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Joy and Flustration with Organofluorine Compounds – A Fluorous Autobiography

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Dedicated to the memory of Professor *Manfred Schlosser*, great chemist, friend and fellow lover of fluoro-organic chemistry[1]

Abstract: An overview is given about our work on fluoro-organic compounds, published or described in PhD theses between 1977 and 2013. After a discussion of structural F-effects and F-tagging applications the material is ordered by the various areas of our research, in which we have used and/or prepared F-derivatives: Li- and Ti-organic compounds and reagents, polylithiated hydroxy-esters and nitroalkanes, the enantiopure trifluoro-lactic, -*Roche*, and -3-hydroxy-butanoic acids as toolbox for the preparation of numerous F_3C-substituted compounds, including natural products and dendrimers, and fluoro-α-, -β-, and -δ-amino acids, as well as peptides with back-bond-bound fluorine. The strong influence on β-peptide folding by fluoro-substituents in the α-position of β-amino-acid residues is discussed in terms of the α-fluoro-amide conformational effect. Finally, some cases of totally unexpected effects on reactivity and structure exerted by fluoro-substitution are presented and taken as examples for our use of the terms flustrate and flustration in connection with organo-fluorine chemistry.

Keywords: CF_3-substituted dendrimers · Enantiopure aliphatic CF_3-derivatives · F-effects on peptide folding · F-labelling and tagging · Fluoro-organic compounds

1. Introduction

When I was invited to contribute an article to the topical *CHIMIA* issue on organofluorine chemistry I was brave enough to accept, without realizing how many papers had been published by us in this area[2–41] over the past 3½ decades, and how many PhD theses had been devoted more or less entirely to this topic in my group:[42–48] it turns out that throughout my career as a methodologically oriented synthetic organic chemist fluorine derivatives exerted an irresistible attraction on me. Fluorine appears in every period of research activities my group had entered: organo-sulfur, organo-lithium, organo-titanium, and nitroorganic chemistry, enzymes as catalysts, electrochemistry, amino-acid and peptide chemistry, dendrimers, the biopolymer PHB, self-regeneration of stereocenters, [-(Arl)$_2$C-O-]-groups[49] in organic synthesis, and organocatalysis. In order to provide a representative overview, I decided to prepare a kind of collage of schemes and figures, with a minimum of text and complete referencing; most of the formulae, diagrams and pictures shown here are actually copied from our corresponding papers. Work of other groups on the same subjects is referred to in our publications and theses[2–48] and will not be cited herein. Also, with few exceptions, no effort is made to update the literature in the various fields. Thus, a very personal fluorous autobiography is presented.

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2. Structural Fluorine Effects and Fluorine as Tagging Element

Fluorine, the most electronegative element, exerts a strong generalized *gauche*-effect, which, in the examples shown in Fig. 1a, can be discussed in terms of anomeric $n_N \rightarrow \sigma^*_{C,F}$ or $\sigma_{C,H} \rightarrow \sigma^*_{C,F}$ interactions.[53] On the other hand, in α-fluoro-amides the *ap*-conformation of the (C,F)- and the (C,O)-bond is strongly favored, an effect that can dominate the structure of F-substituted β-peptides (*vide infra*). – In spite of the big electronegativity difference between C and F and thus polarity of the C,F-bond "organic fluorine hardly ever accepts hydrogen bonds".[54] The still widely taken views that F is a substitute of OH as a hydrogen-bond acceptor, and that F is just a "big hydrogen" are wrong (the A-value of F is 0.15) (Fig. 1 b–d).

The magnetic nucleus ^{19}F (100% abundance) provides unique probes for detection of organofluorine compounds by NMR (and ESR) spectroscopy, and ^{18}F-derivatives are widely used for PET diagnosis. We have used F-tagging for detection and identification of $(RS)_3C^{\cdot}$ radicals and of fluoro-carbenoides (Fig. 2). Introduction of F_3C-groups into oligo(β-hydroxybutyrates) and into β-peptides consisting of 2,2-dimethyl-3-amino-propanoic acid residues was used for obtaining information about the oligomer-backbone structures, also of dendrimers (*vide infra*). Labeling coenzyme A with an F_3C-group gave a valuable NMR probe for studying biochemical processes (Fig. 2). Finally, we have also used the so-called fluorous tagging strategy,[55] which exploits the affinity of fluorocarbons for each other (*cf.* the non miscibility of C_nH_{2n+2} and C_nF_{2n+2}[56]), for peptide synthesis in a microreactor (Fig. 2).

3. Fluorine-containing Organo-Ti- and Organo-Li-reagents

When we turned from organolithium to the much more selective organotitanium reagents[57] in the early 1980s, which was also the period of invention of the TADDOLs[49] we discovered that 2-fluorophenyl titanium compounds are stable at room temperature (Fig. 3) and could be used for highly selective carbonyl additions.

