneously to protect 3-phenyl-1-propanol. On complete consumption of the starting 3-phenyl-1-propanol, the two products (the fluorous MOM ether **1.26** and the standard MOM ether) were separated by flash chromatography. The fluorous tagged adduct and the MOM ether one were isolated in 50% and 49% yields respectively. This corresponds to ca 1:1 ratio of both products. Thus there is no significant difference in reactivity between both reagents.

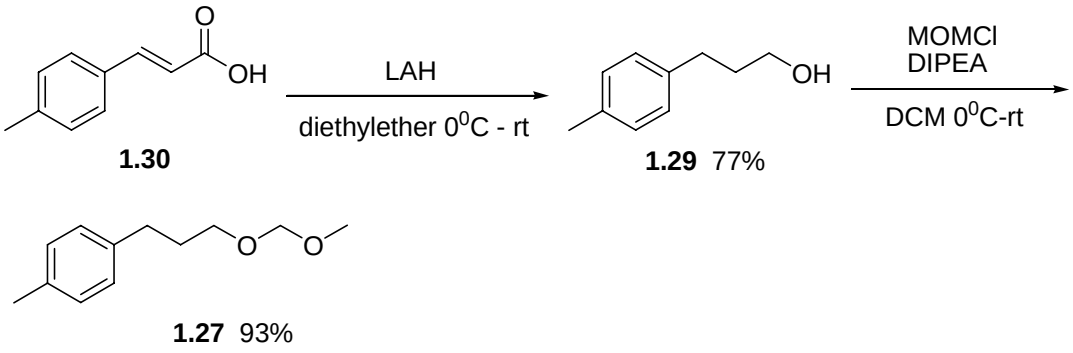
### 1.1.5 Competition studies on detagging of $^{F}$MOM and standard MOM tagged molecules.

It is known that the standard MOM ether group is the most robust of the alkoxymethyl ether compounds.[21a] The electron withdrawing properties of the perfluoroalkyl moiety means that the fluorous MOM ether would be more resistant to detagging. By virtue of this reasoning, we decided to establish the relative stability of the $^{F}$MOM ether and traditional MOM ether compound to a Brønsted acid.

Prior GC experiments had indicated an inability to monitor the disappearance of the starting materials due to inconsistent response factors. As a result, we decided to analyze the

appearance of different (but chemically similar) products from their respective MOM ethers. The products chosen were 3-phenyl-1-propanol **1.28** and 3-(4-methyl) phenyl-1-propanol **1.29**. These products had dissimilar retention times on GC. 3 - phenyl-1-propanol was tagged as its fluorous MOM ether using the established conditions and 3-(4-methyl) phenyl-1-propanol was protected as the MOM ether **1.27**.

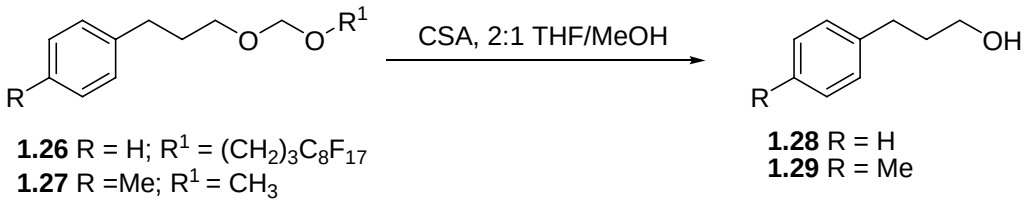
Preparation of 3-(4-methyl)phenyl-1-propoxymethyl ether **1.27** was efficiently done via reduction of the *p*-methyl cinnamic acid **1.30** to provide 3-(4-methyl)phenyl-1-propanol **1.29** in 77% yield with LAH.[38] The product was converted to its MOM ether **1.27** in 93% yield using conditions for the $^{F}$MOM tagging of alcohols. (Scheme 13)




**Scheme 13: Synthesis of 3-(4-methyl)phenyl-1-propoxymethyl-3-perfluorooctylpropyl ether 1.27**

Equimolar amounts (0.5 mmol) of compounds **1.26** and **1.27** dissolved in THF/MeOH and spiked with octadecane were deprotected using 10 equiv CSA. (Scheme 14) Aliquots (100μL) of the reaction mixture were taken in hourly intervals for 5 h and then at 20 and 22 h, quenched with $NaHCO_3$, extracted with ether and the organic layer analyzed on GC. Up to 5 h, the conversions were too small to allow accurate measurement of the product mass. At 20 h, the

amounts obtained for **1.28** and **1.29** were 0.185 mmol (37%) and 0.168 mmol (34%) respectively. The amounts for **1.28** and **1.29** at 22h were 0.206 mmol (41%) and 0.180 mmol (36%). The ratios of yields indicate that both the fluorous MOM and the standard MOM ethers have about the same lability to Brønsted acids.




