question of evolution than a question of the creation of life. As an example, replication and transcription (information transfer) assumes that the double-stranded nucleic acid opens and recloses. The strength of the duplex is defined by the degree of interstrand and intrastrand stacking interactions. In the thermodynamically more stable A form of double-stranded nucleic acids (3′-*endo*-furanose conformation) interstrand stacking is more pronounced than in the less stable B form (2′-*endo*-furanose conformation). Conformational transformation from A type to B type might facilitate the opening of double-stranded nucleic acids and, hence, replication and transcription; this transformation implies conformational flexibility. Such considerations together with the increased chemical stability of DNA might make DNA a better candidate than RNA for information storage (in the way information storage was concepted by nature) and exclude the use of pyranosyl nucleic acids. Similar considerations concerning the catalytic reactivity of RNA restricts considerably the choice of potential structural alternatives for nature's nucleic acid. The reduced conformational flexibility (absence of the 5′-CH_2OH group) might make TNA both an inferior candidate to DNA for storage of information and an inferior candidate to RNA for catalysis.

There is at this moment no indication (or suggestion) that either TNA or pRNA were precursors or former evolutionary competitors of RNA (the opposite cannot be demonstrated either). The investigation of Eschenmoser and co-workers on TNA and its properties provides an additional piece of information to be added to the puzzle which might eventually lead to a general understanding of the genesis of present day life and to the proposition of alternative models of life. It has also become clear that the power of natural selection cannot be understood fully solely on the basis of information generated by the synthesis and analysis of the properties of RNA alternatives.

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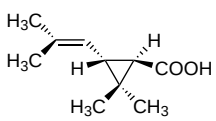
Fascinating Natural and Artificial Cyclopropane Architectures

Rüdiger Faust*

The various facets of the chemistry of cyclopropane derivatives are amazingly diverse and continue to fascinate scientists from a broad range of backgrounds, among them theoreticians, synthetic or structural chemists, and researchers with interests in natural product and/or medicinal chemistry. The challenges posed by the intriguing cyclic arrangement of only three tetravalent carbons are multitudinous, ranging from fundamental aspects of bonding, over the synthesis of highly strained molecules to an understanding of the mode of action of biologically active cyclopropyl derivatives. Selected examples of cyclopropane architectures encountered in compounds either derived from natural sources or prepared for the first time in the laboratory are highlighted below.

That nature has chosen to use a cyclopropane skeleton to design a defense mechanism for certain pyrethrum flowers against insect attack has been known since 1924, when Staudinger and Ruzicka isolated and characterized (+)-*trans*-chrysanthemic acid **1** from the petals of these plants.[1] The active insecticidal ingredients in these plants are in fact



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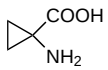

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esters of **1**, which can be easily modified and have been commercially exploited to give birth to one of the most successful classes of biomimetic insecticides, the pyrethroids. In 1997, the market value of this class of insecticides amounted to a staggering 1.5 billion US dollars.[2]

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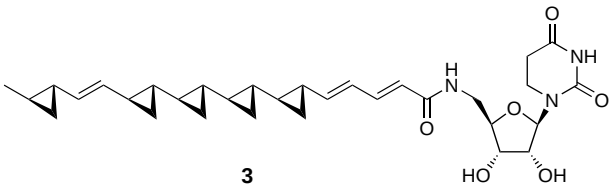
Chrysanthemic acid derivatives are by far not the only examples of cyclopropane-containing structures in nature. In fact, the highly strained three-membered carbocycle is virtually ubiquitous. It occurs, for example, in every green plant in the form of 1-aminocyclopropanecarboxylic acid (ACC) **2**, a direct precursor to the plant hormone ethylene.[3] In addition, the cyclopropane unit is found in a variety of other natural products, including terpenes and various cyclopropanated fatty acids.[4] The biochemical precursors of the latter are unsaturated fatty acids, and in view of the existence of polyunsaturated fatty acids it is perhaps not too surprising that multiply cyclopropanated analogues also occur in nature, and indeed in 1990 Yoshida et al. were able to isolate the potent antifungal agent FR-900848 (**3**) from the fermentation



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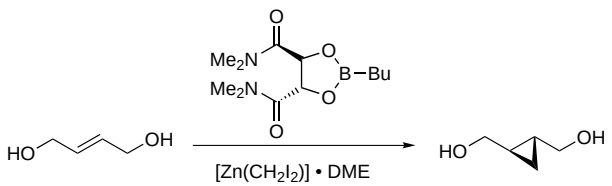
4

broth of *Streptoverticillium fervens*.[5] The unusual architecture of **3**, ultimately proven by total synthesis and X-ray crystallographic analysis,[6, 7] consists of four contiguous and one isolated cyclopropane unit, all of which are arranged on the same face of an all-*trans*-configured carbon backbone. But the amazing array of five cyclopropane units in **3** is not unique. Shortly before the structure of **3** was unequivocally established, chemists at the company Upjohn isolated U-106305 (**4**) from S*treptomyces sp*.[8] This compound had aroused the scientist's interest because it acts as an effective inhibitor of the cholesteryl ester transfer protein in the blood and can thus be envisioned to slow the progression of atherosclerosis. The remarkable structural similarity between compounds **3** and **4**, the latter endowed with five contiguous out of a total of six cyclopropane units, suggests that they are synthesized along the same biochemical pathway. As with **3**, the structure and the absolute configuration of **4** was established by a total synthesis[9, 10] that made use of an enantioselective cyclopropanation reaction of allylic alcohols originally developed by Charette et al. in 1995[11] (Scheme 1). Indeed, Charette and



