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**Synthesis of a New Family of
Chiral Fluorinated Synthons:**

(R)- and (S)-4-Fluoro-1-Alkynes

by

Reese A. Adeney, B.Sc.

A thesis
submitted to the Faculty of Graduate Studies
in partial fulfillment of the requirements
for the degree of
Master of Science

Department of Chemistry

Carleton University
Ottawa, Ontario

Nov 1991

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"Synthesis of a New Family of
Chiral Fluorinated Synthons:
(R)- and (S)-4-Fluoro-1-Alkynes"

submitted by Reese A. Adeney, B.Sc.,
in partial fulfillment of the requirements for the degree of
Master of Science

Dr. Peter H. Buist
Thesis Supervisor

Dr. R. Shigeishi
Chairman, Department of Chemistry
Carleton University

Abstract

Both enantiomers of 4-fluoro-1-decyne were prepared in 32% overall yield from their corresponding optically active alcohols which were in turn prepared from their chromatographically separable (S)-O-methyl mandelate esters. The enantiomeric excess of the title compounds was found to be 90% by NMR and GC analysis of the corresponding 3-fluorononan-1-ol-(R)-MTPA esters. These fluoro-alcohols were obtained by oxidative cleavage of 4-fluoro-1-decyne, followed by LiAlH_4 reduction.

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1.0. Introduction

1.1. General

The synthesis and use of fluorinated organic molecules is currently an area of intense research¹. The current level of interest in the preparation of selectively fluorinated compounds is indicated by the increasing number of publications in this area. Important fluorine-containing compounds include perfluorinated materials² such as (1), fluorine-18 labeled biological intermediates³ such as fluorodopa (2), analogues in which fluorine substitution does not confer an additional chiral centre such as Mosher's acid⁴ (3) and new materials in which fluorine substitution results in an additional chiral centre⁵ (4).

Poly (perfluoropropylene oxide)

(1)

[¹⁸F] 6-fluorodopa

(2)

Mosher's acid

(3)

β-fluorinated aromatic amino acid derivative

(4)

It has been known for some time that fluorine can have profound and unexpected results on biological activity⁶. Fluorine is not a sterically demanding substituent, as its small van der Waals radius (1.35Å) closely resembles that of hydrogen (1.20Å)⁷. In biological systems where a specific substrate conformation is often required for recognition, minimal steric disturbance by a substituent is especially significant⁸. Fluorine can act also as a suitable replacement for hydroxyl and alkoxy groups in some systems, in that fluorine can function as a hydrogen bond acceptor⁹. In studies of the transport of galactose (5) in the intestine, it was determined that 6-fluoro-6-deoxygalactose (6) undergoes active transport while 6-deoxygalactose does not. By systematic substitution of hydrogen and fluorine for hydroxyl, it was, thus, possible to identify which positions of galactose interact with the protein as hydrogen bond donors and acceptors¹⁰.

Replacement of carbon-hydrogen bonds for carbon-fluorine bonds, generally renders a position resistant to electrophilic attack¹¹. This is due to the high electronegativity of fluorine (4) versus that of hydrogen (2.1). This in turn alters the electron distribution in a molecule, and places a large δ^+ on the carbons in the vicinity of the C-F bond. Enhancement of biological activity for the steroid family has been achieved with

fluorinated derivatives (7). Biologically active steroids have improved selectivity

9 α -fluoro-11 β -hydroxyprogesterone

(7)

along with a reduction of undesired properties and side effects. With these improvements, a number of fluorinated steroids are marketed today ¹².

The electron-withdrawing properties of fluorine is manifested in the metabolism of ω -fluorinated fatty acids. Through successive β -oxidations *in vivo*, fluorinated metabolites of the original compound are produced, down to fluoroacetic acid (8)¹³ (See Scheme 1).

Scheme 1

Citrate (si)-synthetase catalyzes the stereospecific abstraction of the pro-S proton from fluoroacetyl-CoA and the condensation of the so formed anion on the si face of oxaloacetate to give (2R, 3R)-fluorocitric acid (9), (See Scheme 2).

Scheme 2

This stereoisomer, which is much more toxic than the other three possible isomers, inhibits the citrate transport in mitochondria and blocks the citric acid cycle by inhibiting the enzyme aconitase. The fluorine atom drastically impedes the acid-catalyzed elimination of water by aconitase on fluoro-citric acid (9), to give fluoro aconitic acid (10). The cycle is thus disrupted by the "lethal synthesis" of an antimetabolite. Even-numbered ω -fluoro fatty acids produce the very toxic final product fluoroacetic acid, while the odd-carbon ω -fluoro fatty acids yield the 100-fold less toxic β -fluoro propionate¹⁴.

The systematic substitution of fluorine can help establish the effect of hydroxylation or other metabolic processes on the action of the molecule, as has been so successfully applied in the synthesis of fluorinated vitamin D₃ analogs^{8a,15} (11). A progress report on the preparation and biological activity of fluorinated analogs of vitamin D₃ has been published in Japanese¹⁶.

Fluorinated vitamin D₃ analogs

The mechanism of biological cyclopropyl fatty acid biosynthesis as it occurs in *Lactobacillus plantarum* has been probed by Buist et. al. using fluorine as a positive charge locator. It was shown that the pattern of rate retardations induced by homoallylic fluorine substitution is numerically the same but opposite in sense for two series of olefinic fatty acid substrates bearing the double bond at either the 9- or the

11-position¹⁷. Fluorine substitution at the 12-position of oleic acid has a substantially greater rate-retarding effect on bio-methylation than fluorine substitution at the 7-position. When the same experiments were performed using vaccenic acid instead of oleic acid, it was found that the pattern of fluorine substitution effects is reversed when the double bond of the substrate is at the 11-position rather than at the 9-position (See Scheme 3)¹⁸.

Scheme 3

Thus, if the carbocation is generated at carbon 12 during methylation of vaccenic acid, then the carbocation must be formed at carbon 9 during methylation of oleic acid. Alternately, if the carbocation is generated at carbon 11 during methylation of vaccenic acid, then it must be formed at carbon 10 during methylation of oleic acid (See Scheme 4). This implies that the absolute configuration of the cyclopropyl products derived from oleic acid and vaccenic acid should be opposite. Indeed, this situation has been confirmed in the case of the non-fluorinated cyclopropyl products (See Scheme 3)¹⁷.

Scheme 4

Using chiral fluorine substituted fatty acids, the switch of enantioselectivity of biomethylation as a function of olefinic position can be probed directly. Biomethylation of the (S)-fluoroolefins should yield quasi diastereomeric cyclopropanes. This pattern should also hold true for the (R)-fluoroolefins (See Scheme 5). The quasi-diastereomers should be distinguishable by ^1H , ^{13}C or ^{19}F NMR. It was the purpose of this thesis to prepare suitable chiral fluorinated synthons for the synthesis of the fluorinated olefinic precursors.

(S)-fluoroolefins

quasi-enantiomers

(R)-fluoroolefins

Scheme 5

1.1.2. Preparation of Chirally Fluorinated Molecules

Useful optically pure synthons bearing a chiral fluoromethylene group remain relatively rare although substantial progress has recently been reported.

1.2.1. Chiral Resolution of α -Fluoro carboxylic acids

The novel synthesis of (2R)- and (2S)-ethyl-2-fluorohexanoates, catalyzed by a bacterial lipase, has afforded these compounds in high enantiomeric purity. The enzyme is specific for the (S) enantiomer. An enantiomeric excess of >99% was achieved for the (R) enantiomer. To prepare the (S) enantiomer, two successive hydrolyses with the same enzyme were required, yielding the other enantiomer in 99% ee¹⁹ (See Scheme 6).

Scheme 6

These enzyme-catalyzed kinetic resolutions constitute an economical method of preparing enantiomerically pure 2-substituted esters and acids on a large scale. Both of these enantiomers have been used as important intermediates in the synthesis of antihypertensive prostaglandins (12) and vasodilator prostacyclins¹⁹ (13).