**1.26** R = H; $R^1 = (CH_2)_3C_8F_{17}$
**1.27** R =Me; $R^1 = CH_3$

**1.28** R = H
**1.29** R = Me

**Scheme 14: Competitive detagging experiment performed on a mixture of 1.26 and 1.27.**

### 1.1.6 Tagging Nitrogen containing compounds as their N,O Acetals.

Amines, amides and carbamates are known to be protected as their N,O acetals using some of the aforementioned reagents such as MOMCl, SEMCl and BOMCl.[21a] Although not as popular due to the often ease of hydrolysis of N,O acetals, nitrogen containing compounds that have less basic nitrogen atoms tend to be stable. As such amides, aromatic amines and carbamates tend to be masked successfully in their aminal forms.

In view of applying the flourous MOMCl as a tagging reagent for nitrogen containing compounds, we protected indole as its fluorous N,O acetal. The indole was deprotonated using 1 equiv of NaH to form the amide and then reacted with $^{F}$MOMCl 1.1 equiv to give the product in 81% yield. Detagging of the fluorous labeled indole with both CSA and TMSI did not provide indole even though the tag was successfully removed. This is presumably due to the incompatibility of indole to the conditions used in the deprotection protocols.

## 1.2 CONCLUSIONS

In conclusion, we have prepared a fluorous version of MOMCl: Perfluorooctyl-1-propoxy methyl chloride. The procedure for the preparation of the γ-perfluorooctylpropoxy-methyl chloride is amenable to a 10 g scale synthesis. Tagging and detagging of both primary and secondary alcohols were achieved in good to excellent yield. Successful detagging was achieved in most cases by employing $ZnBr_2$ and butanethiol or by using CSA. Competition studies on both the classical MOMCl and the fluorous MOMCl reagents indicate that the reactivities of both reagents are similar. Also, GC analysis of products from detagging a mixture of substrates bearing the fluorous MOM ether and the standard MOM ether confirms a similar lability of the standard MOM ether.

Tagging of a heterocyclic aromatic amine was successfully performed and the N,O acetals was obtained in good yield. Our prediction is that perfluorooctyl-1-propoxymethyl chloride, and the homologous perfluoroalkyl-1-propoxymethyl chlorides, will be useful to the field of both synthetic organic chemistry and fluorous chemistry.

## 1.3 EXPERIMENTALS

General: Dichloromethane was distilled from $CaH_2$. Other reagents were used as they were received from Aldrich. 3Å molecular sieves were dried at 150 ºC for at least 24h before use. Unless stated otherwise, all reactions were carried out at room temperature under a positive

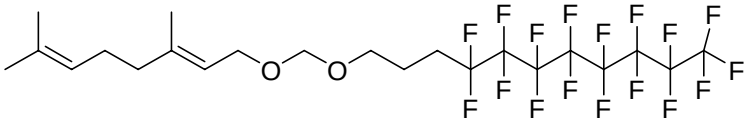
pressure of argon and were monitored by TLC on silica gel 60 $F_{254}$ (0.25 mm, E. Merck). Spots were detected under UV light or by charring with 10% $H_2SO_4$ in ethanol or charring with anisaldehyde. Solvents were evaporated under reduced pressure and below 40 ºC (bath temperature). Organic solutions of crude products were dried over anhydrous $Na_2SO_4$. Column chromatography was performed on silica gel (230-400 mesh ASTM). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). Optical rotations were measured at 21 ± 2 ºC. Melting points are uncorrected. For the characterization of reaction products, $^{1}H$ NMR, $^{13}C$ NMR, and $^{19}F$ NMR spectra were recorded on a Bruker Avance DPX 300 (300 MHz), Avance DRX 500 (500 MHz), and chemical shifts are referenced to either TMS (0.0 ppm, $CDCl_3$) or residual $CHCl_3$ (7.27 ppm) or $CDCl_3$ (77.00 ppm, $CDCl_3$). IR spectra were recorded on a Mattson Genesis Series FTIR and runs as neat films or chloroform solutions. Low resolution and high resolution mass spectra were obtained on a Fision Autospec in EI mode at 70ev and VG Autospec double focusing instrument. Electrospray mass spectra were recorded on samples suspended in mixtures of THF with $CH_3OH$ and added trifluoroacetic acid or NaCl using a quadrupole time of flight (QTOF) detector. HPLC analyses were performed on Waters 600 E system with either UV or light scattering detector and a fluofix 120E column. LC-MS spectra were obtained on a Hewlett-Parkard-1100 LC-MS using APCI mode.