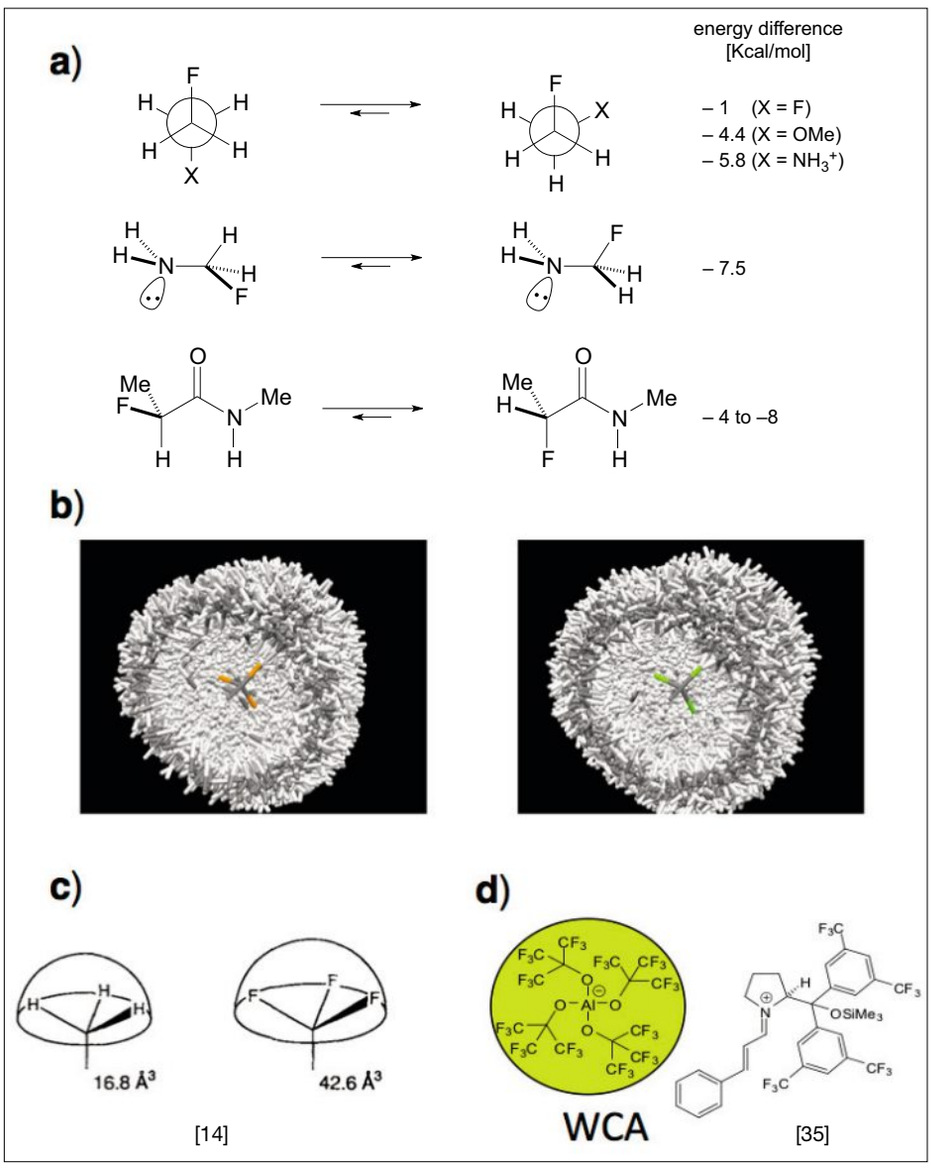

Fig. 1. Structural effects of fluorine. a) *gauche*-Effect in X-CH_2-CH_2-F and *ap*-effect in α-fluoro-amides; the energy differences have been determined experimentally and/or computationally.[31,50] b) Next hydrogen neighbors to CH_3 (left) and F_3C (right); an overlay of *ca*. 2500 X-ray structures each, found in the CSD data base in June 2010, using the CCDC Software *Isostar* (version Nov. 2009),[51] a library of information about non-bonded interactions; in this respect, there is no indication of a fundamental difference between CH_3 and F_3C, except that F_3C is much larger than CH_3;[52] c) *van-der-Waals* volume of CH_3 and F_3C;[14] the latter has approximately the same volume as an isopropyl group. d) Perfluoro tetra-*t*butoxy-aluminate, a weekly or non-coordinating anion (WCA, NCA) for crystallization and X-ray structure determinations[35] – a big ball covered by F atoms with a negatively charged core, engaging in no interactions with the cation.

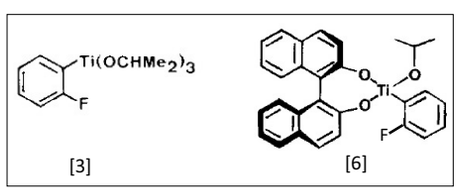

Fig. 3. *ortho*-Fluorophenyl-titanium derivatives. Unlike *ortho*-fluoro-phenyllithium, which is subject to β-elimination and dehydro-benzene formation, the triisopropoxy-titanium analog is stable at room temperature (colorless powder under inert atmosphere).[3] Enantioselective additions to carbonyl compounds have been achieved with the binol derivative.[6] The stability of such compounds is especially surprising when we consider the high Ti,F-affinity (virtual Ti–F bond energy 136 Kcal/mol).

Our long-lasting interest in nitroorganic compounds[58] led to an investigation of di- and trifluoro-nitroethane and trifluoro-2-nitro-propane (Fig. 4), which were generously supplied to us by the *Bayer* company. Like the non-fluorinated analogs, the di- and trifluoro-nitroalkanes could be α,α-doubly deprotonated (to 'supernitronates') or α,β-doubly deprotonated (to 'superenamines'), to give reagents that add to aldehydes and ketones and to α,β-unsaturated carbonyl derivatives. By NO_2 reduction the corresponding amino compounds are accessible (Fig. 4).

