DOI: 10.1002/anie.201304555

Strained Molecules

Fenestranes in Synthesis: Unique and Highly Inspiring Scaffolds

*Aicha Boudhar, Mélanie Charpenay, Gaëlle Blond, and Jean Suffert**

bond angles · fenestranes ·
planar tetracoordinate carbon atom ·
strained molecules · synthetic methods

The scaffold of fenestranes is quite unique, as it contains four condensed cycles and a distorted tetracoordinated central carbon atom with bond angles greater than the regular 109°28“. In this Minireview, a detailed overview on the developments regarding this compound class, including their synthesis, is given for the time period since 2006. In the past years, natural products that belong to the class of hetero-fenestranes have been isolated and their syntheses will also be discussed.

1. Introduction

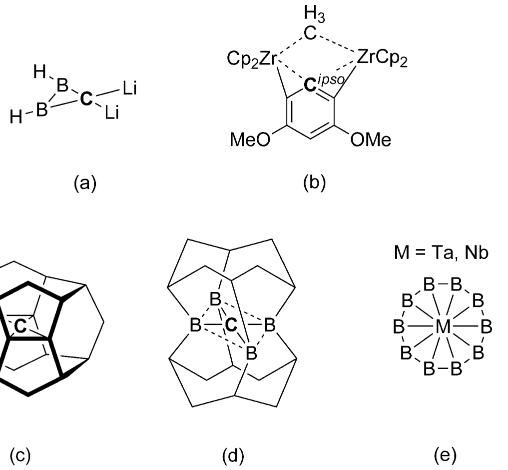


Figure 1. Formation of a planar carbon center through the electronic (a and b) and the mechanical (c and d) approach, and planar compounds with the highest coordination number (e). ptC in bold. Cp = cyclopentadienyl.

Molecular symmetry in general and the symmetry of tetracoordinate carbon atoms perhaps even more have fascinated chemists for more than a century. In 1874, van't Hoff and Le Bel suggested a tetrahedral environment for carbon atoms that bear four substituents.[1] In this manner, they could, for the first time, explain chirality and optical activity that were previously observed for certain compounds. Almost 100 years later, Hoffmann et al. reopened the discussion with the exceptional idea of a planar tetracoordinate carbon atom (ptC).[2] They postulated that such a configuration should in general be possible, and proposed scaffolds in which a central carbon atom would be forced into a planar arrangement. Hoffmann et al. suggested two methods to force a tetracoordinate carbon atom to have a planar instead of a tetrahedral symmetry. The first option, the so-called electronic approach, requires the carbon atom to have an sp^2 hybridization with two electrons located in the 2p orbital,[3] as for example in the calculated 3,3-dilithio-1,2-diboracyclopropane (Figure 1 a)[4–6] or in some synthesized organometallic compounds (e.g. Figure 1 b).[7,8] The second possibility to obtain a ptC is to use mechanical strain or force, also called the mechanical approach. It implies the design of a three-dimensional structure in which the carbon atom is trapped in a rigid cage, and is thus forced into a planar symmetry ,[9] as calculated for dimethanospiro[2.2]octaplane (Figure 1 c).[10,11] The combination of both methods, sp^2 hybridization and mechanical strain, also leads to a ptC. For the compound that bears four boron atoms (Figure 1 d), the calculated angles around the central carbon atom are all 180°.[12] Furthermore, the search for planar configurations is not limited to four substituents on the carbon atom.[13] Most recently, Boldyrev and co-workers found decacoordinated

---

[*] Dr. A. Boudhar, Dr. M. Charpenay, Dr. G. Blond, Dr. J. Suffert
Faculté de Pharmacie, Université de Strasbourg
UMR 7200 CNRS/UDS
74 Route du Rhin, Strasbourg (France)
E-mail: jean.suffert@unistra.fr
Homepage: http://www-chimie.u-strasbg.fr/~lsb/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201304555.