**Preparation of 3-Perfluorooctyl-1-chloromethoxypropane.**

To a solution of perfluoroctyl-1-propanol (10 g, 20.9 mmol) in $CH_2Cl_2$ (21 mL) was added paraformaldehyde powder (0.64 g). Chlorotrimethylsilane (10.8 mL, 83.6 mmol) was added dropwise to the reaction suspension. The suspension, which became clear after ca 10 min, was

stirred at rt for 2 h. The solvent was removed under reduced pressure. Purification of the crude product mixture by vacuum distillation (2 torr, 69-73 ºC) provided the 3-perfuorooctyl-1-chloromethoxy propane as a colorless liquid (8.58 g, 78%): $^{1}$H NMR (300 MHz, $CDCl_3$) δ 5.49 (s, 2 H), 3.77 (t, 2 H, $J$ = 6 Hz), 2.21 (m 2 H), 1.95 (m, 2 H), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 107.5-121.7 (m, $C_8F_{17}$), 82.5, 68.7, 27.8 (t, $J_{FC}$ = 22.2 Hz), 20.2.

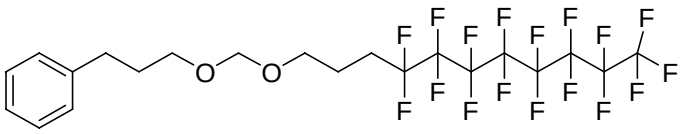
**General procedure for MOM$^{F}$ protection**



**(E)-11-((3,7-Dimethylocta-2,6-dienyloxy)methoxy)-1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-Heptadecafluoroundecane.**

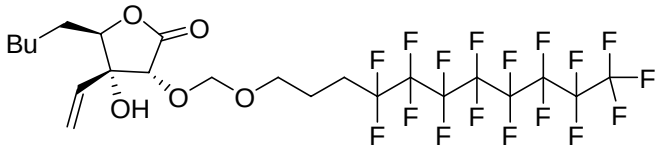
To a solution of geraniol (88.9 µL, 0.5 mmol) in $CH_2Cl_2$ (2.5 mL ) at 0 ºC was added diisopropylethylamine (0.26 mL, 1.5 mmol) and perfluorooctyl-1-propoxy methyl chloride (0.17 mL, 0.55 mmol) dropwise. The reaction mixture was warmed to rt and stirred for 4 h. The reaction was quenched with saturated aq. $NaHCO_3$ and extracted with $CH_2Cl_2$. The organic layer was dried, filtered and evaporated under reduced pressure to yield the crude product. Purification by column chromatography (20:1 hexanes/EtOAc) afforded the target compound in as a colorless oil (0.32 g, 100%): $^{1}$H NMR (300 MHz, $CDCl_3$) δ 5.35 (t, 1H $J$ = 6.9 Hz), 5.10 (t, 1H $J$ = 5.4 Hz), 4.69 (s, 2H), 4.10 (d, 2H $J$ = 6.9 Hz), 3.64 (t, 2H $J$ = 5.9 Hz), 2.04-2.31 (m, 6H), 1.87-1.96 (m, 2H), 1.69 (s, 6H), 1.61 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 141.0, 131.6, 123.8, 119.9,

107.1-119.0 (m, $C_8F_{17}$) 94.2, 66.1, 63.8, 39.5, 28.0 (t, $J_{FC}$ = 21.9 Hz), 26.3, 25.4, 20.8, 17.4, 16.1; HRMS for $C_{22}H_{25}O_2F_{17}$: calc. 644.1583 found: 644.1560.



