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Preface

Fluorinated organic materials have been gaining significant importance among the biologically active and functional materials. Even though several reagents and reaction sequences have been developed for the construction of fluorinated materials in the last decade, the topic remains a specialized field unfamiliar to most chemists. There are a number of problems to be solved, including the handling of the materials, availability of reagents, and selectivity (stereo-, regio-, and/or chemo-). This volume aims to help the nonspecialist in preparing fluorinated materials and reactive intermediates as well as update the specialist on the reagents and reaction sequences in fluorine science.

The task of selecting as diverse references as possible for this volume was very difficult. Since the recent trend is to report important results from prestigious journals as a short communication, we sometimes cannot trace interesting procedures due to very little experimental information in a strictly limited number of printed pages. So, from the standpoint of our initial concept for this volume, we mainly collected the experimental methods from full papers, which usually contain ampler, more detailed, and more practical knowledge, even if the original work was published as a communication. Moreover, the editors only collected information on aliphatic compounds with a few fluorine atoms because works on the preparation of aromatic and heterocyclic materials have already been published.

We are grateful to the kind cooperation of a number of authors who have kindly sent us their detailed procedures or physical properties upon request, or promptly answered our questions. We also thank Mr. Ippei Ohta of Kodansha Scientific Ltd. for his enthusiastic support for this book.

November 1998

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General Remarks

Chapters 2 through 5 deal with the experimental details of the formation of each specific material. Basically, such experimental procedures are described as originally published, but minor changes are sometimes made for consistency throughout the text. One example is the preparation of the famous and widely applicable non-nucleophilic strong base, lithium diisopropylamide (LDA). Because this volume contains many reaction schemes using this versatile base, each procedure only includes a brief description such as "to a solution of LDA (1 mmol) ···", and readers are referred to the following two representative procedures.

Method A: A three-necked, 500-mL, round-bottomed flask is fitted with a nitrogen inlet, a rubber septum, and a 125-mL dropping funnel. The flask is flame-dried, flushed with nitrogen and charged with diisopropylamine (22.0 mL, 0.16 mol) and 100 mL of anhydrous THF. This solution is cooled in an ice bath, and the dropping funnel is charged with a solution of *n*-BuLi (80.0 mL of a 1.88 *M* solution in hexane, 0.15 mol), which is added dropwise over 15 min.

Boeckman, Jr., R. K., *et al. Org. Synth. Coll. VIII* **1993**, 192.

Method B: An oven-dried, 250-mL, round-bottomed flask equipped with a stirring bar and a rubber septum is charged with 100 mL of anhydrous THF and 5.56 g (55 mmol) of anhydrous diisopropylamine. The flask is flushed with argon via a needle inlet-outlet and cooled to -78 °C with a dry ice-isopropyl alcohol bath. To this stirred solution 30 mL (54 mmol) of a 1.8 *M* solution of *n*-BuLi in hexane is added dropwise with a syringe, and stirring is continued at that temperature for 30 min.

Spitzner, D.; Engler, A. *Org. Synth. Coll. VIII* **1993**, 219.

In the case of NMR spectroscopic data, chemical shifts of ^{1}H and ^{13}C NMR in the indicated solvent are reported using tetramethylsilane (TMS) as the internal standard, and the chemical shifts of ^{19}F NMR are tabulated using trichlorofluoromethane ($CFCl_3$) as the reference unless otherwise noted. While downfield shifts in ^{19}F NMR are sometimes designated as negative, their signs are changed by the authors to keep the uniform description of downfield shifts positive.

When a procedure requires the use of poisonous or dangerous materials, readers will find a "*Caution*" section containing remarks on how to handle such compounds. Additional information for readers' convenience is included under the heading *Note*.

