PREFACE

Professor Dr. Ekkehard Winterfeldt

Ekkehard Winterfeldt is emeritus Professor at the Leibniz University of Hannover and an internationally recognized leader in the field of synthetic organic chemistry. In his research he has addressed both, natural products total syntheses and the development of new synthetic methods and strategies. During his active career his focus was on applying the fundamentals of proposed biosyntheses of natural products to the design of new synthetic routes. At the same time he pioneered novel strategies for the selective construction of chiral centers. His perfection to accentuate novel reagents in biomimetic syntheses paved the way for a general approach towards efficient and effective syntheses of biologically active compounds.

Winterfeldt's contributions to organic chemistry are inseparable connected with alkaloid chemistry, the biomimetic synthesis of natural products and the thorough investigation of stereoselective additions to triple bonds (1966). In this context the advent of aluminum based reducing agent (DiBAl-H, TiBAl-H) was taken up by Winterfeldt and his contributions (1975) added significantly to the up-rise of DiBAl-H as the most prominent reducing agent in organic chemistry. Another field which was developed by Winterfeldt was using the retro-Diels-Alder reaction for generating new, structurally diverse compounds for medical applications. An additional strategy using the Diels-Alder reaction was concerned with developing a new strategy for stereoselective transformations. Here the addition to chiral dienes subsequent transformations and its release through retro-Diels-Alder reaction pioneered an unprecedented access to chiral compounds. Looking back to the various research activities that are associated with Winterfeldt it was in almost all cases the combination of elegant stereochemical synthesis applied to the most complex synthetic challenges of natural products that were solved in his own most generic fashion and which became a hallmark of Winterfeldt's oeuvre.

The birthday issue not only honors the concepts and strategies seeded by Winterfeldt but also reflects the way of analyzing synthetical problems the way Winterfeldt has taught a generation of chemists directly as a mentor and indirectly through his imaginative and innovative personality. Lectures delivered early in the morning were always crowded since Winterfeldt had the gift to present chemistry so lifelike and vivid that everybody was already excited attending the lecture on the very next day at 8 am. An impression of the concepts that were central to Winterfeldt and the way he presented chemistry is given in his book on "Stereoselective Synthesis."

In Winterfeldt's early work indole alkaloids were the pivotal class of natural products that he chose at the outset of his independent career. Since he had been trained by Bohlmann on the isolation and structure elucidation of natural products, it was a consequent development that he took on the synthesis of complex natural products with the challenge of providing routes that would be hallmarks of elegancy for constructing the desired stereochemistry. Right from the beginning two major themes were selected by Winterfeldt to be applied in his syntheses. First, established or proposed biosyntheses inspired Winterfeldt's way of designing strategies for the total synthesis of alkaloids. Second, the stereoselective construction was in many aspects in the center of Winterfeldt's research. In particular challenging natural products that were addressed by Winterfeldt are the staurosporines and cephalostatins which exhibit pseudo-symmetrical frameworks and require the novel strategies for stereoselective construction.

The research associated with indole alkaloids began with mechanistic investigations concerned with cyclization reactions of indole derivatives (1964). As a consequence of these investigations the stereoselective syntheses of ajmalicine, 19-epi-ajmalicine, formosanine and isoformosanine were put forward (1969). As one of the first biogenetically orientated total synthesis of an indole alkaloid the syntheses of camptothecin and 7-chlororcamptothecin was reported (1972). In the following years more mechanistic investigations were on the focus of his research. The investigation and stereochemical course of methylene lactam rearrangements in rigid polycyclic systems (1975) is one of the fundamental contributions and has been added to the canon of "standards" in alkaloid chemistry. In addition, his brilliant exploitation of the Witkop-autoxidation of indoles (1971) resulted in a combined one-pot oxidation/Camps-cyclization sequence establishing the autoxidative indole-quinolone rearrangements as a new tool for synthesis of alkaloids. This important strategy, coined the Witkop-Winterfeldt oxidation of indoles has been widely applied for the synthesis of pyrrolo[2,3-c]quinolones starting from 1,2,3,4-tetrahydro-β-carbolines. In order to show its applicability in total synthesis Winterfeldt reported the elegant synthesis of camptothecin model compounds (1972).

The stereoselective total synthesis of octacyclic indole alkaloid roxburghin D was reported stereospecifically (1975) and the enantioselective total synthesis of (+)-geissoschizine and (-)-geissoschizol (1976, 1985) were reported afterwards.

