Tetrahedron. Vol. 34, pp. 3 to 17. Pergamon Press 1978. Printed in Great Britain

TETRAHEDRON REPORT NUMBER 31

INTRODUCTION OF FLUORINE INTO ORGANIC MOLECULES: WHY AND HOW

M. SCHLOSSER
Institut de chimie organique, Université de Lausanne, Rue de la Barre 2, CH-1005 Lausanne, Switzerland

(*Received in UK 9 March 1977*)

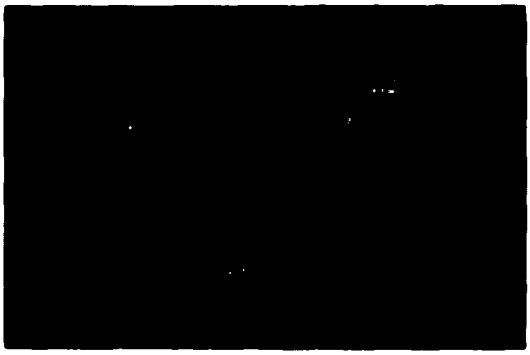


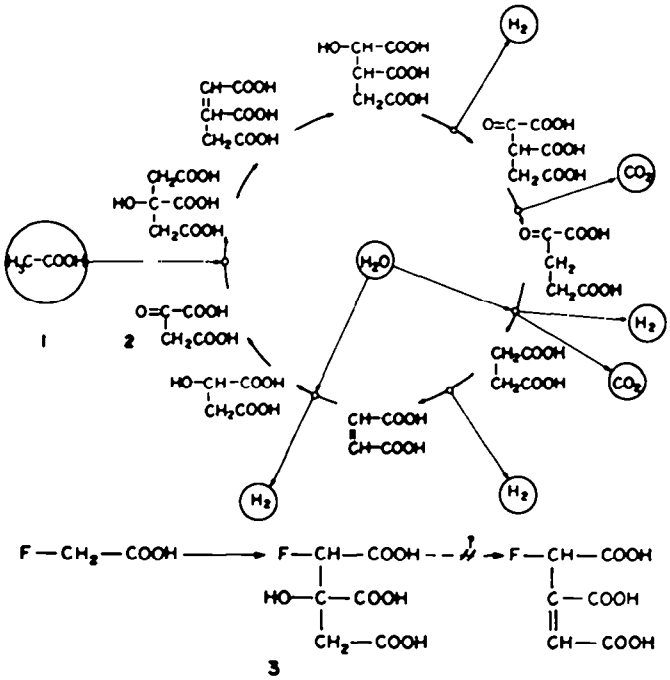
Fig. 1. Stuart/Briegleb/Leybold-models of methane, fluoromethane and chloromethane.

What is special about fluorine? Nothing else than its position in the Periodic Table. The nine protons in the nucleus of the element strongly interact with the same number of electrons, since all of them occupy inner shells. Thus the Van der Waals radius of fluorine ($r_F \sim 1.35$ Å) is contracted to such an extent that it closely ressembles that of an hydrogen atom ($r_H \sim 1.10$ Å). Actually fluorine is the only element which can replace hydrogen without notable steric consequences. Chlorine is already much bigger ($r_{Cl} \sim 1.80$ Å), as Stuart/Briegleb/Leybold-models may illustrate (Fig. 1).

In contrast to their similarity in size, hydrogen and fluorine are quite different in their reactivities. The high effective (unshielded) density of positive charge in the nucleus and the tendency to complete its valence shell render fluorine strongly electronegative. Attached to a reaction center it proves to be a moderately good leaving group. Placed in the vicinity of a reaction center it may substantially influence reaction rates due to its inductive electron-withdrawing effect.

The similarity of steric bulk and the dissimilarity of chemical behavior enable many fluorinated compounds to act as antimetabolites with respect to their corresponding halogen-free natural products. A typical example is given by fluoroacetic acid.[1,2] In biological systems it mimics acetic acid so perfectly well that it can intrude into the tricarboxylic acid cycle (Krebs/Martius/Knoop cycle). This metabolic circuit which burns 1 molecule of acetic acid per turnover to carbon dioxide and water comprises three stages: formation and modification of a C_6-unit, double decarboxylation preceded, accompanied or followed by dehydrogenation steps and, finally, remodelling of the remaining C_4-unit in order to prepare it for the addition of another molecule of acetic acid (1).

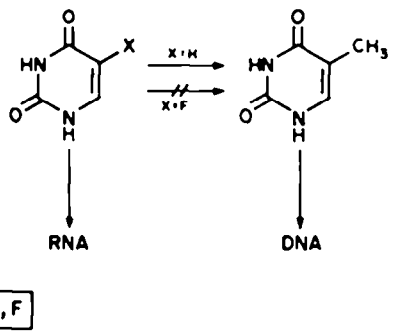
When fluoracetic acid (or a precursor to it, e.g. fluorooleic acid) is ingested, it replaces the natural metabolite and combines with the oxalylacetic acid (2) to give α-fluorocitric acid (3).



According to the metabolic cycle, the subsequent steps are now dehydratation affording aconitic acid and rehydration with reversed orientation yielding isocitric acid. However, neighboring fluorine atoms drastically impede the acid-catalyzed elimination of water as one may deduce from simple laboratory experiments. 1,1,1-Trifluoro-2-propanol[3-5] is not altered by concentrated sulfuric acid at 190°C! Likewise, the dehydrating enzyme aconitase is unable to effect elimination of water from fluorocitric acid.[6]†

Still nothing dramatic would happen if the fluorocitric acid did not bind irreversibly. Once being formed, it can neither be eliminated as such nor "digested", but paralyzes for ever biomolecular key-units. Thus the organism has performed a "lethal synthesis" (*Peters*[11]): the incorporated fluoroacetic acid molecule is converted *in vivo* into an antimetabolite which blocks irrevocably the vital tricarboxylic acid cycle. Actually, thousands of cattle are lost per year mainly in South Africa, Australia and other parts of the Southern hemisphere after eating plants like gifblaar (*Dichapetalum cynosum*), box poison (*Oxylobium parviflorum*) or heart lead poison (*Gastrolobium bilobum*). The toxicity in these plants is due to the presence of fluoroacetic acid, the concentration of which may occasionally exceed 1% of the dry weight of leaves or seeds.

Once the principle of "*antimetabolite formation by introduction of fluorine*" had been recognized, it was tempting to apply it to chemotherapy. With this idea in mind, Heidelberger, Duschinsky *et al.*[12] synthesized 5-fluorouracil and its derivatives. 5-Fluorouracil was found to be incorporated in place of uracil into RNA of bacterial and mammalian cells as well as that of viruses causing mutagenesis, transcription errors and other defects. Still more important, it was demonstrated that 5 - fluoro - 2' - desoxyuridine - 5' - monophosphate, which is produced *in vivo* from 5-fluoro-uracil, acts as an inhibitor of thymidylate synthetase. This enzyme catalyzes the methylation of desoxyuridylate to desoxythymylate. Thymine is one of the four letters of the hereditary alphabet by means of which the complete wiring diagram of life is stored on the DNA ribbon. If thymine (4) is no longer available, no replication of the DNA double helix can be possible and cell division is prevented. By this mechanism the major inhibitory effect of 5-fluorouracil on tumour growth is explained.[13]



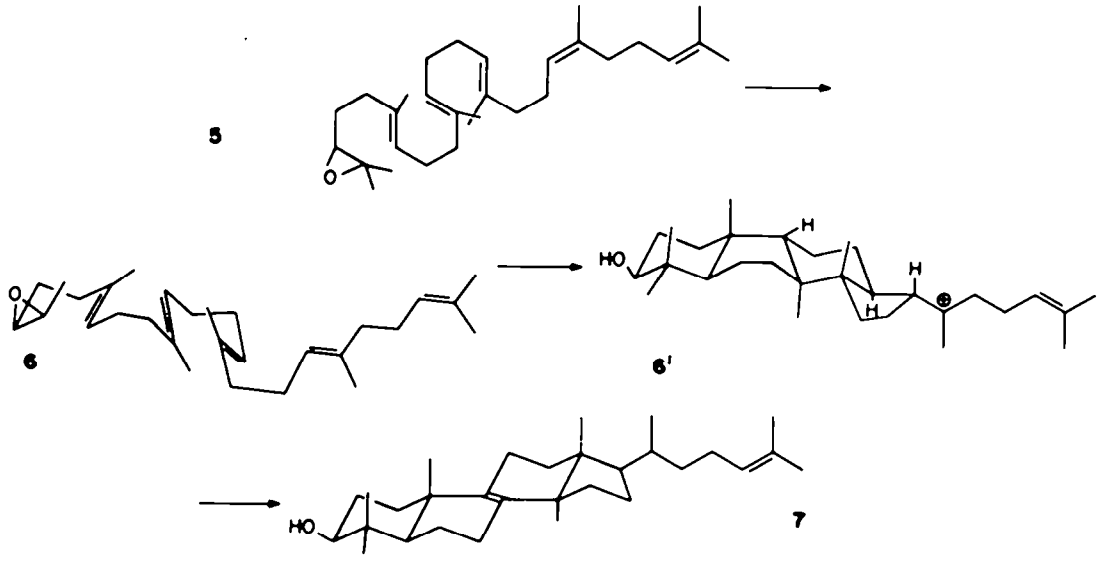
4

5-Fluorouracil and its derivatives belong to the few drugs which are successfully employed in cancer treatment. Unfortunately, however, side effects cannot be avoided and they threaten to affect the entire organism seriously. Particularly the replacement of short-lived normal cells is arrested. Such a low selectivity between benignant and malignant tissues seems to be inevitable, whenever the applied reagent interferes with the living system at only one stage, in other words, when an "all-or-nothing" situation arises. We may hope, however, to produce good overall selectivity by a "snow-ball effect". Let us consider a long biogenetic chain, into which we channel in a fluorinated antimetabolite at an early stage. Let us further assume that the halogen in the antimetabolite will never cause a real breakdown of the biological transformation but rather will perturb them slightly yet continuously, so that a tumour cell may suffer more from such an impact than would a normal cell. Because of the unrestrained tumour proliferation, the emzyme pattern of malignant cells is generally less perfect and balanced than in benign ones. Thus, as biosynthesis goes on, more and more "waste products" may accumulate in the tumour and poison it while in healthy organs the undesired materials are kept under control and are eliminated by rapid degradation.

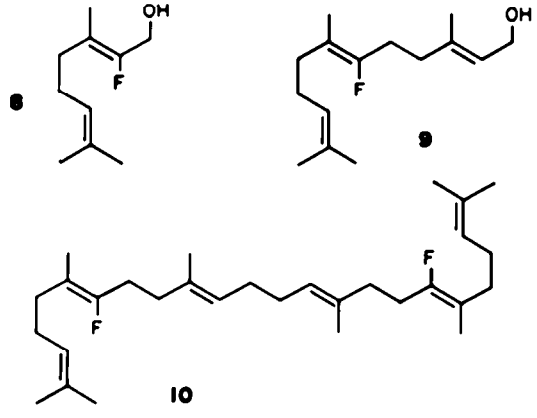
This general strategy led us to prepare a number of fluoroterpenes and to study their cytostatic behavior. Their natural, halogen-free analogs are known as intermediates of steroid biosynthesis,[14,15] the key compound of which is epoxysqualene (5). Several steroid families descend from this oxirane. Their skeletal structure is dictated by the conformation which the C_{30}-epoxide 5 adopts when getting enveloped by the enzyme. For example, when combining with the squaleneoxide cyclase extracted from rat liver or yeast, it folds in order to acquire the conformation 6. In the four ring system 6', which first emerges from the cyclisation process two methyl groups and two hydrogen atoms have to perform a "relay-race" and another hydrogen is cleaved off as a proton in order to adjust the steroid skeleton to its final geometry. The first isolable polycyclic product, lanosterol (7), undergoes a series of subsequent oxidation and degradation reactions which convert it into cholesterol and thence corticoids or other important steroids.