Abbreviations

[α]	specific rotation
Ac	acetyl
Ac_2O	acetic anhydride
AcOEt	ethyl acetate
AcOH	acetic acid
AIBN	2,2'-azobisisobutyronitrile (=2,2'-azobis(2-methylpropionitrile))
Allyl	prop-2-en-1-yl (=C_3H_7)
BINOL	1,1'-bi-2-naphthol
Bn	benzyl (=$C_6H_5CH_2$)
bp	boiling point
br	broad
Bu	butyl (=C_4H_9)
d	day(s); doublet
DAST	diethylaminosulfur trifluoride
DBH	1,3-dibromo-5,5-dimethylhydantoin
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene (=2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepin)
de	diastereomeric excess
DIBAL-H	diisobutylaluminum hydride (=DIBAH or DIBALH)
DIP-Cl	diisopinocampheylboron chloride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (=*N*,*N*'-dimethylpropyleneurea)
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
Et	ethyl (=C_2H_5)
Et_2O	ether (=Diethyl ether)
EtOH	ethyl alcohol (=Ethanol)
F-TEDA-BF_4 bis(tetrafluoroborate)	1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane (=Slectfluor™)
h	hour(s)
HMPA	hexamethylphosphoramide
Hz	hertz
i-	iso
IR	infrared spectrum
LCIA	lithium cyclohexylisopropylamide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide or lithium bis(trimethylsilyl)amide
m	multiplet

*m*CPBA	*m*-chloroperbenzoic acid
Me	methyl (=CH_3)
MeCN	acetonitrile
MEM	(2-methoxyethoxy)methyl
MeOH	methyl alcohol (Methanol)
min	minute(s)
MMPP	magnesium monoperoxyphthalate
MOM	methoxymethyl
mp	melting point
MS	molecular sieves
Ms	methanesulfonyl (=mesyl)
n-	normal
NaHMDS	sodium hexamethyldisilazide or sodium bis(trimethylsilyl)amide
Naph	naphthyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl (=C_6H_5)
PMP	*p*-methoxyphenyl
ppm	parts per million
Pr	propyl (=C_3H_7)
q	quartet
quint	quintet
Red-Al	sodium bis(2-methoxyethoxy)aluminum (=Vitride, SMEAH)
Rf	retention factor
R_f	perfluoro or polyfluoroalkyl groups
s	singlet
sec-	secondary
sept	septet
sex	sextet
t	triplet
TASF	tris(dimethylamino)sulfur (trimethylsilyl)difluoride
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
tert-	tertiary
Tf	trifluoromethanesulfonyl (=triflyl)
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl; tetramethylsilane
Ts	*p*-toluenesulfonyl (=tosyl)

Contents

1 Introduction

When Henri Moissan first isolated elemental fluorine in 1886,[1] could he have imagined the explosive development of fluorine chemistry over these past decades? Recently, fluorine chemistry has been recognized as one of the most significant fields in chemistry. This is because the special properties resulting from the incorporation of fluorine sometimes adds an unexpected quality to organic molecules. The exceptional importance of fluorine chemistry can be readily understood from the fact that many books[2] and reviews in journals[3,4] have been published in this field, especially in the 1990s. On the other hand, its special nature, in particular regarding reactivity and toxicity, can be considered to be one of the main reasons keeping general organic chemists away from this field. However, if such a barrier could be removed, further development of fluorine chemistry with wide application in diverse fields can be anticipated. The primary aim of this publication is to provide as much useful procedural information as possible for easy access to materials readers would like to construct. The various chapters have been compiled from published articles which contain procedures *that do not require any special apparatus or technique.* This is why the present volume contains no scheme directly using F_2 gas, anhydrous HF, SF_4, or similar compounds.

This chapter briefly describes the basic chemistry of fluorine-containing substances discussing physical property changes and effects on the reactivity caused by the introduction of the fluorine atom as well as the care required when handling fluorinated materials.

1.1 Effect of Fluorine on Physical Properties

1.1.1 Mimic and Block Effects

Why has this particular atom been drawing so much attention in recent years? The main reasons stem from the following three special characteristics. Fluorine is

1) the most electronegative element of all,
2) the second smallest element next to hydrogen, and
3) the atom that can form a stronger bond with carbon than hydrogen.

