The Propargylic Route as a Short and Versatile Entry to Optically Active Monofluorinated Compounds

MICHAËL PRAKESCH, DANIELLE GRÉE, AND RENÉ GRÉE*

ENSCR, Laboratoire de Synthèses et Activations de Biomolécules, CNRS UMR 6052, Avenue du Général Leclerc, 35700 Rennes, France

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ABSTRACT

Using selected models and appropriate NMR techniques, it has been demonstrated that dehydroxyfluorination in the propargylic position can be highly regio- and stereoselective. The corresponding propargylic fluorides are very useful intermediates for short preparations of stereodefined unsaturated or polyunsaturated compounds with a single fluorine atom in allylic or propargylic position. This strategy offers good means for the synthesis of chiral, nonracemic monofluorinated analogues of natural products.

Introduction

The introduction of fluorine atom(s) into organic molecules induces major changes in their physical, chemical, and biological properties.[1] It has led already to useful compounds in areas as diverse as new solvents, materials, polymers, agrochemicals, or pharmaceuticals, for instance. In the latter case, powerful drugs and useful pharmacological tools have been reported.[2]

Important information regarding the structure and mechanism of action of enzymatic systems can be obtained by the exchange of strategic C−H bonds with C−F bonds (Figure 1). This replacement occurs with a minimum of steric modification (C−F is only about 20% larger than C−H),[3]but with a strong electronic perturbation due to the high electronegativity of fluorine; furthermore, the C−F bond energy is also larger than that of C−H. Very useful data can be obtained, as well, by replacement of C−OH bonds with C−F. The bond lengths and polarities are very similar.[3] However, although the alcohol is both a hydrogen bond donor (via the H) and acceptor (via the oxygen lone pairs), the fluorine is, at best, only a weak hydrogen bond acceptor.[4]

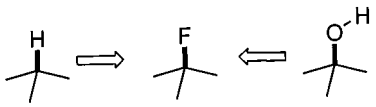

FIGURE 1.

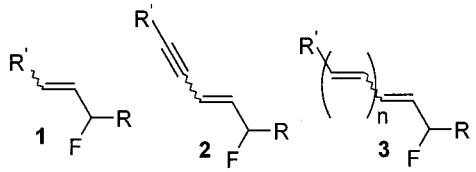

FIGURE 2.

The introduction of fluorine atom(s) is often a key step in the preparation of such molecules; hence, the major advances reported in the discovery and use of fluorinating agents are important aspects for fluoro-organic chemistry. Control of the regio-, stereo-, and enantioselectivity of fluorination still remains a challenging problem in various cases.[5] For example, selective monofluorination in a position vicinal to π systems leads to regioisomers as a result of the delocalized nature of reactive intermediates. Allylic fluorides **1**,[6] as well as the polyunsaturated derivatives **2** or **3**, are representative examples (Figure 2).[7] Very few optically active molecules of this type have been described to date in the literature. However, such compounds would be very attractive intermediates in synthesis, especially for the preparation of fluorinated analogues of several families of natural products (pheromones, terpenes, and various lipids, such as unsaturated fatty acids and corresponding metabolites, for instance). They could also be of much interest in the material sciences, for instance, in the field of liquid crystals.[8] Three elegant methods have been reported to date for the preparation of chiral, nonracemic, allylic fluorides but they have limitations in terms of the scope of the reactions. The asymmetric photodeconjugation process could be applied to a fluoroolefin, giving the allylic fluoride in good yield (84%) but with a lower enantioselectivity (e.e = 40%).[9] Claisen rearrangement was successfully applied in the synthesis of 3′-fluoroapionucleosides. Taking into account the reaction conditions, this method appears to be limited to the preparation of chiral quaternary allylic fluorides.[10] A very interesting approach involves intermediates chiral, nonracemic α-fluoro carbonyl derivatives; it has been successfully applied to the synthesis of 2-deoxy-2-fluoropentoses; However, the very high sensitivity of the latter intermediates to base-catalyzed epimerization will prob-

Michaël Prakesch, born in Saverne (1974), graduated from the Ecole Nationale Supérieure de Chimie et de Physique de Bordeaux (ENSCPB) in 1997. He obtained a Diplôme d'Etudes Approfondies in organic chemistry at the University of Strasbourg with Drs. L. Lebeau and C. Mioskowski (1998). He is currently preparing his Ph.D. thesis at the University of Rennes.