As already outlined, fluorinated antimetabolites may cause a subtle perturbation of the steroid biosynthesis and hopefully damage tumour cells selectively. Besides cancerostatic activity, fluoroterpenes produced *in vivo* may exhibit other pharmaceutical effects. Many fluorosteroids are known to be powerful drugs with anti-

†A closer inspection reveals that the methylene hydrogens in citric acid are pairwise enantiopic or diastereotopic and therefore enzymatically distinguishable. The hydrogen abstracted by aconitase occupies the *re*-side (pro-*R* configuration) and is located on that hydroxycarbonylmethylene branch which, upon substitution, imposes the *R* configuration on the central carbon atom. Thus, the enzyme can by no means accomplish the dehydration of (2*R*, 3*R*) - 2 - fluorocitric acid ((−)erythro-fluorocitric acid). In the three other stereoisomers (2*R*, 3*S*; 2*S*, 3*R*; 2*S*, 3*S*), the halogen does not block a reactive site and may operate only by its electron-attracting, bond-strengthening effect. All three of them were found to be neither substrates nor inhibitors of aconitase to any significant extent.[7,8] More recently the mode of action of fluorocitric acid in the *Krebs* cycle has been fundamentally redefined.[9,10] Although (2*R*, 2*S*)-2-fluorocitric acid indeed is capable of specific aconitase inhibition, this action occurs only reversibly and at relatively high doses ($k_i \sim 0.1$ mM). The extremely poisonous properties of this particular stereoisomer (*in vivo* caused by picomolar quantities!), however are due to a *neurotoxic* effect. Compelling evidence has been presented according to which it is rather the tricarboxylic acid carrier in the inner membrane of mitochondria to which fluorocitric acid binds irreversibly. Probably in this way the citrate outflux from mitochondria of brain cells is stopped and the biosynthesis of the neurotransmitter acetylcholine breaks down.



inflammatory, antiphlogistic, anti-allergic, glucocorticoidal and anabolic properties.[14] In order to examine these hypotheses, we have investigated the synthesis of fluorosqualenes (such as **10**) and the respective epoxides as well as fluorofarnesols (such as **9**) and fluorogeraniols (such as **8**) which are supposed to be biogenetic precursors to **10**.

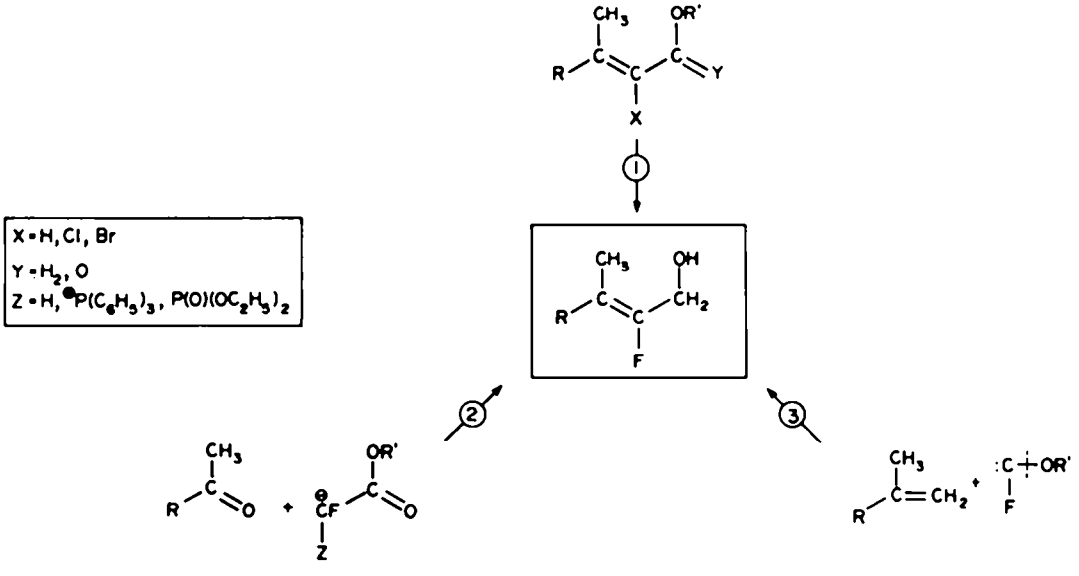


We started out to explore systematically all possible routes promising selective introduction of a fluorine, a problem which soon turned out to be a challenging one. Note that the fluorine should necessarily occupy an olefinic site. All other available positions are allylic ones and an halogen placed there would be far too labile. This restriction considerably reduces the choice of suitable methods for the introduction of one fluorine atom. In addition to that, the proper position and configuration of the CC double bond has to be retained. A systematic analysis of the problems discloses three practical approaches:

(1) Introduction of the fluorine atom by replacement of an electrofugal or nucleofugal leaving group X on a pre-constructed carbon skeleton; no new CC bond has to be formed.

(2) Condensation between an α-fluorocarbanion and a carbonyl compound, i.e. formation of one new CC double bond.

(3) Insertion of a fluoromethine group into a CC double bond and simultaneous addition of an hydroxyl group (or derivative thereof) onto the methylene terminus of this olefinic bond, forming two new CC-linkages.

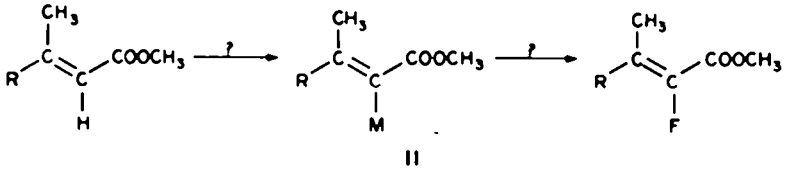


The isoprene unit shown in the middle of the diagram is tacitly understood to bear appropriate functional groups at one end or both ends of its structure in order to present a useful building block for an assembling synthesis of fluoroterpenes.

Substitution reactions for the introduction of a fluorine atom

Clearly the most straightforward method for fluorine introduction would consist of the following reaction sequence: preparation of the halogen-free terpene ester (for example methyl *E*-2,6-octadienoate, geranic acid methyl ester, **11**), metallation at the position adjacent to the carbonyl group and replacement of the metal by fluorine.

The next approach was the addition of elemental fluorine onto the double bond of an α,β-unsaturated ester (such as **11**) or the ring opening of the corresponding oxirane (**12**) with fluorohydric acid,[49,50] boron trifluoride-etherate[50] or diethyl - (2 - chloro - 1,1,2 - trifluoroethyl) - amine‡ and subsequent elimination of hydrogen fluoride or, respectively, water. Immediately one recognized some major obstacles. The regioselective addition of the halogen would require special techniques or precautions, for example, the protection of other double bonds, if present in the starting ester. Moreover both pathways would, in general, lead to a stereoisomeric product mixture. As Merritt[55-57] has already demonstrated, *syn*- and *anti*-eliminations operate simultaneously when *vic*-difluoroalkanes are the substrates. A similar lack of stereo-



11

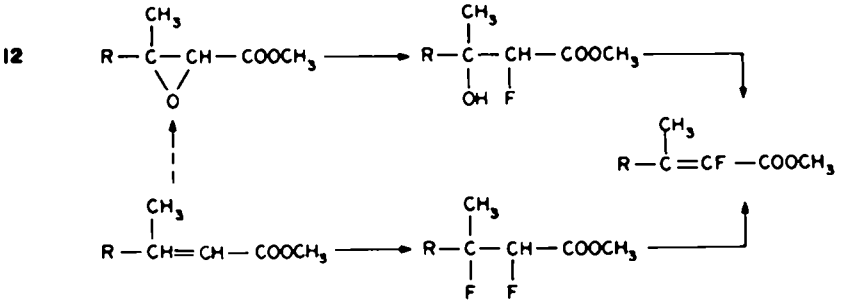
R = $(H_3C)_3C{=}CH{-}CH_2{-}CH_2$
M = Li etc.

Perchloryl fluoride ($FClO_3$) is very convenient source of "positive" fluorine which can be transferred to the negatively charged carbon atom of organometallics of the magnesium and lithium type[17-20]† (see Table 1), phosphorus ylids,[22-25] enolates[19,26-37] or α-nitrocarbanides,[38] enethers, enacetates or enamines.[39-46] α-Metallated α,β-unsaturated esters are also known, although they are only accessible from the corresponding α-bromo α,β-unsaturated ester[47] and not from the unsaturated esters themselves. Exploratory experiments revealed, however, that organometallic intermediates such as **12**, when treated with an electrophile, invariably give rise to a mixture of *Z*- and *E*-isomers of the resulting fluoroolefin. Probably compounds of the type **12** prefer to exist in the metallomeric[48] structure of a ketene hemiacetale that is the metal binds to the electron-rich oxygen-atom of the former carbonyl group. Consequently no stereochemical control can be achieved.

chemical discipline must be anticipated for the dehydration of fluorohydrins. Finally the starting material, unsaturated esters and alkoxycarbonyloxiranes, are commonly available only as a *Z*/*E*-mixture (for example, oxiranes **12** from a Darzens reaction) and the separation of pure isomers is very tedious.

†Neither xenon difluoride nor trifluoromethyl hypofluoride (perfluoromethanol) are efficient reagents for fluorine transfer to organolithium compounds. All identified products were derived from the organic free radical, left behind after homolytic cleavage of the metal (which gives quantitatively LiF).[21]

‡The "Raksha reagent"[51-53] offers a convenient possibility to convert, for example, cyclohexene oxide (7-oxanorcarane) into *cis*-1,2-difluorocyclohexane (40% yield; same result with the corresponding episulfide).[54]



R = H_3C, $(H_3C)_3C{=}CH{-}CH_2{-}CH_2$ etc

Table 1. Reaction between organolithium (organomagnesium) compounds and perchloryl fluoride

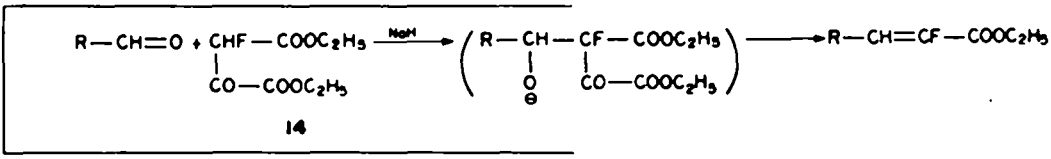
Gross formula	Product Structure	Preparation of the organometallic precursor	Solvent[a]	Yield (%)	Ref.
C_4H_3FS	2-fluorothiophene	thiophene + LiC_4H_9	DEE	49	17
C_5H_5FS	2-fluoro-5-methylthiophene	methylthiophene + LiC_4H_9	DEE	44	17
$C_5H_9FO_2$	α-fluorovaleric acid	valeric acid + $LiN(C_3H_7)_2$	HMPT + THF	18	19
C_6H_5F	fluorobenzene	bromobenzene + Li	THF + DEE	42	19
$C_6H_{11}F$	fluorocyclohexane	chlorocyclohexane + Li	THF + DEE	68	19
C_7H_7F	α-fluorotoluene (benzyl fluoride)	tribenzyltin chloride + $LiCH_3$	THF + DEE	50[b]	19
$C_6H_5FN_2O_2$	*O,O*-dimethyl-5-fluoro-uracil	*O,O*-dimethyl-5-iodo-uracil + LiC_4H_9	DME + THF + DEE	42	20
$C_7H_{11}F$	*anti*-7-fluoronorcarane	bromonorcarane + Li	THF + DEE	83	19
C_8H_5FS	2-fluorobenzo[*b*]thiophene	benzo[*b*]thiophene + LiC_4H_9	DEE	70	17
C_8H_6ClF	*E*-β-chloro-β-fluorostyrene	β-chlorostyrene + LiC_4H_9	THF + DEE	45	19
C_8H_7F	fluorocyclooctatetraene	bromocyclooctatetraene + Li	DEE	10	18
$C_{10}H_7F$	2-fluoronaphthalene	2-chloronaphthaline + Li	THF + DEE	45	19
$C_{12}H_8F_2$	2,2'-difluorobiphenyl	diiodobiphenyl + LiC_4H_9	THF + DEE	94	19
$C_{12}H_{25}F$	fluorododecane	chlorododecane + Li	THF + DEE	39	19

[a] DEE = diethyl ether; DME = 1,2-dimethoxy ethane (ethyleneglycol dimethylether); HMPT = hexamethylphosphorictriamide; THF = tetrahydrofuran.

