

Selective fluorination of natural products

Paige J. Monsen and Frederick A. Luzzio*

Department of Chemistry, University of Louisville, 2320 South Brook Street,
Louisville, KY 40292 United States
Email: frederick.luzzio@louisville.edu

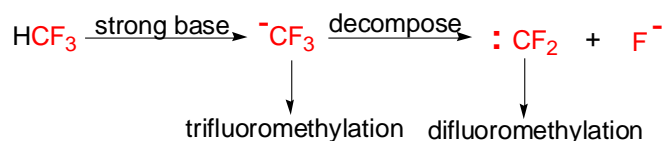
Received 11-01-2016

Accepted 12-08-2016

Published on line 04-02-2017

Abstract

Compounds derived from natural sources including animals, plants, and micro-organisms have been widely used for pharmaceuticals, materials, and agrochemicals. The use of these natural products has grown increasingly over the years and the demand for more improved, biologically active, and safer derivatives of natural products has been investigated by many researchers in the areas of synthetic and medicinal chemistry. Due to the unique characteristics of fluorinated compounds, and the increased or more favorable biological activity which usually accompanies fluorinated analogues of medicinally-important compounds, the fluorination of natural products has gained much attention. This review aims at exploring the range of specific natural product types that have been selectively fluorinated as well as how fluorination was expected to affect their biological activities and physiochemical properties.



Keywords: Natural products, fluorination, biological activity, halogenation

Table of Contents

1. Introduction
2. Fluorination Reagents
 - 2.1 Nucleophilic fluorination reagents
 - 2.2 Electrophilic fluorination reagents
3. Terpenoids
4. Lipid Natural Products
 - 4.1 Aliphatic natural products
 - 4.2 Acetogenins
 - 4.3 Steroids
5. Polyketides
6. Carbohydrates
 - 6.1 Hexopyranosides
 - 6.2 Nucleosides
7. General Oxygen Heterocycles
 - 7.1 Furanoids/benzofuranoids
 - 7.2 Pyranoids/benzopyranoids
8. Aromatic and Cyclic Ketones
9. Amino Acids and Peptides
10. Alkaloids and Nitrogen Heterocycles
11. Tannins/Lignans
12. Conclusions

1. Introduction

Utilizing natural products in the medicinal world has proven to be beneficial in society today. With many pharmaceuticals containing natural products or natural product derivatives as the biologically active compounds of interest, the search to improve these compounds has drawn a great deal of attention. Fluorination of these compounds has been one area of research that has grown tremendously and has been limited by only the types of fluorination reagents, their availability, and the sensitivity of the natural substrate. Fluorine itself exhibits potent characteristics, including a small van der Waals radius of 147 ppm and the highest electronegativity of 3.98 in the periodic table.² Compounds that have been fluorinated therefore display beneficial properties that set them apart. Metabolic stability, binding affinity, lowering of surface tension, hydrophobicity and lipophobicity are just some of the properties that accompany the fluorination of a compound thereby contributing to unique biological properties.³ This overview provides a visualization of several advances in the selective fluorination of natural product with referenced works ranging from the 1980s to the present year. While late-stage fluorinations are emphasized, synthetic schemes showing incorporation of fluorinated intermediates are included for contrast.^{4, 5, 6}

2. Fluorinating Reagents

2.1 Nucleophilic fluorinating reagents

Nucleophilic fluorination is characterized as a fluoride ion behaving as a nucleophile which attacks an electrophilic substrate or its activated complex. Both alkali metal fluorides and HF-based reagents have been utilized as fluoride sources (Figure 1).



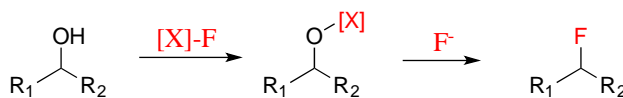
Figure 1. Alkali-metal fluorides and HF-based reagents.

The most straightforward example is an alkyl chain which bears a suitable leaving group that can readily react with a nucleophilic fluoride ion (Scheme 1).



Scheme 1. Nucleophilic fluorination reaction.

Although many traditional nucleophilic fluorination reagents have been used in the past, the majority of natural products have either been fluorinated by HF-based reagents or more commonly were selectively fluorinated by deoxofluorinating reagents. The deoxofluorinating reaction is a modified nucleophilic fluorinating reaction which involves the generation of an activated alcohol as well as a fluoride ion.⁷ The fluoride ion participates in a nucleophilic attack, generally an S_N2 reaction, to produce an alkyl fluoride (Scheme 2). With this form of selective fluorination, many deoxofluorinating reagents have been developed. The reagents that have been developed for such reactions, including DAST⁸, Deoxofluor[®]⁹, Fluolead[™]¹⁰, and PhenoFluor[™]¹¹ are shown in Figure 2.



Scheme 2. Deoxofluorinating Reaction.

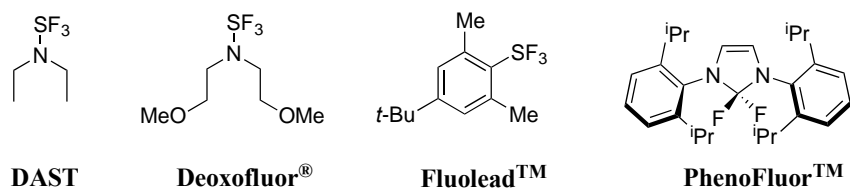


Figure 2. Deoxofluorination reagents.

2.2 Electrophilic fluorinating reagents

An electrophilic fluorination reaction is characterized as the fluorine source behaving as an electrophile and the substrate is that of a nucleophile. The most common form of F^+ originates from fluorine gas, where the electrophilic fluorinating reagents are highly oxidizing,¹² including fluorine gas and hypofluorites. The advance in reagents that can react via electrophilic fluorination and embody a certain specificity of conditions has not only improved the selectivity of fluorination but has also improved the tolerance of functional groups.¹³ The developments of reagents such as *N*-fluoropyridium salts (FP-T300)¹⁴, *N*-fluorobis(phenyl)sulfonimide (NFSI)¹⁵, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2] octane bis(tetrafluoroborate) (Selectfluor[®], F-TEDA-BF₄),¹⁶ and derivative F-TEDA-PF₆¹⁷ have been great innovations to the introduction of a fluorine atom (Figure 3).

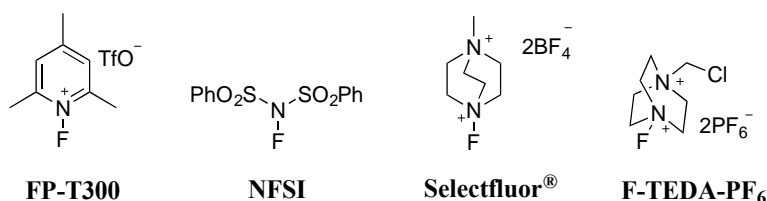
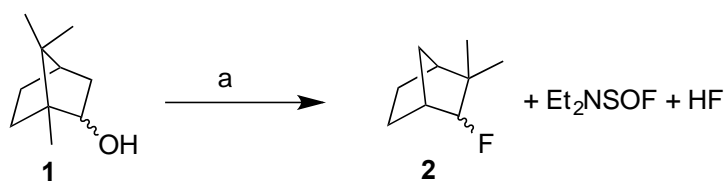


Figure 3. Electrophilic fluorinating reagents.

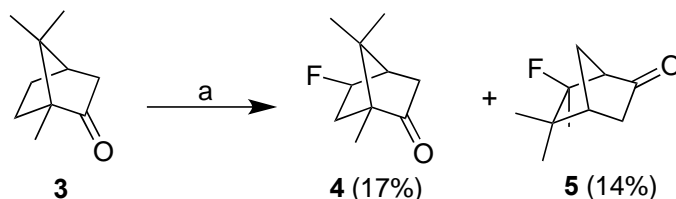
3. Terpenoids

Terpenoids, the largest class of natural products, are diverse in origin, structure and function. Whether derived from plant or animal, such compounds have roles involved in an organism's defense mechanism as well as a form of interaction or chemical communication between organisms. With many terpenes containing natural biological activities, the derivatization of such compounds can lead to enhancing these features and potentially increasing drug like properties. The simplest of terpenoids are the monoterpenes, which consist of two isoprene units and are highly aromatic molecules with limited functionality. Borneol and camphor, both bicyclics, are amongst the simplest of terpenes that have been fluorinated. Borneol **1** was fluorinated by the Middleton group while investigating fluorination reactions which utilize DAST.⁸ As expected, carbonium ion type rearrangements are problems that can occur while replacing an alcohol group with a fluoride. Although carbonium ion type rearrangements are less likely to occur while using DAST as a fluorinating reagent, *exo*- and *endo*-borneol is more easily rearranged in order to yield compound **2**. The fluorination of borneol using DAST led to a rearranged fluoride **2** (Scheme 3).



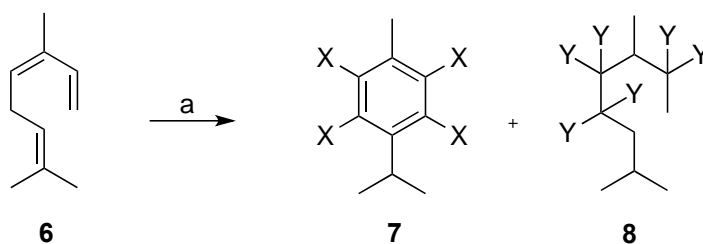
Scheme 3. Fluorination of borneol **1**. Reagents/Conditions: (a) DAST.

Camphor **3** was fluorinated by the Britton group as described in a 2014 communication through the use of a photocatalytic fluorination reaction as detailed in Scheme 4.¹⁸ Fluorination occurred at positions that were most remote from the carbonyl group.



Scheme 4. Fluorination of camphor **3**. Reagents/Conditions: (a) 1.5 equiv NFSI/0.1 equiv NaHCO₃/0.02 equiv TBADT/ MeCN/365 nm, 16 h.

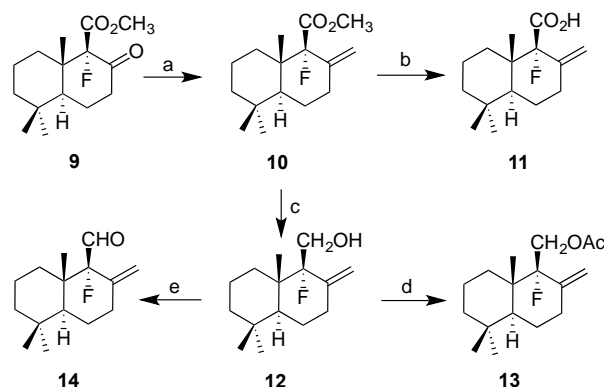
Myrcene, a commercially available monoterpene, has also been fluorinated with the goals of utilizing fluorinated terpenes in a wide variety of general cleaning and degreasing applications.¹⁹ Myrcene **6**, combined with trifluorochloromethane and fluorine gas, was then passed through a sodium fluoride trap to yield fluorinated compounds **7** and **8** (Scheme 5).



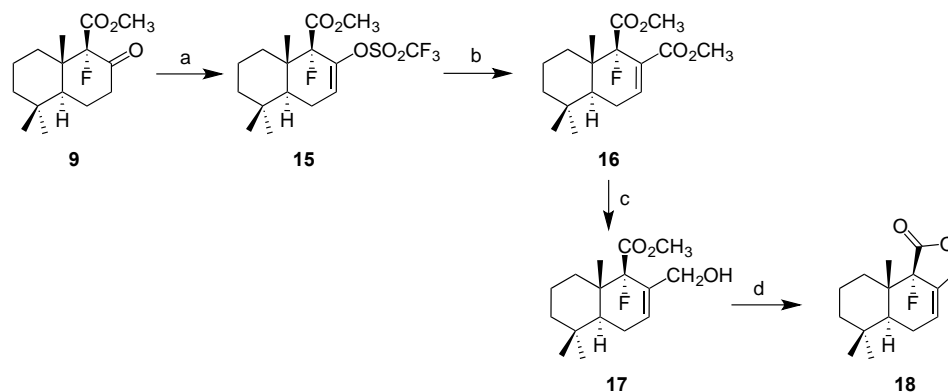
Scheme 5. Fluorination of myrcene **6**. Reagents/Conditions: (a) CFCl₃/F₂. **7**: X is hydrogen or fluorine and at least two of X are fluorine. **8**: Y is hydrogen or fluorine and at least two of Y are fluorine.

The preparation of fluorinated natural sesquiterpenoids based on the drimane system has been reported and has focused on the production of 9- α -fluoro derivatives **9-14**.²⁰ Abad's group sought to prepare several fluorinated analogues of the drimane framework and investigate how these changes could affect their chemical properties and biological activity. Fluorinated albicanic acid **11** was prepared from the starting fluorodecalone **9** which underwent a Wittig methylenation to afford β,γ -unsaturated ester **10** (Scheme 6). Ester cleavage of **10** with NaSPr in DMF yielded 9 α -fluoroalbicanic acid **11**. The 9-fluorinated albicanol **12** was also synthesized from fluorodecalone **9** in which the methylenated compound **10** was reduced with lithium aluminum hydride to provide alcohol **12**. Acetylation of 9 α -fluoroalbicanol, **12**, afforded 9 α -fluoroalbicanyl acetate, **13**. Conversion of alcohol **12** to corresponding aldehyde **14** was performed using the Dess-Martin periodinane oxidation reagent and resulted in 9 α -fluoroalbicanal **14** (Scheme 6).