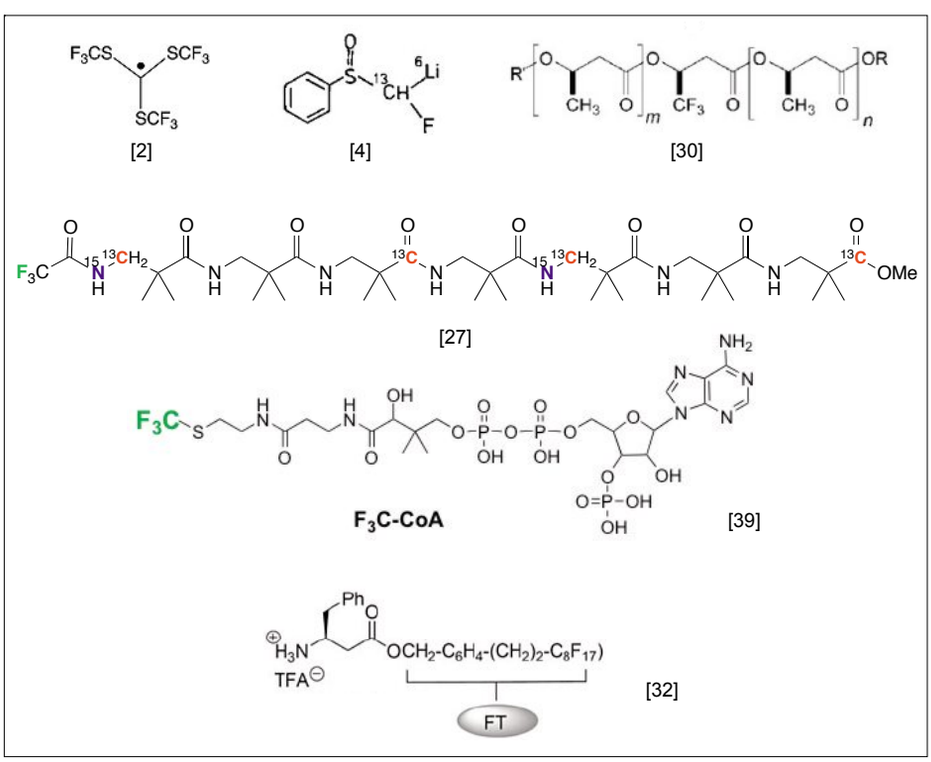

Fig. 2. Use of fluorine tagging. Detection of C,C-dissociation of $(RS)_3C$–$C(SR)_3$; a Li-carbenoid with three magnetic labels; F_3C-analogs of PHB for structural investigations by means of solid-state ^{19}F-NMR techniques; a β-heptapeptide with ^{19}F,^{15}N and ^{13}C labeling for TEDOR/REDOR NMR analysis of the solid-state structure; F_3C-CoA as NMR probe for studying intermolecular chain translocation in ketosynthase; fluorous tagging of H-β^{3}hPhe-benzyl ester, causing solubilization and ease of purification (on fluorous silica gel) in β-peptide synthesis carried out in a microreactor.

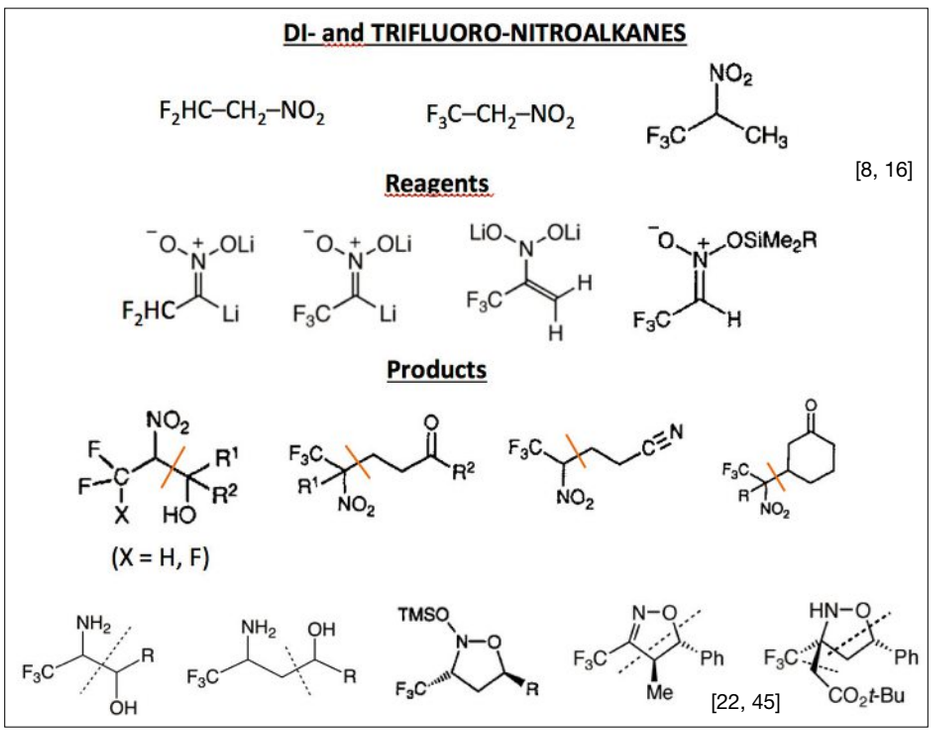

Fig. 4. Doubly deprotonated di- and trifluoro-nitroalkanes and trifluoro-silylnitronates as nucleophiles and for 1,3-dipolar cycloadditions. Surprisingly, there is no fluoride elimination (at low temperatures) from the dilithio derivatives and no F,Si-formation from the silylnitronate (bond energy Li–F and Si–F 138 and 129 Kcal/mol, respectively!). 1,2-Additions, conjugate additions and 1,3-dipolar cycloadditions lead to a variety of F_2HC- and F_3C-derivatives with additional functional groups.