[b] 39% with benzylmagnesiumchloride in THF and in the presence of HMPT.

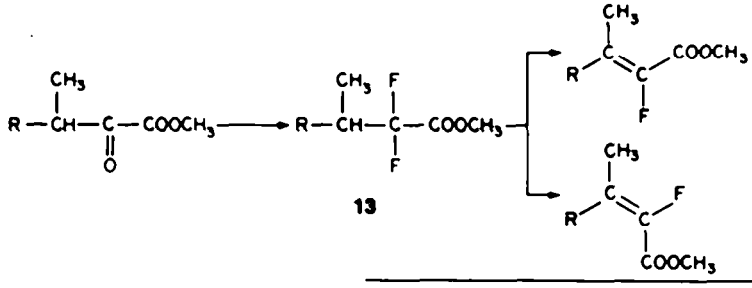
Lack of stereoselectivity advocated also against a further possibility, that is the elimination of hydrogen fluoride form geminal difluorides of the type 13. They are readily obtained by treatment of the corresponding carbonyl compounds with sulfur tetrafluoride or, better, dimethylaminosulfurtrifluoride.[59] Although the dehydrofluorination can be brought about under very mild conditions (by simple filtration over silica, as Boswell[60] has discovered), there is little chance to direct the elimination course towards one of the two isomers.

Therefore, the introduction of fluorine into the preconstructed carbon skeleton was abandoned as a rational solution to our problem.



14

By this method, Bergmann *et al.*[65-67] have prepared a number of α,β-unsaturated α-fluorocarboxylic esters in



13

Condensation reactions for fluorine introduction

Aldol-type condensations are applicable only in very exceptional cases (e.g. benzaldehyde and ω-fluoroacetophenone forming 1,3-diphenyl 2-fluoro-2-propen-1-one in 40% yield[61,62]). Usually they give rise to a complex mixture of products. Even Perkin- and Knoevenagel-type condensations often fail completely or suffer from poor yields. Benzaldehyde and fluoroacetic anhydride in the presence of sodium fluoroacetate do not afford more than 2% α-fluorocinnamic acid.[63] Ethyl fluoroacetate condenses with benzaldehyde, *p*-nitrobenzaldehyde and cinnamaldehyde under the influence of sodium hydride to form 15, 13 and, respectively, 34% of the desired acid or its corresponding ester.[63] Yields obtained under slightly modified reaction conditions were 58, 52, 19 and 32% with benzaldehyde, *p*-anisaldehyde, butanal and isobutyral, respectively.[64] The result can be significantly improved, if diethyl fluoro-oxaloacetate (diethyl fluoro-oxosuccinate 14), a protected and activated fluoroacetic acid, is used as the nucleophilic condensation partner.

fair to good yields (Table 2). Many types of aldehydes, aliphatic and aromatic, unsaturated and heterosubstituted ones, were found to be reactive. However, no successful condensation involving a ketone function was reported.

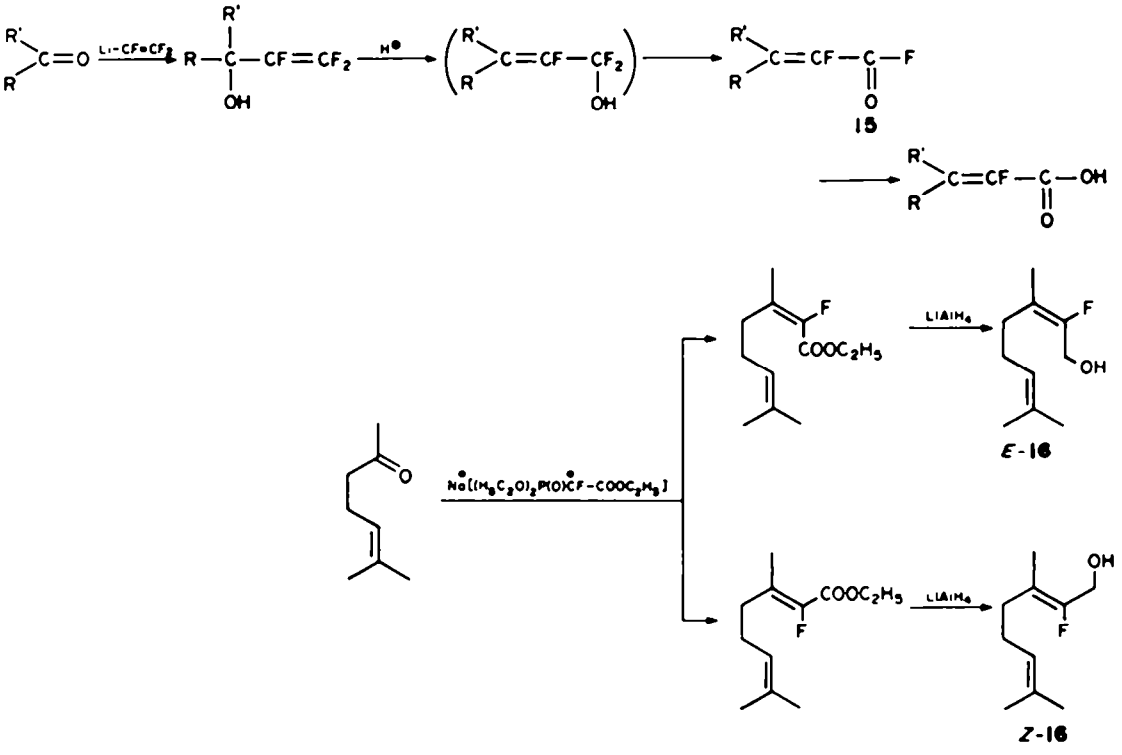
The chain elongation of ketones by a (hydroxycarbonyl)-fluoromethylene unit can quite satisfactorily be achieved by an indirect route. According to Knunyants[68] trifluorovinylmetals (trifluorovinylmagnesiumiodide,[68] trifluorovinyllithium,[69-72] trifluorovinylsodium[73]) may be added to carbonyl compounds

Table 2. Ethyl esters of α,β-unsaturated α-fluorocarboxylic acids (R–CH=CF–$COOC_2H_5$) by base-catalyzed condensation reaction between different aldehydes R–CH=O and diethyl fluoro-oxaloacetate

Gross formula	Product: Structure	Starting material: aldehyde	Yield (%)	Ref.
$C_6H_4Cl_3FO_2$	ethyl 4,4,4-trichloro-2-fluoro-2-butenoate	chloral	51	65
$C_6H_7Cl_2FO_2$	ethyl 4,4-dichloro-2-fluoro-2-butenoate	dichloroacetaldehyde	75	65
$C_6H_9FO_2$	ethyl 2-fluoro-2-butenoate	acetaldehyde	61	64
$C_7H_9FO_3$	ethyl 3-oxiranyl-2-fluoro-2-propenoate	glycinaldehyde	44	65
$C_8H_{11}FO_2$	ethyl 2-fluoro-4-methyl-2,4-pentadienoate	α-methacryl aldehyde	20	65
$C_8H_{13}FO_2$	ethyl 2-fluoro-4-methyl-2-pentenoate	isobutyraldehyde	70	64
$C_8H_{13}FO_2$	ethyl 2-fluoro-2-hexenoate	butyraldehyde	66	64
$C_9H_9FO_2S$	ethyl 2-fluoro-3-(2-thienyl)-2-propenoate	2-formylthiophene	60	65
$C_9H_9FO_3$	ethyl 2-fluoro-3-(2-furyl)-2-propenoate	furfural	38	65
$C_{10}H_{10}FNO_2$	ethyl 2-fluoro-3-(2-pyridyl)-2-propenoate	2-formylpyridine	35	64
$C_{10}H_{10}FNO_2$	ethyl 2-fluoro-3-(3-pyridyl)-2-propenoate	3-formylpyridine	40	64
$C_{10}H_{15}FNO_3$	ethyl 2-fluoro-4-methyl-5-oxo-2-heptenoate	2-methyl-3-oxo-valeraldehyde	60	64
$C_{10}H_{12}FNO_4$	ethyl butyl 2-fluorofumarate	butyl glyoxalate	75	64
$C_{11}H_{10}ClFO_2$	ethyl 2-fluoro-3-*p*-chlorophenyl-2-propenoate	*p*-chlorobenzaldehyde	74	64
$C_{11}H_{10}FNO_4$	ethyl 2-fluoro-3-*p*-nitrophenyl-2-propenoate	*p*-nitrobenzaldehyde	52	65
$C_{11}H_{11}FO_2$	ethyl 2-fluoro-3-phenyl-2-propenoate	benzaldehyde	68	64
$C_{11}H_{15}FO_3$	ethyl 2-fluoro-3-(2-oxocyclohexyl)-2-propenoate	2-formylcyclohexanone	20	65
$C_{12}H_{13}FO_2$	ethyl 2-fluoro-3-*p*-tolyl-2-propenoate	*p*-tolylaldehyde	65	64
$C_{12}H_{13}FO_2$	ethyl 2-fluoro-4-phenyl-2-butenoate	phenylacetaldehyde	63	64
$C_{13}H_{13}FO_4$	ethyl 3-(*o*-acetoxyphenyl)-2-fluoro-2-propenoate	*o*-acetoxybenzaldehyde	61	64
$C_{13}H_{13}FO_4$	ethyl 3-(*m*-acetoxyphenyl)-2-fluoro-2-propenoate	*m*-acetoxybenzaldehyde	62	65
$C_{13}H_{13}FO_4$	ethyl 3(*p*-acetoxyphenyl)-2-fluoro-2-propenoate	*p*-acetoxybenzaldehyde	70	65
$C_{13}H_{15}FO_2$	ethyl 2-fluoro-4-phenyl-2-pentenoate	2-phenylpropanal	50	65
$C_{15}H_{13}FO_2$	ethyl 2-fluoro-3-(1-naphthyl)-2-propenoate	1-naphthaldehyde	48	65
$C_{15}H_{14}FNO_3$	ethyl 3-(*N*-acetyl-3-indolyl)-2-fluoro-propenoate	*N*-acetyl-3-formylindole	60	65
$C_{15}H_{17}FO_3$	ethyl 4-benzoyl-2-fluoro-2-hexonate	α-formylbutyrophenone	40	65

and the resulting alcohol may undergo acid-catalyzed allylic isomerization to afford an α,β-unsaturated α-fluoroacyl fluoride **15** or, after hydrolysis, the corresponding carboxylic acid. Unfortunately ketones with unequal groups R and R' flanking the carbonyl function are inevitably converted to a mixture of *Z*/*E*-isomeric products (unless one of them, R or R', is a tertiary alkyl).