Preparation of 9 α -fluorodrimenin **18** was accomplished from fluorodecalone **9**. Preparation of diester **16** occurred through converting decalone **9** to the corresponding enol triflate **15** with potassium hexamethyldisilazane/*N*-phenyltriflamide. The triflate **15** was then treated with a palladium catalyst to undergo a palladium-catalyzed carbonylation thereby providing the dimethyldiester **16**. Arrival at 9 α -fluorodrimenin **18** was accomplished through lactonization of hydroxester **17** using DBU and molecular sieve (Scheme 7).

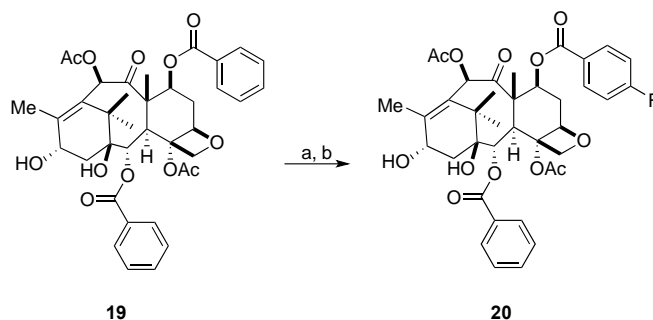


Scheme 6. Preparation of 9- α -fluoro derivatives. Reagents/Conditions: (a) $\text{Ph}_3\text{PCH}_3\text{Br}/\text{KHMDS}/\text{CH}_3\text{Ph}/\text{room temp.}/2\text{h}$; (b) $\text{NaH}/\text{PrSH}/\text{DMF}/80^\circ\text{C}/2\text{h}$; (c) $\text{LiAlH}_4 \cdot 2\text{THF}/\text{CH}_3\text{Ph}/-40^\circ\text{C}$; (d) $\text{Ac}_2\text{O}/\text{DMAP}/\text{Py}/\text{room temp.}/1.5\text{ h}$; (e) $\text{DMP-py}/\text{CH}_2\text{Cl}_2/\text{room temp.}/4.5\text{ h}$.



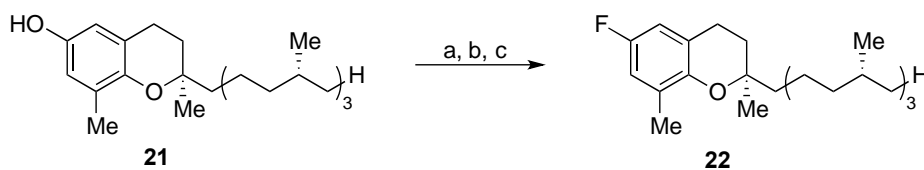
Scheme 7. Synthesis of 9- α -fluorodrimenin **18**. Reagents/Conditions:(a) $\text{KHMDS}/\text{PhNTf}_2/\text{THF}/-78^\circ\text{C}$; (b) $\text{Pd}(\text{OAc})_2/\text{PPh}_3/i\text{Pr}_2\text{Net}/\text{CO}/\text{CH}_3\text{OH}/\text{DMF}/65^\circ\text{C}$; (c) $\text{DIBAL-H}/\text{THF}/\text{C}_6\text{H}_{12}/78^\circ\text{C}$; (d) $\text{DBU}/3\text{\AA MS}/\text{C}_6\text{H}_6/\text{room temp.}$

More complex terpenoids and their derivatives have undergone selective fluorination, including taxol, forskolin, tocopherol, artemisinin, and nerolidol and the potential benefits are self-explanatory, especially when applied to anticancer compounds such as taxol and antimalarials such as the artemisinins. Due to the wide use of fluorinated aromatic compounds in pharmaceuticals, agrochemicals, materials, and as tracers for positron emission tomography (PET), the Ritter group investigated new ways to form carbon-fluorine bonds. The methods were developed while exploring the specific application of silver catalysts. In turn, the mild conditions resulted in good functional group tolerance and wide substrate scope.²¹ Biologically active molecules, including natural products, have been fluorinated using Ritter's catalysis technology successfully and in good yields. The use of the silver catalyst with the electrophilic fluorination can occur with aromatic rings in the presence of other functional groups, such as alcohols, dienones, vinyl ethers, esters, and oxetanes, proving this to be a beneficial fluorinating option for. Taxol **19** has been selectively fluorinated on the aromatic ring using the electrophilic fluorinating reagent, F-TEDA- PF_6 in the presence of a silver catalyst (Scheme 8).



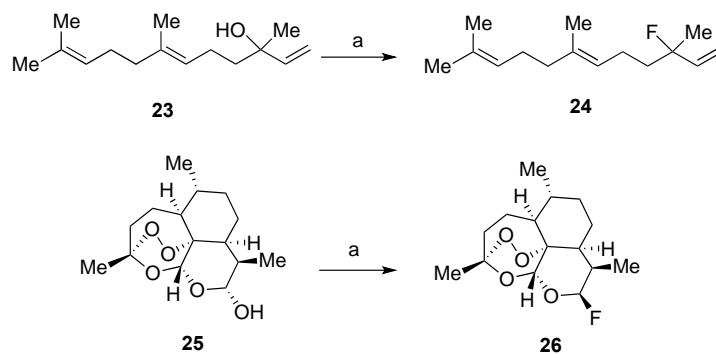
Scheme 8. Fluorination of taxol **19**. Reagents/Conditions: (a) 5.0 mol% Ag₂O/1.0 equiv NaOTf/ 2.0 equiv NaHCO₃; (b) 1.5 equiv F-TEDA-PF₆/acetone/65 °C.

The Ritter group also selectively fluorinated δ -tocopherol, Vitamin E **21** at the hydroxyl position with F-TEDA-PF₆ to afford product **22** (Scheme 9).²²



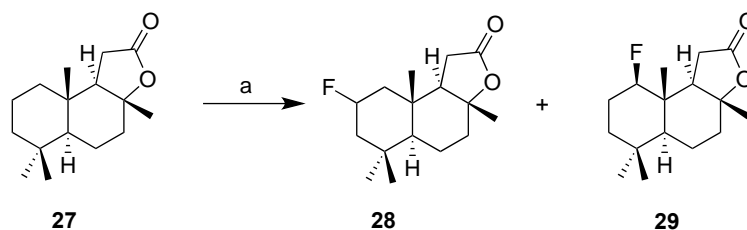
Scheme 9. Fluorination of δ -tocopherol **21**. Reagents/Conditions: (a) Tf₂O/NET₃; (b) LiCl/5 mol% Pd(PPh₃)₄/ⁿBu₃Sn₂; (c) 1.2 equiv F-TEDA-PF₆/2.0 equiv AgOTf/acetone/23 °C/20 min.

Further investigations by Ritter revealed the use of PhenoFluor[®] as a late-stage deoxyfluorination reagent of alcohols in which both terpenoids (*E*-nerolidol **23** and artemisinin **25** were both selectively fluorinated to give products **24** and **26** respectively (Scheme 10).²³



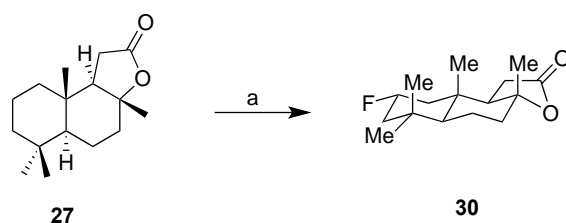
Scheme 10. Fluorination of (*E*)-nerolidol **23** and artemisinin **25**. Reagents/Conditions: (a) PhenoFluor[™]/2.0 equiv. EtNⁱPr₂/ 2.0 equiv. KF/ 2-20h.

The fluorination of natural sclareolide **27** was investigated by Britton's group as shown in Scheme 11. One may note that the fluorination system was highly efficient and the (2*S*)-2-fluorosclareolide **28** was produced as the major product while the 1-fluorosclareolide **29** was the minor product (Scheme 11).¹⁸



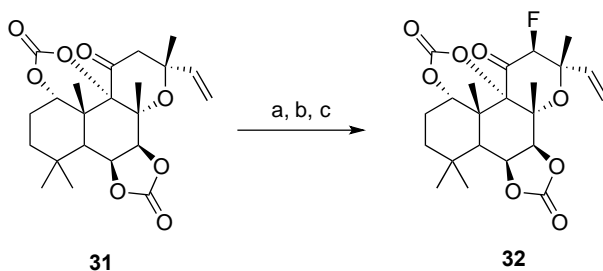
Scheme 11. Fluorination of sclareolide **27**. Reagents/conditions: (a) 1.5 equiv NFSI/0.02 equiv TBADT/ $\lambda=365$ nm/ $\text{NaHCO}_3/\text{MeCN}$.

Sclareolide was also fluorinated by the Groves group using a manganese porphyrin-catalyzed selective C-H fluorination with silver fluoride to yield title tricyclic fluorinated lactone **30** (Scheme 12).²⁴



Scheme 12. Fluorination of sclareolide **27**. Reagents/conditions: (a) $\text{Mn}(\text{TMP})\text{Cl}$ (8 mol%)/ AgF (3 eq.)/TBAF (0.3 eq.)/PhIO (10 eq.).

Forskolin **31**, an adenylyl cyclase activator, was fluorinated utilizing the reaction of its lithium enolate which was generated by lithium hexamethyldisilazide. The enolate was reacted with acetyl hypofluorite to produce 12-fluoroforskolin **32** as a single diastereomer (Scheme 13).²⁵



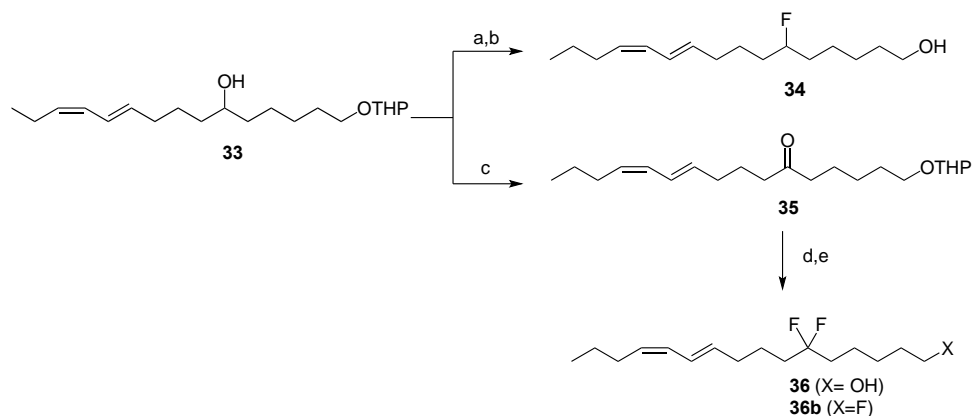
Scheme 13. Fluorination of forskolin **31**. Reagents/Conditions: (a) LiHMDS/THF ; (b) $\text{AcOF}/\text{CFCl}_3/\text{AcOH}/-65^\circ\text{C}$; (c) $\text{NaHCO}_3/\text{THF}/\text{H}_2\text{O}$.

4. Lipid Natural Products

4.1 Aliphatic natural products

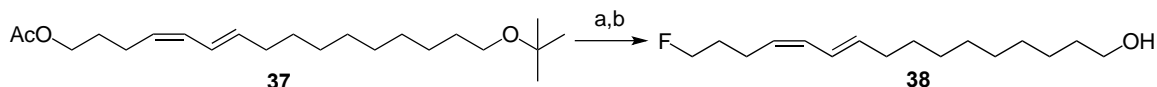
One of the most important subgroups of aliphatic natural products are the semiochemicals. These compounds facilitate communication between many species of organisms and are vastly different amongst themselves in structure but are similar in their functionality, typically alcohols and ethers. With semiochemicals embodying

many of the aliphatic compounds with the greatest biological importance, they are widely studied due to the biological responses they stimulate. Whenever metabolically permissible, semiochemicals can be released on purpose by the organism on an 'as needed' basis so fluorinating these compounds can produce effects on the activity and can therefore cause changes in the response of the individuals especially insects.²⁶ Bombykol **33** is a female sex pheromone of the silkworm moth *Bombyx mori* whereby an understanding of its pheromone biology and chemistry has been widely explored.²⁶ The Svatos group monofluorinated bombykol at two separate positions, at C6 and C16. Bombykol was also difluorinated at C6. The synthesis of both mono and difluoro derivatives of bombykol **34**, **36** respectively is shown in Scheme 14.



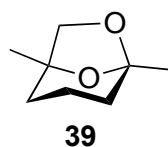
Scheme 14. Fluorination of bombykol **33**. Reagents/Conditions: (a) DAST; (b) PTSA; (c) PCC; (d) DAST; (e) PTSA.