4. Enantiopure Trifluoro-hydroxy-acids Providing a Toolbox for the Preparation of F_3C-Derivatives

Besides carbohydrates and amino acids, the simple hydroxy acids lactic acid, malic acid, 3-hydroxy-butanoic acid, 3-hydroxy-2-methyl-propanoic acid (*Roche*-acid), tartaric acid, and mandelic acid are cheap and readily available enantiopure starting materials (pool of chiral building blocks or 'chiral pool') for organic synthesis. There is a rich body of publications describing elaborations of these chiral compounds to a myriad of products (for reviews from our group see ref. [59]), in many cases this 'source of chirality' is a viable alternative of enantioselective transformations. To make the corresponding trifluoro-derivatives also readily available, we have prepared trifluoro-latic (Fig. 5), trifluoro-*Roche* (Fig. 6) and trifluoro-hydroxy-butanoic acid (Figs. 7a,b,c) in both enantiomeric forms by large-scale resolutions and demonstrated their value as chiral starting materials and valuable building blocks (Figs. 5–7).

5. Fluoro-substituted Amino Acids and Peptides

Not surprisingly, fluorine also 'invaded' our work on amino acids and peptides. Thus, Li-enolates of the chiral, enantiopure glycine derivatives Boc-BMI, Bz-BMI, and 2-*t*Bu-3-Cbz-oxazolidinone were alkylated with benzyl halides or added to aldehydes carrying fluoro- or F_3C-substituents (Fig. 8a). – The unique C_9-amino acid of cyclosporins, Me-Bmt, was synthesized with stereoselective in-

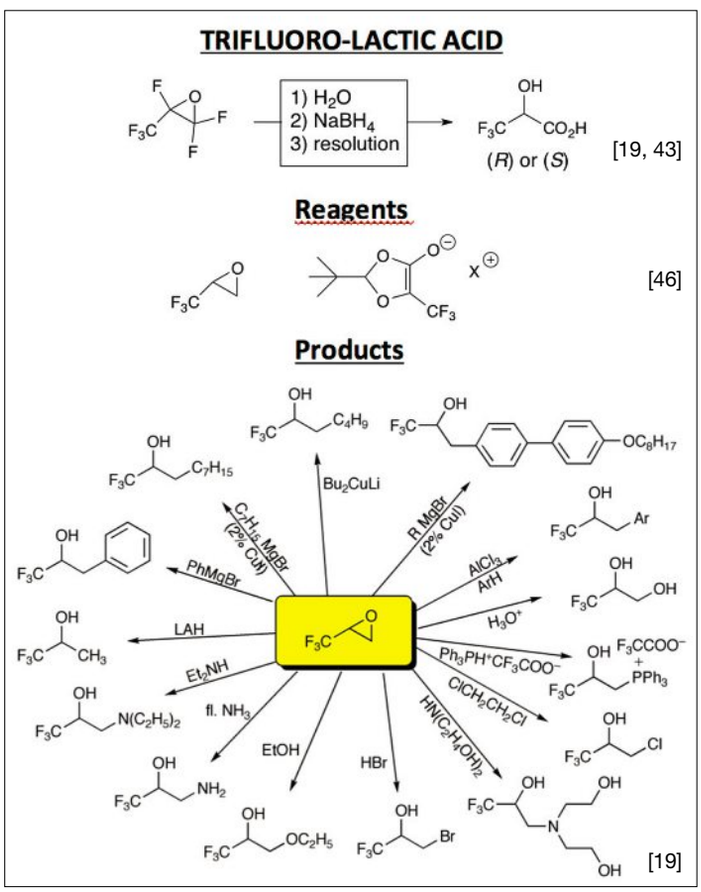

Fig. 5. (*R*)- and (*S*)-Trifluoro-lactic acid and trifluoromethyl-oxirane. Hydrolysis of perfluoro-propylene oxide (cheap monomer of a valuable polymer), reduction and resolution (with 2-amino-1-phenyl-1,3-propandiol) to $F_3CCH(OH)CO_2H$, which is readily converted to the F_3C-oxirane, numerous reactions of which had been published by other groups (see the references in ref. [19]).

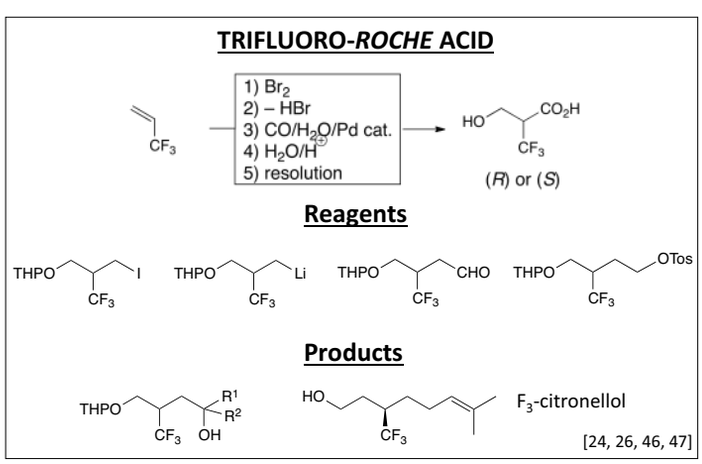

Fig. 6. (*R*)- and (*S*)-2-Trifluoromethyl-3-hydroxy-propanoic acid (F_3-*Roche* acid). Conversion of trifluoro-propene to the corresponding *Roche* acid and resolution (with 2-amino-1-phenyl-1,3-propanediol). The special feature of *Roche* acid (first recognized by the *Hoffmann-La Roche* chemist *A. Fischli*[60]) is its 'hidden' symmetry: from one of its enantiomers either enantiomer of a product is accessible by analogous elaborations on the two enantiotopic carbon atoms C(1) and C(3) (*cf.* $R^1O–CH_2–CHCH_3–CH_2–OR^2$).