16R-fluoroprostaglandin

(12)

16S-fluoroprostacyclin

(13)

These synthons were unsuitable for our purposes as addition of an acetylide to the tosylated derivative of (14) is known to yield a rearranged product (15), with the elimination of fluoride²⁰.

1.2.2. Production of Chiral Fluoro-sulphonyl ketones

The synthesis of a group of three-carbon fluorinated chirons in which C-1, C-2 and C-3 are substituted with fluorine, oxygen and sulphur respectively, has been carried out recently²¹. Mono- and poly-fluorocarboxylic esters or salts were used as the source of the fluoroorganic fragment in the synthesis of several homochiral 1-sulphonyl alkylfluoroalkyl ketones (16). Through regioselective alkylation of the dilithium

derivative of (16), a mono-fluorinated sulphinyl ketone carrying an alkyl residue on the fluorine substituted carbon was created (17). The carbonyl group of the monofluorinated compound (17) was reduced with high diastereoselection to yield (18); the stereochemical course of the process was controlled by the configuration of the auxilliary sulphinyl group²¹. Removal of the auxilliary sulphinyl group from enantiomerically pure ketones or alcohols has afforded several homochiral sulphur-free fluoroorganic compounds (19)²², (See Scheme 7).

Scheme 7

However, these compounds, (19), were also unsuitable for our use in the synthesis of our fluorinated fatty acids as the loss of the sulphinyl group leaves an unwanted methyl group, which would be difficult to remove.

1.3. Fluorination of Chiral Alcohols

A widely used approach to the synthesis of enantiomerically pure drugs and natural products is based on the use of small and easily available compounds from a pool of chirality²³. Fluorination of optically active chiral alcohols has recently received attention as an excellent method for the production of chiral fluorinated compounds. By testing fluorinating agents on optically active 2-octanol, a general assessment of their abilities can be ascertained. A number of reagents capable of stereospecifically replacing an alcohol group by fluorine with a minimum of rearrangement have been used: methyl tri-*n*-butylfluoro phosphorane (20); phenyltetrafluoro phosphorane (21); *N*-(2-chloro-1,1,2-trifluoroethyl) diethylamine - (FAR) (22) and (diethylamino) sulfur trifluoride -(DAST) (23). Potassium fluoride, KF, can also be used, but the hydroxyl group must first be converted to a tosylate derivative²⁴.

A general feature of these reagents is the formation of enyne byproduct. These byproducts predominate when methyl tri-*n*-butylfluoro phosphorane, (20), DAST, (23) and KF are used, but are minor when FAR, (22) is used. For all the fluorinating reagents, except phenyltetrafluoro phosphorane, (21), enantioselectivity, i.e. inversion of configuration, appears to be good (FAR, (22) and KF) or even excellent (methyl tri-*n*-butylfluoro phosphorane, (20) and DAST, (23)). The results obtained with these reagents are consistent with a clean S_N2 step for carbon-fluoride bond formation. For phenyltetrafluoro phosphorane, (21), fluorination proceeds, at least in part, via a carbocation, leading to racemization. Hence, in order to obtain 2-fluorooctane with acceptable yield and good optical purity, use of FAR, (22) or KF has been recommended. Using methyl tri-*n*-butylfluoro phosphorane, (20) or DAST, (23) give the highest optical purity, but the yields are somewhat lower.

compound	stereospecificity	amount of enyne byproduct
methyl tri-n-butylfluoro phosphorane	excellent	predominates

(20)

phenyl tetrafluoro phosphorane

poor
(carbocation intermediate
leading to racemization)

some

(21)

FARN-(2-chloro-1,1,2-trifluoroethyl)
diethylamine

good

minor

(22)

DAST

(diethylamino) sulfur trifluoride

excellent

predominates

(23)

It should be mentioned that these studies were somewhat hampered by the problems associated with determining the optical purity of a simple alkyl fluoride. The optical purities of 2-chloro-, 2-bromo-, and 2-iodooctane are determined without ambiguity. In contrast, however, the maximum optical rotation of 2-fluorooctane remains unknown, as no chemical correlation has been established, owing to the poor leaving-group ability of fluorine in S_N2 reactions. Thus, only an estimate of optical purity has been made for 2-fluorooctane based on the correlation between molecular rotation and bond refraction²⁵.

DAST, (23), is a widely employed reagent to effect the conversion of an alcohol into an alkyl fluoride (See Scheme 8).

Scheme 8

This reaction generally proceeds cleanly with inversion of configuration at the reacting carbon centre (S_N2)²⁶. There are, however, two reported cases of this reaction proceeding with retention of configuration²⁷, in substrates where neighbouring group participation is present^{8a,28}. DAST has been used to elucidate the absolute configuration of fluorinated molecules in ferroelectric liquid crystals^{27a} and has been largely used in carbohydrate chemistry²⁹. More recently, this reagent has been used to prepare fluorinated nucleosides³⁰ where the very mild conditions and the inertness of this reagent toward acid sensitive substances has proved to be very useful. The excellent optical purity of the final product in combination with relatively simple reaction procedures, make DAST the reagent of choice for most fluorinations. DAST was chosen as our fluorinating agent for its very high stereospecificity.

1.4. Goal of Research

Due to the limited number of fluorinated compounds available in the pool of chirality, any highly efficient route to single enantiomers of fluorinated chiralons is looked upon with considerable interest and excitement. Our objective was to synthesize a family of new fluorinated alkynes with known optical purity and absolute configuration. These synthons can be used to prepare chirally fluorinated fatty acids (See Scheme 9).

Scheme 9

These chiral fluoro-fatty acids can then be used to elucidate the mechanism of fatty acid biomodification discussed earlier.

2.0. Results and Discussion

2.1. Synthesis of (R)- and (S)-4-Fluoro-1-decyne

The synthesis of chiral 4-fluoro-1-decyne was accomplished in the first part of this thesis (See Scheme 10). The proof of optical purity is documented in 2.2.

(a) Lithium acetylide; (b) (S)-O-methyl mandeloyl chloride;
(c,d) separation, hydrolysis; (e) DAST.

Scheme 10

2.1.1. Synthesis of Chiral 1-Decyn-4-ol

The synthetic route is based on the availability of chiral homopropargyl alcohols, whose configuration has been unambiguously determined³¹. Our route differed in that we chose to react lithium acetylide with 1,2-epoxyoctane to yield our racemic alcohol (See Scheme 11), while Roy and Deslongchamps chose to use Violo's method³² of condensing propargyl magnesium bromide on propionaldehyde (See Scheme 12).

Scheme 11

Scheme 12

Our use of an epoxide starting material gives us the option of starting with chiral epoxides, which may in future become available. Our racemic alcohols (24) (See Figures 1 and 2) were transformed into their diastereomeric (S)-O-methyl mandelic esters (27) and (28), by reaction with optically active acid chloride (26), (See Scheme 13).

Figure 1. ^1H NMR of ($\pm$)-1-Decyn-4-ol

Figure 2. ^{13}C NMR of ($\pm$)-1-Decyn-4-ol

Scheme 13

The optically active acid chloride, (26), was prepared by reaction of optically active (S)-O-methyl mandelic acid, (30), (See Figure 3), which was in turn prepared from chiral (S)-mandelic acid³³, (29), available commercially from Aldrich³⁴ (See Scheme 14).

Scheme 14

Separation of our 1-decyn-4-ol esters, (27), (28) by preparative HPLC is very time consuming and expensive. Purchasing chiral mandelic acid from Aldrich is very costly (\$1.06/g for 100g; \$2.10/g for 5g; U.S. dollars)³⁴ and methylation gives only a 30% yield using the method of Reeve and Christoffel³⁵ with many hours of laboratory

Figure 3. ^1H NMR of S-O-methyl mandelic acid

time. Commercial O-methyl-mandelic acid (\$5.90/g for 5g; \$7.40/g for 1g; U.S. dollars)³⁴ is also available, but is far too expensive to be used on a large-scale.