Alcohol **33** was synthesized from (*E*)-iodohexan-6-ol followed fluorination using DAST. Cleavage the THP group with *p*-toluenesulfonic acid, yielded title alcohol **34**. The oxidation of alcohol **33** with PCC yields ketone **35**, which then upon fluorination with DAST followed by deprotection with PTSA, the target compound **36** is obtained. Unfortunately, similar fluorination occurred on the terminal alcohol as well to form **36b**. 16-fluorobombykol **38** was synthesized similarly as shown in Scheme 15.

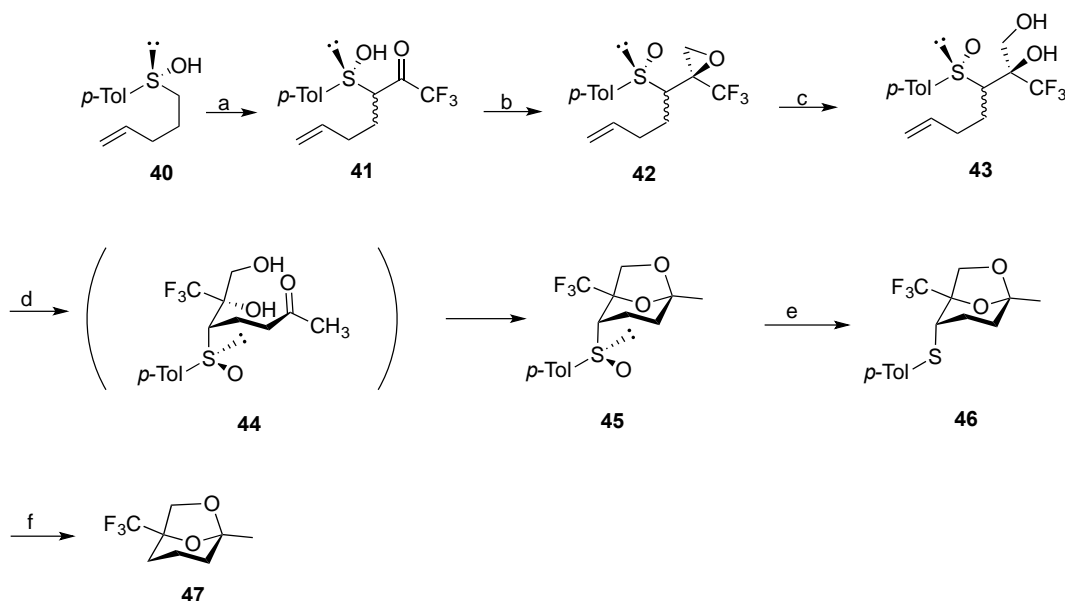


Scheme 15. Synthesis of 16-fluoro derivative **38**. Reagents/Conditions: (a) MeONa; (b) DAST/ Ac₂O/ FeCl₃ /MeONa.

Frontalin **39**, a bioactive compound and aggregation pheromone of the *Scolytidae* insect family, plays a significant role in chemical communication between insects. Replacement of the hydrogen atoms with fluorine atoms in pheromones can cause a variety of effects on an insect's response, thereby altering their activity. Moreover, replacing the hydrogens with fluorine is advantageous in the fact that a large change in electronic distribution occurs without a great steric difference. Along with fluorinated analogues increasing bioactivity, these compounds can be used as tracers for metabolic pathways.²⁷



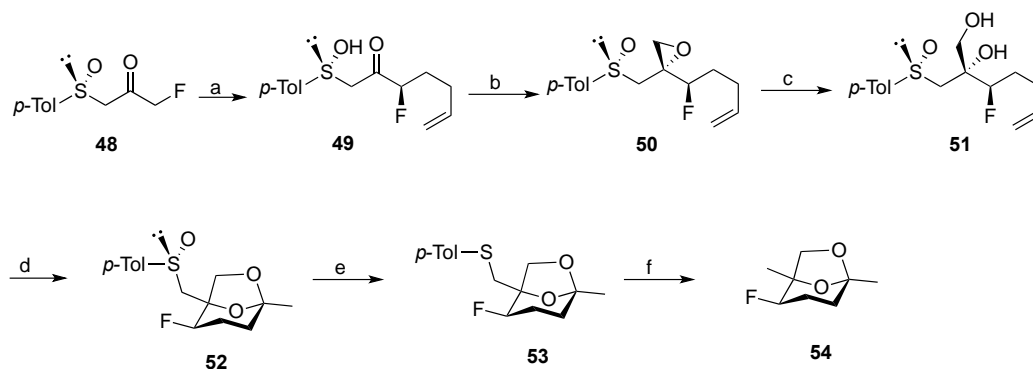
The synthesis of trifluorofrontalin **47** began with enantiopure sulfoxide (*R*_S)-**40**, which was made following the Anderson-modified procedure using 4-pentenylmagnesium bromide and (-)-(1*R*)-menthyl (*S*)-toluene-4-sulfinate (Scheme 16). Treatment of the pentenyl sulfoxide **40** with LDA and ethyl trifluoroacetate resulted in acylation to produce ketosulfoxide **41**. Methylene insertion with diazomethane across the carbonyl group in **41** afforded a diastereomeric mixture of oxiranes **42**. The resulting mixture of oxiranes **42** is then subjected to electrophilic ring opening via aqueous perchloric acid, providing diol **43**. In order to produce the bicyclic core of the frontalin, a Wacker oxidative process was employed on the terminal C=C bond of diol **43** to afford ketodiols **44**. Intramolecular ketalization of the ketodiol intermediate **44** subsequently occurred producing ketalsulfoxide **45**. Compound **47** was obtained through deoxygenation of **45** to sulfide **46** and hydrogenolytic removal of the thiotolyl group led to target compound **47** (Scheme 16).



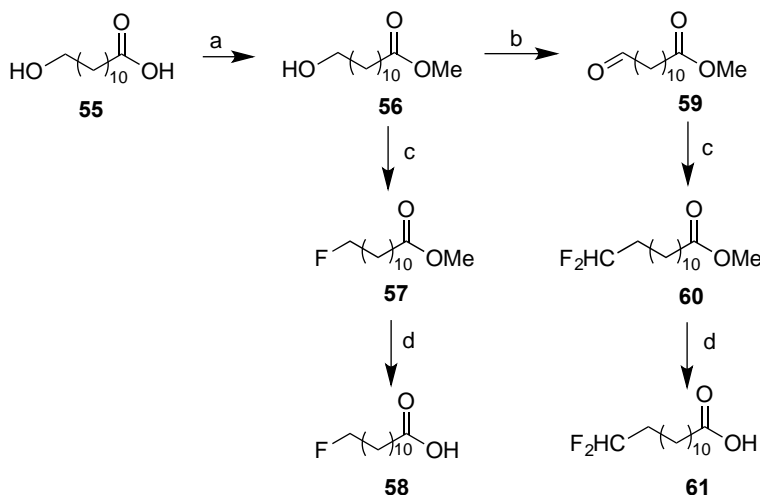
Scheme 16. Synthesis of trifluorofrontalin **47**. Reagents/Conditions: (a) LDA/THF/ CF_3COOEt ; (b) $\text{CH}_2\text{N}_2/\text{MeOH}/-40^\circ\text{C}$; (c) $\text{HClO}_4/\text{THF}/\text{H}_2\text{O}/40^\circ\text{C}/7\text{d}$; (d) $\text{CuCl}_2/\text{PdCl}_2/\text{DME}$; (e) $\text{NaI}/\text{TFAA}/\text{acetone}$; (f) $\text{Raney-Ni}/(\text{HOCH}_2)_2$.

Monofluorofrontalin **54** was synthesized from fluoroketosulfoxide **48** (Scheme 17). Alkylation of **48** with 3-butenyl bromide (LDA/HMPA) gave fluoropentenyl sulfoxide **49**. Treatment of **49** with diazomethane affords oxirane **50** which was hydrolyzed to diol **51** by catalysis with perchloric acid (THF/ H_2O). Further treatment of **51** with $\text{PdCl}_2/\text{CuCl}_2/\text{O}_2$ provided bicyclic sulfoxide, **52**. Deoxygenation of **52** (NaI/TFA) provided sulfide **53** which was then reductively desulfurized with Raney nickel (ethylene glycol/ 110°C) to give the title compound, **54**.

The fluorinated analogues of the C12 fatty acid, lauric acid was prepared recently by the Yu group in 2013. Starting materials 12-Hydroxydodecanoic acid and 12-carboxydodecanal was mono and di-fluorinated respectively at the C12 position with Deoxofluor[®] yielding 12-fluorododecanoic acid **58**, and 12,12-difluorododecanoic acid **61** (Scheme 18).²⁸



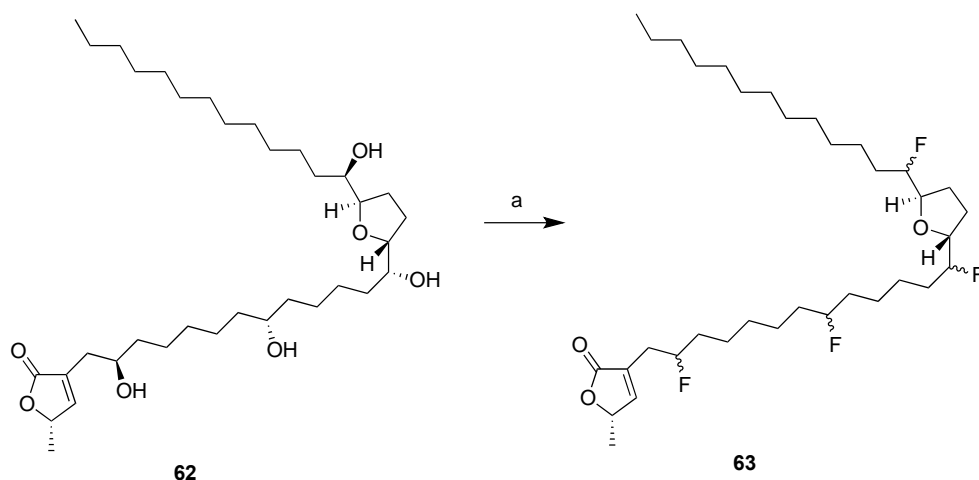
Scheme 17. Synthesis of monofluorofrontalin **54**. Reagents/Conditions: (a) LDA/ *n*-C₄H₇Br/ HMPA /THF/ -60 °C /FC; (b) CH₂N₂/MeOH/ 0 °C; (c) HClO₄/THF/H₂O/40 °C; (d) CuCl₂/PdCl₂/ O₂/diglyme, rt; (e) NaI/ TFAA/ acetone/-20 °C; (f) Raney-Ni/(HOCH₂)₂/110 °C.



Scheme 18. Preparation of lauric acid analogues **58** and **61**. Reagents/Conditions: (a) H⁺/ MeOH/RT/12 h; (b) PCC/ CH₂Cl₂/ rt/ 2 h; (c) Deoxo-Fluor[®]/ CH₂Cl₂/ 0 °C to rt/30 min; (d) LiOH•H₂O/THF/ MeOH /H₂O/ RT/4 h.

4.2 Acetogenins

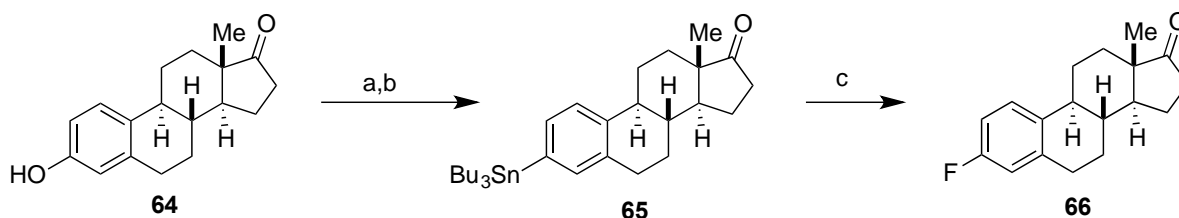
Annonacin **62** is a neurotoxic natural product which was isolated from the fruit pulp of the Caribbean soursop and the North American pawpaw, both species of the family *Annonaceae*. In general, annonacin is a member of the annonaceous acetogenin family of natural products whereby the compounds possess lipid-like structures that may bear single or multiple THF rings as well as a terminal butenolide ring. The compound was found to be toxic to rat cortical neurons and is suspected to cause atypical Parkinson's syndrome in populations in which there is a high consumption rate of the fruit. Naturally-derived annonacin is also antiangiogenic in the rat aortic ring assay at 30 μM. Preliminary results suggest that an excess of DAST in dichloromethane is useful for tetrafluorination of **62** at each of its hydroxyl positions as indicated by ¹H 400MHz spectroanalysis of the reaction product **63** (Scheme 19).²⁹ While one may anticipate inversion of stereochemistry at each of the fluorination sites, it has yet to be determined.