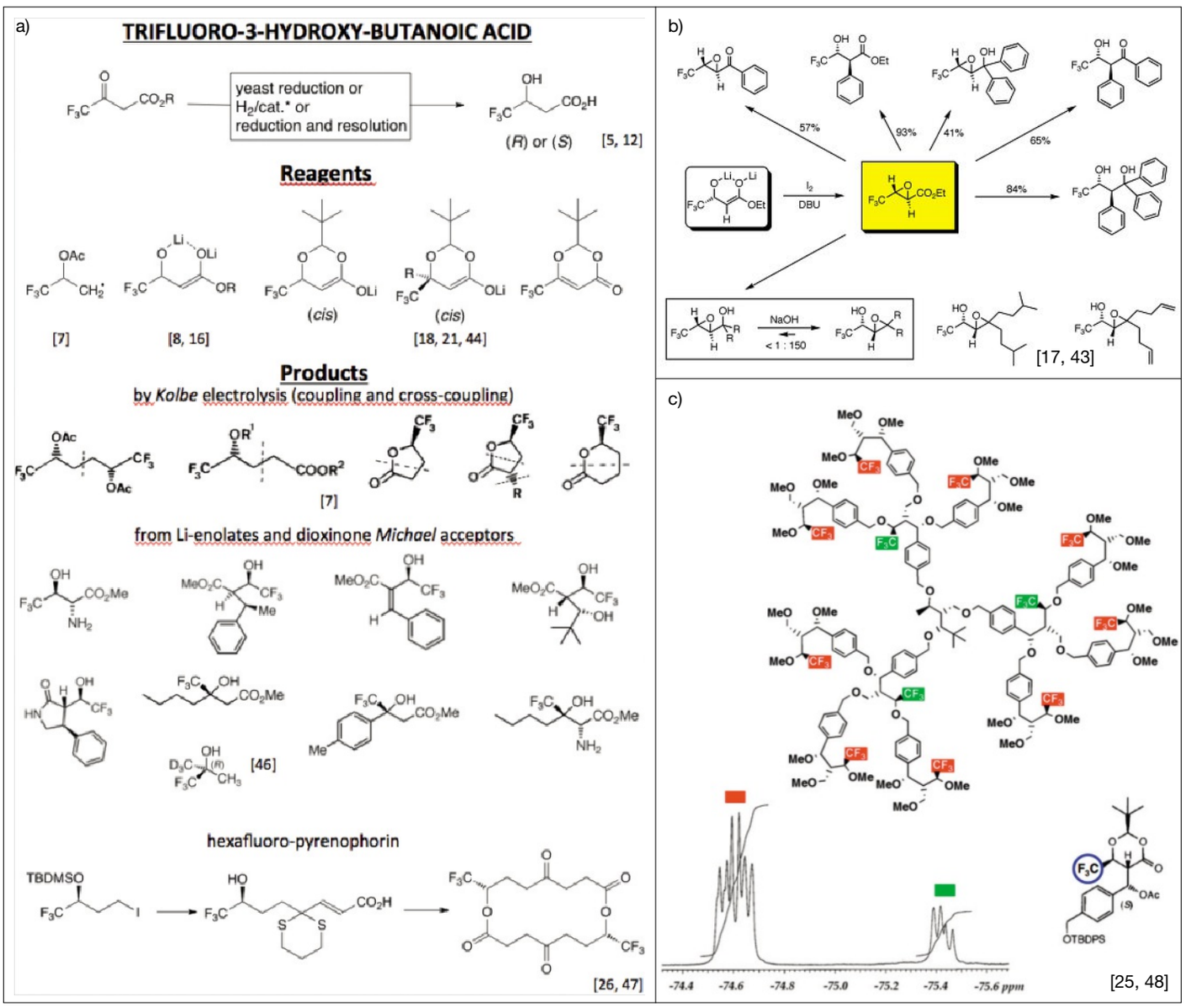

Fig. 7. a) (*R*)- and (*S*)-Trifluoro-3-hydroxy-butanoic acid and products derived thereof through radical, enolate and *Michael* acceptor intermediates. F_3-Acetoacetic ester is a cheap industrial material. The resolution of its reduction product was achieved with 1-phenethyl-amine. *Kolbe* Electrolysis of the acetoxy-acid alone or with excess malonic or succinic half-ester produces the 1,4-diol-diacetate and the γ- and δ-hydroxy-acid derivatives, respectively. Amination, alkylation, aldol addition/condensation, and *Michael* addition (to nitrostyrene), as well as Cu-catalyzed *Michael* addition to the 2-*t*Bu-6-F_3C-5-dioxin-4-one lead to the products shown. In contrast to the parent compound, hexafluoro-pyrenophorin shows no antibiotic activity. b) Preparation of trifluoromethyl-glycidic ester by iodination of the lithioxy-lithium enolate of the β-hydroxyester and cyclization. Reactions of the epoxyester with various nucleophiles and *Payne* rearrangement under basic conditions (in this process, the less acidic epoxy-alcohol is converted to the more acidic one). Dramatic differences of reactivities and properties, as compared to non-fluorinated analogs, have been reported in these investigations.[17] c) A chiral dendrimer consisting of triol ether moieties prepared by addition of the trifluoromethyl-substituted dioxanone Li-enolate to pivalaldehyde (center part) and to 4-TBDPS–O–CH_2-benzaldehyde (branching points). The inner three and the outer nine F_3C-groups are all constitutionally heterotopic, and their ^{19}F-NMR signals are, at least partially, resolved (four of the expected six signals are seen for the inner and eight of the maximum 18 for the outer F_3C groups).[25,48]