Table 1.1 on the following page contains selected data on this atom together with those on a

Table 1.1 Representative physical properties of selected atoms

Atom	Electronegativity	van der Waals radius (Bondi) (Å)	Bond length (CH_3-X) (Å)	Dissociation energy (CH_3-X) (kcal/mol)
H	2.2	1.20	1.09	99
F	4.0	1.47	1.39	110
Cl	3.0	1.75	1.77	85
Br	2.8	1.85	1.93	71
C	2.5	1.70	1.54	83
O	3.5	1.52	1.43	86

few other elements for comparison. Looking at the first column of this table, the strong electronegativity of the fluorine atom is readily understood when compared with the other halogens as well as oxygen. Because of the location of fluorine on the right side of the periodic table (VIIb group), its small size is intuitively and qualitatively expected. Actually, van der Waals (vdW) radius improved by Bondi[5] numerically demonstrated the rather small value of fluorine, only about 20% larger than that of hydrogen (an even smaller difference of *ca.* 10% was previously estimated based on the vdW values by Pauling,[6] H: 1.20 Å, F: 1.35 Å). This element also forms a firm bond with the methyl carbon atom, which is evaluated to be 11 kcal/mol stronger than the methane C-H bond.

These are the basic properties fluorine inherently possesses. The special effects of fluorinated materials brought about by the combination of the above three characteristics are discussed below.

When a fluorine atom is introduced into a molecule, one sometimes expects the enhancement or modification of the original biological activity. Actually, there are a number of cases where just one fluorine causes a tremendous change in the parent physical properties, the most famous and important example being the profound effect of fluoroacetic acid in the original acetic acid metabolic system, the TCA cycle. Compound **1b**,[7] one of the few naturally occurring fluorinated compounds,[3h] is "mistakenly" recognized as acetic acid **1a** by the enzyme due to its already described close steric similarity to hydrogen and is converted to fluorocitric acid (2*R*,3*R*)-**4** by the same biological manipulation of the corresponding fluoroacetyl-CoA **2b** and oxaloacetic acid **3**, as shown in Fig. 1.1. However, different from its prototypic case further transforming the resultant citric acid **5** to isocitric acid **7** *via* the aconitase-catalyzed dehydration, (2*R*,3*R*)-**4** cannot follow the usual process because fluorine is located at the position of the usually abstracted hydrogen atom and the stronger C-F bond cleavage is apparently more difficult, leading to the inhibition of the TCA cycle and accumulation of this fluorinated material. It is quite interesting to note that citrate synthase stereospecifically constructs (2*R*,3*R*)-**4** out of four possible diastereomers and, in spite of the extremely poisonous nature of this isomer, causing convulsions and ventricular fibrillation, the three other stereoisomers are not toxic. Thus, this is expressed as the "lethal synthesis" by citrate synthase.[8] Moreover, use of ω-fluoroalkanoic acid derivatives (F-$(CH_2)_n$-CO_2R) requires similar significant attention when n is an odd number since these substances are metabolically transformed into fluoroacetic acid by the repetitive degradation *via* β-oxidation as a key step.

This is the typical "mimic effect" emerging from the combination of the second and third characteristics of fluorine stated above, which is usually applicable to compounds with