TaB_{10}^- and NbB_{10}^- systems with the highest coordination number in planar clusters known to date (Figure 1).[14]

In 1970, Hoffman et al. proposed a scaffold with four condensed cycles as part of the discussion of a possible tetracoordinate yet planar carbon center (Figure 2a).[2] Only two years later, Georgian and Saltzman joined the challenge with the synthesis of two compounds, tetracyclo[5.5.1.$0^{3,13}$.$0^{10,13}$]tridecan-4-one and tetracyclo[6.5.1.$0^{4,14}$.$0^{12,14}$]tetradecan-11-one (Figure 2b).[15] Based on the resemblance of the schematic structure to a window, they proposed the name fenestrane for this scaffold. The typical reaction of a curious organic chemist to those molecules is to wonder if this kind of scaffold is stable and to ponder on a possible synthesis. As Hoffmann and Hopf stated in their exciting article about the interest of the chemical community for molecules in distress: "*One reason for synthesizing some pretty unhappy molecules is simply the desire to do what has not been done before. And to be praised for it.*"[16]

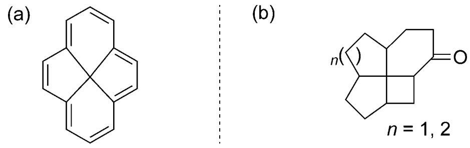


Figure 2. a) Fenestrane scaffold proposed by Hoffmann et al. in 1970.[2] b) First fenestranes synthesized by Georgian and Saltzman in 1972.[15]

Herein, we show how the fenestrane family has grown, particularly during the past decade, and that besides a few naturally occurring fenestranes, a large number of non-natural congeners has become known through challenging syntheses. First, the reader will gain insight on the definition and nomenclature of fenestranes. This will be followed by an account of the natural products with [*m.n.p.q*]fenestrane scaffolds, as well as their recently achieved syntheses. We will also shortly consider the [*m.n.p*]fenestranes, as they are common both in nature and in synthesis. Finally, a comprehensive overview of the recent synthetic efforts leading to fenestranes will complete this update.[17] In addition, a list of all fenestranes synthesized to date is available in the Supporting Information, including the compounds that were obtained earlier, which will not be discussed in detail herein. This compilation also includes the available information on bond angles, and is classified according to the respective synthetic key step.

2. Definition of Fenestranes, Their Nomenclature, and the Bond Angles Around the Central Carbon Atom

Since the beginning of the search for ptCs, a family of compounds that possess four condensed cycles around a shared central carbon atom were suggested (see Figure 2a). In 1972, motivated by the resemblance of the schematized structure with a window that features four panes, Georgian and Saltzman proposed a name derived from the Latin word

Jean Suffert graduated from the Université Louis Pasteur in Strasbourg (1978), where he obtained his Ph.D. (1984) under the supervision of Dr. A. Solladié-Cavallo. After being appointed as a Chargé de Recherches by CNRS (1982–1991), he worked as a postdoctoral associate with Prof. P. A. Wender at Stanford University (1985–1986). He moved to the Faculté de Pharmacie of the University of Strasbourg in 1992, where he is Directeur de Recherches at the CNRS in the Laboratoire d'Innovation Thérapeutique. He currently develops new cascade reactions using transition metals and the synthesis of polycylic complex molecules.

Gaëlle Blond graduated from the University of Nantes in 1999 and obtained her Ph.D. in organic chemistry from the Université Claude Bernard Lyon 1 (2002). She then worked as a postdoctoral associate at the Max Planck Institut for Kohlenforschung in Muelheim an der Ruhr in the group of Prof. A. Fürstner (2002–2003). In 2005, after two additional periods of postdoctoral research (Maine/Bordeaux), she obtained a position as a Chargé de Recherches from the CNRS in the group of Dr. J. Suffert at the University of Strasbourg. Her research focuses on the development of new methodologies using transition metals, leading to complex polycyclic molecules.