The separation of the diastereomers (27) and (28) was carried out by high performance chromatography using 5% ethyl acetate/hexane as the solvent (See Figure 4). After separation, the more polar compound had an $[\alpha]_D^{21} +70.0^\circ$ (c 2.1, CHCl_3) and the less polar had an $[\alpha]_D^{21} +18.1^\circ$ (c 2.2, CHCl_3), which is in close agreement with Roy and Deslongchamps work³¹, where their more polar and less polar compounds had $[\alpha]_D^{25}$ values of $+86^\circ$ (c 1.1, CHCl_3) and $+28^\circ$ (c 1.9, CHCl_3) respectively. Thus, we were able to predict that the more polar diastereomer would correspond to (28) and the less polar to (27), having respectively the SR and the SS absolute configuration.

This same phenomenon was observed when the ^1H NMR of our diastereomers (27) and (28) were run (See Figure 5). Our more polar diastereomer, (28), SR, had an acetylenic hydrogen peak at 1.95ppm, whereas the less polar diastereomer, (27), SS, had a peak at 1.80ppm. Thus, our results correlated well with Roy and Deslongchamps work^{31a}. This assignment is based on the fact that (a) the protons at C-1 and C-2 in (31) absorb at a higher field than those in (32), and (b) the protons at C-4 and C-6 in (31) absorb at a lower field than those in (32).

Figure 4. Prep LC separation of (±)-1-Decyn-4-ol, (S)-O-methyl mandelates

Figure 5. ^1H NMR of the acetylenic group present in (+)-1-Decyn-4-ol, (S)-O-methyl mandelates

The rather large chemical shift differences for acetylenic protons (0.15ppm) between the diastereomers is due to their steric and electronic nonbonded interactions as well as the anisotropy of the aromatic ring. The aromatic ring is sufficiently close in one diastereomer for shielding to occur³⁶.

Thus, assignment of the ¹H NMR was straightforward (See Figure 6). The diastereomeric excess of the esters was determined from the OCH₃ peaks present on the mandelyl moieties, yielding 3.40 and 3.42 ppm for the SR and SS esters respectively (See Figures 7 and 8), both in >99% ee. The diastereomeric excess was confirmed by ¹³C NMR (See Figures 9 and 10), with results of the octyn series being shown.

The configurational assignments by Roy and Deslongchamps were based on Mosher's work³³. In his work, both diastereomeric o-methylmandelate esters of secondary carbinols were considered, (33) and (34).

(33)

(34)

$L^2 = \text{alkyl}$

$L^3 = -\text{CH}_2\text{C}\equiv\text{CH}$

This single conformational model represents a crucial arrangement in which the α -phenyl substituent of the acid moiety is preferentially oriented toward the L^3 vs. L^2 groups attached to the carbinyl carbon of the alcohol moiety of each diastereomer. Thus, for (33), L^3 (alkyne) is juxtaposed in the α -phenyl group, while in the opposite diastereomer, (34), it is L^2 (alkyl) which is juxtaposed with the α -phenyl group³⁶.

This model provides an empirical correlation of extensive data which show that the mandelate diastereomer specified by (33) will have the resonance for L^3 upfield (more shielded) from that for L^3 in the alternate diastereomer (34); at the same time diastereomer (34) will have the resonance for L^2 upfield (more shielded) from that for L^2 in diastereomer (33). This is quickly and conveniently determined from the model by observing which group is juxtaposed with phenyl.

Figure 6. ^1H NMR of the ($\pm$)-1-Decyn-4-ol, (S)-O-methyl mandelate

Figure 7. ^1H NMR of the OCH_3 group present in (S)-1-Decyn-4-ol, (S)-O-methyl mandelate

Figure 8. ^1H NMR of the OCH_3 group present in (R)-1-Decyn-4-ol, (S)-O-methyl mandelate

Figure 9. ^{13}C NMR of (S)-1-Octyn-4-ol, (S)-O-methyl mandelate

Figure 10. ^{13}C NMR of (R)-1-octyn-4-ol, (S)-O-methyl mandelate

The configurational assignments by Roy and Deslongchamps were rigorously established by preparing a chiral sample of (37) starting from D-glucose (35), using (36), a known intermediate³⁸ (See Scheme 15).

Scheme 15

The basic hydrolysis of the mandelate esters, (31) and (32), yielded chiral alcohols, of which the optical rotation of (R)-5-hexyn-3-ol was identical to (37), confirming that the configurational assignment of (31) was correct.

Our (R)- and (S)-1-decyn-4-ols had $[\alpha]_D^{21}$ values of $+14.5^\circ$ (neat) and -14.4° (neat) respectively. The optical rotations of our alcohols could not be measured at normal concentrations (1-2% w/v). Attempts were made to determine the optical rotations at various concentrations. No clear linear relationship emerged from the results.

Table 1: Polarimetry data of (S)-1-Decyn-4-ol in CHCl_3

% concentration	observed rotation	specific rotation
100	-14.40°	-14.40°
50	-2.99°	-5.98°
40	-1.88°	-4.70°
10	-0.07°	-0.70°
5	-0.01°	-0.20°
0	0°	0°

Although these results are the first reported, their values were somewhat unexpected as optical rotations by Roy and Deslongchamps on the hexyn-ol compounds were -4° (c 1.1, CHCl_3) and $+4^{\circ}$ (c 2.1, CHCl_3) for (R) and (S) enantiomers respectively. These values are opposite in sign to our series ! However, other cases have been reported where associations, dissociations and solute-solvent interactions have caused nonlinear behaviour⁷. An example is (-)-2-ethyl-2-methylsuccinic acid in CHCl_3 where the $[\alpha]_D^{24}$ values changed from -5.0° at c 16.5, to -0.7° at c 10.6, to $+1.7^{\circ}$ at c 8.5, and $+18.9^{\circ}$ at c 2.2.

2.1.2. Synthesis of Optically Active 4-Fluoro-1-decyne

DAST was selected as the fluorinating agent because of its ability to introduce fluorine with clean inversion at unactivated secondary carbinol centers²⁴ (see 1.0. Introduction). The (S)- (38) and (R)- (39)-decyn-ols were each transformed into their corresponding (R)- (40) and (S)- (41)-fluoro-yne counterparts, each in 32% isolated yield. (See Scheme 16).

Scheme 16

One of the general features of this fluorination step is the formation of enyne byproduct (42). Fortunately, (42) is less polar than (40) and (41), and can be separated easily by flash chromatography (2.5% CH_2Cl_2 /Hexane). The final product was then distilled bulb-to-bulb to yield a colourless free-flowing liquid which was analytically pure and possessed the following NMR (See Figures 11 and 12) and mass spectral data (See Figure 13).

Figure 11. ^1H NMR of ($\pm$)-4-Fluoro-1-decyne

Figure 12. ^{13}C NMR of ($\pm$)-4-Fluoro-1-decyne

(R)- and (S)-4-Fluoro-1-decyne yielded $[\alpha]_D^{21}$ values of $+12.3^\circ$ (c 1.1, CH_2Cl_2) and -10.2° (c 1.3, CH_2Cl_2) respectively. (R)- and (S)-4-Fluoro-1-decyne are new compounds, and a manuscript describing this work has recently been accepted for publication in the Journal of Organic Chemistry³⁹.

This reaction was not optimized⁴⁰, although recent attempts to use TMS ethers has not significantly increased the efficiency of this reaction⁴¹. The reaction was performed with pentane as solvent at -78°C and 0°C , both with limited success. At -78°C , the solution thickened to the extent that it seemed frozen, and it looked as though the DAST reagent had frozen. The yields here were much lower than if the reaction had been performed at -45°C . Running the reaction at 0°C yielded primarily enyne byproduct, thus greatly reducing the amount of fluorinated product.

2.2. Determination of Enantiomeric Excess of 4-Fluoroalkynes

At the commencement of this thesis, the determination of the optical purity of simple fluorinated synthons containing only one chiral CHF centre was unknown. Since this time, Mosher's acid (α -methoxy- α -(trifluoromethyl)phenyl acetate, (3)) has been used to determine the enantiomeric purity of 2-fluorohexanoic acids¹⁹.