Danielle Grée, born in Fougères (1947) graduated from the Ecole NationaleSupérieure de Chimie de Rennes (ENSCR) in 1969. After working in the group of Professor R. Carrié at the University of Rennes, she joined the ENSCR where she holds a CNRS position as Ingénieur de Recherche. Her main current research interest is fluorine chemistry and the use of transition metal complexes in organic synthesis.

René Grée, born in Rennes (1948), graduated from ENSCR in 1970. After a Ph.D. thesis with Pr. R. Carrié (1975) and a post-doctoral fellowship in the U.S. (Pr. L. A. Paquette), he returned first to the University of Rennes and then to ENSCR. He holds a position as Directeur de Recherche CNRS and, since 1990, he has also held a part-time professor position at the Ecole Polytechnique (Paris). The major research interests of his group are organometallic chemistry directed toward organic synthesis, fluorine chemistry, chemistry on soluble supports, ionic liquids, and total synthesis of bioactive natural products and structural analogues.

* To whom correspondence should be addressed. Phone: 33 (0) 2 23 23 80 70. Fax: 33 (0) 2 23 23 81 08. E-mail: rene.gree@ensc-rennes.fr.

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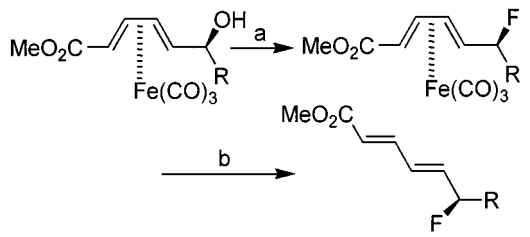
Scheme 1[a]



[a] (a) DAST, CH_2Cl_2, −50 °C, R = Me (86%), R = $-CH_2-C\equiv CH$ (79%), R = $-CH_2-CH=CH_2$ (76%). (b) Me_3NO, CH_2Cl_2, Δ (45%).

ably limit their use in the synthesis of optically active allylic fluorides.[11] Therefore, more general and versatile routes toward type **1**−**3** fluorinated compounds are clearly needed before applying them to the preparation of natural product analogues.

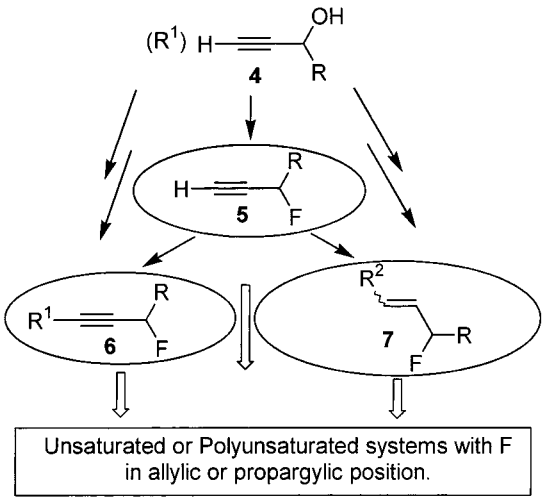
A first strategy toward the regio- and stereocontrol of monofluorination was to take advantage of temporary complexation of the π system by appropriate transition metal complexes. We have demonstrated for the first time that fluorination with diethylaminosulfur trifluoride (DAST) of alcohols vicinal to diene tricarbonyl iron complexes indeed yielded the desired fluorides with good to complete regio- and stereoselectivity (Scheme 1).[12] This new methodology was extended later to rhenium[13] (for allylic systems) and chromium[14] complexes (for benzylic fluorides). This strategy was efficient, especially in terms of stereocontrol, allowing the introduction of a single fluorine atom in the desired position and with the required absolute configuration. However, this approach needed access to starting materials in optically pure form, a process that could be difficult, time-consuming, and expensive for some of these organometallic complexes. Therefore, we envisaged a complementary strategy using small chiral key fluorinated intermediates. On the basis of the versatility of the C−C triple bond in organic synthesis, especially in transition metal mediated coupling reactions,[15] we selected the propargylic fluorides, such as **5** and **6**, as our key intermediates. Directly related structures were derivatives **7** either as vinylmetals or as functionalized systems that are to be used for the next C−C bond connections. Dehydroxyfluorination with DAST or related reagents, such as Deoxo-Fluor, was selected for our purpose, since it is usually a rapid and efficient process, even at very low temperature. The optically active propargylic alcohols **4** are easily accessible either by resolution[16] or by asymmetric synthesis.[17] Therefore, they appeared to be logical starting materials in this strategy (Scheme 2).