The same stereochemical non-selectivity is observed when ketones are condensed with α-fluorinated ylids. Thus, Machleidt *et al.*[74] obtained from 6-methyl-5-hepten-2-one, diethyl (ethoxycarbonyl)-fluoromethanephosphate and sodium hydride a 1:1 mixture of *Z*- and *E*-ethyl 2 - fluoro - 3,7 - dimethyl - 2,6 - octadienoate which was reduced with lithium aluminium



hydride to yield 2-fluorogeraniol (*Z*-**16**) and 1-fluoronerol (*E*-**16**). In the same manner geranylacetone was converted to a 1:1 mixture of *Z,E*- and *E,E*-α-fluorofarnesol (consult Tables 3 and 4 for a survey on Wittig reactions involving α-fluorinated ylids).

A modification of the Wittig reaction (SCOOPY[61-63] technique, "three-dimensional" Wittig reaction) permits perfect control over the olefin stereochemistry, provided that an aldehyde is chosen as the carbonyl component. α-Metallated β-lithiumoxyalkylphosphonium halides, so-called "betaine-ylids" (**17**), are the key intermediates in this reaction sequence. At this stage, diastereomeric mixtures equilibrate due to rapid pyramidal inversion of the carbanionic center adjacent to the phosphorus atom. If an aliphatic or aromatic group R' and an hydrogen atom (R" = H) compete for the sterically less hindered position, the quasi-*threo* configuration (*RS* + *SR*, R" being alkyl) is favored to the extent of approximately 99.5%.

Table 3. Wittig reactions utilizing α-fluorinated ylids with a C_1-unit as the side chain: replacement of carbonyl oxygen by a fluoromethylene, a difluoromethylene or a chlorofluoromethylene group

Formula	Product Structure	Starting material: carbonyl compound[a]	Olefin yield %	Mode of ylid generation
$C_6H_4F_2O$	2-(2,2-difluorovinyl)-furan	furfural	69	*b*
$C_7H_9ClF_4$	2-trifluoromethyl)-1-chloro-1-fluoro-hexene	1,1,1-trifluoro-2-hexanone	34	*c*
$C_7H_{11}F$	(fluoromethylene)-cyclohexane	cyclohexanone	69	*d*
$C_7H_{13}F$	1-fluoro-1-heptene	hexanal	55	*d*
$C_8H_2F_6$	1-fluoro-2-pentafluorophenylethylene	pentafluorobenzaldehyde	65	*e*
$C_8H_5F_2NO_2$	1-fluoro-2-(*p*-nitrophenyl)-ethylene	*p*-nitrobenzaldehyde	2[h]	*b*
$C_8H_5F_3$	1,1-difluoro-2-*p*-fluorophenylethylene	*p*-fluorobenzaldehyde	65	*b*
C_8H_6ClF	2-*p*-chloro-1-fluoro-phenylethylene	*p*-chlorobenzaldehyde	65	*d*
C_8H_6DF	[β-^{2}H]-β-fluorostyrene	benzaldehyde	64	*d*
$C_8H_6F_2$	β,β-difluorostyrene	benzaldehyde	74	*b*
C_8H_7F	β-fluorostyrene	benzaldehyde	65[i]	*d,f*
$C_8H_{14}F_2$	1,1-difluoro-1-octene	heptanal	52	*b*
$C_8H_{15}F$	1-fluoro-1-octene	heptanal	54	*d,e*
$C_9H_4BrF_5$	2-(*m*-bromophenyl)-pentafluoropropene	*m*-bromophenyl tripluoromethyl ketone	83[j]	*g*
$C_9H_4ClF_5$	2-(*p*-chlorophenyl)-pentafluoropropene	*p*-chlorophenyl trifluoromethyl ketone	86[k]	*g*
$C_9H_4Cl_2F_4$	2-(*p*-chlorophenyl)-1-chloro-1,3,3,3-tetrafluoropropene	*p*-chlorophenyl trifluoromethyl ketone	53[e]	*c*
$C_9H_4F_6$	2(*p*-fluorophenyl)-pentafluoropropene	*p*-fluorophenyl trifluoromethyl ketone	27	*c*
$C_9H_5ClF_4$	2-phenyl-1-chloro-1,3,3,3-tetrafluoropropene	phenyl trifluoromethyl ketone	56	*c*
$C_9H_5Cl_2F_3$	2-phenyl-1,3-dichloro-1,3,3-trifluoropropene	chlorodifluoromethyl phenyl ketone	29	*c*
$C_9H_6F_5$	2-phenyl-pentafluoropropene	phenyl trifluoromethyl ketone	85[l]	*g*
$C_9H_6F_4$	1-fluoro-2-(*m*-trifluoromethyl phenyl)-ethylene	*m*-trifluoromethylbenzaldehyde	25	*d*
$C_9H_6F_4$	2-phenyl-1,3,3,3-tetrafluoropropene	phenyl trifluoromethyl ketone	80	*d,e*
$C_9H_6F_2O$	2(*p*-anisyl)-1,1-difluoroethylene	*p*-anisaldehyde	60	*b*
C_9H_6F	1-fluoro-2-phenylpropene	acetophenone	49	*d*
$C_9H_{11}ClF_4$	2-cyclohexyl-1-chloro-1,3,3,3-tetrafluoropropene	cyclohexyl trifluoromethyl ketone	70	*c*
$C_{10}H_4BrF_7$	2-(*m*-bromophenyl)-heptafluoro-1-butene	*m*-bromophenyl pentafluoro ketone	87[m]	*q*
$C_{10}H_5ClF_6$	2-phenyl-1-chloro-1,3,3,4,4,4-hexafluoro-1-butene	pentafluoroethyl phenyl ketone	42	*c*
$C_{10}H_5F_7$	2-phenyl-bentafluoro-1-butene	pentafluoroethyl phenyl ketone	82	*g*
$C_{10}H_7ClF_4$	2-(*p*-tolyl)-1-chloro-1,3,3,3-tetrafluoropropene	*p*-tolyl trifluoromethyl ketone	48	*c*
$C_{10}H_7ClF_4$	2-benzyl-1-chloro-1,3,3,3-tetrafluoropropene	benzyl trifluoromethyl ketone	37	*c*
$C_{10}H_7ClF_4O$	2-(*p*-anisyl)-1-chloro-1,3,3,3-tetrafluoropropene	*p*-anisyl trifluoromethyl ketone	67	*c*
$C_{11}H_5ClF_8$	2-phenyl-1-chloro-1,3,3,4,4,5,5,5,-octafluoro-1-pentene	heptafluoropropyl phenyl ketone	41	*c*
$C_{14}H_{11}F$	1-fluoro-2,2-diphenylethylene	benzophenone	69	*d*
$C_{28}H_{37}FO_2$	17-fluoromethylene-5-androsten-3β-yl 2-tetrahydropycanyl ether	5-androsten-17-on-3β-yl 2-tetrahydropyranyl ether	16	*d*

[a] Invariably as a *Z*/*E*-mixture, if the new double bond is unsymmetrically substituted.

[b] Aldehyde, triphenylphosphine and sodium chlorodifluoroacetate bis-(1-methoxy-ethoxy)-ether ("diglyme") at 160°C.[73]

[c] Polyfluoroketone, triphenylphosphine and sodium dichlorofluoroacetete in 1,2-bis-2-methoxy-ethoxy)-ethane ("triglyme") at 90°C.[77]

[d] Carbonyl compound and triphenylphosphonio fluoromethylid in tetrahydrofuran, temperature range from −78°C to 0°C or 25°C.[23,79]

[e] Carbonyl compound, (fluoroiodomethyl)-triphenylphosphonium iodide and zinc-copper couple in dimethylformamide at 0°C.[79]

[f] 60% Yield, if the "*SCOOPY*" method[22] was applied.

[g] Carbonyl compound, triphenylphosphine (2 equiv.) and dibromodifluoromethane in bis-(2-methoxy-ethoxy)-ether at 70°C.[78]

[h] Together with 20% 1,1,1-trifluoro-2-*p*-nitroethane, resulting from base-catalyzed addition of HF to $C_8H_5F_2NO_2$.

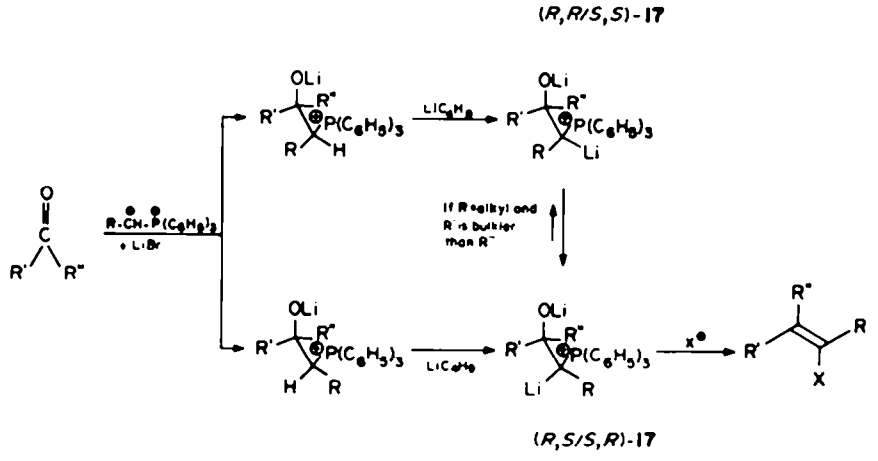
[i] 63% β-fluorostyrene, together with 12% styrene, when a solution of (fluoromethyl)-triphenylphosphonium iodide and benzaldehyde in dichloromethane was treated with potassium *t*-butoxide (2 equiv.) at 25°C.[24]

[j] 2% $C_9H_4BrF_5$ accompanied by 65% $C_9H_5BrF_6$ (base-catalyzed HF-addition!), if *m*-bromophenyl trifluoromethyl ketone, triphenylphosphine and sodium chlorodifluoroacetate were allowed to react.[76]

[k] 32% $C_9H_4ClF_5$ accompanied by 37% $C_9H_5ClF_6$ (base-catalyzed HF-addition !), if *p*-chlorophenyl trifluoromethyl ketone, triphenylphosphine and sodium chlorodifluoroacetate were allowed to react.[76]

[l] The yield reached only 33%, when phenyl trifluoromethyl ketone was treated with (bromodifluoromethyl)-triphenylphosphonium bromide in the presence of potassium fluoride.[80]

[m] 42% 2-(-Bromopbenyl)-heptafluoro-1-pentene accompanied by 54% 2-(*m*-bromophenyl)-heptafluoro-2-pentene, resulting from a base-catalyzed isomerisation.[76]



Treatment with a proton donor leads exclusively to *trans*-alkenes, reaction with an electrophile X give rise to a single isomer of an trisubstituted ethylene.