Scheme 19. Tetrafluorination of annonacin **62**. Reagents/Conditions: Excess DAST/MeOH.

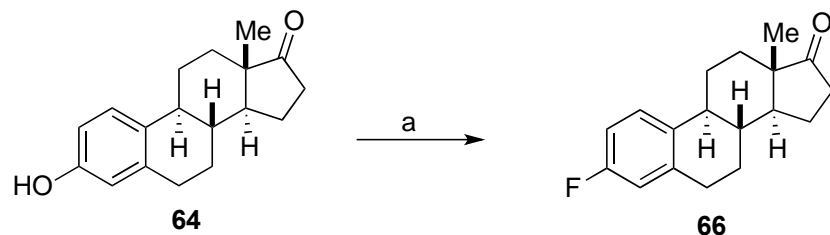
4.3 Steroids

Fluorinated steroids are active components of a number of important pharmaceuticals.³⁰ Studying the fluorination of naturally occurring steroids can lead to new innovations in hormone medicine as well as discovering new methods of fluorinating these polycyclic lipids. Estrone **64**, one of several naturally occurring estrogens, is a hormone secreted from the ovaries. This well-known steroid has been fluorinated in multiple accounts by Ritter's group utilizing a silver catalyst.^{21,22} In their first account Ritter's group utilized a similar approach that they used to fluorinate δ -tocopherol (Scheme 9) in order to selectively fluorinate estrone **64** (Scheme 20).



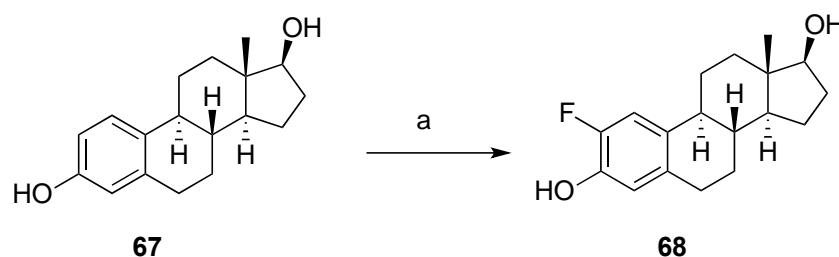
Scheme 20. Fluorination of estrone **64**. Reagents/Conditions: (a) $\text{F}_2\text{O}/\text{Et}_3\text{N}$; (b) $\text{LiCl}/\text{Pd}(\text{PPh}_3)_4/(\text{Bu}_3\text{Sn})_2$; (c) $\text{AgOTrif}/\text{F-TEDA-PF}_6$.

The conversion of estrone **64** to 3-fluoro-3-deoxyestrone **66** first involves the triflation of estrone followed by a palladium-mediated stannylation giving the intermediate stannylated steroid **65**. Fluorodestannylation of the aromatic ring leading to the title compound employed the electrophilic fluorinating agent F-TEDA- BF_4 or F-TEDA- PF_6 in the presence of silver triflate (Scheme 20).²² One year later, Ritter's group performed another late stage fluorination on estrone (Scheme 21).²¹



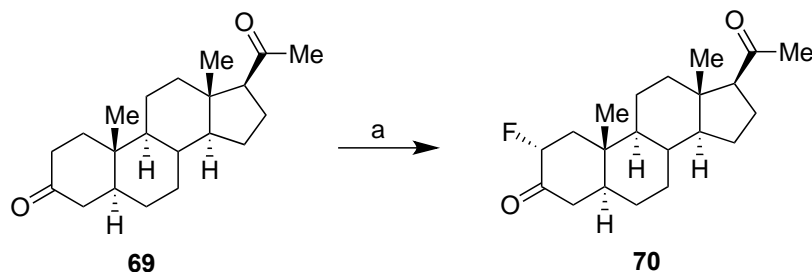
Scheme 21. Fluorination of estrone **64**. Reagents/Conditions: (a) 5.0 mol% Ag₂O/2.0 equiv NaHCO₃/1.0 equiv NaOTf/1.5 equiv F-TEDA-PF₆/acetone/ 65 °C.

Estradiol **67** another naturally occurring estrogen, has also been fluorinated in multiple accounts, in which Selectfluor[®] is utilized as an electrophilic fluorinating reagent (Scheme 22).^{31,32}



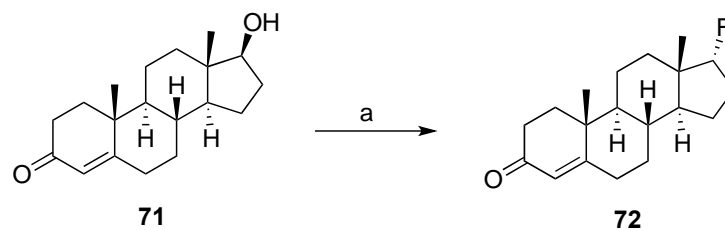
Scheme 22. Fluorination of estradiol **67**. Reagents/Conditions: (a) Selectfluor[®] /bmimBF₄ /CH₃OH/20 °C.

Allo-Pregnanedione **69** an endogenous progestogen, has been fluorinated by the MacMillan group utilizing an enantioselective organocatalytic α -fluorination reaction to give product **70**.³³ After successfully investigating multiple cyclohexanone compounds, the MacMillan group utilized their findings to fluorinate a more complex cycloketone as seen in Scheme 23. Depending on which catalyst is used the selectivity of fluorination can be manipulated.

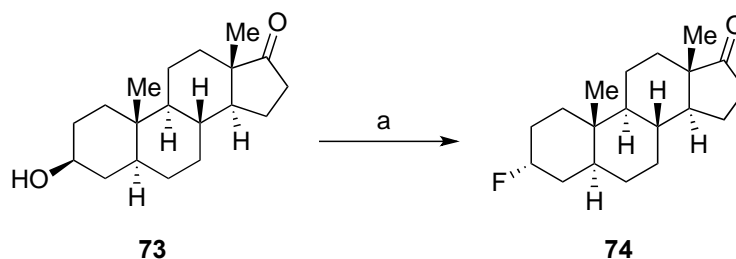


Scheme 23. Fluorination of *allo*-pregnanedione **69**. Reagents/Conditions: (a) NFSI/Na₂CO₃/ THF/DCM.

The Ritter group selectively fluorinated steroids, testosterone **71** and *epi*-androsterone **73** as reported in 2013 and employed a late-stage deoxyfluorination of alcohols with Phenofluor[™] as previously mentioned earlier.²³ Both compounds underwent replacement of the alcohol group with a fluorine atom in which inversion of stereochemistry occurred to provide **72** and **74** (Schemes 24, 25).

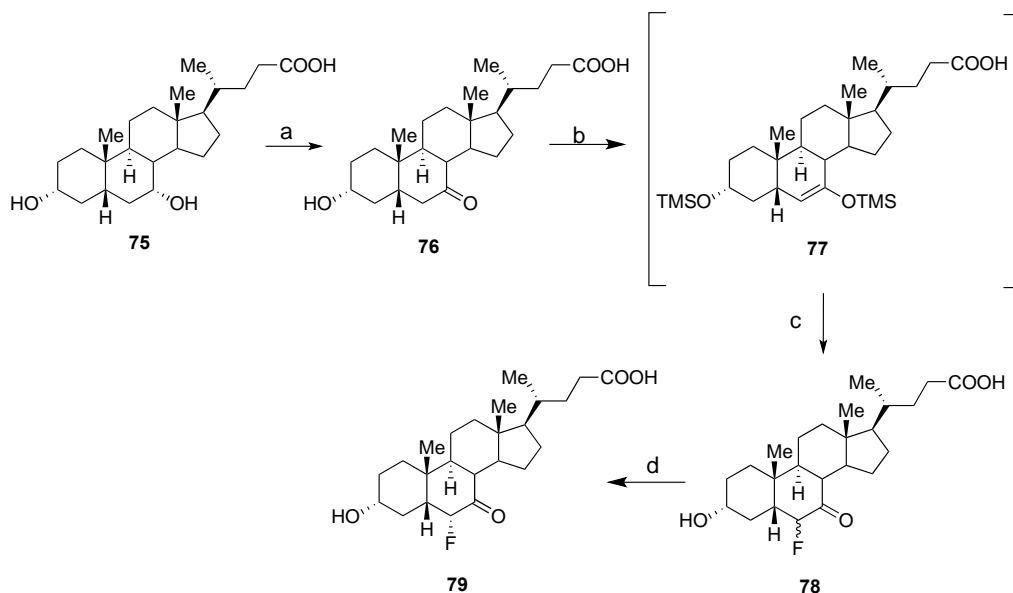


Scheme 24. Fluorination of testosterone **71**. Reagents/Conditions: (a) PhenofluorTM/2.0 equiv EtNⁱPr₂/2.0 equiv KF/2-20 h.



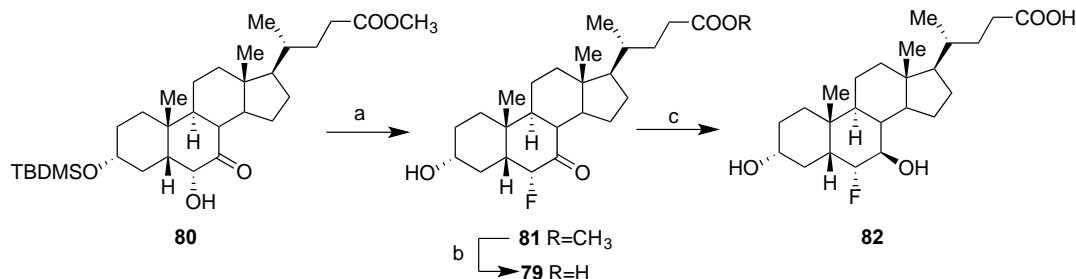
Scheme 25. Fluorination of *epi*-androsterone **73**. Reagents/Conditions: (a) PhenofluorTM/2.0 equiv EtNⁱPr₂/2.0 equiv KF/2-20 h.

In the concise synthesis of 6- α -fluoroursodeoxycholic acid **79** (Scheme 26), a Novartis process group used Selectfluor[®] to fluorinate the enol ether of **77** which resulted in total desilylation and provided the α -fluoroketone **78** (Scheme 26).³⁴ Subsequent steps which gave a key intermediate included equilibration to the 6 α -fluoroketone with sodium methoxide/methanol, formation of the methyl ester using methanol/chlorotrimethyl silane, acetylation of the 3-hydroxyl group (Ac₂O/DMAP). 6 α -Fluoroketone **78** was then reduced with H₂/platinum oxide followed by mesylation (mesyl chloride/DMAP) and mesyl displacement (KO₂/DMSO) giving inversion at C-7 and thus the title compound **79**.



Scheme 26. Fluorination of chenodeoxycholic acid **75**. Reagents/Conditions: (a) NaOCl/ Bu₄N⁺Br⁻/NaBr; (b) TMSCl/ NaI; (c) Selectfluor[®]; (d) NaOMe/MeOH/TMSCl/MeOH/Ac₂O /DMAP.

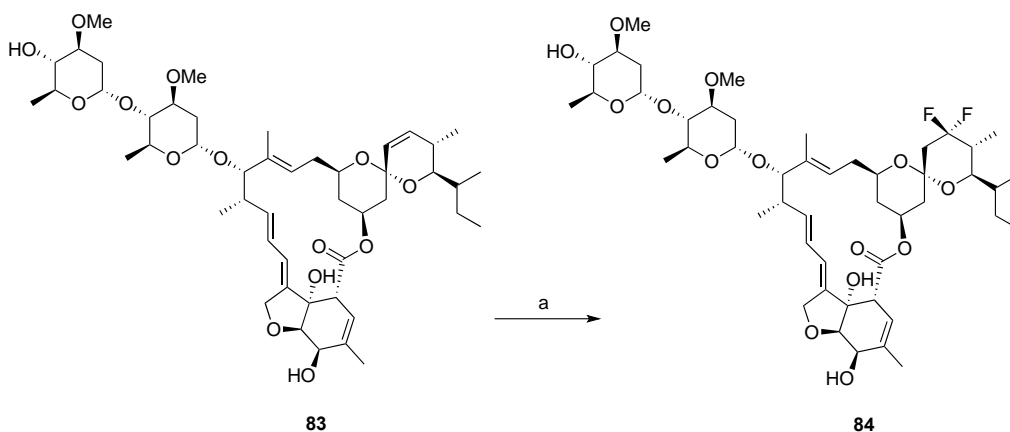
The Novartis synthesis was in contrast to the previous synthesis of **79** by an Italian group whereby DAST in dichloromethane was used to fluorinate followed by desilylation of TBDMS-protected hydroxyketone **80** (Scheme 27).³⁵ The resulting α -fluoroketone **81** was saponified with KOH in methanol which afforded ketocarboxylic acid **79**. The 6-ketogroup of **79** was then reduced with sodium borohydride in methanol to give title compound **82**.



Scheme 27. Fluorination of chenodeoxycholic acid **75**. Reagents/Conditions: (a) DAST/DCM; (b) KOH/MeOH; (c) NaBH₄/MeOH.