Optical purity can be defined as the percent excess of one enantiomer over the other (e.e.):

$$\begin{aligned}\text{Optical purity} &= \text{percent excess} = \frac{[R] - [S]}{[R] + [S]} \quad 100 \\ &= \% R - \% S\end{aligned}$$

Thus, if a solution contains 80% (+) and 20% (-) isomer, the (-) isomer cancels an equal amount of (+) isomer, and the mixture behaves as if 60% of it were (+) and the other 40% inactive.

If a compound is synthesized, and had previously been made and proven to be 100% optically pure, then the enantiomeric excess of the newly synthesized compound can be calculated from its $[\alpha]_{\text{obs}}$.

$$\text{e.e.} = \frac{[\alpha]_{\text{obs}}}{[\alpha]_{\text{max}}} \quad 100$$

Thus, for the case above, if $[\alpha]_{\text{max}}$ for the (+) isomer is $+80^\circ$, then $[\alpha]$ for the above mixture would be 60% of $+80^\circ$, or $+48^\circ$. If the value of $[\alpha]_{\text{max}}$ is not known, then the optical purity of the sample is unknown. However, the conversion of a mixture of enantiomers into a mixture of diastereomers using an optically pure reagent, will yield a mixture that can be analyzed by NMR or chromatography. For instance, if O-methyl mandelic acid is used, the o-methyl protons can be examined, yielding two singlets. From the intensity of the two peaks, the relative proportions of the two diastereomers (and hence of the original enantiomers) can be determined. If the peaks are too close together for resolution, the use of a different optically pure reagent (i.e. Mosher's acid)

may yield proper resolution. ^{13}C NMR has been used in the same manner. The use of Mosher's acid give the experimenter the added bonus of using ^{19}F NMR to resolve the mixture by observing the trifluoromethane group.

A related method that does not require conversion of enantiomers to diastereomers is the addition of chiral lanthanide shift reagents, such as tri[3-trifluoroacetyl-d-camphorato] europium-(III). Lanthanide shift reagents have the property of spreading NMR peaks of compounds with which they can form coordination compounds, e.g. alcohols, carbonyl compounds, amines, etc. Chiral lanthanide shift reagents shift the peaks of the two enantiomers of many such compounds to different extents.

Also, the direct separation of enantiomers by gas or liquid chromatography on a chiral column has been used to determine optical purity. An alternative is to again convert the enantiomeric solution into a diastereomeric one, using an optically pure reagent and use gas or liquid chromatography. Here, a chiral column is not necessarily required⁷.

The determination of the enantiomeric purity of the homopropargyl fluorides (40) and (41) was attempted from various fronts. All chiral shift reagents known to interact with halogen²⁵ ($\text{Yb}(\text{fod})_3$, and $\text{Eu}(\text{fod})_3$) and multiple bonds⁴² (binuclear complex of lanthanide(III) β -diketonate and silver(I) β -diketonate) had failed previously to distinguish the two enantiomers. In order to encourage better shift reagent/substrate interaction, the conversion of the fluoro-decyne to their corresponding ketones was attempted. Hydration of the triple bond of 1-decyne, using standard methods⁴³ worked well, but were unsuccessful when applied to the fluorinated derivatives. The strong electronegative nature of fluorine has been known to interfere with or alter the course of a reaction⁴⁴ (See 1.0. Introduction).

Oxidative dimerization is a well known reaction, and coupling of our racemate

would yield us two products, *dl* (*SS* and *RR*) and *meso* (*RS* and *SR*). This method would be very elegant as it does not require an additional chiral compound, as the compound itself can act as its own chiral derivatizing agent. A trial oxidative coupling of 1-decyne according to the method of Hay⁴⁵ using an O₂ bubbler for 24hr was uneventful, yielding a dimer evident by tlc (monomer *rf* 0.20; dimer *rf* 0.49) in 10% CH₂Cl₂/Pentane and ¹H NMR. Dimerization of racemic 4-fluoro-1-decyne yielded a mixture of *meso* and *dl* dimers. This reaction was deemed complete after 1hr by tlc (monomer *rf* 0.24; dimer *rf* 0.53) in 10% CH₂Cl₂/Pentane without the aide of external oxygen. Again the characteristic loss of the acetylenic hydrogen was visible by ¹H NMR (See Figure 14). Unfortunately, these dimers were undistinguishable from each other by high field ¹³C NMR (See Figure 15), ¹⁹F NMR (only 1 signal visible), nor by capillary GC or reversed phase HPLC.

Encouraged by a recent report¹⁹ that the enantiomeric purity of 2-fluorohexanoic acids could be evaluated by Mosher esterification of their corresponding fluoroalcohols, oxidative cleavage of the triple bond was attempted, (See Scheme 17).

(f) acidic 0.4M KMnO₄; (g) LiAlH₄; (h) (R)-MTPA-chloride

Scheme 17

Figure 14. ^1H NMR of the dimer of ($\pm$)-4-Fluoro-1-decyne

Figure 15. ^{13}C NMR of the dimer of ($\pm$)-4-Fluoro-1-decyne

By treating the fluoro-decynes with acidic KMnO_4 solution⁴⁶, we were able to cleave one-carbon unit to prepare analytically pure 3-fluorononanoic acid (43) as a white crystalline material in 45% yield. Looking at the ^1H NMR (See Figure 16) and ^{13}C NMR (See Figure 17), it was difficult to determine the extent of purity of (43). The mass spectrum of the methyl ester (See Figure 18) was characteristic, and the compound, (43), was found to be analytically pure by elemental analysis (See Experimental 3.2.7.).

Reduction of 3-fluorononanoic acid, (43), to the corresponding alcohol, 3-fluoro-1-nonanol, (44), with LiAlH_4 yielded an analytically pure viscous colourless liquid in quantitative yield. The ^1H (See Figure 19) and ^{13}C (See Figure 20) NMR data were characteristic of the compound, as was the mass spectrum (See Figure 21).

Conversion of the terminal alkyne of 4-fluoro-1-decyne to an acid, and further, an alcohol, yielded some interesting chemical shifts in the ^{13}C NMR. C2 of 4-fluoro-1-decyne had a shift of 79ppm (JCF 10Hz), but was shifted downfield to 176ppm (JCF 6Hz) when converted to an acid, and then shifted back upfield to 59ppm (JCF 4Hz) when reduced to an alcohol.

The carbon atom bearing the pendant fluorine atom also experienced various shifts. In the terminal alkyne, a chemical shift of 91ppm with a JCF of 174Hz was observed. However, conversion again to an acid group moved the signal to 90ppm, but with a coupling constant of 170Hz due to the presence of the acid group. This interaction is present again when the acid group is reduced to an alcohol, yielding a chemical shift of 92ppm with a JCF of 166Hz, similar to that of the acid group interaction.

Esterification of our racemic alcohol, 3-fluoro-1-nonanol, (44), to (R)-MTPA-chloride^{4a}, (45), was uneventful and gave two products, (46) and (47), (See Scheme 18).

Scheme 18

Figure 16. ^1H NMR of ($\pm$)-3-Fluoro-1-nonanoic acid

Figure 17. ^{13}C NMR of ($\pm$)-3-Fluoro-1-nonanoic acid

Figure 18. Mass spectrum of (+)-3-Fluoro-1-nonanoic acid (methyl ester)

Figure 19. ^1H NMR of ($\pm$)-3-Fluorononan-1-ol

Figure 20. ^{13}C NMR of ($\pm$)-3-Fluorononan-1-ol

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MTPA has its many advantages in determining enantiomeric compositions: (a) the generally excellent separation of both proton and fluorine NMR signals of the diastereomers; (b) the presence of the CF_3 group, permitting the use of fluorine NMR, which occurs in an uncongested region of the spectrum; (c) its marked stability toward racemization even under severe conditions of acidity, basicity, and temperature; (d) its relative ease of preparation and resolution; and (e) its inherent volatility which allows lower molecular weight derivatives to be purified, as well as analyzed, by glpc^{4a}.