On the other hand, a primary alkyl and methyl group differ little in steric requirement. Therefore, when 2-methyl-2-hepten-6-one, instead of an aldehyde, was subsequently treated with triphenylphosphonio - 4 - (1,3 - dioxolan - 2 - yl) - 1 - pentylid (18), butyllithium, perchloryl fluoride and dilute acid, (2-fluoroneryl)acetone and (2-fluorogeranyl)acetone were identified in nearly equal amounts.[84]

Thus, the condensation approach also turned out to be inappropriate for our proper purpose.

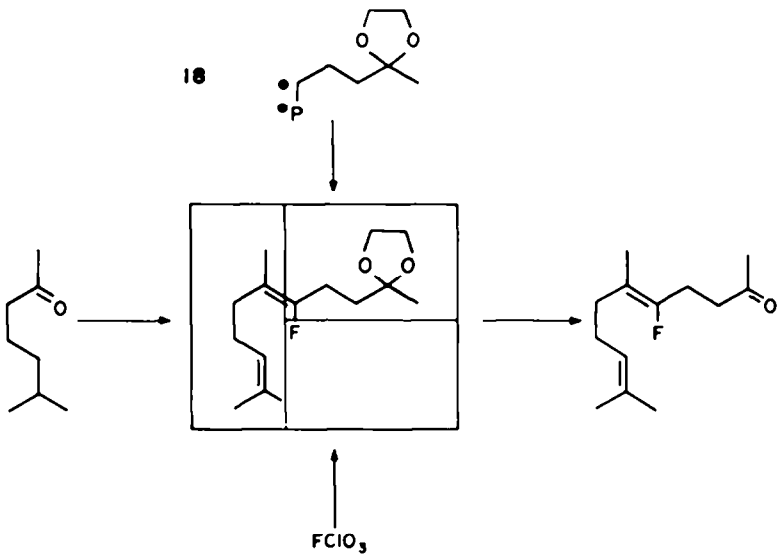
Table 4. Wittig and Wittig/Horner reactions leading to 1-enefluoro compounds and utilizing ylid intermediates with a C_7-unit or longer side chain

Gross formula	Product Structure	Starting material: Carbonyl compound[a]	Olefin yield %	Mode of ylid generation
$C_7H_9F_3O$	ethyl 2,4-difluoro-3-fluoromethyl-2-butenoate	α,α'-difluoroacetone	54	*b*
$C_7H_{11}FO_2$	ethyl 2-fluoro-3-methyl-2-butenoate	acetone	63	*b*
$C_7H_{13}F$	4-fluoro-3-heptene	propanal	52	*c*
$C_8H_{13}FO_2$	ethyl 2-fluoro-4-methyl-2-pentanoate	isobutyral	55	*b*
$C_{10}H_9F$	1-fluoro-4-phenyl-1,3-butadiene	cinnamaldehyde	25	*c*
$C_{12}H_{19}F_3O_2$	ethyl 2,4-difluoro-3,7-dimethyl-2,6-octadienoate	5-fluoro-2-methyl-2-hepten-6-one	53	*b*
$C_{12}H_{19}FO_2$	ethyl 2-fluoro-3,7-dimethyl-2,6-octadienoate	2-methyl-2-hepten-6-one	58	*b*
$C_{14}H_{21}FO_2$	ethyl 2-fluoro-3-(2,6,6-trimethyl-1-cyclohexenyl)-propenoate	2,6,6-trimethyl-1-cyclohexenyl-carbaldehyde ("β-cyclocitral")	50	*b*
$C_{15}H_{25}FO_2$	7-fluoro-2,6-dimethyl-10-(1,3-dioxol-2-yliden)-2,6-undecadien	2-methyl-2-hepten-6-one	30	*c*
$C_{17}H_{25}FO_2$	ethyl 2-fluoro-3-methyl-5-(2,6,6-trimethyl-1-cyclohexenyl)-,24-pentadienoate	1-(2,6,6-trimethyl-1-cyclohexenyl)-1-buten-3-one ("β-ionone")	40	*b*
$C_{17}H_{27}FO_2$	ethyl 2-fluoro-3,7,11-trimethyl-2,6,10-dodecatrienoate	*E*-2,6-dimethyl-2,6-undecadien-10-one ("geranylacetone")	48	*b*
$C_{29}H_{45}FO_2$	17β-(3-fluoro-2-pentenyl)-5-androsten-3β-yl 2-tetrahydropyranyl ether	5-pregnen-17-on-3β-yl 2-tetrahydropyranyl ether	29	*c*

[a] If an unsymmetrically substituted double bond is going to be constructed, the two possible configurational isomers will generally be formed with fairly equal probability. Exceptions are found when aldehydes are submitted to *SCOOPY* olefination reactions, the halo-alkenes formed having almost exclusively *Z*-configuration[81] (unless a radical chain mechanism intervenes) or aldehydes are condensed with diethyl (ethoxycarbonyl)-fluoromethanephosphonate, the esters being obtained predominantly (~90%) as *E*-isomers.[74]

[b] Carbonyl compound and "PO-ylid" prepared from diethyl ethoxycarbonylmethanephosphonate and sodium hydride, in diethyl ether at 35°C.[74]

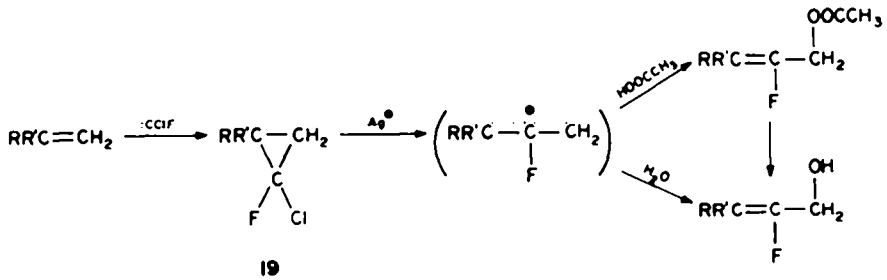
[c] "*SCOOPY*" technique.[22,83]



Cycloaddition reactions for fluorine introduction

The general synthetic concept was already outlined in the Introduction (p. 5): insertion of a fluoromethine moiety into a CC double bond and the addition of an hydroxyl group to the newly constructed allylic system. Of course, one cannot arrive at this goal by one-step process. The practical realization relied on the preparation[85] and subsequent ring-opening of chlorofluorocyclopropanes **19**.

1,1 - dibromo - 2 - phenylcyclopropane as the starting material. As anticipated from related studies with monochloro- and *gem*-dichlorocyclopropanes,[88] chlorofluorocyclopropanes proved to be much more reluctant towards ring opening. Silver acetate alone was not effective. Only in the presence of small amounts of silver perchlorate or silver tetrafluoborate did a still relatively slow reaction take place around 100°C to give 1-fluoroallyl acetates in satisfactory yields.[89,90] The cor-

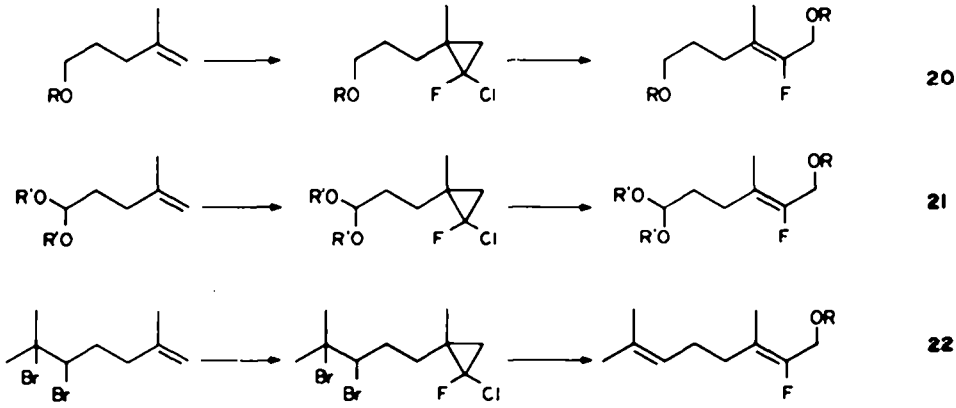


19

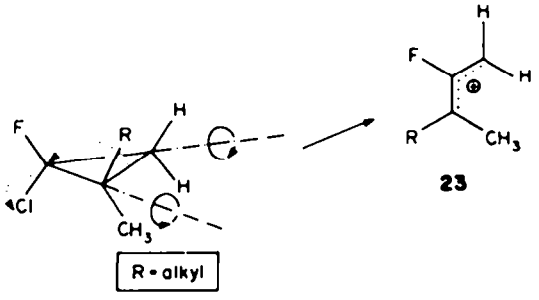
Skell and Sandler previously described an analogous reaction with 1,1-dibromocyclopropanes, which were found to hydrolyze readily upon interaction with silver acetate in acetic acid in the temperature range of 50–120°C.[86,87] Thus, for example, *Z* - 1 - acetoxy - 2 - bromo - 3 - phenylpropene was isolated in a 53% yield based on

responding 1-fluoroallyl alcohols were either obtained by acetate hydrolysis[89,90] or, directly, by solvolytic ring-opening in aqueous dioxane.[91] In this way, a whole series of 2-fluoroallyl derivatives has been prepared, among them the acetates (R = $OCCH_3$) **20**, **21** and **22**.

Let us consider now the stereochemistry of the cy-



cloaddition/ring-opening sequence. Upon addition of chlorofluorocarbene, a 1,1-disubstituted ethylene with two unlike alkyl groups is converted into two diastereomeric chlorofluorocyclopropanes. In the course of solvolysis each of them undergoes a specific motion.[92,93] The ligand occupying a *trans*-position with respect to the leaving chlorine atom invariably ends up at the *exo*-side of the emerging allyl cation **23**, while the ligand holding a *cis*-neighborship rotates to the *endo*-position. Consequently, *syn*- and *anti*-chlorofluorocyclopropanes must generate configurationally different 2-fluoroallylic cations and hence should lead to configurationally different 2-fluoroallyl acetates (or alcohols).



23

However, when diastereomeric mixtures for *syn*- and *anti*-cyclopropanes were separated by gas phase chromatography and submitted to the usual ring-opening procedure, both *Z*- and *E*-2-fluoro-1-allyl acetates always resulted. The reason is that the major primary product of solvolysis is the regio-isomeric 2-fluoro-3-allyl acetate (**24**), which in acetic acid solution undergoes a consecutive structural reorganisation to the thermodynamically more stable primary acetates (*Z*- and *E*-**25**).

If the chlorofluorocyclopropanes are ring-opened in aqueous medium containing pyridine rather than in acetic acid, again solvent attack to the alkyl-bearing allylic carbon atom is favored. The tertiary 2-fluoroallyl alcohols thus produced are stable, however, and may be isolated.[91] Tertiary allyl acetates equally survive, if the temperature for the reaction can be lowered, as evidenced by the silver acetate-induced acetolysis of 1,1 - dibromo - 2,2 - dimethylcyclopropane. At 50°C, 50% 2 - bromo - 3 - methyl - 1 - buten - 3 - yl acetate together with 31% 2 - bromo - 3 - methyl - 2 - buten - 1 - yl acetate are obtained.[87]

The intermediacy of tertiary 2-fluoroallyl acetates in the acetolysis of chlorofluorocyclopropanes has been demonstrated by gas chromatography analysis of the product evolution as a function of time.[91] Thus, 2 - fluoro - 3 - methyl - 1 - buten - 3 - yl acetate was recognized to prevail considerably over the isomeric primary acetate in the early stages of the acetolytic ring-opening of 1 - chloro - 1 - fluoro - 2,2 - dimethylcyclopropane (Fig. 2).