Consequently, the main questions to be studied were the following:

(I) What are the factors governing the regio- and stereoselectivity in fluorination of propargylic alcohols (such as **4** → **5** or **4** → **6**)?

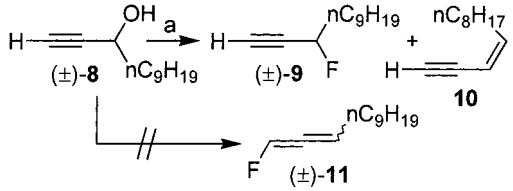
(II) Will it be possible to functionalize propargylic fluorides, such as **5**, for instance, by using hydrometalation reactions? What will be the regio- and stereoselectivity of such processes?

Scheme 2[a]



[a] R = alkyl group; R^1 = alkyl or functional group; and R^2 = functional group or Bu_3Sn, I, etc.

Scheme 3[a]



[a] (a) DAST, CH_2Cl_2, RT, (±)-**9** (51%), and **10** (11%).

(III) Will the propargylic or allylic fluorides be compatible with the various reaction conditions involved in the multistep synthesis of fluorinated target molecules?

Stereoselective Synthesis of Propargylic Fluorides. Very limited data have been reported on the regio- and stereoselectivity of nucleophilic monofluorination in propargylic systems,[18] including optically active derivatives.[19] Therefore, we designed three simple and representative models for such studies.

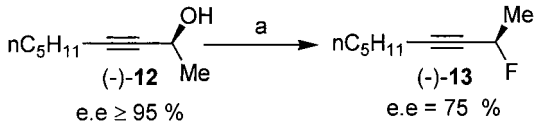
Alcohol (±)-**8** reacted with DAST[20] to yield propargylic fluoride (±)-**9** with a small amount of enyne **10** separated by chromatography (Scheme 3). It is important to note that no allene (±)-**11** was obtained in this reaction.[21] The same regiocontrol has been observed with all of the propargylic alcohols studied. From the literature and from our own experience, it appears that formation of fluoroallenes by SN_2' processes is rare and limited to very peculiar systems: in particular, reactions of derivatives with two perfluoro alkyl chains on the carbinol center have been reported.[22] It is possible to speculate that this exclusive SN_2 pathway could be related to the fact that F^- is a very hard nucleophile, contrary to most nucleophilic reagents (like cuprates) used to prepare allenes by such a route. A thermodynamic control could be another possibility, if we admit that fluoroallenes are less stable than the respective propargylic fluorides.[23] Therefore, the explanation of this intriguing result needs further experimental and computational studies.

The enantioselectivity studies in the reaction shown in Scheme 3 were very difficult, since low-molecular-weight

Scheme 4[a]

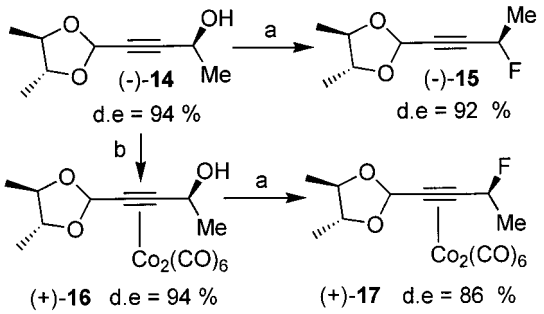
[a] (a) DAST, CH_2Cl_2, −50 °C (51%).

Scheme 5[a]



[a] (a) DAST, CH_2Cl_2, −95 °C (55%).

Scheme 6[a]



[a] (a) DAST, CH_2Cl_2, −50 °C, (−)-**15** (87%), and (+)-**17** (80%); (b) $Co_2(CO)_8$, THF, RT (88%).