Both diastereomers, (46) and (47) were distinguished by ^1H , ^{13}C and ^{19}F NMR as well as by capillary GC⁴⁷. Two equal-sized signals were observed in the ^{19}F NMR for the CF_3 groups (4.254 and 4.310ppm, $\Delta\delta=0.056\text{ppm}$), (See Figure 22). Mirror image patterns for these signals were obtained when each chiral fluoroalcohol was used separately ((46) 4.254: (47) 4.310ppm), (See Figures 23 and 24). The mono fluorine in the diastereomers (46 and 47) was undistinguishable and could not be resolved as it coupled with all of its neighbouring hydrogens, (See Figure 25). In addition, the signals due to the methoxyl groups appear as overlapping quartets (3.533 and 3.528ppm, $\Delta\delta=0.005\text{ppm}$) in the 500MHz ^1H NMR spectrum (See Figure 26). This pattern again simplified to one quartet in the ^1H NMR spectrum of the ester derived from each enantiomer [(46) 3.533ppm, (See Figure 27): (47) 3.528ppm, (See Figure 28)]. The ^{13}C NMR data was also in agreement with the other results (See Figures 29 and 30). From these sets of data, we were able to estimate the enantiomeric excess of our fluoroalkynes to be ~90%. The enantiomeric excess is calculated in the same manner as the optical purity in 2.2., i.e. $([\text{R}]-[\text{S}]) / ([\text{R}]+[\text{S}])$. Hence, one enantiomer here contributed 95% to the overall total relative signal in figures 27 and 28. A recent report⁴⁸ has found the enantiomeric purity of Mosher's Acid to be between 97.89% and 99.80%. This finding in conjunction with the possible racemization of the mandelates, puts some speculation on the use of exact results (hence, ~90%). If during the methylation of the mandelates (See Experimental section 3.2.2.) racemization occurred due to the basic conditions, it is possible that an (R), instead of an (S), configuration for the mandelates could be created.

Figure 22. ^{19}F NMR of CF_3 groups in MTPA-esters

Figure 23. ^{19}F NMR of the CF_3 group of (R)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl acetate.

Figure 24. ^{19}F NMR of the CF_3 group of (S)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl acetate.

Figure 25. ^{19}F NMR of the mono fluorine in (S)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl acetate.

Figure 26. ^1H NMR of OCH_3 groups in MPTA-esters

Figure 27. ^1H NMR of the CF_3 group of (R)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl acetate.

Figure 29. ^{13}C NMR of (R)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl acetate

Figure 30. ^{13}C NMR of (S)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl acetate

This configuration would be hidden during the chromatographic separation and would cause impurities. (SR) and (RR) would be concealed chromatographically by (RS) and (SS) respectively .

This optical purity of the fluoro-decynes has been corroborated recently by running the GC of (46) and (47) on a DB 17 column as previously recommended^{19b} : The (RS)-Mosher ester, (46), eluted 0.29min. later than did the (RR)-ester, (47), (See Figure 31); the ratio of the two diastereomers was estimated to be 94(RS):6-(RR), (46) and 95 (RR):5(RS), (47)-in good agreement with the NMR results. EI and CI mass spectra of the esters were also run (See Figure 32).

The proof of configuration of our fluorinated synthon has generated great interest in those seeking to solve similar problems. A group at the Los Alamos National Laboratory has been trying to apply the chemical shift sensitivity of the selenium-77 nucleus for the detection and quantitation of remotely disposed centres. Louis A. Silks, III (Ph. D) of the group has stated "Your observation of the two MTPA diastereomers is quite remarkable considering the chiral centre is 7 bonds removed from the observing fluorine nucleus". The group plans to use our synthon in their studies.

Figure 31. GC of both MTPA-esters

Figure 32. Mass spectrum of MTPA-esters

2.3. Conclusions

Both enantiomers of 4-fluoro-1-decyne were synthesized in 32% overall yield from their corresponding optically active homopropargyl alcohols whose absolute configuration have been determined. The chromatographic separation of the chiral alcohols was accomplished by esterification with (S)-O-methyl mandeloyl chloride. The enantiomeric excess of the title compounds was found to be 90% by NMR and GC analysis of the corresponding 3-fluorononan-1-ol-(R)-MTPA esters. The fluoro-alcohols were obtained by oxidative cleavage of 4-fluoro-1-decyne, followed by LiAlH_4 reduction.

An optically pure chiral fluorinated synthon has been synthesized which can now be used in the elucidation of the mechanism of biological cyclopropyl fatty acid biosynthesis or any synthesis requiring a simple fluorinated alkyl chain with a terminal alkyne that can easily be transformed. This synthon and its acid derivative are, to our knowledge, novel, and can be produced with assurance as to optical purity. The synthetic route is versatile in that a variety of alkyl chain lengths can be employed. Our 3-fluorocarboxylic acid compounds may be of pharmaceutical interest owing to their possible inhibitory effects on fatty acid β -oxidation.

3.0. Experimental

3.1. General

The low field ^1H NMR spectra (60MHz) in this work were recorded on a Varian EM360-A instrument. The high field ^1H NMR (200, 300, and 500MHz), ^{13}C NMR (50.286MHz and 75.429MHz) and ^{19}F NMR (282.2MHz) spectra were recorded on Varian XL200, Varian XL300 and Bruker AM500 spectrometers. The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; db, broad; dist, distorted. All chemical shifts are reported with reference to tetramethylsilane (TMS) using CDCl_3 as solvent (unless otherwise noted), and are quoted in δ (ppm) values. The elemental analyses were obtained on a Perkin Elmer Elemental Analyzer 240C by Ann Webb at NRC. The mass spectra were obtained on a VG7070 E mass spectrometer at 70eV, using a direct introduction probe at 10^{-7} mm pressure or on a GC inlet system for GC-MS (Varian GC-3300, 30m, megabore DB-5 column, (temperature programmed from 100°C to 300°C at 10°C/min., carrier gas He at 20mL/min.). The MS and GC-MS data were collected using a DEC PD P8 system. Optical rotations were measured at 21°C on a Perkin Elmer model 141 polarimeter equipped using a 1mL sample cell (l 10cm) at 589nm. Melting point determinations were performed on a Buchi SMP-20 melting-range apparatus.

Several chromatographic techniques were used in this work:

Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh). Both analytical and preparative thin layer chromatography were performed using Merck precoated Silica Gel G/UV254 glass plates. Visualization of UV-inactive compounds was accomplished by spraying with water: hydrophobic spots appeared as white spots on a grey background. Mosher and mandelate esters could be observed on TLC plates using a UV lamp at 254nm.

Separation of the (S)-(+)-O-methyl-mandelic esters of 1-decyne-4-ol was accomplished by HPLC on a Waters prep LC/System 500 chromatograph with a Waters 410 differential refractometer as detector. Two sealed 500mL silica gel columns and

5% Ethyl acetate/Hexane were used as stationary and mobile phases respectively. A column pressure of 20atm, solvent pressure of 100psi, and 100mL/min. flow rate, allowed near baseline resolution.

The capillary GC chromatograms of the Mosher esters were obtained by using FID detection and a 30m, J&W DB 17 column (0.25mm ID, 0.25 μ m film) which was temperature programmed from 100°C to 210°C at 2.0°C/min. All solvents used for chromatography were previously distilled. Reagents and starting materials were purchased from Aldrich Chemical Company (unless otherwise stated) and used without purification. Chiral materials were used without improving their optical purity. Reactions were performed under N₂. DMSO was distilled from CaH in vacuo prior to use and stored over molecular sieves under N₂. A rotary evaporator (Buchi, rotovapor R) was used to remove solvents *in vacuo*.