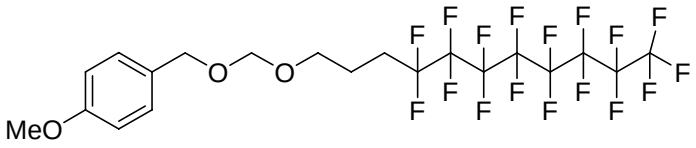
**1-(3-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyloxy)methoxy) propyl) benzene.**

This was synthesized using the general procedure for $^{F}$MOM protection. 3-phenyl-1-propanol (80 µL, 0.5 mmol) was used to obtain, after purification by column chromatography (20:1 hexanes/EtOAc) , the target compound as a colorless oil (0.31 g, 100%): $^{1}$H NMR (300MHz, $CDCl_3$) δ 7.16-7.30 (m, 5H), 4.67 (s, 2H), 3.60 (t, 2H *J* = 6.0 Hz), 3.54 (t, 2H *J* = 6.4 Hz), 2.71 (t, 2H *J* = 7.4 Hz), 2.09-2.26 (m, 2H), 1.83-1.96 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 141.8, 128.5, 126.0, 110.5-119.1 (m, $C_8F_{17}$), 95.5, 67.3, 66.3, 32.5, 31.4, 28.1 (t, $J_{FC}$ = 22.6 Hz), 20.9; HRMS for $C_{21}H_{19}O_2F_{17}$: calc. 626.1114 found: 626.1100.



**(3R,4R,5R)-3-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyloxy) methoxy)-4-hydroxy-5-pentyl-4-vinyldihydrofuran-2(3H)-one.**

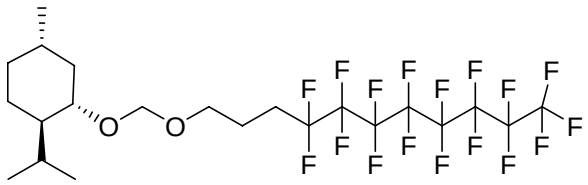
This was synthesized using the general procedure for $^{F}$MOM protection. Lactone (20 mg, 0.10 mmol) was used to obtain, after purification by column chromatography (10:1 hexanes/EtOAc), the target compound as a colorless oil (48.6 mg, 69%): $^{1}$H NMR (300 MHz, $CDCl_3$) δ 5.94 (dd, 1H *J* = 17.0, 10.6 Hz), 5.67 (dd, 1H *J* = 17.1, 1.2 Hz), 5.42 (dd, 1H *J* = 10.6, 1.2 Hz), 5.07 (d, 1H *J* = 6.9 Hz), 4.80 (d, 1H *J* = 6.9 Hz), 4.46 (s, 1H), 4.30 (dd, 1H *J* = 10.7, 3.4 Hz), 3.76 (t, 2H *J* = 6.1 Hz), 2.10-2.32 (m, 2H), 1.83-1.95 (m, 2H), 1.24-1.68(m, 8H), 0.89 (t, 3H *J* = 6.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 172.6, 135.2, 118.6, 115.3, 95.0, 86.5, 78.5, 67.3, 31.9, 31.3, 28.0, 25.5, 22.5, 20.7, 14.0; (the signals from the $C_8F_{17}$ group were obscured due to their low intensity); HRMS for $C_{23}H_{25}O_5F_{17}$: calc. 704.1431 found: 704.1415.




**1-(((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyloxy)methoxy) methyl)-4-methoxybenzene.**

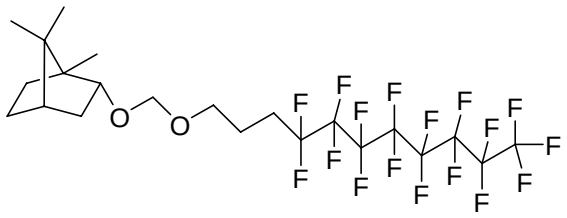
This was synthesized using the general procedure for $^{F}$MOM protection. *p*-methoxybenzyl alcohol (34.5 mg, 0.25 mmol) was used to obtain, after purification by column chromatography (20: 1 hexanes/EtOAc), the target compound as a colorless oil (0.14 g, 87%): $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, 2H *J* = 8.3 Hz), 6.89 (d, 2H *J* = 8.4 Hz), 4.75 (s, 2H), 4.55 (s, 2H), 3.81 (s, 3H), 3.65 (t, 2H *J* = 5.8 Hz), 2.11-2.27 (m, 2H), 1.88-1.93 (m, 2H); $^{13}$C NMR (75 MHz,

$CDCl_3$) δ 159.5, 129.9, 129.6, 113.9, 94.5, 69.3, 66.4, 55.2, 28.1 (t, $J_{FC}$ = 21.9 Hz), 20.9; HRMS for $C_{20}H_{17}O_3F_{17}$: calc. 628.0906 found: 628.0922.