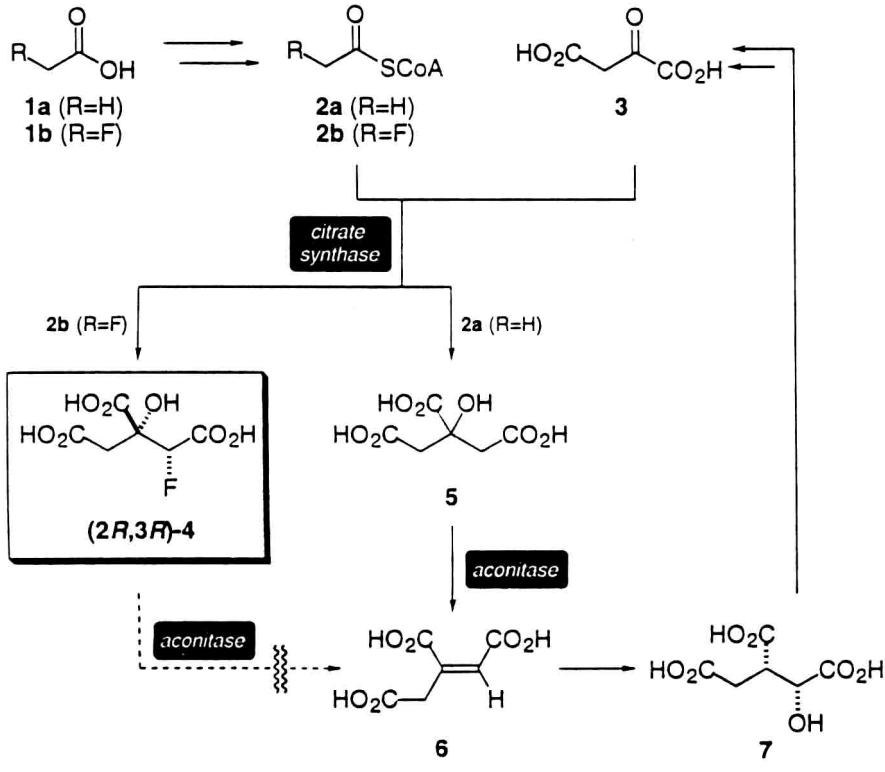


Fig. 1.1 Citric acid cycle with fluoroacetic acid **1b** as a substrate.

only one fluorine atom, but there are a few examples of the mimic effect for di-[9] as well as trifluoromethylated compounds.[10]

Apart from the metabolic pathway and from the synthetic point of view, the appearance of toxicity of (2*R*,3*R*)-**4** in Fig. 1.1 is also interpreted as a possible result of the introduction of a fluorine atom to **5** instead of the enzymatically labile hydrogen. Such replacement constitutes one of the important strategies effectively inhibiting the usual conversion pathways. This is sometimes classified as the "block effect." The slower oxidative metabolic degradation of *p*-fluorophenylalanine, about one-sixth of the parent phenylalanine,[11] was explained in a similar fashion, which suggests increased durability by the incorporation of a fluorine atom.

1.1.2 Effect of the Electron-withdrawing Nature of Fluorine

1.1.2.1 Deactivation Effect

It has been proved that the second and third characteristics play important roles for the mimic and block effects. Moreover, the electronegative quality of fluorine has also been widely utilized for alteration of the original physical properties along with the inherent

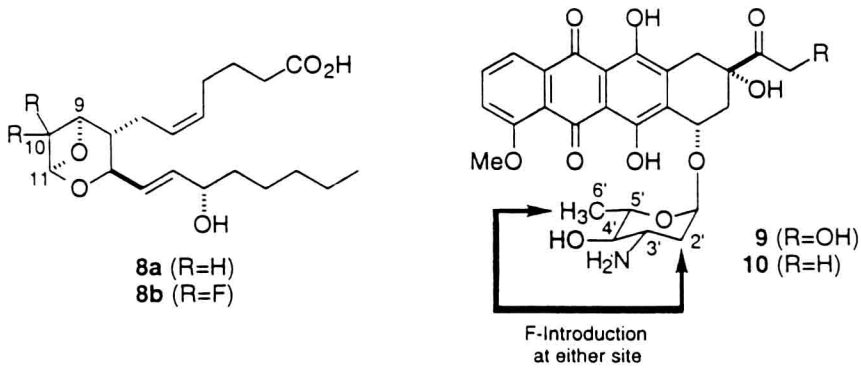


Fig. 1.2 Thromboxane A_2 and anthracyclines as fluorine-modified targets.

increase in its lipophilic nature.

For example, Fried and co-workers reported excellent resistance to hydrolysis when two fluorine atoms were introduced at the 10 position of thromboxane A_2 (TXA_2, **8a**, Fig. 1.2).[12] Their study stemmed from the necessity of finding more stable analogs of **8a** because of its powerful vasoconstricting and platelet aggregating ability but only 30 sec of half life at pH=7.4. However, Fried came to the conclusion that such inherent lability of oxetane acetal could be overcome by these two fluorines, which would effectively decrease the electron density of the neighboring oxygen atoms and also destabilize the possible formation of the cation at the 11 position on hydrolysis under acidic conditions (*vide infra*). This was indeed the case and **8b** attained dramatically greater chemical stability (*a half life of 270 years at physiological pH!*) retaining the same or even better biological activity than the parent **8a**.[13]