3.2. Synthesis

3.2.1. (±)-1-Decyn-4-ol

To an oven-dried 2L r.b. flask, equipped with a large football stirring bar, rubber septum, and N_2 flow, was added Lithium acetylide-EDA complex (83.5g, 0.91mole) under a blanket of N_2 , dry DMSO (400mL) and finally, 1,2-Epoxyoctane (60.0mL, 0.39mole) via syringe with stirring over a 5 minute period. To control the highly exothermic reaction, the reaction flask was cooled with an ice-water bath. The solution slowly turned to a very deep brown colour with emerging bubbles. The slurry was stirred overnight at room temperature, at which time it was poured onto ice (~800g). The basic solution was neutralized with 3N H_2SO_4 (~150mL) until a pH of 7 was reached. The aqueous layer was extracted with 4x300mL of ether. Precipitated salts formed, and were also washed with ether after being collected on a Buchner funnel. The combined golden-coloured ethereal layer was washed with 2x50mL sat. $NaHCO_3$, 2x50mL sat. $NaCl$, dried over $MgSO_4$, and evaporated *in vacuo* at 40°C to yield the crude alcohol as a golden free-flowing liquid (50.6g): bp 106-110°C (90mm), (lit.⁴⁹ 107-112°C (112mm)).

Table 2. ^1H NMR of ($\pm$)-1-Decyn-4-ol

a	b	c	d	e	f	f'	g	h
0.87 t, 3	1.35 bd m, 8	1.35 bd m, 2	3.73 m, 1	2.33 m, 2			2.03 m, 1	3.20 s, 1

Table 3. ^{13}C NMR of ($\pm$)-1-Decyn-4-ol

a	b	c	d	e	f	g	h	i	j
69.82	81.09	36.15	70.58	29.19	27.26	25.52	31.75	22.56	14.00

3.2.2. (S)-(+)-O-Methyl mandelic acid

To a three-necked 1L r.b. flask, equipped with a large football stirring bar, a reflux condensor, drying tube, a 250mL pressure-equalizing dropping funnel, and a thermometer, was added water (280mL), followed by NaOH pellets (87g, 2.2mole). A highly exothermic reaction resulted, which was cooled with a large ice-water bath. The solution was cooled to 45°C, at which time (S)-(+)-Mandelic acid (25.0g, 164mmole) was added via a dry large-mouthed powder funnel and quickly dissolved. Into the dropping funnel was placed dimethyl sulfate (85mL) via a 50mL glass syringe. The dimethyl sulfate was added dropwise at a rate of 3 drops/10 seconds, keeping the solution at a constant temperature of 40-45°C. A flocculent white solid slowly began to precipitate out after the addition of 20mL. The total time taken for the addition of the methylating agent was 2 hrs. Addition of the methylating reagent faster than that time specified created a further exothermic reaction, which also had to be controlled with an ice-water bath.

The solution was filtered by suction, with the filtrate being used repeatedly to wash the round bottomed flask. The white solid was transferred to a 500mL beaker and dissolved in hot water (100mL). The filter paper, stirring bar and filter were also washed with hot water. The hot solution was acidified to pH 3.0 (MN paper) using 3M H₂SO₄. As the solution cooled, some white solid had precipitated out. Once all the solid had precipitated out (3 days), it was suction filtered to yield small white crystals.

NaCl (6g) was added to the filtrate, cooled to 5°C and left to precipitate overnight. These solids were also filtered and added to the previous crystals. These combined solids were dissolved in hot water (85mL) and the pH lowered by the addition of conc. HCl (2mL) which caused immediate precipitation. This new solution was allowed to cool to room temperature, at which time another aliquot of conc. HCl (3mL) was added. An oily solid was extracted with 3x80mL ether, washed with 40mL water, dried over MgSO₄, and evacuated *in vacuo*. Dry acetonitrile was then added and rotovaped off until a constant weight was achieved, yielding (9.50g) of white solid as the product.

$[\alpha]_D^{21} = +135.8$ (experimental; c 1.1, ethanol)

$[\alpha]_D^{21} = +144.1$ (commercial; c 1.0, ethanol)

$[\alpha]_D^{21} = +150$ (accepted literature value)³⁵

Table 4. ¹H NMR of (S)-O-Methyl mandelic acid

a	b	c	d
3.3	4.7	7.4	10.8
s,3	s,1	bd m,5	bd s,1

3.2.3. ($\pm$)-1-Decyn-4-ol, (S)-O-methyl mandelates

To (S)-O-Methyl mandelic acid (35.77g, 215mmole) in a 1L r.b. flask was added Oxalyl chloride (35mL, 400mmole). With fast stirring, the white solid dissolved slowly (~2hrs), while under N₂. When all the acid had been converted to acid chloride, the excess oxalyl chloride was removed via a water aspirator pump using a dry ice/isopropyl bath. This was continued (~1hr) until no apparent volume change could be detected. A faintly yellow coloured free-flowing liquid remained. To the ($\pm$)-1-Decyne-1-ol (29.24g, 190mmole) was added dry benzene (45mL) and dry pyridine (25mL). To the acid chloride was added dry benzene (140mL) followed by the alcohol solution. A highly exothermic reaction ensued, which was controlled with an ice-water bath. A white precipitate formed, and the solution was left stirring for a further 48 hours under N₂, at which time water (300mL) was added to dissolve the precipitate. The aqueous layer was extracted with 3x100mL of ether. The combined

yellow ethereal layer was washed with 100mL of 2M HCl, 200mL sat. NaCl, dried over MgSO_4 , and evaporated *in vacuo* at 40°C to yield the product as a crude yellow oil (53.92g).

3.2.4. Resolution of (R)- and (S)-1-Decyn-4-ol, (S)-O-methyl mandelates

Premixed solvent (10 litres of 5% Ethyl acetate/Hexane) was placed into an airted reservoir complete with magnetic stirring bar. Two sealed 500g silica gel columns were set up in series with a column pressure of 20atm, solvent pressure of 100psi and flow rate of 100mL/min.. The columns were equilibrated until a steady baseline was reached. The diastereomeric mixture (3.46g) was put onto the first column (using a 25mL glass syringe fitted with a preinjection filter), after having been filtered through a 3cm pad of silica gel with ethyl acetate as eluent. Almost baseline resolution was achieved with the two diastereomers eluting at the 3rd and 4th column volumes (15% yield each). The first diastereomer (less polar of the two) off the column remained a liquid at 0°C while the second froze.

Data for (S)-1-Decyn-4-ol, (S)-O-methyl mandelate

rf 0.30: silica gel, 10% EtOAc/Hexane

$[\alpha]_D^{21} = +18.1$ (c 2.2, CHCl_3)

Table 5. ^1H NMR of (S)-1-Decyn-4-ol, (S)-O-methyl mandelate

a	b	c	d	e	f	f'	g	h	i	j	k
0.75 t,3	1.13 bd m,8	1.57 bd m,2	4.97 p,1	2.31 m,2			1.80 t,1		4.76 s,1	3.42 s,3	7.15-7.35 m,5

Table 6. ^{13}C NMR of (S)-1-Octyn 4-ol, (S)-O-methyl mandelate

a	b	c	d	e	f	g	h	i
70.40	79.22	32.68	72.61	27.18	23.73	22.34	13.89	

j	k	l	m	n
	170.36	82.68	57.38	127.11, 128.49, 128.60, 136.28

Data for (R)-1-Decyn-4-ol, (S)-O-methyl mandelate

rf 0.28: silica gel, 10% EtOAc/Hexane

$[\alpha]_D^{21} = +70.0$ (c 2.1, CHCl_3)

Table 7. ^1H NMR of (R)-1-Decyn-4-ol, (S)-O-methyl mandelate

a	b	c	d	e	f	f'	g	h	i	j	k
0.72 t,3	0.97 bd m,8	1.45 bd m,2	4.94 p,1	2.45 m,2			1.95 t,1		4.75 s,1	3.40 s,3	7.15-7.35 m,5

Table 8. ^{13}C NMR of (R)-1-Octyn-4-ol, (S)-O-methyl mandelate

a	b	c	d	e	f	g	h	i
70.54	79.49	32.59	72.49	26.76	24.06	22.15	13.75	

j	k	l	m	n
	170.25	82.48	57.23	127.27, 128.51, 128.68, 136.38

3.2.5. (R)- and (S)-1-Decyn-4-ol

In a 250mL r.b. flask, equipped with a stirring bar and reflux condensor was placed the (R)-1-Decyn-4-ol, (S)-O-methyl mandelate ester (4.31g, 14mmole) and 1.5M $\text{NaOCH}_2\text{CH}_3$ (30mL). The clear colourless solution became cloudy white within 30 seconds of stirring with the base. A gentle reflux was created and left for 1.5hrs. During the reflux, the solution turned a bright yellow and became clear. The reaction was quenched with the addition of water (40mL). The aqueous layer was then extracted with 3x30mL ether. The yellow ethereal layer was washed with 30mL sat. NaCl, dried over MgSO_4 , and evaporated *in vacuo* to yield a yellow free-flowing liquid (2.15g). The hydrolysis was deemed complete after 1.5hrs by running the starting ester and product together on a TLC plate in 20% EtOAc/Hexane. The starting ester had an *rf* value of 0.28 while the alcohol had an *rf* value of 0.21.