Aicha Boudhar specialized in organic synthesis and obtained both a French Engineering Degree at the European Engineering School of Chemistry, Polymers and Materials Science in Strasbourg (2007) and the German Degree Diplomchemiker (2008) at the TU Dresden. She then moved back to Strasbourg for her Ph.D. studies on the synthesis of heterofenestranes and cyclooctatrienes in the group of Dr. J. Suffert (2009–2012). She is currently working at the National University Singapore, where she is a postdoctoral fellow in the group of K. S. W. Tan.

Mélanie Charpenay studied organic chemistry at the European Engineering School of Chemistry, Polymers and Materials Science in Strasbourg and graduated in 2009. In the same year, she obtained her Masters Degree at the University of Strasbourg. Her Ph.D. studies under the supervision of Dr. J. Suffert focused on the development of new synthetic methodologies to reach highly strained polycyclic structures using palladium-catalyzed cascade reactions (2009–2012). She then joined the group of K. M. Brummond at the University of Pittsburgh as a postdoctoral fellow.

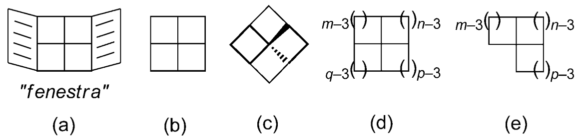


Figure 3. a) Idea for the name of fenestranes and b–e) schematic structures of the scaffolds.

fenestra and the term alkane for hydrocarbon: *fenestra* + alkane = "fenestrane" (Figure 3 a).[15] Their definition implies that each of the condensed cycles must share three carbon atoms with the neighboring cycles, and that the central carbon atom must be common to all four cycles (Figure 3 b). The scaffold can also be described as a double-bridged spiroalkane (Figure 3 c). The classification of polycycles following the IUPAC nomenclature is quite complex, thus Liebman and Greenberg proposed another nomenclature for this scaffold using the prefix [*m.n.p.q*] to define the size of the four cycles (Figure 3 d).[18] The compound in Figure 3 b is then a [4.4.4.4]fenestrane, which is much more convenient. Similar tricyclic structures, that is, spiroalkanes with only one bridge (Figure 3 e), are in consequence [*m.n.p*]fenestranes. In analogy to a window with four panes, these compounds with only three condensed cycles have a missing pane and can be called broken windows.[17a]

The smallest possible member of the fenestrane family is the [3.3.3.3]fenestrane, which is particularly strained and should possess some kinetic stability under a pyramidal configuration, as shown by MINDO/3 calculation (Figure 4 a).[3d] This fenestrane was studied in detail and named pyramidane. In contrast, for the [4.4.4.4]fenestrane, calculations indicate a preference for the flattened tetrahedral configuration D_{2d} (Figure 4 b) over the pyramidal one C_{4v} (Figure 4 c).

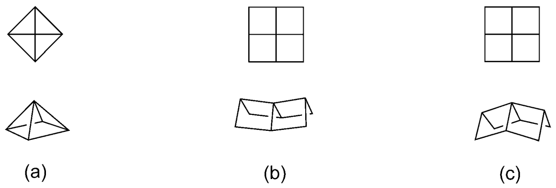


Figure 4. Predicted structures of [3.3.3.3]fenestrane (a) and [4.4.4.4]fenestrane (b, c).

In order to describe fenestranes, the numbering of the scaffold and its substituents must also be defined. In the past, this was not done following a specific rule, because common numbering systems cannot be applied without difficulties. As a general rule, the numbering starts at the bridgehead carbon atom with the highest priority, follows the outer periphery, and ends with the central carbon atom (Figure 5 a). The position C1 also defines the starting point for the association of the ring sizes following the [*m.n.p.q*] definition, which then follows the cycles in a clockwise manner. Often, the attribution of the bridgehead carbon atom with the highest priority and thus C1 is not trivial. In those cases, the numbering is defined so that the name of the fenestrane starts with the smallest ring: [4.5.5.5]fenestrane (Figure 5 b) is better than [5.5.5.4]fenestrane (Figure 5 c) or [5.5.4.5]fenestrane (Figure 5 d).