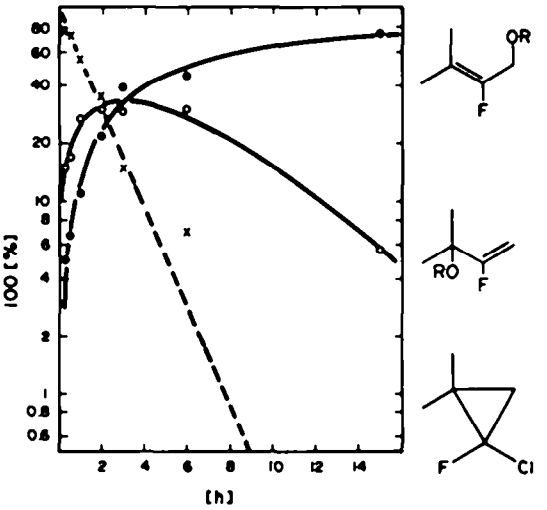
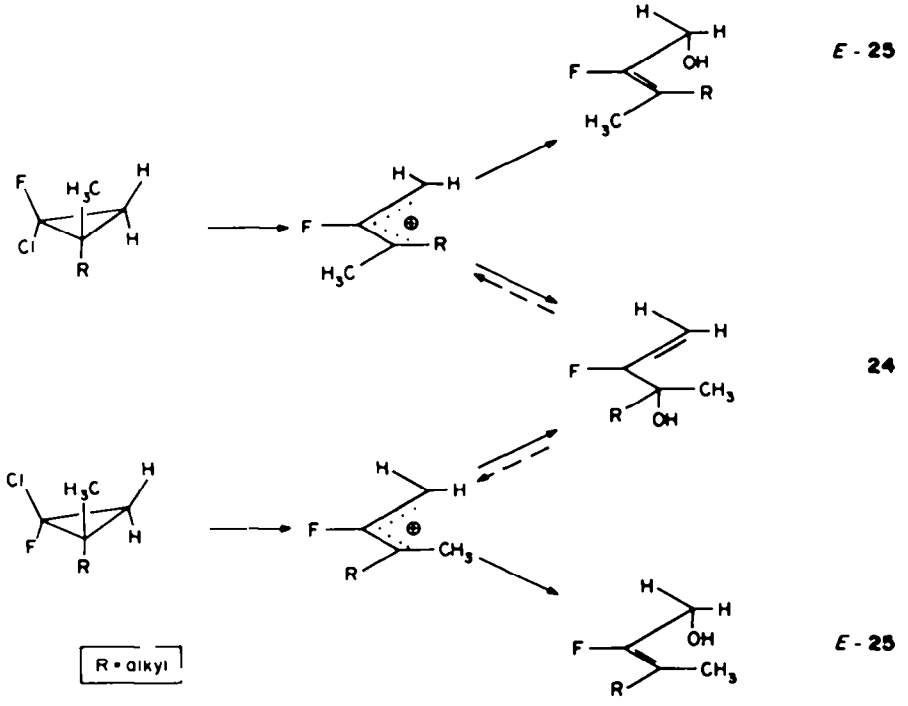


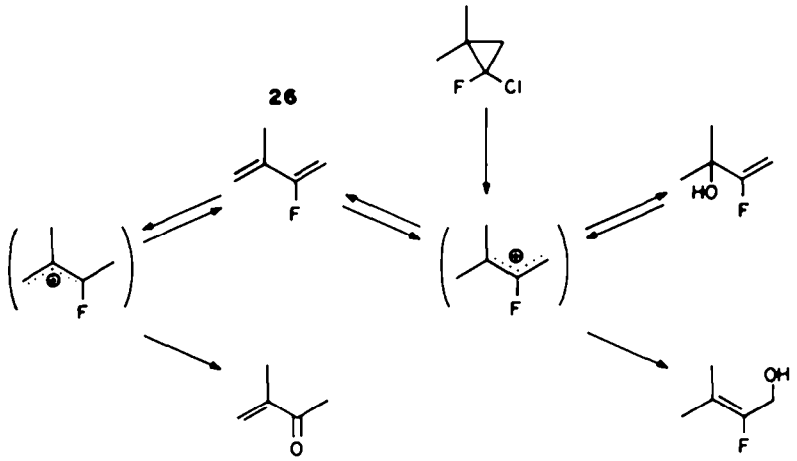
Fig. 2. Acetolytic ring-opening of 1 - chloro - 1 - fluoro - 2,2 - methylcyclopropane: progress of the reaction as a function of time. --x--, starting material; —○—, tertiary allylacetate; —●—, primary allylacetate.



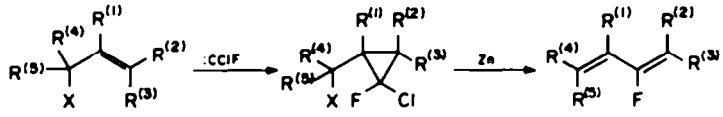
The same kinetic study revealed, that with prolonged reaction times 2-fluorodienes (such as **26**) and α-fluoroenones (such as **27**) are formed in noticeable quantities. Apparently the 2-fluoroallylic cations can lose a proton to give the diene. Reprotonation of the diene may generate a thermodynamically favored 3-fluoroallylic cation, which can add an acetoxy group and than collapse to afford the α,β-unsaturated α-fluorocarbonyl compound.[90]

sis of the carbon-halogen linkage. The cycloaddition product **28** contains the structural element of an 1,4-dihaloalkane and, consequently is prone to a fragmentation process.[94,95] Under the influence of zinc the halide X (chlorine, bromine or, after an eventual Finkelstein exchange, iodine) are eliminated and the carbon–carbon bond opposite to the fluorine-bearing ring atom is ruptured.[96,97]

2 - Fluoro - 3 - methyl - 1,3 - butadiene ("fluoroisoprene") looked particularly attractive as a potential construction unit for fluoroterpene syntheses. When treated with bromine at −80°C, *Z* - 1,4 - dibromo - 2 - fluoro - 3 - methyl - 2 - buten (**30**) was detected by NMR spectroscopy and gas chromatography as the sole product. Only when the reaction mixture was warmed up to room



2-Fluorodienes, previously almost unknown were found to be generally and readily accessible by a related, but highly efficient and specific method (Table 5). Under two-phase conditions allyl chlorides and even allyl bromides can be converted into the corresponding chlorofluorocyclopropanes without appreciable hydroly-



28

Table 5. Fluoro-1,3-dienes by reductive ring-opening of chlorofluoro-α-halogenmethylcyclopropanes

Gross formula	Product Structure	Allyl halide precursor	Yield[a] %
C_5H_7F	2-fluoro-3-methyl-1,3-butadiene	2-methylallyl chloride[b]	98
C_6H_9F	3-fluoro-2-methyl-1,3-pentadiene[c]	*E*-2-methyl-2-butenyl acetate[d,e]	50
C_6H_9F	3-fluoro-4-methyl-1,3-pentadiene	3-methyl-2-butenyl bromide	80
$C_7H_{11}F$	3-fluoro-2,4-dimethyl-1,3-pentadiene	2,3-dimethyl-2-butenyl chloride	54
$C_8H_{11}F$	1-fluoro-2-methyl-1,3-cycloheptadiene[f]	1-methyl-3-cyclohexenyl acetate[d]	20

[a] Based on the chlorofluorocyclopropane, obtained from the allyl halide precursor.

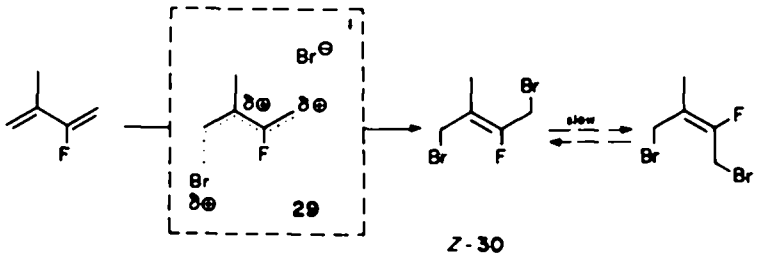
[b] Exchange of the (exocyclic) chloride against iodide at the stage of the chlorofluorocyclopropane intermediate.

[c] Stereochemistry: *Z*/*E* = 87:13 (49% yield after 2 hr 120°C) starting out with a *syn*/*anti*-cyclopropane ratio of 97:3; *Z*/*E* = 35:65 (68% yield after 90 min 130°C) starting out with a *syn*/*anti*-cyclopropane ratio of 1:99.

[d] Two-step replacement of acetoxy against bromine at the stage of the chlorofluorocyclopropane intermediate.

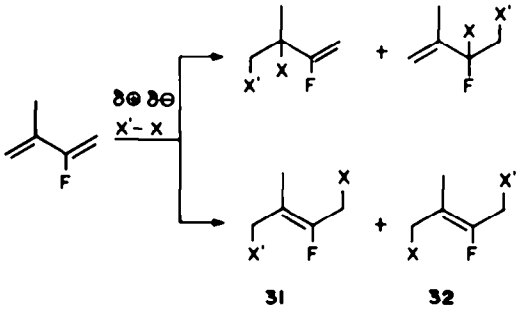
[e] Tiglic acetate.

[f] Obviously formed from the original 2-fluoro-1-methyl-1,3-cycloheptadiene by two consecutive [1,5]-hydrogen shifts.



temperature did another product appear which was probably the corresponding *E*-isomer.

The only remaining problem was now to selectively replace one of the heteroelements at the terminal positions by another halogen or another functional group. Then an assembly synthesis could be carried out by combining it first with a suitable building block at the more reactive side of the fluoroisoprene derivative and, subsequently, by attacking the less reactive side in order to complete the target structure. However, all "unsymmetrical" electrophiles failed to add regioselectively. Numerous reagents and reaction conditions have been tested, but invariably a product mixture was obtained composed of two pairs of 1,2-adducts (eventually as secondary products) and 1,4-adducts.

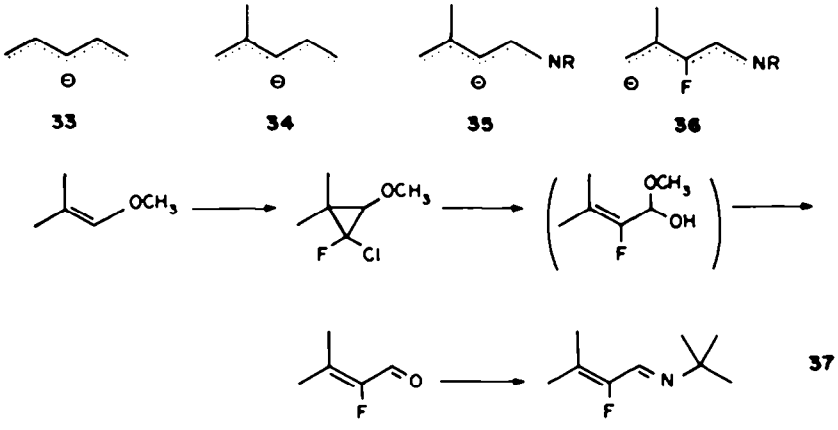


Notice, however, that both 1,4-adducts (**31** and **32**) have conserved the *Z*-configuration. This stereoselectivity is probably due to the delocalization of positive charge at the transition state of the addition reaction (as illustrated in **29**). Such a delocalization requires coplanarity of the original diene system, which can be achieved satisfactorily only in an out-stretched *anti*-periplanar geometrical arrangement. Delocalization of *negative* charge finally laid the foundation for the desperately sought stereoselective synthesis of fluoroterpenes.