(R)-1-decyn-4-ol $[\alpha]_D^{21} = +14.5^\circ$ (neat)

(S)-1-decyn-4-ol $[\alpha]_D^{21} = -14.4^\circ$ (neat)

No appreciable optical rotation could be measured at normal concentrations (1-2% w/v) in CHCl_3 . This behaviour is in contrast with that reported for the corresponding optically active 1-hexyn-3-ols^{31a}.

3.2.6. (±)-4-Fluoro-1-Decyne

To a 100mL r.b. flask containing 20mL CH_2Cl_2 in a dry-ice/ acetonitrile bath at -45°C under N_2 , was added with stirring via a disposable syringe, Diethylaminosulfurtrifluoride (DAST), (4.2g, 26mmole), creating a clear yellow liquid solution. (±)-1-Decyn-4-ol (2.15g, 13.9mmole) was added slowly (10 min.). A vigorous reaction commenced and was controlled with the bath. The reaction was left stirring for 24 hrs under N_2 , until an orange-brown liquid resulted. This solution was then pipetted into a separatory funnel containing water and CH_2Cl_2 (10mL each). No exothermicity was noted. The layers were separated and 2x10mL CH_2Cl_2 extractions were performed. The combined ethereal layer was washed with repeated sat. NaHCO_3 aliquots until the aqueous layer remained basic, then dried over MgSO_4 , evaporated *in vacuo*, passed through a pad of florisil and evaporated again *in vacuo* to yield 1.78g of dried product. This golden coloured free flowing liquid was flash chromatographed using a medium-sized column (~100g silica) and 2.5% CH_2Cl_2 /Hexane used as the eluent to remove a considerable amount of eneyne byproduct (fractions 1-9). Collecting 25mL fractions, the pure fluoro-decyne was collected in the 10-21 fractions evident by TLC. The purified title compound was evaporated *in vacuo* to yield a clear colourless free flowing liquid (0.68g, 32% isolated yield) μ 82°C (43mm). Calc'd for $\text{C}_{10}\text{H}_{17}\text{F}$: C, 76.92; H, 10.90. Found: C, 76.83; H, 10.63.

It has been reported⁵⁰ that DAST can decompose violently upon contact with water and by heating at temperatures higher than 50°C .

R-4-fluoro-1-decyne $[\alpha]_D^{21} = +12.3$

S-4-fluoro-1-decyne $[\alpha]_D^{21} = -10.2$

Table 9. ^1H NMR of (+)-4-Fluoro-1-decyne

a	b	c	d	e	f	f'	g
0.89 t, 3	1.30 bd m, 8	1.70 d of m, 2 $J(\text{HF}) = 20\text{ Hz}$	4.59 d of m, 1 $J(\text{HF}) = 48\text{ Hz}$	2.53 d of m, 2 $J(\text{HF}) = 19\text{ Hz}$			2.03 t, 1

Table 10. ^{13}C NMR of (+)-4-Fluoro-1-decyne

a	b	c	d	e	f	g	h	i	j
70.50	79.23 $J(\text{CF}) = 10\text{ Hz}$	34.07 $J(\text{CF}) = 20\text{ Hz}$	91.50 $J(\text{CF}) = 174\text{ Hz}$	25.08 $J(\text{CF}) = 24\text{ Hz}$	29.03	24.80	31.69	22.56	14.00

The yield of this reaction has recently been increased to 70% by Dr. P.H. Buist.

Table 11. ^1H NMR of ($\pm$)-3-Fluoro-1-nonanoic acid

a	b	c	d	e	f	f'
0.87 t,3	1.24 bd m,8	1.66 bd m,2	4.92 d of m,1 $J(\text{HF})=44\text{Hz}$	2.64 m,2		5.80 bd s,1

Table 12. ^{13}C NMR of ($\pm$)-3-Fluoro-1-nonanoic acid

a	b	c	d	e	f	g	h	i	j
176.32 $J(\text{CF})=6\text{Hz}$	40.22 $J(\text{CF})=24\text{Hz}$	90.06 $J(\text{CF})=170\text{Hz}$	34.82 $J(\text{CF})=21\text{Hz}$	24.78 $J(\text{CF})=41\text{Hz}$		31.66	28.95	22.54	14.01

3.2.8. (±)-3-Fluorononan-1-ol

All glassware had been oven-dried and was immediately set up and left to cool under N_2 . To a 50mL three-necked r.b. flask, fitted with a rubber stopper, a reflux condensor, dropping funnel, drying tube, and stirring bar, was added $LiAlH_4$ powder (200mg, 5.3mmole). Dry ether (1mL) was used to transfer any remaining LAH to the rbf. ($\pm$)-3-Fluoro-nonanoic acid (24mg, 0.14mmole) was dissolved in minimal ether and placed into the dropping funnel. The mixture was added slowly to the reducing agent. A little more ether (2mL) was added to the dropping funnel to wash down any last traces of acid. No visible reaction or exothermicity could be seen. Ether was added as needed to replenish that evaporated during a 10 minute stirring period. After the 10 minutes, excess LAH was decomposed by the slow addition of water. This addition created fuming, bubbles, and solid white particulate formation. When the addition of water ceased to have any effect, the two layers were separated and each backwashed. The ethereal layer was dried over $MgSO_4$ and evaporated *in vacuo* to yield a clear colourless liquid (22mg, 0.13mmole). Calc'd for $C_9H_{19}FO$: C, 66.62; H, 11.80. Found: C, 66.86; H, 11.83.

Table 13. ^1H NMR of ($\pm$)-3-Fluorononan-1-ol

a	b	c	d	e	f
0.87 t,3	1.28-1.85 bd m,10	4.68 d of m,1 J(HF)= 49Hz	1.88 m,2	3.78, 3.61 dist t, each 1	

Table 14. ^{13}C NMR of ($\pm$)-3-Fluorononan-1-ol

a	b	c	d	e	f	g	h	i	j
	59.44 $J(\text{CF}) = 4 \text{ Hz}$	37.89 $J(\text{CF}) = 20 \text{ Hz}$	92.63 $J(\text{CF}) = 166 \text{ Hz}$	35.40 $J(\text{CF}) = 21 \text{ Hz}$	25.01 $J(\text{CF}) = 4 \text{ Hz}$	29.11	31.73	22.58	14.04

3.2.9. ($\pm$)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl acetates

To (R)-(+)-methoxytrifluoromethylphenylacetic acid (39.8mg, 0.17mmole) in a 5mL r.b. flask, equipped with stirring bar and N_2 flow, was added oxalyl chloride (1mL, 11mmole). The solid acid showed little signs of dissolving, so was left stirring overnight under N_2 , at which time it had dissolved. The excess oxalyl chloride was removed via a water aspirator pump using a dry ice-isopropyl bath. This was continued for a full 2 hrs, until no further volume change could be detected. The ($\pm$)-Fluoro-alcohol (20mg, 0.13mmole) was dissolved in dry pyridine (1mL), and dry benzene (2mL). To the acid chloride was added dry benzene (1mL), followed by the fluoro-alcohol solution. The solution turned cloudy, and was left for 72hrs under N_2 . Water (3mL) was added to the solution. Three 2mL portions of ether was used to extract, followed by two 3mL aliquots of 2M HCl and sat. NaCl. This was then dried

over MgSO_4 and evaporated *in vacuo* to yield the product as a clear colourless liquid. TLC showed starting reagent was still present, r_f 0, compared to the product with an r_f value of 0.4 in 20% EtOAc/Hexane. The crude product was flash chromatographed using 20% EtOAc/Hexane as eluent, yielding pure compound (46.9mg, 0.12mmole).

racemic Mosher ester

Mass spectrum (CI, ether), m/e 453 ($(M+75)^+$).