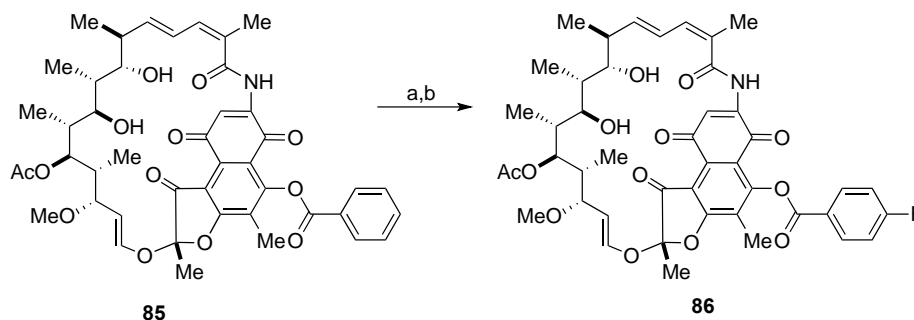
5. Polyketides

Structurally complex as well as highly bioactive, the polyketide family has become a great area of research within the biochemical community. This class of secondary metabolites, produced by living organisms, are structurally diverse from one another and are potent pharmaceuticals. Avermectin B_{1A} **83** is a representative polyketide that has been widely used for the treatment of parasites in animals, plants, and humans and is known for its high biological activity and complex structure. Based on this knowledge, new derivatives that even further enhance these properties have been developed. The fluorination technique of naturally occurring Avermectin B_{1A} was carried out by the Meinke group.³⁶ As part of their initiative to determine new avermectin derivatives with enhanced biological activity, the Meinke group explored the option of preparing a *gem*-difluoro derivative of the parent natural product. Starting compound **100** was fluorinated at position 23 across the alkene, using fluorinating reagent, DAST, noted in Scheme 28. Title compound **83** was successfully fluorinated and analyzed in a pentamethylenetetrazole (PTZ) mouse epilepsy model. The results portrayed a three-fold increase for the difluoro derivative in protecting against PTZ induced seizures compared to ivermectin, a non-fluorinated avermectin derivative. Although the fluorination derivative did not display greater activity than known drug, diazepam, compound **84** lacks the sedative effects of diazepam, a notable positive feature.



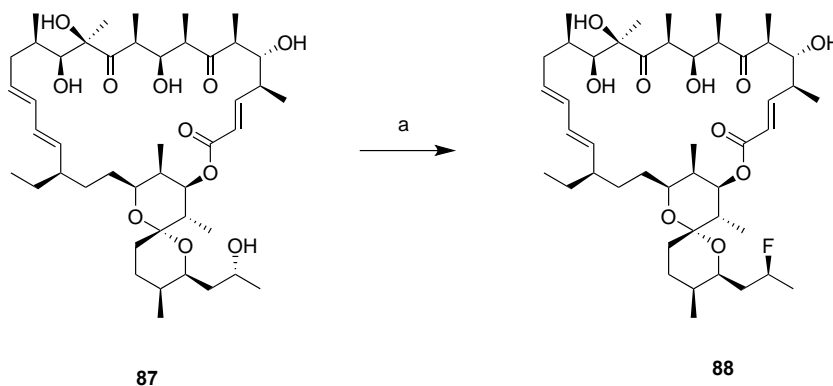
Scheme 28. Fluorination of avermectin **83**. Reagents/Conditions: (a) excess DAST.

The natural polyketide antibiotic, rifamycin S **85** has been fluorinated on the aromatic ring using the electrophilic fluorinating reagent, F-TEDA-PF₆, in the presence of a silver catalyst (Scheme 29). The formation of the carbon-fluorine bond in **86** was performed in the last synthetic step, where the fluorination occurs with exclusive regioselectivity.²²



Scheme 29. Fluorination of rifamycin S **85**. Reagents/Conditions: (a) 20 mol% AgOTf/2.0 equiv NaOTf/5.0 equiv MeOH; (b) 1.5 equiv F-TEDA-PF₆/acetone/65 °C.

Again, the Ritter group investigated the fluorination of natural products to generate optimized derivatives that can be optimized with increased pharmacological profiles.²³ Specifically, late stage fluorination is being examined, where oligomycin A **87** was fluorinated with commercially available PhenoFluor™, a deoxyfluorinating reagent that can be utilized on a multi-functional group level. The selective deoxyfluorination of polyketide oligomycin A is shown in Scheme 30, and is an example of a chemoselective introduction of fluorine into a complex molecule thereby yielding secondary fluoride **88**.

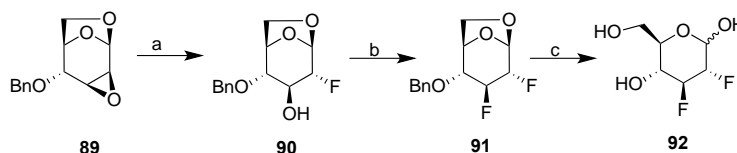


Scheme 30. Fluorination of oligomycin **87**. Reagents/Conditions: (a) PhenoFluor™/2.0 equiv. EtNⁱPr₂/ 2-20 h.

6. Carbohydrates

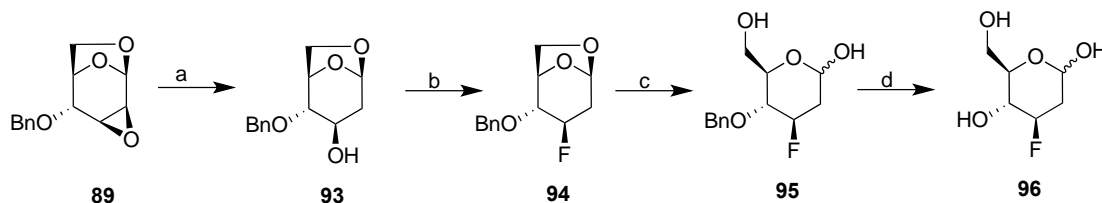
6.1 Hexopyranosides

Being central to many fundamental biological processes, carbohydrates are an important class of compounds to investigate in terms of fluorinated analogues. Selectively-fluorinated carbohydrates may be used as tools to elucidate glycoprocessing mechanisms and have been useful in medicinal chemistry, pharmacology and biochemistry. Research groups have looked into decreasing polarity of sugars through replacing CHOH groups with CF₂ groups, therefore creating a more hydrophobic environment.³⁷ Linclau's group sought to synthesize mono- and difluorinated 2,3-deoxy-D-glucopyranoses. Starting epoxide **89** was obtained from D-glucal. As shown in Scheme 31, **89** underwent a regioselective epoxide opening with potassium hydrogen bifluoride to yield fluoroalcohol **90**. Fluoroalcohol **90** was then treated with DAST to afford *trans* 1,2-difluoride **91**. Benzyl deprotection of **91** was accomplished with BCl₃ followed by quenching with water to yield 2,3-dideoxy-2,3-difluoro-D-glucose **92** (Scheme 31).



Scheme 31. Synthesis of 2,3-dideoxy-2,3-difluoro-D-glucose **92**. Reagents/Conditions: (a) KHF₂/(CH₂OH)₂/reflux; (b) DAST/toluene/reflux; (c) BCl₃/H₂O.

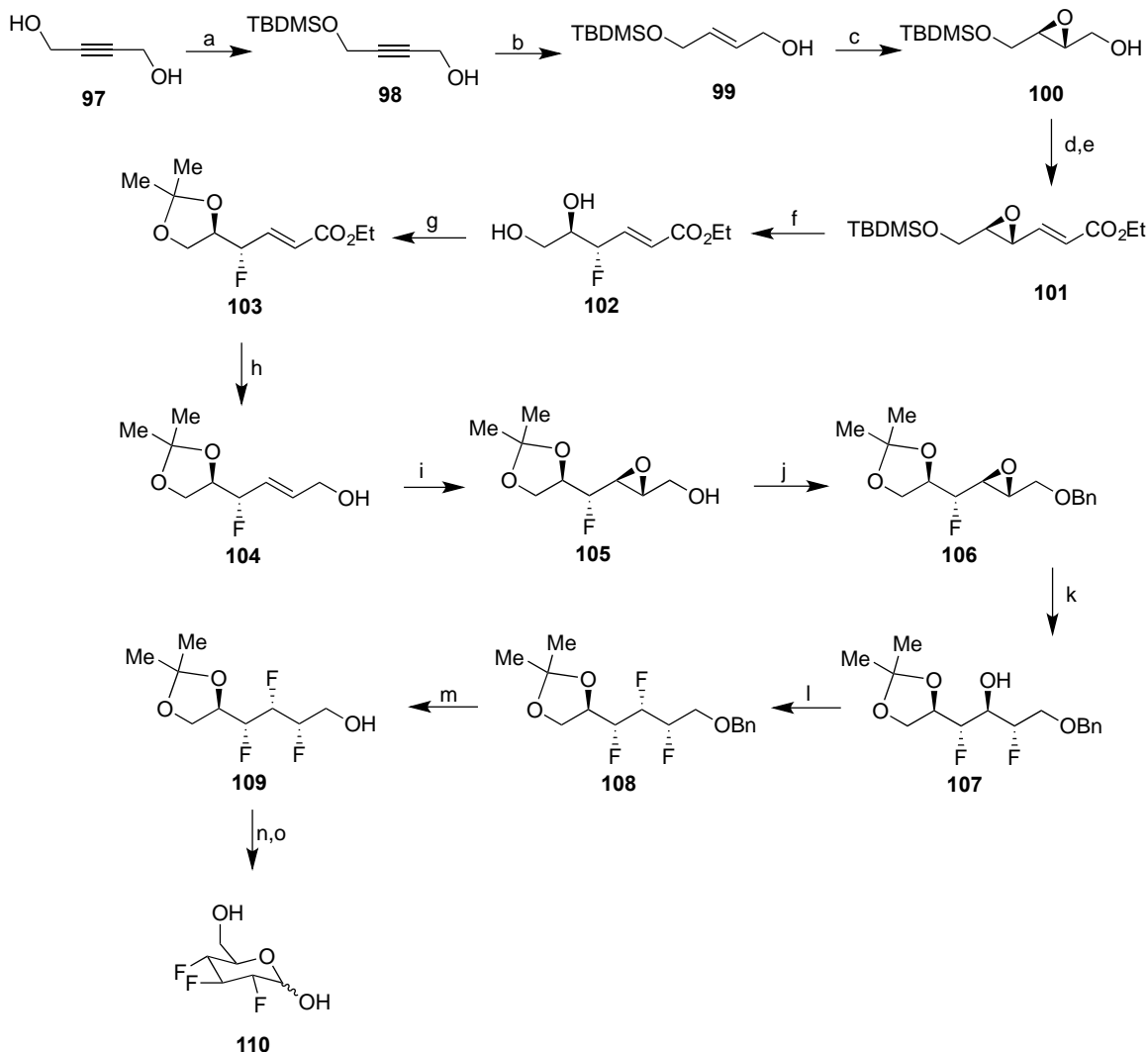
The synthesis of 2,3-dideoxy-3-fluoro-D-glucose **96** is outlined in Scheme 32. Again a deoxofluorination of benzyloxyalcohol **93** with DAST was utilized to provide benzyloxyfluoride **94**. The bicyclic ether moiety of **94** was then hydrolyzed with sulfuric acid to yield diol **95**. Hydrogenolysis of diol **95** resulted in cleavage of the benzyl group and gave the title compound **96**.



Scheme 32. Synthesis of 2,3-dideoxy-3-fluoro-D-glucose **96**. Reagents/Conditions; (a) LiAlH₄/ THF/reflux/2h; (b) DAST/toluene/reflux/24h; (c) 1M H₂SO₄/dioxane/75 °C; (d) H₂/ Pd(OH)₂/ MeOH.

A *de novo* synthesis of trifluoroglucose **110** was reported by O'Hagan's group in an effort to provide a more expedient route to this target compound (Scheme 33).³⁸ Butynediol **97** was monosilylated to afford butynyl silylether **98** which was then reduced to the TBDMS-protected *trans*-silyl ether **99**. Sharpless epoxidation of **99** gave TBDMS-protected epoxyalcohol **100**. Swern oxidation of **100** followed by Emmons-Horner olefination gave the TBDMS-protected α,β -unsaturated epoxyester **101**. Fluorinative epoxide ring-opening of **101** provided α,β -unsaturated fluorodiols **102** which was protected to afford fluoroketal ester **103**. Selective reduction of the ester function of **103** gave fluoro allylic alcohol **104** which was then epoxidized using the Sharpless method to fluoro epoxyalcohol **105**. The alcohol group of **105** was protected to give the fluoro epoxy benzyl ether **106** with the dimethyl ketal intact. Fluorinative epoxide opening of benzyl ether **106** was done with hydrogen fluoride triethylamine to provide benzyl-protected difluoroalcohol **107**. Deoxyfluorination of difluoroalcohol **107** to give benzyl-protected trifluoride **108** employed Deoxofluor[®] at 0 °C. The benzyl group was removed from trifluoride

108 giving trifluoroalcohol **109**. Finally, **109** was oxidized and deprotected to give the target 2,3,4-trifluorosugar **110** (Scheme 33).