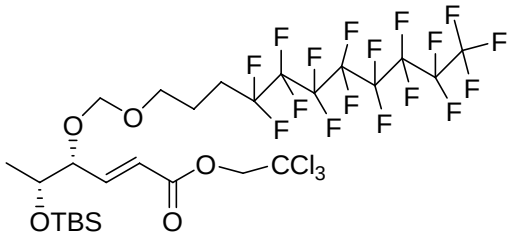
**(1R,2S,4S)-2-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyloxy) methoxy)-1-isopropyl-4-methylcyclohexane.**

This was synthesized using the general procedure for $^F$MOM protection. (+)-menthol (78.2 mg, 0.50 mmol) was used to obtain, after purification by column chromatography (20: 1 hexanes/EtOAc), the target compound as a colorless oil (0.29 g, 91%): $[\alpha]_D^{25}$ + 33.3 (c 1.10, $CHCl_3$): $^1$H NMR (300 MHz, $CDCl_3$) δ 4.83 (d, 1H *J* = 7.0 Hz), 4.65 (d, 1H *J* = 7.1 Hz), 3.57-3.70 (m, 2H), 3.34 (t,d 1H *J* = 20.9, 4.2 Hz), 2.05-2.29 (m, 3H), 1.85-1.94 (m, 2H), 1.59-1.67 (m, 3H), 1.32-1.40 (m, 1H), 1.19-1.27 (m, 2H), 0.83-1.04(m, 8H), 0.78 (d, 3H *J* = 6.9 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 107.1-119.0 (m, $C_8F_{17}$), 93.9, 77.5, 66.4, 48.3, 41.5, 34.3, 31.5, 28.1 (t, $J_{FC}$ = 22.7 Hz),, 25.3, 22.9, 22.0, 20.9, 20.7, 15.5; HRMS for $C_{22}H_{27}O_2F_{17}$: calc. 644.1740 found: 646.1717.



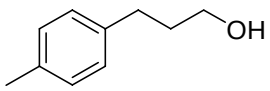
**2-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyloxy)methoxy)-1,7,7-trimethylbicyclo[2.2.1]heptane.**

This was synthesized using the general procedure for $^{F}$MOM protection. Endo-borneol (78 mg, 0.50 mmol) was used to obtain, after purification by column chromatography (20:1 hexanes/EtOAc), the target compound as a colorless oil (0.27 g, 83%): $[\alpha]_D^{25}$ - 22.5 (c 0.80, $CHCl_3$): $^1$H NMR (300 MHz, $CDCl_3$) δ 4.73 (d, 1H *J* = 6.8 Hz), 4.66 (d, 1H *J* = 6.8 Hz), 3.86 (dd, 1H *J* = 9.6, 1.3 Hz), 3.55-3.69 (m, 2H), 2.11-2.29 (m, 2H), 1.85-2.00 (m, 3H), 1.63-1.79 (m, 2H), 1.24-1.27 (m, 2H), 1.05 (d, 1H *J* = 3.3 Hz), 1.00 (d, 1H *J* = 3.3 Hz), 0.86 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 104.8-122.1 (m, $C_8F_{17}$) 95.0, 82.7, 66.4, 49.3, 47.9, 47.6, 45.3, 36.7, 28.5 (t, $J_{FC}$ = 21.8 Hz), 26.9, 21.1, 19.9, 18.9, 13.8; HRMS for $C_{22}H_{25}O_2F_{17}$: calc. 644.1583 found: 644.1560.



**(4R,5R,E)-2,2,2-trichloroethyl-5-(tert-butyldimethylsilyloxy)-4-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)methoxy)hex-2-enoate.**