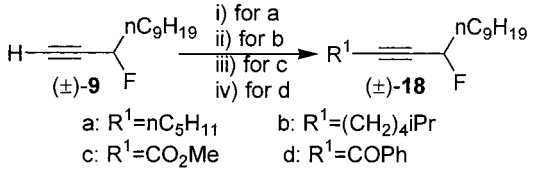
and nonfunctionalized propargylic fluorides, such as **9**, are highly volatile, nonpolar compounds. Therefore, we failed in using the standard techniques (HPLC, GC) to measure the e.e in type **9** compounds.[24] Only the recently developed method, NMR in chiral liquid crystals,[25] allowed us to discriminate the two enantiomers of (±)-**9**. Using this novel technique and starting from (+)-**8** we could establish that the reaction is highly enantioselective, but only at low temperature (−50 °C) (Scheme 4).[26] A slight loss of selectivity was observed at higher temperatures (e.e = 60% at room temperature). From the literature data, inversion of configuration was assumed in this reaction using DAST.[27,28]

The second model compound, (−)-**12**, was easily accessible in optically pure form from (*S*)-butynol. Using the same NMR analysis, a strong temperature dependence was observed for the enantioselectivity of fluorination, with the highest e.e obtained at −95 °C (Scheme 5).[26]

Further, with the pentyl group in terminal position, the selectivity is high but not complete. Such an electron-donating group in this terminal position should probably better stabilize a carbenium ion intermediate; therefore, competition with an SN_1 process could probably explain this result.

A third model, (−)-**14**, as prepared in optically active form from (*S*)-butynol and (2*R*, 3*R*)-butane diol yielded fluoride (−)-**15**, again with complete regiocontrol and a very high stereoselectivity at low temperature (Scheme 6).[29] The reaction of the corresponding cobalt−carbonyl complex (+)-**16** was particularly interesting. It occurred in excellent yield with a very good selectivity at low temperature but with overall retention of configuration giving (+)-**17**. This is in agreement with the usual nucleophilic additions on carbenium ions stabilized by cobalt carbonyl complexes,[30] but this appears to be the first extension to fluorination of the well-known Nicholas reaction.[30a] The decomplexation of (+)-**17** led to (+)-**15**, allowing the preparation of both of the enantiomers of propargylic fluorides **17** from the same chiral alcohol, (−)-**14**.

Scheme 7[a]



[a] (i) *n*-BuLi, THF-HMPA (3:1), −78 °C → −40 °C, then *n*-$C_5H_{11}Br$, −60 °C → −30 °C, (±)-**18a** (76%); (ii) *n*-BuLi, THF-HMPA (3:1), −50 °C, then 5-methyl-1-bromohexane, (±)-**18b** (74%); (iii) *n*-BuLi, THF, −78 °C, then $ClCO_2Me$, then RT, (±)-**18c** (66%); (iv) $Pd(PPh_3)_4$, CuI, PhCOCl, Et_3N, RT, (±)-**18d** (41%).

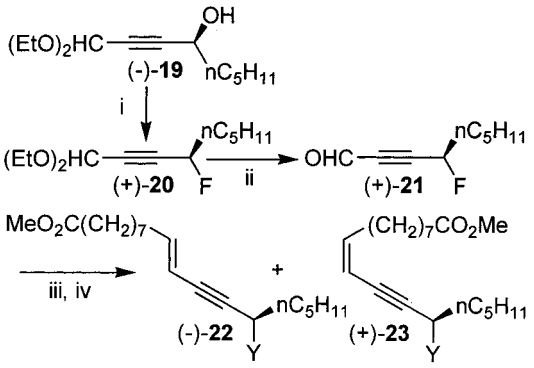
Thus, for such secondary alcohols, the stereoselectivity of fluorination is clearly dependent upon the nature of substituents on the triple bond. Furthermore, it can be modified by the use of cobalt−carbonyl complexes.

With type **5** derivatives being easily accessible, both in racemic and optically active form, the introduction of alkyl groups or various functionalities became an important issue. Propargylic fluoride (±)-**9** was selected as a representative example (Scheme 7).

In fact, alkylations, alkoxycarbonylation or Sonogashira-type reactions could be performed under classical conditions to yield compounds **18a**−**d** in fair to good yields.[21] These propargylic fluorides were stable under the reaction conditions employed. This was particularly useful in the case of alkyl-substituted derivatives (such as **18a** or **18b**), since we had established earlier that the dehydroxyfluorination was not completely stereoselective for such derivatives. On the contrary, the two-step sequence (**4** → **5** → **6**) will allow their preparation with a very high enantiocontrol.