The pentadienyl anion (**33**) and its organometallic derivatives exist almost exclusively in the out-stretched zig-zag conformation ("W-form"), the alternative "S"- and "U"-shaped torsional isomers being present only in non detectable quantities.[98,99] The introduction of a methyl group into the 2-position (anion **34**) may suffice to alter this stereochemical preference, however.[100] It was completely unknown whether and how the conformational equilibrium would be affected upon further replacement of one methylene terminus by an isolectronic imino group (anion **35**) and, in addition, substitution of the hydrogen at the 3-position by a fluorine atom (anion **36**).

The preparation of the required starting material, the eneazomethine **37**, again relied on a cycloaddition/ring-opening sequence. The chlorofluorocyclopropane obtained from methyl 2-methyl-1-propenyl ether readily hydrolyzed to afford 2-fluoro-3-methyl-2-butenal (75%),[101] which was condensed with *t*-butylamine to afford the azomethine **37** (70%).

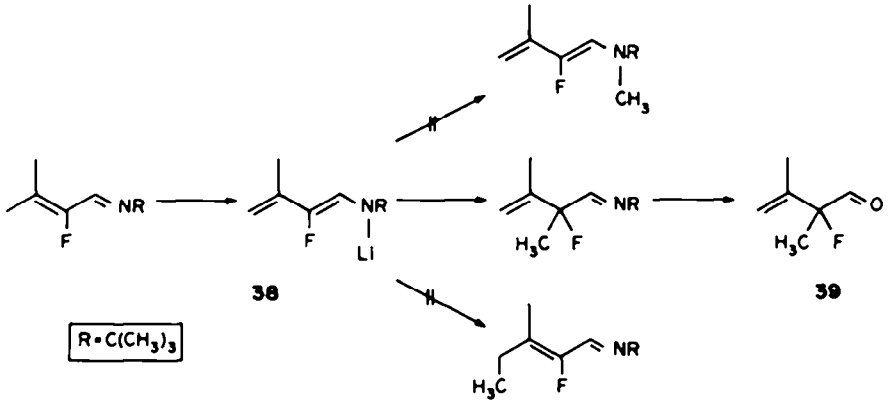
Lithium diisopropylamide in tetrahydrofuran solution and in the presence of hexamethylphosphoric triamide effected a clean deprotonation of one allylic methyl group. The resulting metallated species **38** furnished one single product upon treatment with methyl iodide.[102] Although the nitrogen is the most probable binding site for the lithium atom (as illustrated in formula **38**), the methyl group was not expected to be attached there. Only when metallated azomethines are subjected to *acylation* is the electrophile preferentially fixed at the heteroatom.[103,104] The remaining possibilities were either chain elongation by methyl attack on the terminal methylene group or branching of the carbon skeleton by methyl binding to the fluorine-bearing inner carbon atom. As was an-



ticipated from analogous behavior[105] of the lithium derivative of the structurally equivalent but halogen-free anion 35 the new carbon–carbon bond was exclusively formed at the central position. Hydrolysis gave pure fluoro - 2,3 - dimethyl - 3 - butenal[102] (39).

prenyl bromide gave rise to one isomer, the desired *Z*-form (*Z*-40b) exclusively.

Meerwein/Ponndorf-type reduction of this compound by means of isopropanol/alumina[107] furnished *Z* - 2 - fluoro - 3,7 - dimethyl - 2,6 - octadien - 1 - ol (2-fluorogeraniol, 41).

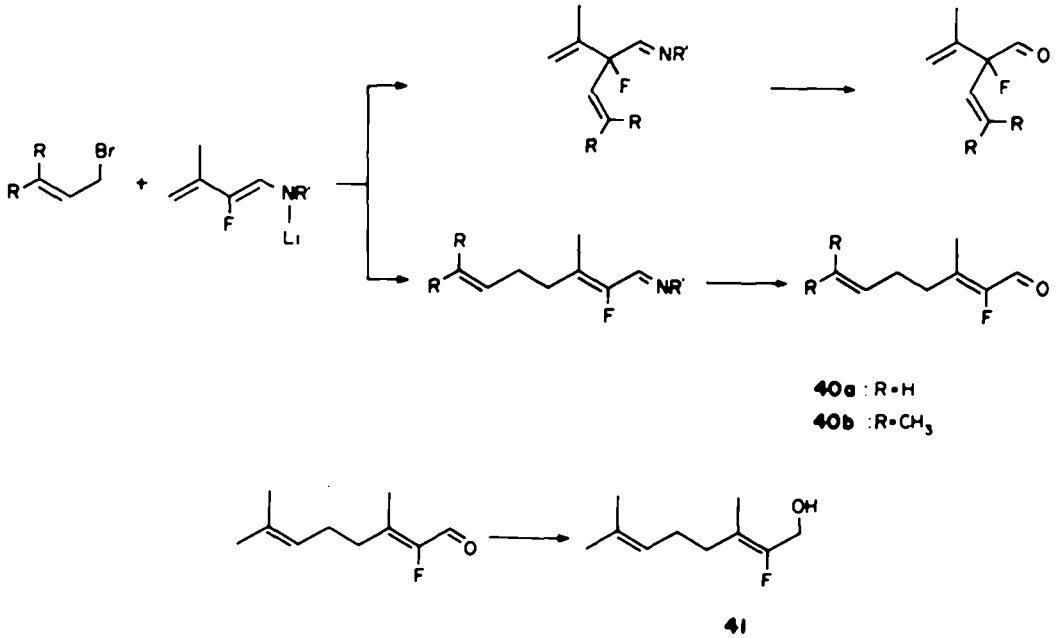


Fortunately the regioselectivity of the alkylation reaction with allylbromide and 3-methyl-2-butenyl bromide ("prenyl bromide") turned out to be much less unfavorable than in the case of quenching with methyl iodide. The branched and the chain-elongated products were formed in approximately equal amounts.† Moreover, the separation of the regioisomers was found to be facile, once the azomethines had been hydrolyzed to the corresponding aldehydes. Surprisingly, the stereochemical outcome of the alkylation reaction varied profoundly as a function of the chosen reagent. With allyl bromide a 1:1 mixture of *Z*- and *E* - 2 - fluoro - 3 - methyl - 2,6 - heptadienal (40a) was obtained, whereas

Analogously 2-fluorofarnesol has been prepared by alkylation with geranyl bromide and the synthesis of 11,14-difluorosqualene is under way.

FINAL REMARKS AND ACKNOWLEDGEMENTS

Obviously this was the report of an Odyssey. If it is true that our little boat has finally reached a safe harbour, one should not praise the captain who only indulged in the adventure but the crew who bore the hardship of a harsh undertaking: Y. Bessière, K. F. Christmann, G. Fouquet, G. Heinz, V. Ladenberger, Le Van Chau, B. Spahić, Truong Thi My Thu, M. Zimmermann. We gratefully remember those who helped



†According to a recent report,[106] the lithium derivative of anion 35 condenses at −78°C with prenyl chloride to yield a mixture containing three products. The minor component (roughly 10%) is the chain-elongated imine corresponding to 40b but with hydrogen in place of fluorine. Apparently the stereochemistry of the product has not been elucidated.

with equipment and supplies at the time when the expedition embarked (*Deutsche Forschungsgemeinschaft*, Bonn-Bad Godesberg) and through all the years of going astray (*Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung*, Bern). And one should, of course, be aware of the incompleteness and subjectivity

of any reminiscence: although we have arrived at many coasts and seen many horizons, large unknown areas have yet to be explored. (For guide books offering complementary and more comprehensive information see, e.g. Refs. 108–112).