After establishing general strategies of indole alkaloids syntheses he moved to subtle stereochemical implications of the important protein kinase inhibitor staurosporine. Here the pseudo-symmetrical dimeric indole compounds had to be differentiated and the synthesis of an aglycon was reported (1983). Later the first regioselective synthesis of a monosubstituted staurosporine precursor was reported and opened the way for the selective construction of this protein kinase inhibitor (1994).

Continuing with synthesis that addressed such subtle stereochemical problems he approached in an enantiodivergent route both vincamine enantiomers which were synthesized based on a common precursor (1987).

The second theme on which Winterfeldt started his independent career was to unravel the scope and limitations of additions to acetylenic triple bonds. Here as well, stereochemical aspects were on the special focus of his research (1965). His creativity made him also realize that the triple bond would serve as a formidable starting point for constructing heterocycles (1966) and consequently a variety of papers covering various stereochemical aspects of additions to triple bonds were reported. In order to value his contribution one has to realize that nowadays most transformation based on triple bonds employed in polyketide synthesis refer at least in parts on results reported by Winterfeldt in his early career.

Inspired by natural products Winterfeldt was one of the pioneers who introduced the aspects of efficient synthesis combined with stereochemical control to synthetic organic chemistry. Being involved into the chemistry of biologically active compounds he developed a novel strategy for the stereoselective construction of such natural products. This synthetic approach is based on reactions with 4-acetoxy-2-cyclopenten-1-one (1977) and is the pivotal transformation for the synthesis of compounds such as prostaglandins. Cyclopentenone derivatives of 4-oxo-2-cyclopentenyl acetate served as intermediates for various syntheses (1982) and consequently an elegant entry to brefeldin A was reported (1980, 1984).

The fact that Winterfeldt anticipated very early new concepts in biologically-driven organic chemistry is demonstrated by his work on the synthesis of ansa-seco-steroids (1987). This concept that involved ring-opening of the steroid skeleton by means of retro-Diels-Alder reaction was also used by others to build up macrocyclic compounds for structurally diverse libraries.

His concept of using the retro-Diels-Alder reaction as a new transformation that allows incorporation and even more important removal of chiral auxiliaries was subsequently reported. Based on the Hajos-Wiechert ketone phenyl derivatives were transformed to enantiomerically pure cyclopentadienes (1993). These dienes served as chiral as chiral templates (1989) which could be transformed in face and endo-selective cycloadditions with enantiomerically pure cyclopentadienes (1994). Subsequent transformations could be performed diastereoselectively and finally the product was released through the retro-Diels-Alder process (1990).

In the 1990ies marine natural products became a new field of endeavor for Winterfeldt. In particular the cephalostatins, dimerized from two steroids through a pyrazine and extraordinarily strong cytostatics, provided new challenges. As in staurosporins, the two parts of the dimeric structure exhibited only subtle differences in their structure. Here it was important to provide access to unsymmetrically

substituted derivatives which could not be accessed through standard condensation reactions (1993, 1998).

Winterfeldt solved this problem by applying one component as an azirine, ultimately derived from the corresponding azide, and the second as the aminoketone. Subsequent azirine opening through the amino ketone and condensation furnished the desired heterodimeric cephalostatin analogues as first biologically active analogues (1996).

Winterfeldt's contributions to natural product and stereoselective synthesis have paved the way for important future developments in organic chemistry. As a teacher he had the unmatched ability to bring chemistry alive and to inspire the next generation of chemists in his very special way.

Nevertheless, the Winterfeldt-family is most grateful for having the privilege sharing parts of our lives with an exceptional chemist and a warm and wonderful person.

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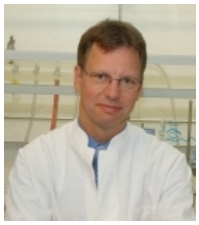

Markus Kalesse, born in 1961, was awarded the Dr. rer. nat. in the group of Dieter Schinzer at the University of Hannover in 1991. Between 1991 and 1992 he undertook two postdoctoral investigations at the University of Wisconsin (Madison) with Steven D. Burke and Laura L. Kiessling. After returning to the University of Hannover he completed his habilitation with Ekkehard Winterfeldt as the mentor in 1997. He was visiting professor at the University of Wisconsin (Madison) between 1998 and 1999 and had a temporary chair in Organic Chemistry at the University of Kiel in 1999. He was offered the chair in Organic Chemistry at the University of Oslo before he accepted a call from the Free University of Berlin (2002). Since July 2003 he holds the chair (C4) of Organic Chemistry at the University of Hannover and became Head of Medicinal Chemistry at the Helmholtz Centre for Infection Research (HZI) in 2005. He was Novartis lecturer in 2004/2005.