corporation of a fluoro-substituent in the 4-position (Fig. 8a), to see whether the thus increased acidity and reduced nucleophilicity of the neighboring OH-group would lead to increased stability and/or activity of the immunosuppressive cycloundecapeptide; the activity in three standard tests was only slightly higher than that of CS A itself, and the stability *in vivo* was actually never tested.[61] – Leucine was converted to a possible dipeptide isostere (5-amino-4,4-difluoro-7-methyl-octanoic acid, Fig. 8b).

Most efforts were devoted to the stereospecific preparation of α-fluoro- and α,α-difluoro-β-amino acids (Fig. 8b) and their incorporation into β-peptides. Since α-peptides with fluoro-substituents on back-bone positions are non-existent the β-peptides containing, or consisting entirely of, fluoro-amino-acid residues allowed us to study, for the first time, the effect of fluoro-groups on peptidic secondary structures. It turned out that the conformational preference of α-fluoro-amide groups, alluded to in Fig. 1a, is strong enough to stabilize or destabilize helices or turns (by incorporation of a single (!) fluoro-amino-acid residue, see Fig. 8c).

6. Non-rationalized Reactivities and Structural Effects Observed with Organofluorine Compounds

Again and again it happened that the chemical behavior of fluoro-derivatives completely baffled us. At first sight, the unexpected result of an experiment can be frustrating, even more so, when we have