REFERENCES

[1]R. Peters, *Carbon-Fluorine Compounds*, p. 1–27. A CIBA Foundation Symposium, Elsevier, Amsterdam (1972).
[2]B. C. Saunders, *Carbon-Fluorine Compounds*, p. 55–70. A CIBA Foundation Symposium, Elsevier, Amsterdam (1972).
[3]F. Swarts, *Bull. Soc. Chim. Belg.* **38**, 99 (1929).
[4]Impeded dehydration of ethyl 2 - fluoromethyl - 2 - hydroxypropionate: H. Machleidt, V. Hartmann and H. Bünger, *Justus Liebigs Ann. Chem.* **667**, 35 (1963).
[5]Note also that hexafluoroacetone and other fluorinated carbonyl compounds form stable hydrates, hemiacetals and hemiaminals, C. G. Krespan and W. J. Middleton, *Fluorine Chem. Rev.* **1**, 145 (1967).
[6]R. A. Peters, P. Buffa, R. W. Wakehn and L. C. Thomas, *Proc. Roy. Soc.* **B140**, 497.
[7]D. W. Fransbier, L. K. Gottwald and E. Kun, *J. Biol. Chem.* **237**, 3588 (1962); **239**, 425 (1964).
[8]R. J. Dummel and E. Kun, *Ibid.* **244**, 2966 (1969); also cf. H. L. Carrell and J. P. Glusker, *Acta Crystallogr.* **29**, 4364 (1973).
[9]E. Kun, *Carbon-Fluorine Compounds*, pp. 70–73. A CIBA Foundation Symposium, Elsevier, Amsterdam (1972). E. Kun, *ACS Symposium Series* Number **28** (Edited by R. Filler). *Am. Chem. Soc.*, Washington (1976); R. Z. Eanes, D. M. Skilleter and E. Kun, *Biochem. Biophys. Res. Commun.* **46**, 1619 (1972), also cf. V. Guarriera-Bobyleva and P. Buffa, *Biochem. J.* **113**, 853 (1969).
[10]E. Kun, personal communication to the author (1977).
[11]R. A. Peters, *Proc. Roy. Soc.* **B139**, 143 (1952).
[12]C. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. R. Duschinsky, R. J. Schnitzer, E. Pleven and J. Scheiner, *Nature* **179**, 663 (1957); R. Duschinsky, E. Pleven und C. Heidelberger, *J. Am. Chem. Soc.* **79**, 4559 (1957).
[13]C. Heidelberger, *Carbon-Fluorine Compounds*, pp. 125–137. A CIBA Foundation Symposium, Elsevier, Amsterdam (1972).
[14]R. B. Clayton, *Quart. Rev.* **19**, 168 (1965).
[15]L. J. Mulheirn and P. J. Ramm, *Chem. Soc. Reviews* **1**, 259 (1972).
[16]O. Scherer, *Fortschr. Chem. Forschung*, Vol. 14/2, Springer Verlag, Heidelberg (1970).
[17]R. D. Schuetz, D. D. Taft, J. P. O'Brien, J. L. Shea and H. H. Mork, *J. Org. Chem.* **28**, 1420 (1963).
[18]D. E. Gwynn, G. M. Whitesides and J. D. Roberts, *J. Am. Chem. Soc.* **87**, 2862 (1965).
[19]M. Schlosser and G. Heinz, *Chem. Ber.* **102**, 1944 (1969).
[20]M. Schlosser and K. R. Rutz, unpublished results, cf. K. R. Rutz, *Diplomarbeit*, Universität Heidelberg (1969).
[21]M. Schlosser and A. H. Rehan, unpublished results (1969).
[22]M. Schlosser and K. F. Christmann, *Synthesis* **38** (1969).
[23]M. Schlosser und M. Zimmermann, *Synthesis* **75** (1969). *Chem. Ber.* **104**, 2885 (1971).
[24]2 - (2 - Fluoropropyl) - triphenylphosphonium iodide: M. Schlosser and M. Zimmermann, unpublished results, see also M. Zimmermann, *Thesis*, Universität Heidelberg (1970).
[25](1 - Fluorocyclohexyl) - triphenylphosphonium iodide: M. Schlosser and Le Van Chau, unpublished results, see also Le Van Chau, Thesis, Universität Heidelberg (1972).
[26]C. E. Inman, R. E. Oesterling and E. A. Tyczkowski, *J. Am. Chem. Soc.* **80**, 6533 (1958).
[27]A. H. Nathan, B. J. Magerlein and J. A. Hogg, *J. Org. Chem.* **24**, 1517 (1959).
[28]A. H. Nathan, J. C. Babcock and J. A. Hogg, *J. Am. Chem. Soc.* **82**, 1436 (1960).
[29]H. M. Kissman, A. M. Small and M. J. Weiss, *Ibid.* **82**, 2312 (1960).
[30]J. P. Freeman, *Ibid.* **82**, 3869 (1960).
[31]H. Schechter and E. B. Roberson, *J. Org. Chem.* **25**, 175 (1960).
[32]A. S. Kende and P. MacGregor, *J. Am. Chem. Soc.* **83**, 4197 (1961).
[33]C. E. Holmlund, L. I. Feldman, H. M. Kissmann and M. J. Weiss, *J. Org. Chem.* **27**, 2122 (1962).
[34]H. Machleidt, *Justus Liebigs Ann. Chem.* **667**, 24 (1963); **676**, 66 (1964).
[35]H. Gershon, J. A. A. Renwick, W. K. Wynn and R. D. Ascoli, *J. Org. Chem.* **31**, 916 (1966).
[36]H. Gershon and R. Parmegiani, *J. Med. Chem.* **10**, 187 (1967).
[37]H. Gershon, S. G. Schulman and A. D. Spevack, *Ibid.* **10**, 536 (1967).
[38]H. Lange and M. Lipp, *Naturwissenschaften* **47**, 397 (1960).
[39]R. B. Gabbard and E. V. Jensen, *J. Org. Chem.* **23**, 1406 (1958).
[40]S. Nakanishi, K. Morita and E. V. Jensen, *J. Am. Chem. Soc.* **81**, 5259 (1959).
[41]J. S. Mills, J. Barrera, E. Olivares and H. Garcia, *Ibid.* **82**, 5882 (1960).
[42]G. R. Allen, Jr. and N. A. Austin, *J. Org. Chem.* **26**, 5245 (1961).
[43]S. Nakanishi and E. V. Jensen, *Ibid.* **27**, 702 (1962).
[44]S. Nakanishi, *J. Med. Chem.* **7**, 108 (1964).
[45]B. J. Magerlein, J. E. Pike, R. W. Jackson, G. E. Vandenberg and F. Kagan, *J. Org. Chem.* **29**, 2982 (1964).
[46]Y. Osawa and M. Neeman, *Ibid.* **32**, 3055 (1967).
[47]H. L. Elbe and G. Köbrich, *Tetrahedron Letters* 2557 (1974), *Chem. Ber.* **107**, 1654 (1974).
[48]M. Schlosser, *Struktur und Reaktivität polarer Organometalle*, Springer Verlag, Heidelberg (1973).
[49]E. Forche, *Houben/Weyl*, Methoden der Organischen Chemie (Edited by E. Müller), Vol. 5/3, pp. 115–117. G. Thieme Verlag, Stuttgart (1962).
[50]J. Fried and N. A. Abraham, In J. Fried/J. A. Edwards, *Organic Reactions in Steroid Chemistry*, Vol. 1, pp. 425–436. Van Nostrand Reinhold, New York (1972).
[51]N. N. Yarovenko and M. A. Raksha, *Zhur. Obshch. Khim.* **29**, 2159 (1959); *Chem. Abstr.* **54**, 9724h (1960).
[52]D. E. Ayer, *Tetrahedron Letters* 1065 (1962).
[53]L. H. Knox, E. Velarde, S. Berger, D. Cuardriello and A. D. Cross, *Ibid.* 1249 (1962); *J. Org. Chem.* **29**, 2187 (1964).
[54]M. Schlosser and G. Fouquet, unpublished results (1973).
[55]R. F. Merritt and F. A. Johnson, *J. Org. Chem.* **31**, 1859 (1966).
[56]R. F. Merritt, *Ibid.* **31**, 3871 (1966).
[57]R. F. Merritt and T. E. Stevens, *J. Am. Chem. Soc.* **88**, 1822 (1966).
[58]R. F. Merritt, *Ibid.* **89**, 609 (1967).
[59]W. J. Middleton, *J. Org. Chem.* **40**, 574 (1975).
[60]D. R. Strobach and G. A. Boswell, *Ibid.* **36**, 818 (1971).
[61]F. Bergmann, A. Kalmus and S. Vromen, *J. Am. Chem. Soc.* **77**, 2494 (1955).
[62]Also cf. D. L. E. Bronnert and B. C. Saunders, *Tetrahedron* **21**, 3325 (1965).
[63]E. D. Bergmann and J. Schwarcz, *J. Chem. Soc.* 1524 (1956).
[64]E. D. Bergmann and I. Shahak, *Ibid.* 5261 (1960).
[65]E. Elkik, *Bull. Soc. Chim. Fr.* 2258 (1964).
[66]E. D. Bergmann and I. Shahak, *J. Chem. Soc.* 4033 (1961).
[67]E. D. Bergmann, I. Shahak, E. Sali and Z. Aizenshtat, *Ibid.* 1232 (C1968).
[68]R. N. Sterlin, R. D. Yatsenko and I. L. Knunyants, *Khim. Nauka i Promy.* **3**, 540 (1958); *Chem. Abstr.* **53**, 4195 (1959).
[69]D. Seyferth, T. Wada and G. Raab, *Tetrahedron Letters* 20(22), (1960).
[70]P. Tarrant, P. Johncock and J. Savory, *J. Org. Chem.* **28**, 839 (1963).
[71]F. G. Drakesmith, R. D. Richardson, O. J. Stewart and P. Tarrant, *Ibid.* **33**, 286 (1968).
[72]J. F. Normant, J. P. Foulon, D. Masure, R. Sauvêtre and J. Villeras, *Synthesis* 122 (1975).
[73]*U.S. Pat.* 3 751 492 (S. Y. Delavareane, Union Carbide Corp.), 7 Aug. 1973 (appl. 18 Dec. 1970).
[74]H. Machleidt and R. Wessendorf, *Justus Liebigs Ann. Chem.* **674**, 1 (1964).
[75]S. A. Puqua, W. G. Duncan and R. M. Silverstein, *J. Org. Chem.* **30**, 1027 (1965).
[76]D. J. Burton and F. E. Herkes, *Ibid.* **33**, 1854 (1968).
[77]D. J. Burton and H. C. Krutzsch, *Ibid.* **35**, 2125 (1970).
[78]D. G. Naae and D. J. Burton, *J. Fluorine Chem.* **1**, 123 (1971).

[79]D. J. Burton and P. E. Greenlimb, *J. Org. Chem.* **40**, 2796 (1975).
[80]K. S. Kesling and D. J. Burton, *Tetrahedron Letters* 3355 (1975).
[81]M. Schlosser, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger), Vol. 5, pp. 17–27. Wiley-Interscience, New York (1970).
[82]A. S. Arora and I. K. Ugi, *Houben/Weyl*, Methoden der organischen Chemie (Edited by E. Müller), Vol. 5/1b, pp. 887–893, G. Thieme Verlag, Stuttgart (1972).
[83]M. Schlosser, *Methodicum Chimicum* (Edited by F. Korte, K. Niedenzu and H. Zimmer), Vol. 7, p. 551. G. Thieme Verlag, Stuttgart/Academic Press, New York (1976).
[84]M. Schlosser, K. F. Christmann, G. Müller, A. Piskala and Huynh Ba Tuong, unpublished results.
[85]Le Van Chau and M. Schlosser, *Synthesis* 112 (1973).
[86]P. S. Skell and S. R. Sandler, *J. Am. Chem. Soc.* **80**, 2024 (1958).
[87]S. R. Sandler, *J. Org. Chem.* **32**, 3876 (1967).
[88]S. J. Cristol, R. M. Sequeira and C. H. DePuy, *J. Am. Chem. Soc.* **87**, 4007 (1965).
[89]Le Van Chau and M. Schlosser, *Synthesis* 115 (1974).
[90]M. Schlosser and Le Van Chau, *Helv. Chim. Acta* **58**, 2595 (1975).
[91]Y. Bessière and M. Schlosser, *Ibid.* **59**, 969 (1976).
[92]S. J. Cristol, R. M. Segueira and C. H. DePuy, *J. Am. Chem. Soc.* **87**, 4007 (1965).
[93]P. v. R. Schleyer, G. W. VanDine, U. Schöllkopf and J. Paust, *Ibid.* **88**, 2868 (1966).
[94]C. A. Grob and P. W. Schiess, *Angew. Chem.* **79**, 1 (1967); *Ibid.* internat. **6**, 1 (1967).
[95]C. A. Grob, *Ibid.* **81**, 543 (1969); *Ibid.* internat. Edit. **8**, 535 (1969).
[96]M. Schlosser, B. Spahić, C. Tarchini and Le Van Chau, *Ibid.* **87**, 346 (1975); *Ibid. internat. Edit.* **14**, 365 (1975).
[97]B. Spahić and M. Schlosser, unpublished results.
[98]H. Kloosterziel and J. A. A. van Drunen, *Rec. Trav. Chim. Pays-Bas* **89**, 270 (1970).
[99]J. Hartmann, R. Muthukrishnan and M. Schlosser, *Helv. Chim. Acta* **57**, 2261 (1974).
[100]See M. Schlosser and G. Rauchschwalbe, paper submitted for publication.
[101]Y. Bessière, Dang Ngoc-Huê Savary and M. Schlosser, *Helv. Chim. Acta* **60**, 1739 (1977).
[102]M. Schlosser and Truong Thi My Thu, unpublished results.
[103]G. Wittig and H. Reiff, *Angew. Chem.* **80**, 8 (1968); *Ibid.* internat. Edit. **7**, 7 (1968).
[104]W. Oppolzer and W. Frőstl, *Helv. Chim. Acta* **58**, 587 (1975).
[105]G. R. Kieczykowski, R. H. Schlessinger and R. B. Sulsky, *Tetrahedron Letters* 597 (1976).
[106]K. Takabe, H. Fujiwara, T. Katagiri and J. Tanaka, *Ibid.* 1237 (1975).
[107]G. H. Posner, A. W. Runquist and M. J. Chapdelaine, *J. Org. Chem.* **42**, 1202 (1977).
[108]W. A. Sheppard and C. M. Sharts, *Organic Fluorine Chemistry*. W. A. Benjamin, New York (1969).
[109]M. Hudlický, *Organic Fluorine Chemistry*. Plenum Press, New York (1971).
[110]R. D. Chambers, *Fluorine in Organic Chemistry*. Wiley, New York (1973).
[111]C. M. Sharts and W. A. Sheppard, *Organic Reactions*, Vol. 21, p. 125. Wiley, New York (1974).
[112]G. A. Boswell, W. C. Ripka, R. M. Scribner and C. W. Tullock, *Organic Reactions*, Vol. 21, p. 1, Wiley, New York (1974).