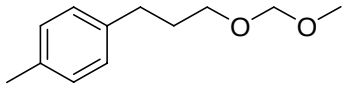
To a solution of TBS alcohol (100.0 mg, 0.26 mmol) in DCE (2.6 mL ) at 0 ºC was added diisopropylethylamine (0.18 mL, 1.04 mmol), TBAI (96 mg, 0.26 mmol) and perfluorooctyl-1-propoxy methyl chloride (0.17 mL, 0.55 mmol) dropwise. The reaction mixture was warmed to rt and then to 50 ºC and stirred for 24 h. The reaction was cooled to rt and then quenched with saturated aq. $NaHCO_3$ and extracted with $CH_2Cl_2$. The organic layer was dried, filtered and evaporated under reduced pressure to yield the crude product. Purification by column chromatography (30:1 hexanes/EtOAc) afforded the target compound in as a colorless oil (0.18 g, 81%): $[\alpha]_D^{25}$ + 0.83 (c 0.01, $CHCl_3$): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.15 (dd, 1H *J* = 15.8, 4.9 Hz), 6.17 (dd 1H *J* = 15.8, 1.6 Hz), 4.82 (s, 2H), 4.76(d, 1H *J* = 7.0 Hz), 4.70 (d, 1H *J* = 7.0 Hz), 4.17-4.21 (m, 1H), 3.97 (app qn, 1H *J* = 6.1 Hz), 3.66-3.75 (m, 1H), 3.55-3.62 (m, 2H), 2.09-2.27 (m, 2H), 1.84-1.95 (m, 2H), 1.10 (d, 3H *J* = 6.2 Hz), 0.90 (s, 9H), 0.08 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 164.3, 148.2, 121.1, 95.1, 94.7, 79.9, 74.1, 69.8, 66.8, 28.1, 25.8, 20.9, 18.8, 18.1, -4.65, -4.81; (the signals from the $C_8F_{17}$ group were obscured due to their low intensity). HRMS for $C_{26}H_{32}O_5F_{17}Na_{23}SiCl_3$: calc. 903.0711 found: 903.0799.




**3-(4-Methyl) phenyl-1-propanol 1.29.**

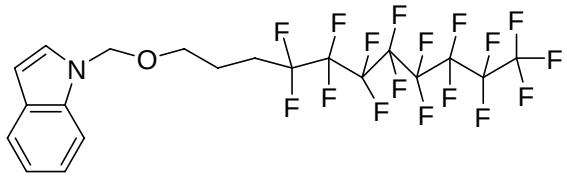
To a solution of *p*-methylcinnamic acid (1.0 g, 6.2 mmol) in anhydrous diethylether (31 mL) at 0 ºC was added LAH (1.0M in diethylether, 31.0 mL, 31 mmol) dropwise. The reaction mixture was warmed to rt and allowed to stir for 24 h. The reaction was cooled back to 0 ºC, quenched

by careful dropwise addition of $H_2O$ (6 mL), sat. aqueous NaOH (6 mL), and $H_2O$ (12 mL). The suspension was filtered, the filtrate was dried with magnesium sulfate and evaporated under reduced pressure to yield the crude product. Purification by column chromatography (3:1 hexanes/EtOAc) yielded the product as a colorless oil (0.72 g, 77%); The $^1H$ NMR spectra was consistent with an authentic sample.[38]




**3-(4-methyl) phenyl-1-propoxymethylmethylether 1.27**

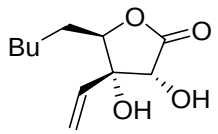
To a solution of alcohol 1.29 (0.3 g, 2.0 mmol) in $CH_2Cl_2$ (3.2 mL ) at 0 ºC was added diisopropylethylamine (1.8 mL, 8.0 mmol) and methoxy methyl chloride (0.52 mL, 6.0 mmol) dropwise. The reaction mixture was warmed to rt and stirred for 3 h. The reaction was quenched with saturated aq. $NaHCO_3$ and extracted with $CH_2Cl_2$. The organic layer was dried, filtered and evaporated under reduced pressure to yield the crude product. Purification by column chromatography (10:1 hexanes/EtOAc) afforded the target compound in as colorless oil (0.36 g, 93%): The $^1H$ and $^{13}C$NMR spectra were consistent with an authentic sample.[39]




**1-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)methyl)-1H-indole.**

To a suspension of NaH (95%, 16.4 mg, 0.65 mmol) in THF (4 mL) at 0 ºC was added a THF solution (1mL) of indole (58.6 mg, 0.5 mmol). The mixture was stirred at 0 ºC for 2 h after which perfluorooctyl-1-propoxy methyl chloride (0.18 mL, 0.55 mmol) was added dropwise to the mixture. The reaction mixture was warmed to rt and stirred for 12h. The reaction mixture was poured into $H_2O$, and extracted with ethyl acetate. The organic layer was dried and ethyl acetate was removed under reduced pressure to give the crude product. Purification by column chromatography (20:1 hexanes/EtOAc) yielded the product as a light yellow oil. (0.25 g, 81%); $^1$H NMR (300 MHz, Acetone-d6) δ 7.52-7.59 (m, 2H), 7.35 (d, 1H *J* = 3.2 Hz), 7.18 (m, 1H), 7.08 (m, 1H), 6.49 (d,d 1H *J* = 3.2, 0.7 Hz), 5.60 (s, 1H), 3.49 (t, 2H *J* = 6.0 Hz), 2.07-2.28 (m, 2H), 1.73-1.82 (m, 2H) $^{13}$C NMR (75 MHz, Acetone-d6) δ 136.4, 129.3, 128.4, 121.7, 120.6, 119.9, 109.9, 102.0, 75.8, 66.2, 27.4, 20.4; (the signals from the $C_8F_{17}$ group were obscured due to their low intensity). HRMS for $C_{20}H_{14}NO_1F_{17}$: calc. 607.0804 found: 607.0798.