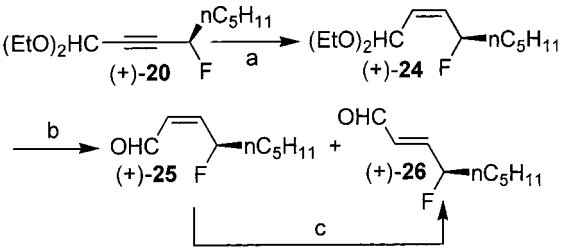
Synthetic Applications of Propargylic Fluorides. Derivatives with propargylic systems are found in various families of natural products. For instance, cytotoxic polyacetylenic alcohols are common in marine species.[31] Thus, having developed new and short routes to various type of propargylic fluorides, the preparation of fluorinated analogues of naturally occurring propargylic alcohols was considered. Polyunsaturated fatty acid metabolites **22b** and **23b** were selected as representative examples, since they have interesting biological activities as rice blast fungus inhibitors.[32] On the basis of our previous results, fluorination of acetal (−)-**19** yielded, after deprotection, key aldehyde (+)-**21** in 96% e.e. A Wittig reaction led to the desired fluorinated analogues as a mixture of (*E*)-(−)-**22a** and (*Z*)-(+)-**23a** derivatives separated by chromatography (Scheme 8).[33] Comparison of biological properties should help to elucidate the role of the hydroxyl group as hydrogen bond donor in such derivatives.

Scheme 8[a]



[a] (a) Y = F; (b) Y = OH; (i) DAST, CH_2Cl_2, −78 °C (85%); (ii) HCOOH, CH_2Cl_2, RT, (92%); (iii) Br-$^+Ph_3P(CH_2)_8COOMe$, LiHMDS, HMPA, THF, −20 °C to −45 °C; (iv) (+)-**21**, −70 °C to −10 °C ((+)-**23**: 37% and (−)-**22**: 15%).

Scheme 9[a]



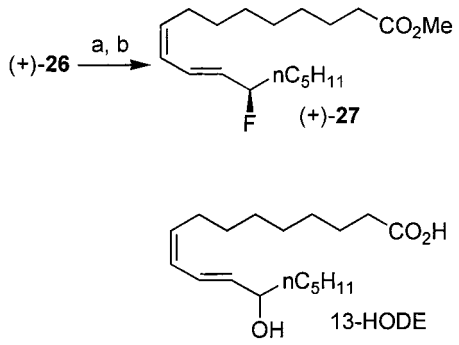
[a] (a) Pyridine, Lindlar catalyst, H_2, *n*-pentane, RT (99%); (b) HCOOH, CH_2Cl_2, RT, (+)-**25** (87%) and (+)-**26** (8%); (c) DMSO, 80 °C (84%).

These propargylic fluorides appeared also to be attractive starting materials for systems having a single fluorine in the allylic position. For this purpose, two main strategies have been developed, depending on whether the lateral chain has to be introduced at the propargylic stage (i.e., synthesis starting from type **6** derivatives) or later (approaches starting from **5**). These two approaches will be discussed in the next two parts of this Account.

Synthesis of Allylic Fluorides Starting from Disubstituted Propargylic Derivatives. Allylic alcohols are also very common in natural products. Therefore, short, selective routes to allylic fluorides appear to be of much interest. The most straightforward transformation of propargylic fluorides into allylic systems is semi-hydrogenation. Lindlar's catalyst proved to be compatible with a single fluorine in propargylic position.[18b,34] Starting from (+)-**20**, it quantitatively yielded (+)-**24** and, after deprotection, a 9:1 mixture of (*Z*)-(+)-**25** and (*E*)-(+)-**26** enals was obtained. They were separated by chromatography and isolated in a 96% e.e (Scheme 9).