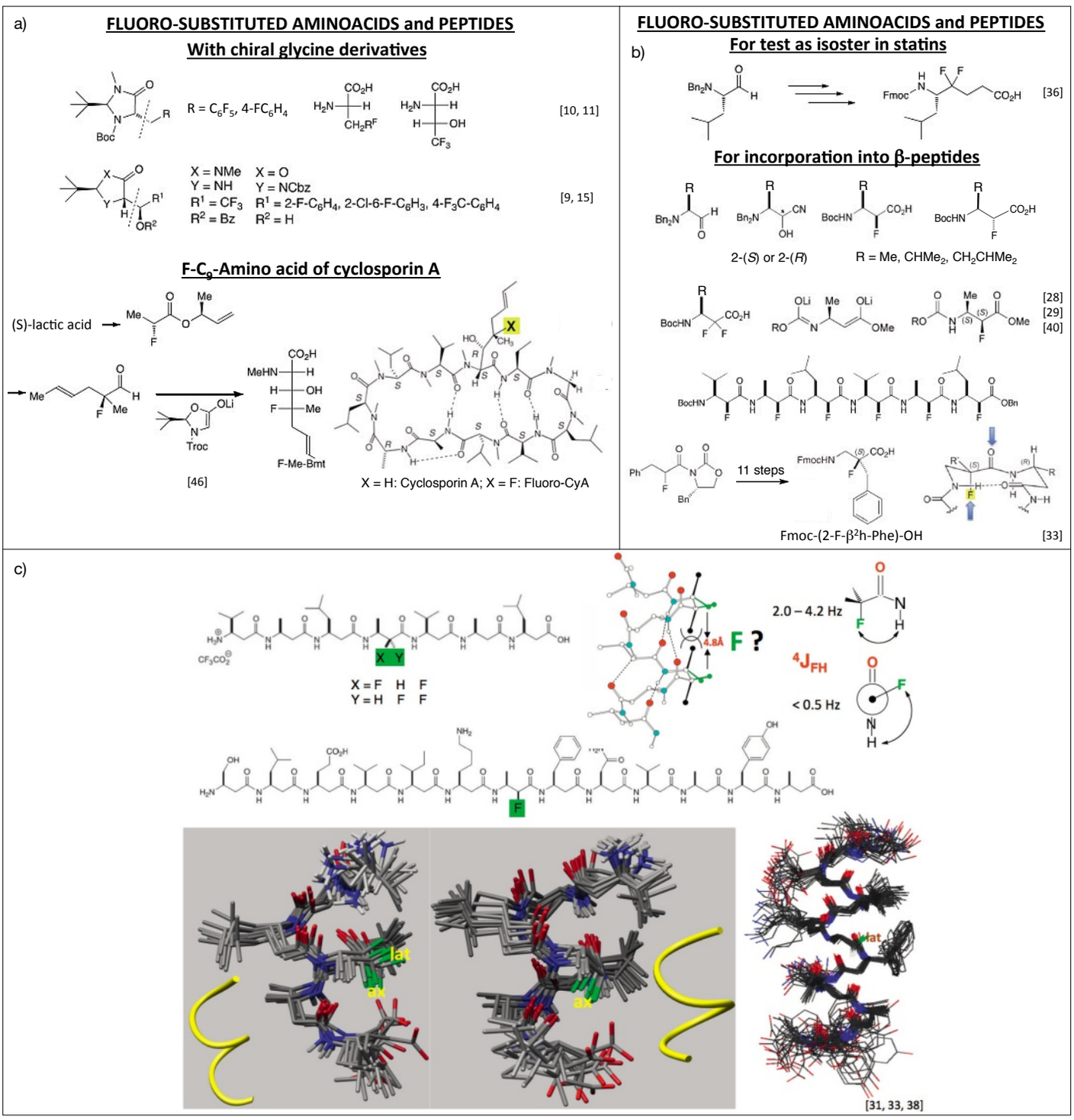

Fig. 8. a) F-Containing α-amino acids by alkylation or hydroxyalkylation of enantiopure imidazolidinone and oxazolidinone enolates and hydrolytic cleavage of the primary products (top). Hitherto unpublished synthesis of F-Bmt for incorporation into cyclosporine (bottom); (*R*)-fluoro-propanoic acid was allylated by *Claisen* rearrangement of its (*S*)-2-but-3-enyl ester and the product reduced to an aldehyde, to which the Troc-oxazolidinone enolate was added diastereoselectively with formation of the threonine-type substructure of Bmt.[46] As with other Bmt analogs, incorporation of the F-Bmt into Cy A was achieved by 'offering' it to Cy A-producing microorganisms.[61] b) Preparation of a δ- and of a series of β-amino acids carrying fluorine in the γ- and α-position, respectively, and synthesis of β-peptides containing a single fluoro-substituent (*cf*. Fig. 8c) or a fluorine atom in every residue. From alanine, valine and leucine the *Reetz* aldehydes were prepared and converted to either (*S,S*)- or (*R,S*)-cyanohydrins; the hydroxyesters resulting from a *Pinner*-type methanolysis were then treated with DAST to give (with retention of configuration) 3-amino-2-fluoro-substituted esters, and finally *N*-Boc-protected acids were prepared for peptide synthesis in solution. Alternatively an (*S,S*)-derivative of β^{3}h-alanine is also accessible by diastereoselective fluorination with $(PhSO_2)_2NF$ of the doubly lithiated Boc- or Cbz-protected methylester. Geminal difluoro-amino acids were prepared by DAST treatment of the corresponding carbonyl compounds ('keto'-amino acids). c) Incorporation of (*S,S*)- or (*R,S*)-2-fluoro- and of (*S*)-2,2-difluoro-3-amino-acid residues in the center position of a hepta- and a trideca-β-peptide and NMR structure determination in MeOH. In the 3_{14}-helix of β^3-peptides each tetrahedral (sp^3) center of the backbone has an axial and a lateral position for substituents. The distance between two such centers lying on top of each other is *ca*. 4.8 Å, enough for two axial hydrogen substituents (the sum of two covalent and two *van-der-Waals radii* for C–H···H–C is *ca*. 4.4 Å). An axial Me group is forbidden,[62] how about a fluorine (C–H···F–C distance > 5 Å)? The NMR analysis of the corresponding peptide structures indicates that an axial F is possible in the helix of the heptapeptide while a lateral F is not (the preferred fluoroamide conformation 'breaks' the helix!). It takes the cooperativity of the tridecapeptide to force a fluorine atom into the lateral position, with the unfavorable fluoroamide conformation. Like almost all our β-peptide NMR structures this analysis is due to a wonderful collaboration with *B. Jaun*.[31,33,38]

no rationale to offer. On the other hand, a central element of science is the discovery of new facts, in chemistry particularly the "creation of new objects", as *Berthelot* put it in his definition of chemistry.[63] Thus, there was always a mixture of frustration and excitement (fluster, flutter) when a coworker reported an unexpected result, which was hard to understand or could not be rationalized at all – and this was the case especially frequently with fluoro-substrates. This is why our group started using the term "flustrate",[14] which *Roald Hoffmann* appreciated – for poetic and linguistic reasons. In Figs. 9a and b just a few examples are collected of non-rationalized results or effects we experienced with fluorine derivatives over the years.

Thus, β-fluoro-nitroalkanes are poor substrates in classical base-catalyzed nitroaldol reactions (because of HF elimination: F^- is a good leaving group only in protic solvents). We found that di- and trifluoro-nitroalkanes can be doubly lithiated or silylated with butyllithiums or with DMAP/$ClSiR_3$ without loss of fluoride. On the other hand, treatment of $F_3CCH(NO_2)CH_3$ with the silylating reagents $Me_2NCO_2SiR_3$ led to complete loss of all three fluorine atoms with formation of 1,1-bisdimethylamino-2-nitro-propene (Fig. 9a, a)). A total change of mechanism must occur when the CH_3-group of the dioxinone *Michael* acceptor shown in Fig. 9a, b) is replaced by F_3C in the Cu(I)-mediated addition of benzyl *Grignard* reagent! No clue is offered to explain the effect of a single fluorine atom in the *Michael* addition of *N*-Me-indol to cinnamaldehyde catalyzed by the so-called *MacMillan* generation I organocatalyst (Fig. 9a, c)). The 'transacetalization' of an