**Detagging Protocols**

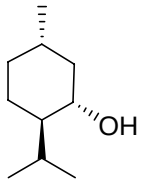



**(3R, 4S, 5R)-3,4-dihydrixy-5-pentyl-4-vinyl-dihydrofuran-2(3H)-one.**

**General Procedure for Lewis acid deprotection:**

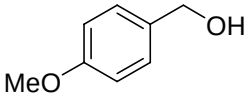
To a stirred solution of the $^F$MOM tagged pentyl lactone (0.14 g, 0.20 mmol) in anhydrous $CH_2Cl_2$ (0.4 mL) at 0 ºC was added butanethiol (44.3 µL, 0.40 mmol) followed by $ZnBr_2$ (0.135

g, 0.60 mmol). The reaction mixture was warmed to rt and stirred for 1 h. The reaction mixture was diluted with $CH_2Cl_2$ (5 mL), cooled to 0 ºC and quenched with saturated aqueous $NaHCO_3$ (2 mL). The crude mixture was filtered through celite. The filtrate was separated into the organic and aqueous layers. The organic layer was dried, $CH_2Cl_2$ was removed under reduced pressure and the crude oil was purified by flash chromatography (2:1 hexane/EtOAc) to afford the pentyl lactone as a white solid (39 mg, 91%). The $^{1}H$ and $^{13}C$ NMR spectra were consistent with an authentic sample.




**(1S, 2R, 5S)-2-isopropyl-5-methylcyclohexanol.**

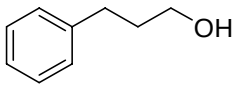
This was obtained using the general procedure for $^{F}$MOM deprotection under Lewis acid conditions. The protected alcohol (0.2 g, 0.31 mmol) was used to obtain, after purification by column chromatography (10:1 hexanes/EtOAc), the target compound as a white solid (43 mg, 89%). The $^{1}H$ and $^{13}C$ NMR spectra were consistent with an authentic sample.




**4-(methoxyphenyl)methanol.**

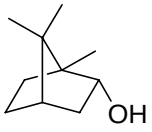
This was obtained using the general procedure for $^{F}$MOM deprotection under Lewis acid conditions. The protected alcohol (59.0 mg, 0.09 mmol) was used to obtain, after purification by

column chromatography (4:1 hexanes/EtOAc), the target compound as a colorless liquid (11 mg, 82%). The $^{1}H$ and $^{13}C$ NMR spectra were consistent with an authentic sample.



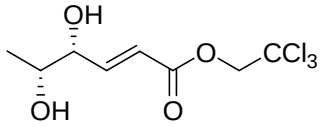

**3-phenylpropan-1-ol.**

This was obtained using the general procedure for $^{F}$MOM deprotection under Lewis acid conditions. The protected alcohol (0.14 g, 0.22 mmol) was used to obtain, after purification by column chromatography (4:1 hexanes/EtOAc), the target compound as a colorless liquid (26.7 mg, 89%). The $^{1}H$ and $^{13}C$ NMR spectra were consistent with an authentic sample.



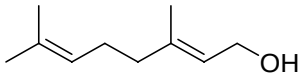

**1,7,7-trimethylbicyclo [2.2.1]heptan-2-ol.**

This was obtained using the general procedure for $^{F}$MOM deprotection under Lewis acid conditions. The protected alcohol (0.10 g, 0.31 mmol) was used to obtain, after purification by column chromatography (10:1 hexanes/EtOAc), the target compound as a white solid (21 mg, 91%). The $^{1}H$ and $^{13}C$ NMR spectra were consistent with an authentic sample.



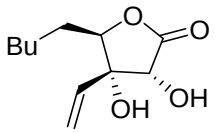

**(4R, 5R, E)-2,2,2-trichloroethyl 4,5-dihydrohex-2-enoate.**

This was obtained using the general procedure for $^{F}$MOM deprotection under Lewis acid conditions. The protected alcohol (0.07 g, 0.08 mmol) was used to obtain, after purification by column chromatography (2:1 hexanes/EtOAc), the target compound as a colorless oil (20 mg, 91%). The $^{1}$H and $^{13}$C NMR spectra were consistent with an authentic sample.