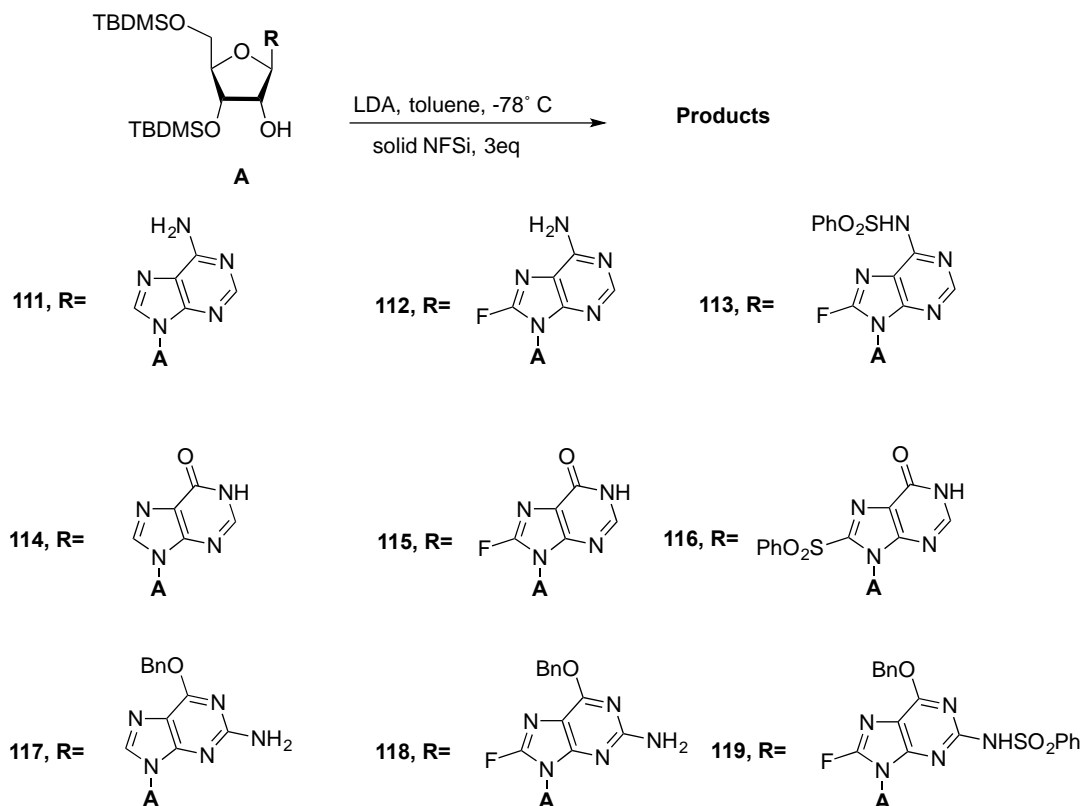


Scheme 33. Synthesis of trifluoroglucose **110**. Reagents/Conditions: (a) TBDMSOTf/ NaH/ THF/ 0 °C to RT / 18.5 h; (b) Red-Al/ THF/ 0 °C to RT/4 h; (c) Ti(OiPr)₄/ (-)-DIPT/ tBuOOH / DCM/4Å MS /25 °C to -20 °C/ 19.5 h; (d) Oxalyl chloride/ DMSO/ NEt₃/ 78 °C to 0 °C/ 2 h; (e) C₈H₁₇O₅P / NaH/ THF/ 0 °C to 78 °C/ 2.5 h; (f) 3HF•NEt₃/ 90 °C /24 h; (g) (CH₃)₂C(OCH₃)₂/ CSA/ DMF/ RT/18 h; (h) DIBAL-H/ THF/ 78 °C to RT; (i) Ti(OiPr)₄/ (-)-DIPT/ tBuOOH/ DCM/ 4Å MS/ 25 °C to 20 °C/ 19.5; (j) BnBr/ NaH/ DMF/ 0 °C to RT/ 18.5 h; (k) 3HF•NEt₃/ NEt₃/ 100 °C / 3 days; (l) Deoxofluor™ (in THF)/ DCM/ 0 °C to RT/ 19 h; (m) NaBrO₃/ Na₂S₂O₄/ H₂O/ EtOAc/ RT/ 1.5 h; (n) DMP/ DCM/ 0 °C to RT/ 1 h; (o) SnCl₂/ DCM/ RT/ 1 h.

6.2 Pyranosides

Carbohydrates, including sugars and fatty acids are widely abundant in the natural product arena, providing the energy sources for organisms through fueling their metabolism. Due to their biological activity, fluorinated nucleosides and their analogues are of interest in the science community-especially as antivirals. The substitution at the carbon-8 position has not received much attention, and the few that have been reported utilize the halox reaction with the substitution occurring by a bromine or a chlorine. Protected 8-fluoro

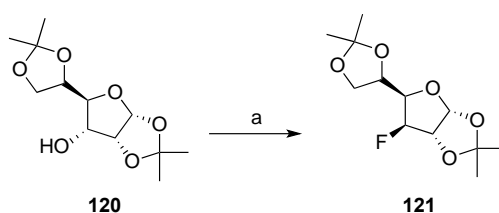
derivatives of deoxyadenosine **111**, deoxyinosine **114**, and deoxyguanosine **117** via a direct metalation-fluorination have been reported for the first time by Zajc and coworkers (Scheme 34).³⁹



Scheme 34. Fluorination of purine nucleosides.

Protected 2'-deoxyadenosine **111** was fluorinated via metalation-electrophilic fluorination to form two fluorinated products that were separated by column chromatography. The fluorinated products were confirmed by ¹⁹F-NMR and ¹H-NMR and exhibited a fluorine resonance at δ 102.1 ppm **112** and δ 99.1 ppm **113**. The purine C8 proton resonance at δ 8.14 ppm disappears with the fluorinated products, which was indicative of a protected 8-fluoro-adenosine. Protected 2'-deoxyinosine **114** was also fluorinated via metalation-electrophilic fluorination to form 8-fluoro-2'-deoxyinosine **115** as the major product. **115** exhibited a fluorine resonance at δ 101.8 ppm in the ¹⁹F-NMR; however, the minor product **116** did not display a fluorine resonance, but instead showed aromatic protons representing the phenyl ring in ¹H-NMR. Protected O⁶-benzyl 2'-deoxyguanosine **117** was fluorinated to form two fluorinated products, **118** and **119** that were separated by column chromatography and unfortunately very low yields of these were isolated.

Ritter's group fluorinated protected D-allofuranose **120** at C-3 by means of the deoxofluorinating reagent PhenofluorTM in 83% yield and obtained the fluorosugar derivative **121** (Scheme 35).²³

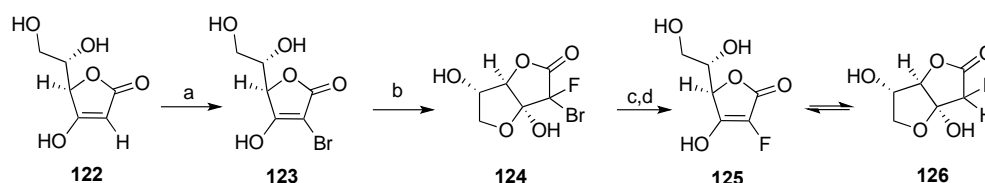


Scheme 35. Fluorination of *D*-allofuranose **120**. Reagents/Conditions: (a) Phenofluor™/ 2.0 equiv. EtNⁱPr₂/ 2.0 equiv. KF/ 2-20 h.

7. General Oxygen Heterocycles

7.1 Furanoids/benzofuranoids

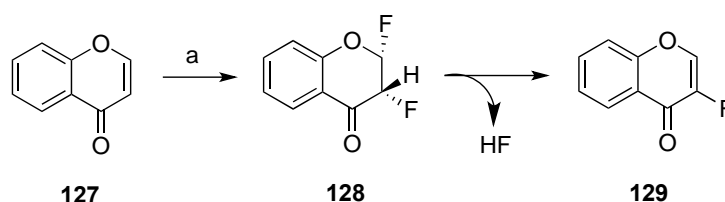
Ascorbic acid **122**, or better known as Vitamin C, is a compound well known to the science community as well as to the public. With research into the biochemistry involving ascorbic acid new insights have been revealed, including the information that the 6-hydroxy group is unimportant while the 2-hydroxy group is at the center of the reaction site in redox mechanisms of ascorbic acid.⁴⁰ With this in mind chemical manipulation at the 2-position of ascorbic acid can have an effect on the biological properties of this compound. 2-Fluoro-2-deoxy-L-ascorbic acid **126** was prepared through halogenation of 2-deoxy-L-ascorbic acid **122** by Kirk and coworkers using NBS (Scheme 39). Fluorination of **123** using F-TEDA-BF₄ resulted in a 95% yield of **124**, in which reductive debromination using tri-*n*-butyltin hydride followed and resulted in the formation of 2-deoxy-2-fluoro-L-ascorbic acid **126** after workup. Unfortunately, the desired 2-fluoro analogue **125** was not the sole product, and tautomerization between the enol **125** and the hemiketal **126** was a result, primarily due to the strong electronegativity of the fluorine atom (Scheme 36).



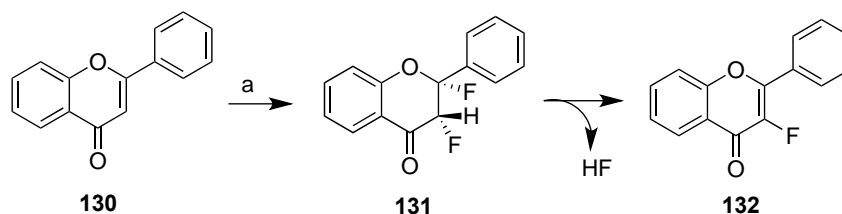
Scheme 39. Synthesis of fluorinated ascorbic acid **125**. Reagents/Conditions: (a) NBS; (b) Selectfluor® / THF; (c) *n*-Bu₃SnH; (d) 10% HOAc.

7.2 Pyranoids/benzopyranoids

Flavones and chromones are found in many plants and are abundant chemical components of the human diet.⁴¹ These naturally occurring compounds are beneficial to the human body, decreasing the risks of multiple diseases. Unfortunately, recent studies have proven that these compounds have a very short lifetime in the body for 10 hours before being metabolized. With that in mind, Rozen's group examined the fluorination of flavones and chromones in an attempt to provide derivatives which are somewhat resistant to normal metabolic processes.⁴¹ Treatment of chromone **127** with fluorine gas resulted in a mixture of difluorinated products in which spontaneous elimination of hydrogen fluoride from intermediate **128** resulted in the formation of 3-fluorochromone **129** (Scheme 37). Fluorination of isoflavone **130** occurred similarly to that as **127** and gave fluoroisoflavone **132** through intermediate difluoride **131** (Scheme 38).

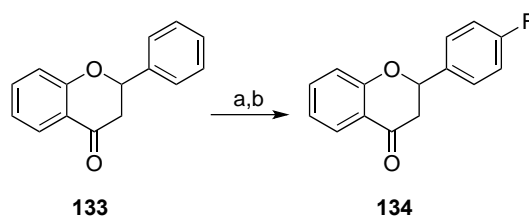


Scheme 37. Fluorination of chromone **127**. Reagents/Conditions: (a) F₂/N₂.



Scheme 38. Fluorination of isoflavanone **130**. Reagents/Conditions: (a) F₂/N₂.

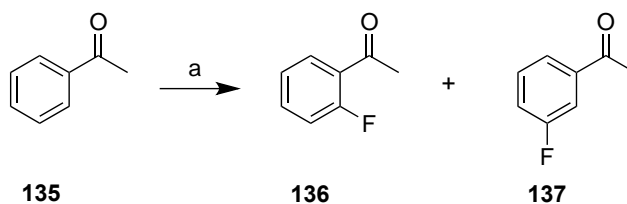
The fluorination of flavanone **133** was investigated by the Ritter group in 2010 and utilized the electrophilic fluorinating reagent, F-TEDA-PF₆ in the presence of a silver catalyst. The fluorination occurs on the aromatic ring to afford **134** as shown in Scheme 39.²¹



Scheme 39. Fluorination of flavanone **133**. Reagents/Conditions: (a) 5.0 mol% Ag₂O/ 2.0 equiv NaHCO₃/1.0 equiv NaOTf; (b) 1.5 equiv F-TEDA-PF₆/acetone/65 °C.

8. Aromatic Natural Products and Cyclic Ketones

Acetophenone **135**, a simple organic compound which occurs naturally occurring in certain foods, underwent an electrochemical aromatic fluorination as shown in Scheme 40.⁴² The main fluorination products were *ortho*- and *meta*-isomers **136** and **137** respectively.



Scheme 40. Electrochemical fluorination of acetophenone **135**. Reagents/Conditions: (a) anhydrous HF/ CHCl₃ or CH₃CN.