Scheme 1. Enantioselective cyclopropanation of allylic alcohols developed by Charette et al.[11]

Lebel published the enantioselective synthesis of the non-natural enantiomer of U-106305 shortly thereafter.[12] The cyclopropanation procedure they devised involves the complex $[Zn(CH_2I_2)] \cdot DME$ (DME = 1,2-dimethoxy ethane) and the presence of a chiral dioxaborolane ligand derived from tartaric acid diamide (see Scheme 1). The same methodology was used to make the non-natural, all-*trans* septicyclopropane derivative **5**,[10] the most highly cyclopropanated linear structure prepared to date.

5

Multiple cyclopropyl groups can also be arranged in a spiro-fused fashion around a core carbocycle, giving rise to the structurally fascinating classes of the so-called rotanes and triangulanes.[13] These hydrocarbons have been investigated extensively by the groups of Conia and de Meijere. In 1973, Fitjer and Conia prepared the smallest system in this series, the highly strained [3]rotane **6**.[14] More recently, de Meijere's team presented a succession of milestones in this area, including the first synthesis of an enantiomerically pure [4]triangulane **7**,[15] the stunning perspirocyclopropanated [3]rotane **8**,[16] and even the [15]triangulane **9**,[17] a record-breaking arrangement of fifteen spiro-linked cyclopropane rings.

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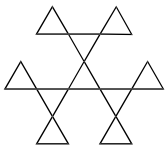
7



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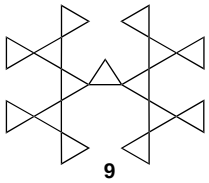

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Compound **7**, prepared to test the hypothesis that chiral, unfunctionalized and completely saturated hydrocarbons can show optical activity if sufficiently rigid, was found to have a remarkably high specific rotation ($[\alpha]_{365}^{20} = -648.2$), which the authors attribute to the helical arrangement of the σ C–C bonds in **7**. It was therefore suggested that **7** is a σ bond analogue of the aromatic [*n*]helicenes, a class of compounds with similarly large optical rotations resulting from a helical arrangement of their π-bond backbone.[18]

Most recently, de Meijere and co-workers have climbed yet another mountain in cyclopropane architecture and prepared tetracyclopropylmethane **10** (Figure 1).[19] Many organoelement derivatives with the maximum number of cyclopropyl groups are known, and in fact the heavier (and larger) homologues of **10**, namely tetracyclopropylsilane, -germane, and -stannane had been made before.[20] However, the

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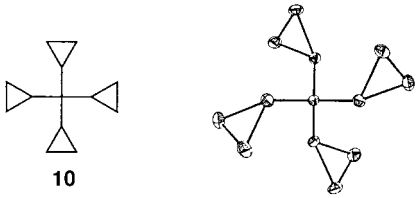

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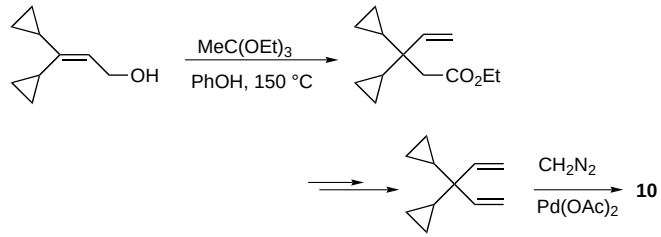
Figure 1. Molecular structure of tetracyclopropylmethane.[19]

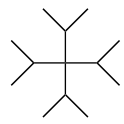
corresponding hydrocarbon has remained elusive until now, and earlier attempts to generate the compound using standard cyclopropanation methods failed. The key steps in the successful synthesis of **10** are the formation of its quaternary center (Scheme 2) by an orthoester Claisen rearrangement



Scheme 2. Synthesis of tetracyclopropylmethane.

and the twofold cyclopropanation of dicyclopropylpentadiene with diazomethane. The larger steric crowding in **10** compared to that in the higher homologues also affects its conformation in the solid-state. Whereas the molecules in crystals of the corresponding silicon, germanium, and tin derivatives have D_{2d} symmetry, **10** has S_4 symmetry (Figure 1).

Compound **10** is not only of structural interest, it also serves as a starting point to make one of the most sterically congested methane derivatives prepared to date: palladium-catalyzed selective hydrogenolysis of the least-substituted cyclopropane bonds in **10** furnishes tetraisopropylmethane **11** in almost quantitative yield. X-ray crystallographic analysis of **11** reveals that the shortest nonbonded H···H distances are 2.008 Å, significantly shorter than those observed in **10** (shortest H···H distance 2.135 Å). The elegance of the synthetic route to the highly crowded **11** becomes apparent when one ponders the fact that the sterically even more fraught tetra-*tert*-butylmethane remains elusive.



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This short excursion into the diverse field of natural and artificial cyclopropane architectures highlights the fact that cyclopropanes continue to provide stimuli for, and challenges to, current concepts of synthesis, structure, and theory. It is amazing what three carbons can do!

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