Mass spectrum (EI, 70eV), m/e 378 (M^+).

Data for (R)- and (S)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl acetate

Table 15. ^{19}F NMR of (R)- and (S)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl acetate

(R)

a	b
-108.2	4.313
bd m,1	bd s,3

(S)

a	b
-107.8	4.258
bd m,1	bd s,3

Data for (R)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl acetate

capillary GC (DB 17), retention time: 47.97 min.

Table 16. ^1H NMR of (R)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl acetate

a	b	c	d	e	f	f'	g	h	i	j	k
0.86 t,3	1.236 bd m,8	1.236 bd m,2	4.45 m,1	1.97 m,2	4.45 m,2					3.533 q,3 J(HF)= 1.2Hz	7.40, 7.48 m,5

Table 17. ^{13}C NMR of (R)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl acetate

a	b	c	d	e	f	g	h	i
	62.45 J(CF)= 5Hz	35.13 J(CF)= 20Hz	90.60 J(CF)= 168Hz	34.02 J(CF)= 21Hz	24.92 J(CF)= 5Hz	29.02	31.70	22.60

j	k	l	m	n
14.11	166.33		55.45	127.16, 128.35, 129.55, 132.11

Data for (S)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl acetate

capillary GC (DB 17), retention time: 48.28 min.

Table 18. ^1H NMR of (S)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl

a	b	c	d	e	f	f'	g	h	i	j	k
0.86 t,3	1.234 bd m,8	1.234 bd m,2	4.45 m,1	1.97 m,2	4.45 m,2					3.528 q,3 J(HF)= 1.2Hz	7.40, 7.48 m,5

Table 19. ^{13}C NMR of (S)-3-Fluorononan-1-ol, (R)- α -methoxy- α -(trifluoromethyl)phenyl

a	b	c	d	e	f	g	h	i
	62.66 J(CF)= 5Hz	35.14 J(CF)= 20Hz	90.68 J(CF)= 168Hz	34.02 J(CF)= 21Hz	24.92 J(CF)= 5Hz	29.02	31.70	22.60

j	k	l	m	n
14.16	166.49		55.56	127.18, 128.35, 129.55, 130.24

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Table 20. ^1H NMR of the dimer of (+)-4-Fluoro-1-decyne

a	b	c	d	e
0.87 1,6	1.32 bd m, 16	1.80 d of m, 4 20Hz	4.50 d of m, 2 48Hz	2.54 d of m, 4 19Hz

Table 21. ^{13}C NMR of the dimer of (+)-4-Fluoro-1-decyne

a	b	c	d	e	f	g	h	i	j
67.10	72.70 J(CF)= 101Hz	34.24 J(CF)= 20Hz	91.31 J(CF)= 175Hz	25.87 J(CF)= 26Hz	24.77 J(CF)= 3Hz	28.96	31.65	22.52	14.00

Table 20. ^1H NMR of the dimer of (+)-4-Fluoro-1-decyne

a	b	c	d	e
0.87 t, 6	1.32 bd m, 16	1.80 d of m, 4 20Hz	4.50 d of m, 2 48Hz	2.54 d of m, 4 19Hz

Table 21. ^{13}C NMR of the dimer of (+)-4-Fluoro-1-decyne

a	b	c	d	e	f	g	h	i	j
67.10	72.70 $J(\text{CF}) = 10\text{Hz}$	34.24 $J(\text{CF}) = 20\text{Hz}$	91.31 $J(\text{CF}) = 175\text{Hz}$	25.87 $J(\text{CF}) = 26\text{Hz}$	24.77 $J(\text{CF}) = 3\text{Hz}$	28.96	31.65	22.52	14.00

4.0. Appendix

Overall Sequence

Table 22. Comparison ^1H NMR table for overall sequence

compound	a	b	c	d	e	f	f'	g	h	i	j	k
1	0.87 t,3	1.35 bd m,8	1.35 bd m,2	3.73 m,1	2.33 m,2			2.03 m,1	3.20 s,1			
2-S	0.75 t,3	1.13 bd m,8	1.57 bd m,2	4.97 p,1	2.31 m,2			1.8 t,1	4.76 s,1	3.42 s,3	7.15-7.35 m,5	
2-R	0.72 t,3	0.97 bd m,8	1.45 bd m,2	4.94 p,1	2.45 m,2			1.95 t,1	4.75 s,1	3.4 s,3	7.15-7.35 m,5	
3 J(HF)	0.89 t,3	1.3 bd m,8	1.7 d of m,2 20Hz	4.59 d of m,1 48Hz	2.53 d of m,2 19Hz			2.03 t,1				
4 J(HF)	0.87 t,3	1.24 bd m,8	1.66 bd m,2	4.92 d of m,1 44Hz	2.64 m,2		5.8 bd s,1					
5 J(HF)	0.87 t,3	1.28-1.85 bd m,10		4.68 d of m,1 49Hz	1.88 m,2	3.78, 3.61 dist t, each 1						
6-S J(HF)	0.86 t,3	1.234 bd m,8	1.234 bd m,2	4.45 m,1	1.97 m,2	4.45 m,2				3.528 q,3 1.2Hz	7.40, 7.48 m,5	
6-R J(HF)	0.86 t,3	1.236 bd m,8	1.236 bd m,2	4.45 m,1	1.97 m,2	4.45 m,2				3.533 q,3 1.2Hz	7.40, 7.48 m,5	

Table 23. Comparison ^{13}C NMR table for overall sequence

compound	a	b	c	d	e	f	g	h
1	69.82	81.09	36.15	70.58	29.19	27.26	25.52	31.75
2-S *	70.40	79.22	32.68	72.61	27.18	23.73	22.34	13.89
2-R *	70.54	79.49	32.59	72.49	26.76	24.06	22.15	13.75
3	70.50	79.23	34.07	91.50	25.08	29.03	24.80	31.69
J(CF)		10Hz	20Hz	174Hz	24Hz			
4		176.32	40.22	90.06	34.82	24.78	31.66	28.95
J(CF)		6Hz	24Hz	170Hz	21Hz	4Hz		
5		59.44	37.89	92.63	35.40	25.01	29.11	31.73
J(CF)		4Hz	20Hz	166Hz	21Hz	4Hz		
6-S		62.66	35.14	90.68	34.02	24.92	29.02	31.70
J(CF)		5Hz	20Hz	168Hz	21Hz	5Hz		
6-R		62.54	35.13	90.60	34.02	24.92	29.02	31.70
J(CF)		5Hz	20Hz	168Hz	21Hz	5Hz		

compound	i	j	k	l	m	n
1	22.56	14.00				
2-S *			170.36	82.68	57.38	127.11, 128.49, 128.60, 136.28
2-R *			170.25	82.48	57.23	127.27, 128.51, 128.68, 136.38
3	22.56	14.00				
J(CF)						
4	22.54	14.01				
J(CF)						
5	22.58	14.04				
J(CF)						
6-S	22.60	14.16	166.49		55.56	127.18, 128.35, 129.55, 130.24
J(CF)						
6-R	22.60	14.11	166.33		55.45	127.17, 128.35, 129.55, 132.11
J(CF)						

* octyn series

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