A similar concept was applied to increase the stability of anthracyclines such as doxorubicin **9** or daunorubicin **10** by Tsuchiya's group (Fig. 1.2).[14,15,16] Based on the fact that these compounds are also susceptible to acid hydrolysis and that the resultant aglycones themselves do not show any antitumor activity, incorporation of one or two fluorine(s) at the 2' position[14a,b] or three fluorines at the 6' position[14c] was investigated

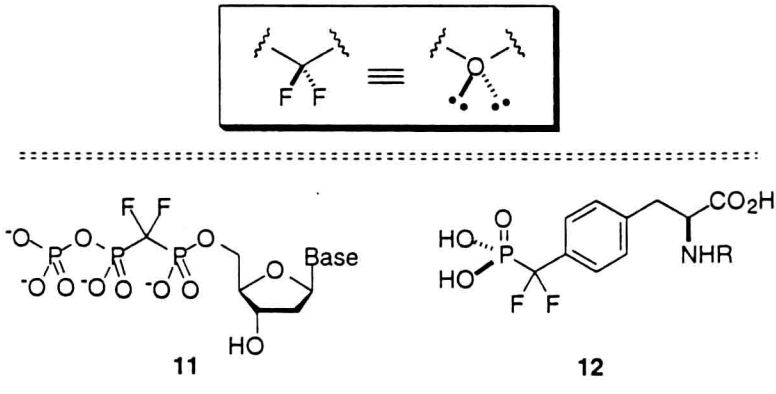


Fig. 1.3 Representative difluorophosphonates.

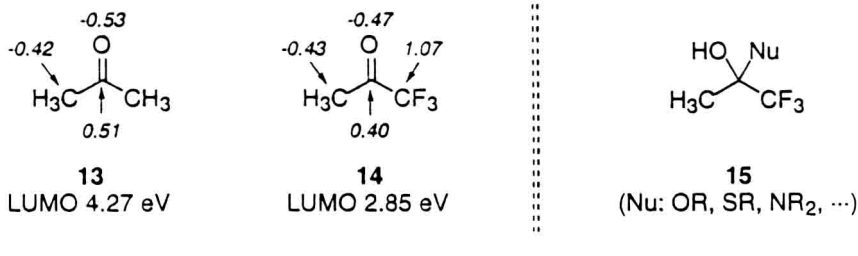
along with the modification of functional groups at the 3' and/or 4' positions to successfully suppress the unfavorable cleavage of the sugar moieties while maintaining their excellent original activities.

Substitution of biologically attractive phosphate intermediates for the corresponding phosphonates becomes the major protection strategy from undesirable hydrolysis. Recently, difluoromethylene phosphonates rather than the nonfluorinated counterparts have drawn significant attention due to the isosteric as well as isoelectronic nature of a CF_2 moiety to the ether oxygen with elimination of the hydrolysis susceptibility,[17] and such analogs lead to attainment of second pK_a values much closer to those of the parent materials.[18] Based on this concept, Blackburn demonstrated[19] the construction of difluoromethylene-substituted 2'-deoxyadenosine and 2'-deoxythymidine 5'-triphosphates **11** along with the corresponding monofluorinated counterparts as the DNA polymerase inhibitors (Fig. 1.3). On the other hand, two research groups[20] manipulated 4-(phosphonodifluoromethyl)phenylalanine **12** as the mimetics of the original phosphate as the phosphotyrosine phosphatase inhibitor.[21,22] In addition to the pK_a values, another advantage of oxygen substitution for a CF_2 group is the retention of the hydrogen bonding acceptance ability, which is completely lost in the corresponding CH_2 derivatives.

1.1.2.2 Activation Effect

The above constitutes the typical application of a difluoromethylene moiety as the mimic of oxygen, and the deactivation by the electronic acceptance from the neighboring functionalities results in the final stabilization of molecules. In sharp contrast to this concept, there exists another strategy activating the original substrates by incorporation of fluorine.