A recent report from the O'Hagan group described the multistep *de novo* syntheses of nine civetone and five muscone analogues **138-140** containing the difluoromethylene motif. The fluorinated analogues were prepared for structure/conformation and odor comparisons. The key steps in the macrocycle synthesis utilized DAST for difluorination of intermediate carbonyls as well as Grubbs-type strategies to close the 15-17 membered rings. Some selected examples of O'Hagan's target compounds are shown in Figure 4.⁴³

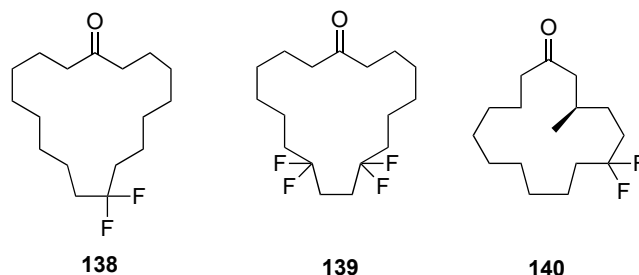


Figure 4. Fluorinated civetone **138**, **130**, and muscone **140** analogues.

9. Amino acids and peptides

Hunter's group recently investigated the stereoselective syntheses of α,β -difluoro- γ -amino acids in order to provide a scalable reaction sequence.⁴⁴ Deoxofluor[®] and HF in pyridine were employed in a series of reactions in order to provide new synthetic approaches toward the backbone-fluorinated amino acids **141** and **142** (Figure 5).

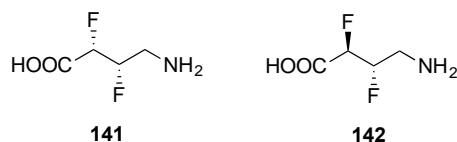
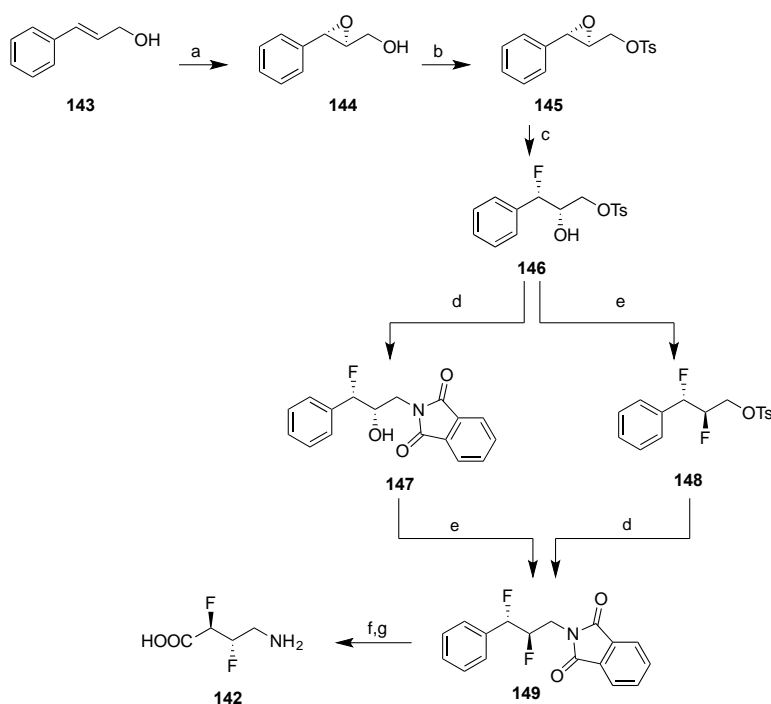


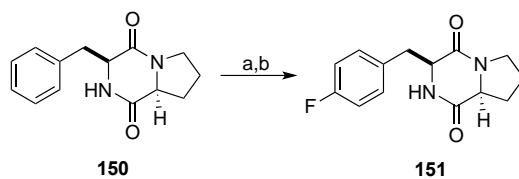
Figure 5. α,β -Difluoro- γ -amino acids.

α,β -Difluoro- γ -amino acid **142** was synthesized in a seven-step sequence and resulted in a vast improvement over previous synthetic ventures (Scheme 41). However, amino acid **141** is still under investigation to fully improve the synthesis, a venture which requires more steps, though still achieving good chemoselectivity. Cinnamyl alcohol **143** was stereoselectively epoxidized via the Sharpless method to afford epoxy alcohol **144**. The *p*-toluenesulfonyl ester **145** of epoxyalcohol **144** was then prepared followed by fluorination of **145** to give tosyloxy-fluoroalcohol **146**. Phthalimide displacement of **146** gave the *N*-phthalimidofluoroalcohol **147**; or alternatively, fluorination of tosyloxy fluoroalcohol **146** gave the tosyloxy difluoride **148**. Toward the common intermediate *N*-phthalimdidifluoride **149**, the *N*-phthalimidofluoroalcohol **147** was fluorinated, or alternatively the tosyloxydifluoride **148** was submitted to phthalimide displacement. Finally, the phthalimide group of **149** was removed to obtain the α,β -difluoro- γ -amino acid **142**.



Scheme 41. Synthesis of α,β -difluoro- γ -amino acid **142**. Reagents/Conditions: (a) D-(-)-DET/t-BuOOH/Ti(Oi-Pr)₄/CH₂Cl₂/ -20 °C; (b) Et₃N/ DMAP/ TsCl/ 0 °C; (c) BF₃•OEt₂/CH₂Cl₂/ -20 °C; (d) Deoxofluor[®] (neat)/ 70 °C; (e) phthalimide/potassium phthalimide/DMF/90 °C; (f) NaIO₄/ RuCl₃/ H₂O CH₂Cl₂/CH₃CN/RT; (g) H₂NNH₂•H₂O/ EtOH/ reflux.

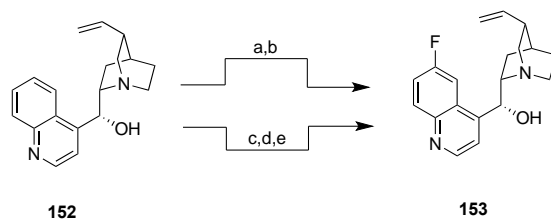
The cyclic peptide, maculosin **150** was fluorinated by Ritter's group in 2010 by utilizing F-TEDA-PF₆ in the presence of a silver catalyst, (Scheme 42).²¹ Maculosin is formed from tyrosine and proline and is a fungal and bacterial metabolite.



Scheme 42. Fluorination of maculosin **150**. Reagents/Conditions: (a) 5.0 mol% Ag₂O/2.0 equiv NaHCO₃/1.0 equiv NaOTf; (b) 1.5 equiv F-TEDA-PF₆/acetone/65 °C.

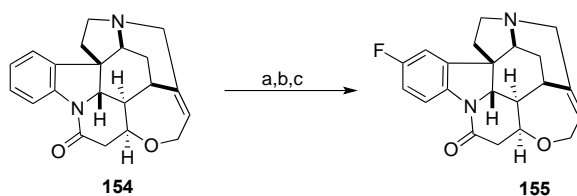
10. Alkaloids and Nitrogen Heterocycles

Alkaloids are a large class of nitrogen-containing naturally occurring compounds which arguably have the greatest range of biological activities. Naturally-occurring quinine **152**, one of the simpler alkaloids, was fluorinated by Ritter's group according to two different reports.^{21, 22} Both reactions embody the use of an electrophilic fluorinating reagent, F-TEDA-PF₆ in the presence of a silver catalyst. The overall reaction provides for the addition of a fluoride atom to the 6¹-position of the aromatic ring thereby giving analogue **153** (Scheme 43).

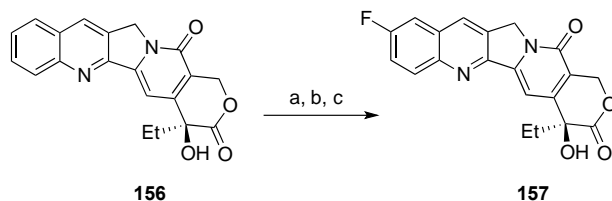


Scheme 43. Selective fluorination of quinine **152**. Reagents/Conditions: (a) 20 mol% AgOTf /2.0 equiv NaOTf; (b) 2.0 equiv F-TEDA-PF₆/acetone/90 °C; (c) Tf₂O/NEt₃; (d) LiCl/5 mol% Pd(PPh₃)₄ /(ⁿBu₃Sn)₂; (e) F-TEDA-PF₆ /AgOTf / acetone/23 °C /20 min.

Strychnine **154** was also selectively fluorinated by the Ritter group and utilized a similar protocol as that employed with quinine as described above (Scheme 44).²¹ Strychnine's structure was difficult for Ritter's group to fluorinate utilizing a silver catalyst due to the fact it doesn't contain a phenol functionality. Utilization of an in situ *N*-benzylation followed by the silver-catalyzed fluorination resulted in an ammonium salt derivative of strychnine which immediately underwent hydrogenolysis yielding 2-fluorostrychnine **155**. The fluorination of camptothecin **156**, another natural product with anticancer activity, was accomplished by utilizing Ritter's silver catalyzed fluorination approach as well and gave 10-fluorocamptothecin **157** (Scheme 45).²²

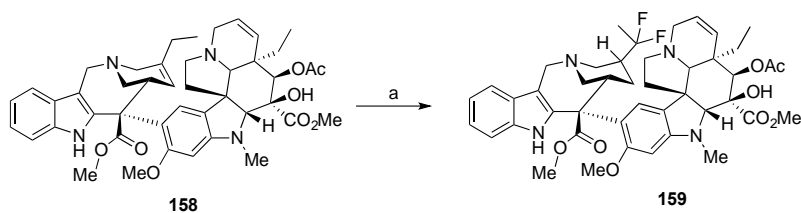


Scheme 44. Fluorination of strychnine **154**. Reagents/Conditions: (a) 1. Et₃N/ 5 mol % Pd(PPh₃)₄ /(n-Bu₃Sn)₂/dioxane/100 °C; (b) BnBr/acetone/AgOTf/Ag₂O (5 mol %)/ NaHCO₃/ NaOTf/ F-TEDA-PF₆/65 °C; (c) 1,4-cyclohexadiene/Pd/C/ MeOH/40 °C/ 60% (2 steps).



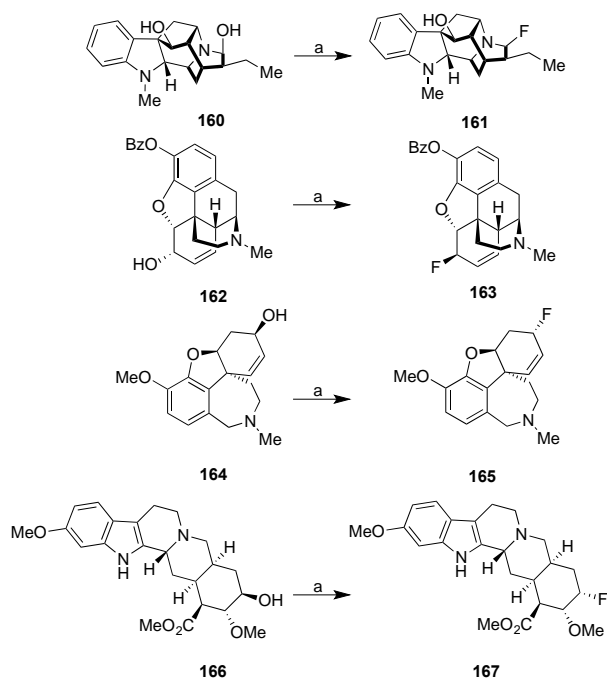
Scheme 45. Fluorination of camptothecin **156**. Reagents/Conditions: (a) Tf₂O/ NEt₃; (b) LiCl/ 5 mol% Pd(PPh₃)₄/(ⁿBu₃Sn)₂; (c) F-TEDA-PF₆/AgOTf /acetone/23 °C/20 min.

Vinca alkaloids such as vinorelbine **158** are established useful chemotherapeutic agents, and the fluorinated derivatives of such compounds have been explored to optimize the therapeutic value of these natural products. The preparation of vinoflunine **159** using HF-SbF₅ occurs through an essentially one-pot sequential superacid-mediated chlorination at the allylic C-20' followed by sequential fluorination. Advantage was taken of the ability of the intermediate chloroalkyls, in the presence of superacids to form highly electrophilic intermediates where the nucleophilic fluoride can then attack (Scheme 46).⁴⁵



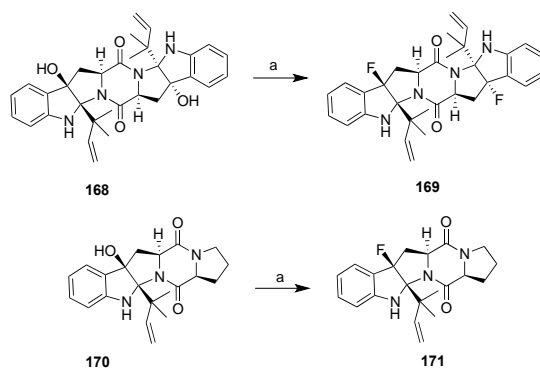
Scheme 46. Fluorination of vinorelbine **158**. Reagents/ Conditions: (a) HF-SbF₅/CCl₄/ -40 °C.