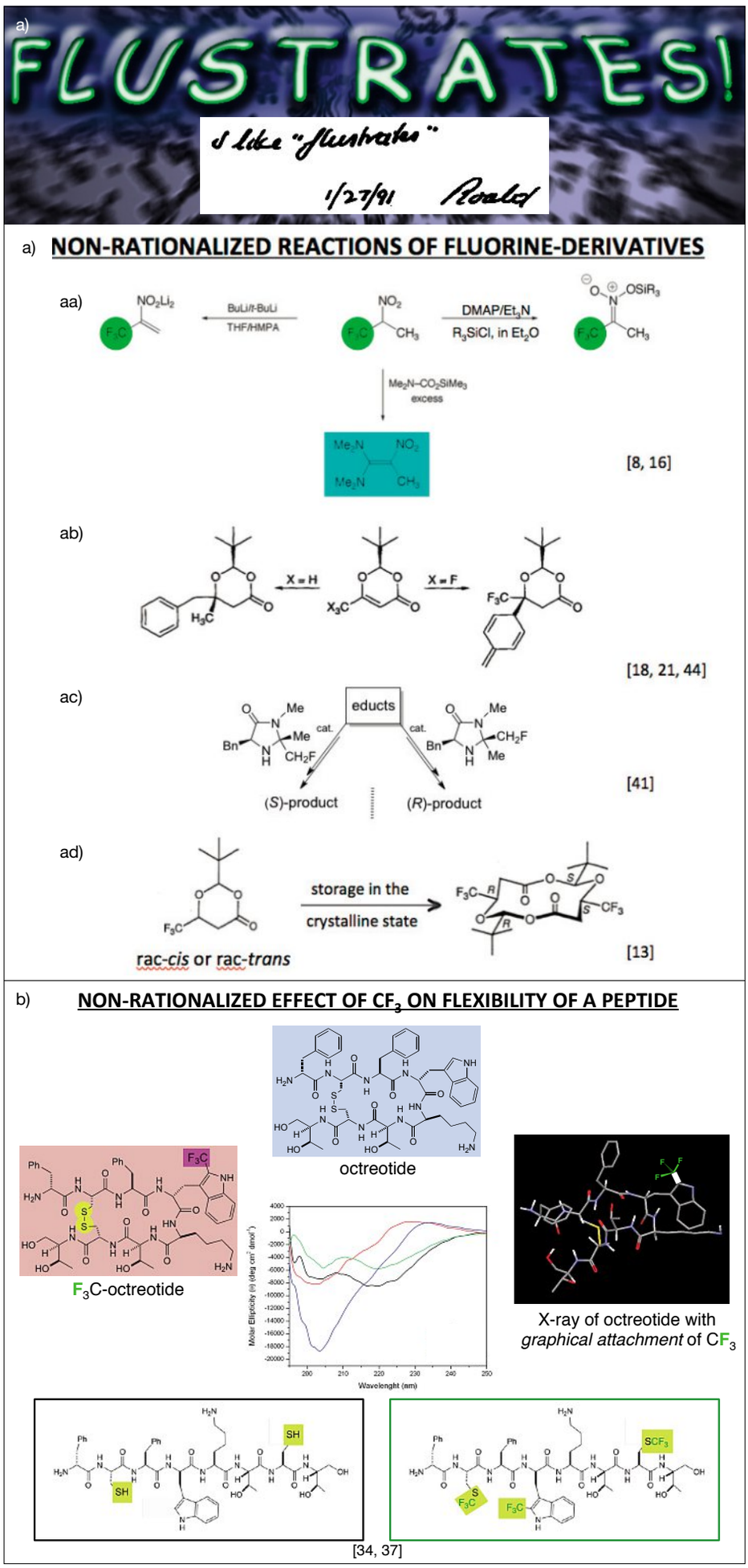

Fig. 9. a) Some unexpected reactions of fluoro-derivatives. aa) No LiF- or R_3SiF-elimination from 1,1,1-trifluoro-2-nitro-propane with BuLi or DMAP, but complete loss of all three fluorines with $Me_2NCO_2SiMe_3$ in a series of β-eliminations/conjugate additions. ab) *trans*-Benzylation of the CH_3-substituted dioxinone and coupling in the *para*-position with the F_3C-analog (BnMgCl/CuCl). ac) Reversal of the stereochemical course of an organocatalytic reaction with *cis*- and *trans*-5-benzyl-2-fluoromethyl-2,3-dimethyl-imidazolidinone. ad) Reaction in the solid state of *rac*-*t*Bu-trifluoromethyl-dioxanone to form a 12-membered ring; the enantiopure *cis*- and *trans*-forms and the CH_3-analogs are stable compounds of dioxanone structure. b) Octreotide (Sandostatin®), the corresponding dithiol and F_3C-derivatives obtained with the *Togni* reagent. The strong *Cotton* effect of octreotide (blue CD curve) disappears upon trifluoromethylation in 2-position of the indolyl group (red CD curve). Concomitantly, a dynamic NMR analysis reveals that the rigid backbone conformation of octreotide becomes highly flexible by introduction of the F_3C-group.

F_3C-substituted dioxanone in the crystalline state is yet another example causing flustration (Fig. 9a, d)). Finally, laymen[34] and specialists[37] are equally surprised about the backbone flexibilization of the octreotide backbone by introduction of an F_3C-group in the tryptophane side chain (Fig. 9b) – albeit a comparison within the H_3C-analog has not been made as yet.

It remains for us to cite a doggerel about fluorine by *V. O. J. Newton*:[64]

The ultimate combiner
Fervid Fluorine, though just Nine
Knows her aim in life: combine!
In fact, of things that like to mingle,
None's less likely to stay single.

Acknowledgements

I thank all the coworkers and collaborators, who took the risk of flustration with me over the years; their names are given in the list of references.[2-48] I ask those, whose work was not published, to forgive me, but also those, whose results were published 'only' in German, and thus remained almost unnoticed in the literature. Finally, my special thank goes to Albert K. Beck for his F-contributions and for his help in producing the manuscript of this autobiography.

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