How then are functionalities in the vicinity of fluorine or fluorine-containing groups activated? The solution was suggested by a comparison of two model compounds, acetone **13** and 1,1,1-trifluoroacetone **14**, based on *ab initio* molecular orbital calculations (Fig. 1.4).[23] It might be intuitively understood that the carbonyl carbon atom of the latter is electronically more deficient than the one of **13** due to the direct attachment of the strongly electron-withdrawing CF_3 group. However, MO calculations by Linderman's group[23] unambiguously manifested the opposite tendency, *i.e.* the carbonyl carbon of **14** is less cationic than the one of **13**, and this theoretical result is experimentally supported by ^{13}C NMR chemical shifts of these carbon atoms in question, 206.0 ppm for **13** and 188.8 ppm for **14**. Instead of the partial charge, fluorines are considered to be responsible for about 1.4 eV lowering of the LUMO energy level, producing the quite different electrophilic

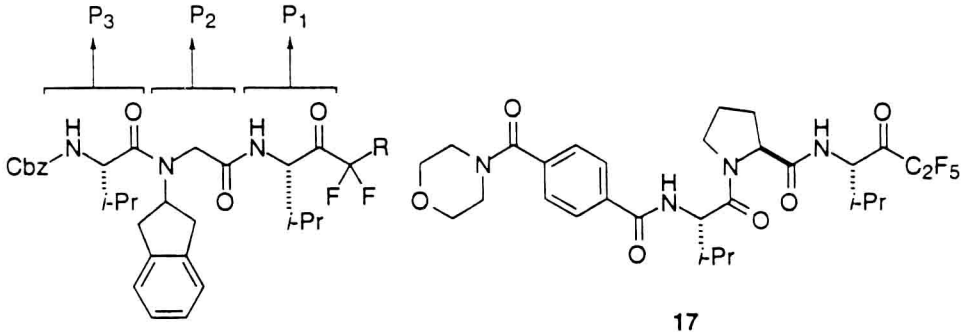


13
LUMO 4.27 eV

14
LUMO 2.85 eV

15
(Nu: OR, SR, NR_2, ···)

Fig. 1.4 *Ab initio* (HF/6-31G**) analysis of acetone and trifluoroacetone.
(*italic number*: point charge)



16a (R=F)
16b (R=CO_2Et)

17

Fig. 1.5 Protease inhibitors with fluorinated ketone functions.

circumstance between **13** and **14**.

This quality allows **14** to very easily react with a variety of nucleophiles to form the adduct **15**. Although this type of product is less stable than the starting carbonyl compound when such materials do not contain any fluorine atoms, a tetrahedral intermediate like **15** is extraordinarily stable for substances with two or three fluorines next to the original carbonyl group. This stability originates from the significant reluctance to form carbocations α to the CF_3 group and also the strong stability of the alkoxide from **15** for the electrostatic reason (*vide infra*), both inhibiting its hydrolysis under acidic and basic conditions, respectively. It is well known that trifluoroacetaldehyde CF_3CHO demonstrates a characteristic behavior: only its hydrate ($CF_3CH(OH)_2$) or hemiacetal ($CF_3CH(OH)(OR)$) forms are available from commercial suppliers, and *both forms must be heated to 120 °C or more in concentrated H_2SO_4 for the liberation of the desired aldehyde!*[24]

Application of this unique activation concept based on the stability of a tetrahedral intermediate like **15** has been realized in a recent intensive investigation of protease inhibitors which mimic the tetrahedral hydrolysis transition states by the stable hemiketal formation with the hydroxy group of the active site Ser^{195}.[25] The representative examples are described in Fig. 1.5. Skiles and his co-workers reported[26] the preparation of **16a** as the human leukocyte elastase (HLE) inhibitor and the effectiveness of the achiral indan substituent on nitrogen instead of L-proline at the P_2 site as well as the importance of the valine-derived trifluoromethyl ketone structure at P_1 for the accomplishment of the acceptable *in vitro* inhibition. They further carried out the modification of **16a**[27] to construct the α,α-difluoro-β-ketoester **16b** and succeeded in enhancing the activity to a level about twice that of cephalosporins.[28]

Another research group studied[29] a similar type of compound **17** for the human neutrophil elastase (HNE) inhibitors. NMR study clarified the ready hydrate formation of pentafluoroethyl and the corresponding trifluoromethyl ketones (the latter is more active than the former) and it is interesting to note that even substrates with five fluorines were found to be effective as the inhibitor.