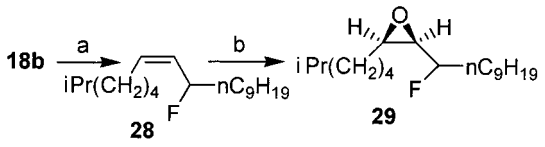
Aldehyde (+)-**26** is the monofluorinated analogue of 4-hydroxynonenal,[35] a well-known fatty acid metabolite with potent biological properties;[36] it is the first enantioselective synthesis of this fluorinated lipid analogue. Its enantiomer has been prepared similarly from (−)-**20**.[33] Both enals appear also as versatile building blocks in synthesis. For instance, (+)-**26** has also been used for the first enantioselective synthesis of (+)-**27**,[33] which is (as the methyl ester) the fluorinated analogue of 13-hydroxyoctadecadienoic acid (13-HODE, also called coriolic acid)

Scheme 10[a]



[a] (a) Br-$^+Ph_3P(CH_2)_8COOMe$, LiHMDS, HMPA, THF, −20 °C to −45 °C; (b) (+)-**26**, −70 °C to −10 °C (+)-**27** (70%).

Scheme 11[a]

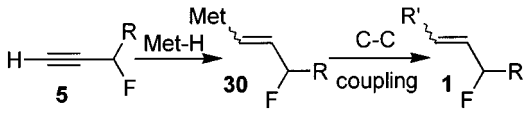


[a] (a) pyridine, Lindlar catalyst, H_2, *n*-pentane, RT (95%); (b) *m*-CPBA, CH_2Cl_2, 40 °C, (73%).

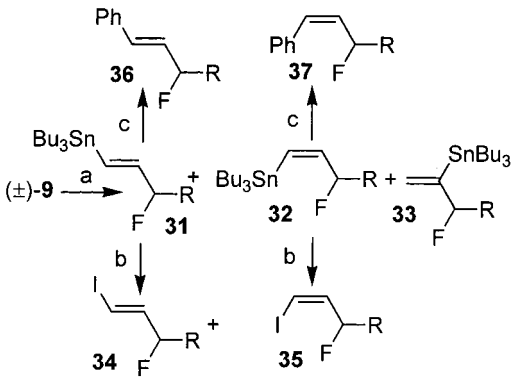
(Scheme 10). The latter is a metabolite of linoleic acid involved in various human diseases.[37] Saponification of (+)-**27**, under carefully controlled conditions, led to the *R*-fluoro analogue of 13-HODE. The *S* enantiomer was prepared similarly, starting from (−)-**20**. Preliminary biological studies on these fluoro analogues yielded very interesting results: both enantiomers have higher antiaggregant properties (2−4 times) than the natural products, with the *S* enantiomer being slightly more active than the *R* fluoride.[38] This is a good indication that hydrogen bonding from the alcohol function does not play a major role in the antiaggregant properties of the natural 13-HODE. A similar conclusion could be drawn from the action of these monofluorinated derivatives on the nuclear receptor PPARα:[37e,39] the fluoro analogues are very potent activators of this important receptor.[40] Furthemore, in that case, a relatively unusual observation was made, since the racemic compound has higher affinity for the receptor than either of the isolated enantiomers.[40] Although preliminary, these data indicate that the exchange of OH for F can afford useful structure−activity relationships for such unsaturated fatty acid metabolites. It can be expected that similar approaches can be used for other families of natural products.

Finally, it is also clear that the *Z* double bond obtained during the hydrogenation of propargylic fluorides can be of further synthetic use. The *Z* alkene **28** obtained by reduction of **18b** is a representative example. The epoxidation of **28** yielded a 1:1 mixture of the syn and anti isomers of **29** easily separated by chromatography (Scheme 11).[41] Those derivatives are the 9-fluoro analogues of disparlure, a well-known pheromone.[42] It is interesting to note that the 9,9-difluoro analogue has not only potent pheromone-like activity, but it is also an inhibitor of epoxide hydrolase.[34] Therefore, it will be interesting to

Scheme 12



Scheme 13[a]



[a] R = *n*-C_9H_{19}; (a) Bu_3SnH, AIBN, 90 °C, **31** (39%), **32** (30%), **33** (8%); (b) I_2, $CHCl_3$, RT, **34** (69%), **35** (62%); (c) $Pd(PPh_3)_4$, CuI, PhI, DMF, RT, **36** (14%), **37** (9%).

study the effect of a single fluorine atom on the biological activity for both the syn and anti isomers.

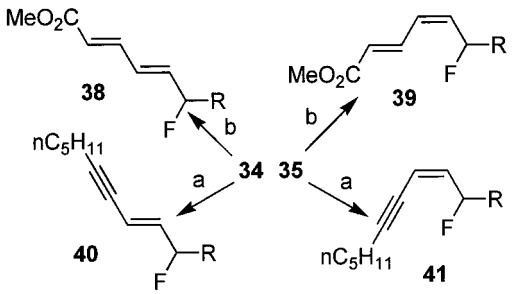
Although much work remains to be done in this area, it is clear that these very easily accessible type **6** propargylic fluorides will offer flexible entries toward a large variety of chiral monofluorinated compounds.