**(E)-3,7-dimethylocta-2,6-dien-1-ol.**

This was obtained using the general procedure for $^{F}$MOM deprotection under Lewis acid conditions. The protected alcohol (70.0 mg, 0.11 mmol) was used to obtain, after purification by column chromatography (6:1 hexanes/EtOAc), the target compound as a colorless liquid (2 mg, 13%). The $^{1}$H and spectra was consistent with an authentic sample.

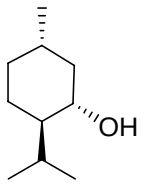



**(3R, 4S, 5R)-3,4-dihydrixy-5-pentyl-4-vinyl-dihydrofuran-2(3H)-one.**

**General Procedure for Brønsted acid deprotection:**

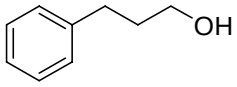
To a stirred solution of the $^{F}$MOM tagged pentyl lactone (0.12 g, 0.17 mmol) in THF/MeOH (1.2 mL: 0.6 mL) at rt was added CSA (0.40 g, 1.7 mmol). The reaction mixture was stirred at rt for 11 h. The reaction mixture was cooled to 0 ºC quenched by careful addition of sat. aqueous $NaHCO_3$ (1 mL). The reaction mixture is diluted with diethyl ether (10 mL) and the organic layer is separated from the crude mixture. The organic layer is dried, removed in vacuo followed

by purification by flash chromatography (2:1 hexanes/EtOAc) to yield the pentyl lactone as a white solid (33.6 mg, 92%). The $^{1}H$ and $^{13}C$ NMR was consistent with an authentic sample.



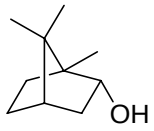

**(1S, 2R, 5S)-2-isopropyl-5-methylcyclohexanol.**

This was obtained using the general procedure for $^{F}$MOM deprotection under Brønsted acid conditions. The protected alcohol (0.07 g, 0.11 mmol) was used to obtain, after purification by column chromatography (4:1 hexanes/EtOAc), the target compound as a white solid (14 mg, 84%). The $^{1}H$ and $^{13}C$ NMR spectra were consistent with an authentic sample.



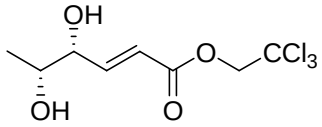

**3-phenylpropan-1-ol.**

This was obtained using the general procedure for $^{F}$MOM deprotection under Brønsted acid conditions. The protected alcohol (0.14 g, 0.22 mmol) was used to obtain, after purification by column chromatography (4:1 hexanes/EtOAc), the target compound as a colorless liquid (26.0 mg, 85%). The $^{1}H$ and $^{13}C$ NMR spectra were consistent with an authentic sample.



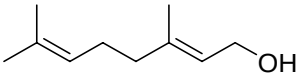

**1,7,7-trimethylbicyclo [2.2.1]heptan-2-ol.**

This was obtained using the general procedure for $^{F}$MOM deprotection under Brønsted acid conditions. The protected alcohol (0.20 g, 0.31 mmol) was used to obtain, after purification by column chromatography (7:1 hexanes/EtOAc), the target compound as a white solid (42 mg, 90%). The $^{1}$H and $^{13}$C NMR spectra were consistent with an authentic sample.




**(4R, 5R, E)-2,2,2-trichloroethyl 4,5-dihydrohex-2-enoate.**

This was obtained using the general procedure for $^{F}$MOM deprotection under Brønsted acid conditions. The protected alcohol (0.09 g, 0.10 mmol) was used to obtain, after purification by column chromatography (2:1 hexanes/EtOAc), the target compound as a colorless oil (5 mg, 17%). The $^{1}$H was consistent with an authentic sample.




**(E)-3,7-dimethylocta-2,6-dien-1-ol.**

This was obtained using the general procedure for $^{F}$MOM deprotection under Brønsted acid conditions. The protected alcohol (0.15 g, 0.23 mmol) was used to obtain, after purification by column chromatography (4:1 hexanes/EtOAc), the target compound as a colorless liquid (28 mg, 79%). The $^{1}$H and $^{13}$C NMR spectra were consistent with an authentic sample.

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