Although Ritter's group successfully fluorinated multiple complex alkaloids utilizing a silver catalyzed fluorination reaction, they also fluorinated several complex alkaloids utilizing a nucleophilic, deoxygenating fluorinating reagent, phenofluor™. Ajmaline **160**, morphine **162**, galanthamine **164**, and reserpine **166** were all complex alkaloids that were fluorinated using Phenofluor™ to provide fluorinated analogues **161**, **163**, **165** and **167** (Scheme 47).²³



Scheme 51. Fluorination of ajmaline **160**, morphine **162**, galantamine **164**, and reserpine **166**. Reagents/Conditions: (a) Phenofluor™/ 2.0 equiv EtNⁱPr₂/2.0 equiv KF/2-20 h.

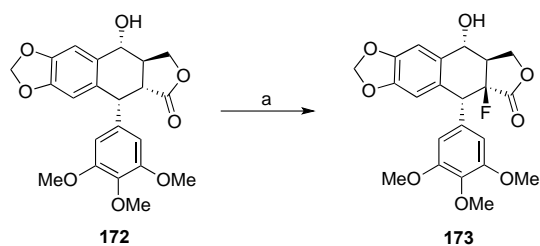
Both gypsetin **168**, an inhibitor of acyl-Co-A cholesterol transferase, and brevinamide E **170**, a cytotoxin, are two complex alkaloids which were both fluorinated. The strategy was to selectively replace the angular hydroxyl groups with angular fluorines thereby retaining stereochemistry in the fluorinated products **169** and **171**. The selective fluorinations of **168** and **170** utilized the electrophilic fluorination reagent, FP-T300 (Scheme 48).⁴⁶



Scheme 48. Fluorination of gypsetin **168** and brevianamide E **170**. Reagents/Conditions: (a) FP-T300/THF/65 °C.

11. Tannins/Lignans

Podophyllotoxin **172**, a non-alkaloid toxic lignan, is an effective topical treatment of external genital warts caused by the human papillomavirus (HPV). Podophyllotoxin was fluorinated using NFSI to form 2-fluoropodophyllotoxin **173**.²⁵ This potent antitumor agent was obtained by a completely diastereoselective fluorination of the sodium enolate formed with NFSI (Scheme 49).



Scheme 49. Fluorination of podophyllotoxin **172**. reagents/Conditions: (a) NFSI.

12. Conclusions

The synthesis and biological evaluation of fluorinated analogues and derivatives of natural products provides new in-roads in the field of medicinal chemistry and developmental therapeutics. Natural products are continuously being altered or modified in an effort to optimize their efficacy or probe their biochemical disposition. The development of new reactions and reagents have allowed for the fluorination of many sensitive substrates and have been useful on a drug discovery scale. On a manufacturing or otherwise process scale, the procedures for carbon-fluorine bond-forming reactions will still rely on older, more established technology due to costs and procedural ease. The examples of more recently employed techniques and strategy for the introduction of fluorine into natural products take into account the complexity of some of the chemical intermediates and late-stage substrates and may possibly be applied to starting materials used in the pharmaceutical industry once optimized. The selective fluorination of natural products has proven beneficial to date, and research will be continuing into the most prime 'areas' of fluorination of these complex molecules as the science advances.

References

1. Corey, J. E.; Czakó, B.; Kürti, L. *Molecules and Medicine*; Wiley: New Jersey, 2007.
2. Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006.
3. Kirsch, P.; *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd ed.; Wiley-VCH: Weinheim, 2013.
4. Isanbor, C.; O'Hagan, D.; *J. Fluorine Chem.* **2006**, *127*, 303–319.
<https://doi.org/10.1016/j.jfluchem.2006.01.011>
5. Bégué, J-P.; Bonnet-Delpon, D.; *J. Fluorine Chem.* **2006**, *127*, 992–1012.
<https://doi.org/10.1016/j.jfluchem.2006.05.006>
6. O'Hagan, D.; Harper, D.B.; *J. Fluorine Chem.* **1999**, *100*, 127–133.
[https://doi.org/10.1016/S0022-1139\(99\)00201-8](https://doi.org/10.1016/S0022-1139(99)00201-8)
7. Champagne, P. A.; Desroches, J.; Hamel, J.; Vandamme, M.; Paquin, J. *Chem. Rev.* **2015**, *115*, 9073–9174.
<https://doi.org/10.1021/cr500706a>
8. Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574–578.
<https://doi.org/10.1021/jo00893a007>
9. Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonc, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048–7054.
<https://doi.org/10.1021/jo990566>
10. Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* **2010**, *132*, 18199–18205.
<https://doi.org/10.1021/ja106343h>
11. Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482–11484.
<https://doi.org/10.1021/ja2048072>
12. Barton, D. H. R.; Ganguly, A. K.; Hesse, R. H.; Loo, S. N.; Pechet, M. M. *Chem. Commun.* **1968**, 806–808.
<https://doi.org/10.1039/C19680000806>
13. Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–264.
<https://doi.org/10.1002/anie.201206566>
14. Umemoto, T.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 3271–3274.
[https://doi.org/10.1016/S0040-4039\(00\)84772-3](https://doi.org/10.1016/S0040-4039(00)84772-3)
15. Differding, E.; Ofner, H.; *Synlett.* **1991**, 187–189.
<https://doi.org/10.1055/s-1991-20673>
16. Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Commun.* **1992**, 595–596.
<https://doi.org/10.1039/C39920000595>
17. Jin, Z.; Xu, B.; Dimagno, S. G.; Hammond, G. B. *J. Fluorine Chem.* **2012**, *143*, 226–230.
<https://doi.org/10.1016/j.jfluchem.2012.05.010>
18. Halperin, S. D.; Fan, H.; Chang, S.; Martin, R. E.; Britton, R. *Angew. Chem. Int. Ed.* **2014**, *53*, 4690–4693.
<https://doi.org/10.1002/anie.201400420>
19. Keyser, G.E. U.S. Patent 5 510 544, 1993.
20. Abad, A.; Consuelo, A.; Cuñat, A. C.; González-Coloma, A.; Pardo, D. *Eur. J. Org. Chem.* **2010**, 2182–2198.
<https://doi.org/10.1002/ejoc.200901499>
21. Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150–12154.
<https://doi.org/10.1021/ja105834t>
22. Furuya, T.; Storm, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662–1663.
<https://doi.org/10.1021/ja8086664>

23. Sladojevich, F.; Arlow, S. I.; Tang, P.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 2470–2473.
<https://doi.org/10.1021/ja3125405>
24. Liu, W.; Xiongyi, H.; Cheng, M.; Nielsen, R. J.; Goddard III, W. A.; Groves, J. T. *Science*. **2012**, *337*, 1322–1325.
<https://doi.org/10.1126/science.1224953>
25. Ma, J.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119–6146.
<https://doi.org/10.1021/cr030143e>
26. Mansurova, M.; Klusák, V.; Nešňerová, P.; Muck, A.; Doubský, J.; Svatoš, A. *Tetrahedron*. **2009**, *65*, 1069–1076.
<https://doi.org/10.1016/j.tet.2008.10.106>
27. Ambrosi, P.; Arnone, A.; Bravo, P.; Bruché, L.; Cristofaro, A. D.; Francardi, V.; Frigerio, M.; Gatti, E.; Germinara, G. S.; Panzeri, W.; Pennacchio, F.; Pesenti, C.; Rotundo, G.; Roversi, P. F.; Salvadori, C.; Viani, F.; Zanda, M. *J. Org. Chem.* **2001**, *66*, 8336–8343.
<https://doi.org/10.1021/jo0055640>
28. Chiang, C.; Ramu, R.; Tu, Y.; Yang, C.; Ng, K.Y.; Luo, W.; Lu, y.; Liu, C.; Yu, S. S. *Chem. Eur. J.* **2013**, *19*, 13680–13691.
<https://doi.org/10.1002/chem.201302402>
29. Monsen, P. J.; Luzzio, F A. unpublished results.
30. Jasem, Y. A.; Thiemann, T.; Gano, L.; Oliveira, M.C. *J. Fluorine Chem.* **2016**, *185*, 48–85.
<https://doi.org/10.1016/j.jfluchem.2016.03.009>
31. Bogautdinov, R. P.; Fidarov, A. F.; Morozkina, S. N.; Zolotarev, A. A.; Starova, G. L.; Selivanov, A. I.; Shavva, A. G. *J. Fluorine Chem.* **2014**, *168*, 218–222.
<https://doi.org/10.1016/j.jfluchem.2014.09.030>
32. Heravi, M. R. P. *J. Fluorine Chem.* **2008**, *129*, 217–221.
<https://doi.org/10.1016/j.jfluchem.2007.11.006>
33. Kwiatkowski, P.; Beeson, T. D.; Conrad J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 1738–1741.
<https://doi.org/10.1021/ja111163u>
34. Königsberger, K.; Chen, G.; Viveló, J.; Lee, G.; Fitt, J.; McKenna, J.; Jenson, T.; Prasad, K.; Repic, O. *Org. Process Res. Dev.* **2002**, *6*, 665–669.
<https://doi.org/10.1021/op0255433>
35. Roberto, P. Eur. Pat. Appl. 393 493 1995
36. Meinke, P. T.; Shoop, W. L.; Michael, B. F.; Blizzard, T. A.; Dawson, G. R.; Fisher, M. H.; Mrozik, H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3643–3646.
<https://doi.org/10.1021/jo962394b>
37. Mtashobya, L.; Quiquempoix, L.; Linclau, B. *J. Fluorine Chem.* **2015**, *171*, 92–96.
<https://doi.org/10.1016/j.jfluchem.2014.08.023>
38. Corr, M. J.; O'Hagan, D. *J. Fluorine Chem.* **2013**, *155*, 72–77.
<https://doi.org/10.1016/j.jfluchem.2013.06.003>
39. Ghosh, A. K.; Lagisetty, P.; Zajc, B. *J. Org. Chem.* **2007**, *72*, 8222–8226.
<https://doi.org/10.1021/jo0711211>
40. Ge, P.; Kirk, K. L. *J. Org. Chem.* **1997**, *62*, 3340–3343.
<https://doi.org/10.1021/jo962394b>
41. Vints, I.; Rozen, S. *J. Org. Chem.* **2014**, *79*, 7261–7265.

<https://doi.org/10.1021/jo5009542>

42. Shainyan, B.A.; Danilevich, Y.S.; Grigor'eva, A.A.; Chuvashov, Y.A. *Russian Journal of Organic Chemistry*. **2003**, 39, 11, 1581-1586.
<https://doi.org/10.1023/B:RUJO.0000013131.19936.5e>
43. Callejo, R.; Corr, M. J.; Yang, M.; Wang, M.; Cordes, D. B.; Slawin, A. M. Z.; O'Hagan, D. *Chem. Eur. J.* **2016**, 22, 8137-8151.
44. Patel, A. R.; Hu, X.-G.; Lawer, A.; Ahmed, M. I.; Au, C.; Jwad, R.; Trinh, J.; Gonzalez, C.; Hannah, E.; Bhadbhade, M. M.; Hunter, L. *Tetrahedron*. **2016**, 72, 3305–3317.
<https://doi.org/10.1016/j.tet.2016.04.070>
45. Kirk, K.L. *Org. Process Res. Dev.* **2008**, 12, 305-321.
<https://doi.org/10.1021/op700134j>
46. Shibata, N.; Tarui, T.; Doi, Y.; Kirk, K.L. *Angew. Chem. Int. Ed.* **2001**, 40, 4461-4463.
[https://doi.org/10.1002/1521-3757\(20011203\)113:23<4593::AID-ANGE4593>3.0.CO;2-8](https://doi.org/10.1002/1521-3757(20011203)113:23<4593::AID-ANGE4593>3.0.CO;2-8)

Authors Biographies



Paige Monsen was born in 1993 in Cortland, New York. She received her Bachelor's degree in chemistry from the University of Louisville in 2015. She entered the Ph.D. graduate program at the University of Louisville the following semester, joining the group of Dr. Frederick Luzzio where she is currently working as a Ph.D. student. Her research interests are focused on the natural compound annonacin which is isolated from the pawpaw, a fruit native to the area.



Frederick Luzzio was born in Lawrence, Massachusetts and raised near Ft. Knox, Kentucky. He graduated from Vanderbilt University (BS, 1976) where he majored in chemistry and biology. He worked as a development chemist at Arthur D. Little, Inc. in Cambridge, Massachusetts until entering Tufts University where he earned his MSc and PhD degrees in organic chemistry under the mentorship of Frank S. Guziec, Jr. After finishing graduate study, he spent three years of study with Professor E. J. Corey as a post-doctoral fellow, followed by two years in the Biomedical Products Department of DuPont. Since 1988 he has served on the faculty of the University of Louisville where he is currently Professor. His research interests are in the areas of organic synthesis, natural products and medicinal chemistry.