Synthesis of Allylic Fluorides Starting from Monosubstituted Propargylic Fluorides. Any preparation of chiral allylic fluorides starting directly from compounds **5** must involve both the introduction of a lateral chain and the transformation of the triple bond into a double bond. An attractive strategy for that purpose appeared to be a sequence of hydrometalation followed by transition metal catalyzed C−C coupling reactions (Scheme 12). Therefore, the main questions were the regio- and stereoselectivity of hydrometalation as well as the compatibility of C−F bond in both steps.

Hydrostannylation affords a first solution. Starting from (±)-**9**, selected as a simple model, a 5:4:1 mixture of vinylic tin derivatives **31**, **32**, and **33** was obtained. After separation by chromatography, reactions of **31** and **32** with I_2 yielded stereospecifically the interesting new vinylic iodides **34** and **35** (Scheme 13).[21] The tin derivatives could be used in Stille coupling reactions. Those were stereospecific, even if only modest yields of **36** and **37** were obtained in that case. Better results were obtained starting from vinylic iodides **34** and **35**, which could be used both in Heck and Sonogashira type reactions. They led to desired dienes **38** and **39** and enynes **40** and **41** in good yields and in a stereospecific manner (Scheme 14).

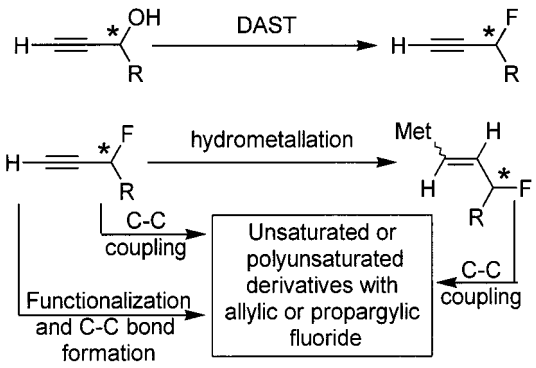
Although preliminary, these results already demonstrate that such a strategy starting directly from **5** type compounds could afford another short and versatile route to polyunsaturated systems with a single fluorine atom in allylic position. Further research remains to be done in order to improve the selectivity of the hydrostannylation step, to study the extension to other metals, and to look at possible carbometalation processes.

Scheme 14[a]



[a] R = *n*-C_9H_{19}; (a) $Pd(PPh_3)_4$, CuI, heptyne, NEt_3, RT, **40** (53%), **41** (48%); (b) $Pd(OAc)_2$, methyl acrylate, K_2CO_3, NBu_4Br, DMF, RT, **38** (65%), **39** (60%).

Scheme 15



Conclusion

This research, based on simple models, contributed to delineate the factors governing the stereoselectivity of dehydroxyfluorination in propargylic systems. It has been demonstrated that chiral secondary fluorides are not only easily accessible but also are very useful starting materials in synthesis. Using this new strategy, the fluorinated target molecules can be obtained in very few steps from easily available propargylic alcohols (Scheme 15). Although the selectivity of the hydrometalation remains to be improved, it should be noted that both the dehydroxyfluorination and the C−C coupling reactions are highly stereoselective. Furthermore, these fluorinated derivatives could be useful intermediates,[43] for instance, for labeled compounds (with D or T).

Future studies will follow several directions:

- The efficiency of the preparation of propargylic fluorides and corresponding allylic derivatives has to be improved in several cases. Extension of their synthetic use will have to answer the key issue of the compatibility of the C−F bond with various chemical reagents.
- The synthesis of chiral nonracemic monofluorinated analogues of biomolecules will continue. It will contribute to a better understanding of the structure−activity relationships in such derivatives. This novel approach to chiral monofluorinated compounds will probably also be of interest in the material sciences.

• Finally, compounds of this sort will also contribute to a better understanding of the effect of the C−F bond on the reactivity of neighboring π-systems. For that purpose, a combination of experimental and high-level computational studies are necessary. A first representative example has been reported recently in the case of Diels Alder reactions.[44]

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