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FOREWORD

Fluorine is an element with unique properties and an unusual history. If it is possible to imagine a man who possesses the features of fluorine (small, but very greedy and violent), it is easy to expect that such a person would be ostracised from society or would govern it. Indeed, Nature has synthesized a dazzling array of halogen-containing natural products, but failed to handle fluorine having produced only a dozen fluorinated molecules which mostly are very toxic for living creatures. In contrast to this in the man-made continuation of Nature - organic chemistry, fluorine figures prominently and this part of its history is almost legendary. Thus, in 1992, compounds containing a carbon-fluorine bond constituted 6.2% of the ten million registered by Chemical Abstracts. Quite recently, Seebach in his excellent review *Organic Chemistry. Where now?* has emphasized the significant position of organofluorine chemistry in the current movement of organic chemistry and gave a birth to new term "flustrates" which reflects the unexpected and generally unusual reactivity and biological activity of fluorine-containing compounds. To our mind, one of the most important events in the history of fluorine happened about half century ago; the isolation of potassium fluoroacetate from the leaves of the South African shrub *Dichapetalum cymosum* in 1943 by Marais which was followed by the discovery of the "lethal synthesis" by Peters. A decade later, in 1954, with the preparation of 9-α-fluorohydrocortisone acetate by Fried, the idea of *modification of biological activity by fluorine substitution for hydrogen* had been successfully demonstrated and has become a cornerstone of fluoroorganic chemistry directed towards the creation, synthesis and investigation of the metabolism of fluorinated analogs of natural products - *fluorobioorganic chemistry.* During the past quarter of a centrury this area of research has reached a position of prominence in the life science fields, most notably with fluorinated carbohydrates, vitamin D_3 analogues, and nucleic and amino acids. Despite the understanding of the influence of the basic physical properties of fluorine (size of atom, its electronegativity, energy of C-F bond and lipophilicity of fluorine) on the physiological behaviour of fluorinated compounds, the biological activity of fluorine-containing molecules is mostly unpredictable. The rapid development of the field is closely linked to the state of the art of fluoroorganic synthesis which is required to provide the varied fluorinated materials to allow systematic structure-activity and molecular recognition studies. Nowadays, the scientific community have fully recognized the necessity of investigating the biological activity of stereochemically pure compounds, and this has been reflected in the recent guidelines of Food, Drug and Agrochemical regulatory authorities of many countries. As a consequence, the development of efficient approaches to enantiomerically pure fluorine-containing analogues of natural products has become an area of research of crucial importance. The results achieved so far on the synthesis of fluoroorganic compounds have clearly shown that fluorine and fluorine containing groups cannot be considered as merely substituents. The strongly electronegative nature of fluorine can disturb or alter the course of reactions established for hydrocarbon patterns. Moreover, there are a number of examples which demonstrate the abilities of fluorine and fluorine-containing groups to play the role of enantiodirecting factors inverting the stereochemical results of reactions. Thus, being on the border of asymmetric synthesis and organofluorine chemistry the *enantiocontrolled synthesis of fluroorganic compounds* is the point of intensive growth and we consider that the time is now ripe for the Special Issue devoted to this subject.

The present collection of papers by leading investigators in the field gives a fair description about the goals currently of interest and methodologies used to reach them. The selection of papers for this issue reflects the efforts being devoted to the different approaches such as asymmetric synthesis, chiral pool elaboration, classical and biocatalytic resolutions and their potential for the preparation of homochiral fluorine containing compounds. Current activity in the field is reflected by the large proportion of papers dealing with asymmetric synthesis. However, in the present limited collection it has not been possible to give some areas full justice relative to their significance.

One of the major targets of fluoroorganic chemistry - the direct introduction of fluorine and the trifluoromethyl group into the already formed carbon skeleton of a designed molecular, in the much more difficult asymmetric version, are exemplified by Davis and Iseki contributions. Related to this theme the enantioselective addition of molecular fluorine to alkenes, is represented by Sato. Another approach to the formation of stereogenic carbon centers being fluorine - substitution of hydroxy group by fluorine, is exemplified by Fritz-Langhals. Chiral building blocks (fluorinated chiral synthons) methodology being developed by Bravo is represented by the synthesis of optically active polyfluoroalkyl-containing oxiranes which could be easily transformed to enantiopure fluorinated analogues of amines, hydroxy amines, amino and hydroxy acids. New applications of fluorinated β-lactam chemistry by Welch are given in his contribution devoted to the synthesis of peptide analogues containing the fluorinated retroamide isostere. Sorochinsky reports on how fluorinated analogues of such complex molecules as coriolic acid can be prepared from readily available starting fluorine-containing building blocks. The highly stereoselective intramolecular cycloaddition reactions of nitrone, oxime and nitrile oxide, derived from 3-fluoro-5-hexenals, which lead to enantiomerically pure fluorinated aminocyclopentanols are reported by Resnati. Kitazume demonstrates the use of chiral fluorinated Schiff bases in the asymmetric aza-Diels-Alder reaction which offers a convenient entry to fluorine-containing 1,6-deoxyazasugar derivatives. The general route to compounds possessing fluorinated quaternary stereogenic centers via diastereoselectvie alkylations of chiral derivatives of fluoromalonate is described by Fukumoto. Diastereoselective additions of organometallic reagents to highly electrophilic C=N double bond of chiral cyclic trifluoromethyl-containing acylimines resulting in preparation of dipeptide esters with *N*-terminal α-trifluoromethyl substituted amino acids is reported by Sewald and Burger. A systematic study of the asymmetric reduction of α-acetylenic α'-fluoroalkyl, and aryl, alkyl α-fluoroalkyl ketones providing an excellent route to enantiopure fluorinated secondary alcohols is represented in two contributions from Brown. Brown also presents his rationale for the unexpected influence of the fluorine atom(s) on the enantioselection process in these reactions. An extension of homogeneous catalytic asymmetric syntheses to flustrates is exemplified by the Mikami and the Hayashi contributions. Thus, Mikami reports highly diastereo- and enantioselective catalytic carbonyl-ene reaction of fluoral with internal olefins, which provides an efficient route to homochiral trifluoromethyl-containing compounds. The use of gold(I)-catalyzed asymmetric aldol reaction for the asymmetric synthesis of fluorinated β-phenylserines is described by Hayashi. Enzymatic catalytic synthesis via bakers' yeast reduction of aryl trifluoromethyl ketones is presented by Fujisawa. Finally, the potential of resolution methods are also represented. Bégué reports an example of the preparation of all possible stereoisomers of β-peptidyl trifluoromethyl alcohols by chromatigraphic resolution of diastereomeric derivatives which have shown surprisingly different biological activities. The biocatalytic resolution of fluorinated tertiary alcohols using lipase and β-polyflyoroalkyl-β-amino acids by means of penicillin acylase are reported by O'Hagan and Švedas, Soloshonok, respectively.

The present collection of papers on the enantiocontrolled synthesis of fluoroorganic compounds shows the range and level of research efforts to date and gives new ideas and goals for future research rather than completed themes and results. Much remains to be understood and to be done before homochiral fluoroorganic compounds become readily available in the structural and conformational variety needed for the sophisticated problems of fluorobioorganic chemistry. We believe, the next few years will be rich in exciting results in the field and we optimistically look forward to a next Special Issue on this subject.

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