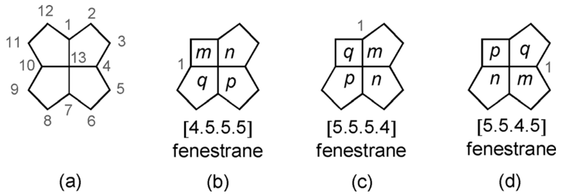


Figure 5. Numbering of the fenestrane scaffold.

It is important to comment on the stereochemistry of this scaffold and its resulting nomenclature.[17b,19] For clarity reasons, fenestrane scaffolds will be drawn in Fischer projections throughout this Minireview. The fenestranes possess a minimum of five stereocenters (Figure 6 a and b), with the sole exception being a fictive fenestrane shown in Figure 6 c. With four equal substituents and a perfectly planar central carbon atom, the latter possesses an internal plane of symmetry and would thus not be chiral, but a *meso* compound. As is true for all polycyclic molecules, the Cahn–Ingold–Prelog system and *R*/*S* nomenclature are cumbersome and lead to inconveniently long and complex molecule names, which are only suitable for experimental sections. In order to facilitate this, the relation between the different bonds has been described by using the terminology for polycycles and their substituents (*syn* and *anti*), or for sugars (α and β).[17a] However, we feel that both these nomenclatures can still be quite complex and confusing.

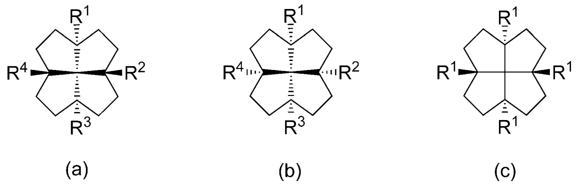


Figure 6. Stereocenters in fenestranes.

Another nomenclature has been introduced by Keese, who defined the relationship between the bonds as *cis* or *trans*.[17c] After declaring one bridgehead as C1 in accordance with the highest priority and the ring size, the set of H1-C1-C13-C7 bonds is the first to be assigned as *cis* or *trans* to each other. As an example, see the fenestrane shown in Figure 7 a,

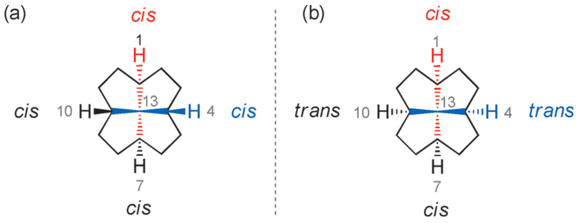


Figure 7. *cis*/*trans* Nomenclature by Keese and co-workers.

in which the relation between the bonds H1-C1-C13-C7 is *cis* (in red). Then, the attribution of the other bonds follows, always as sets of three (H4-C4-C13-C10, H7-C7-C13-C1, and finally H10-C10-C13-C4). According to the Keese nomenclature, the compound in Figure 6a is a *cis,cis,cis,cis*-[5.5.5.5]fenestrane, or even all-*cis*-[5.5.5.5]fenestrane, and the compound in Figure 6b is a *cis,trans,cis,trans*-[5.5.5.5]fenestrane. The shorter nomenclature *c,c,c,c*-[5.5.5.5]fenestrane and *c,t,c,t*-[5.5.5.5]fenestrane can also be used for these two examples, respectively, and we chose to use this nomenclature throughout this Minireview.

In order to analyze the relationship between the structure of the fenestrane and the planarization of the central carbon atom, various modifications and their consequences have been studied. While altering the hypothetical structures, the values of the opposite angles α and β have been calculated by different methods: ab initio methods of quantum chemistry, density functional theory (DFT), semi-empiric methods (AM1, MNDO, PM3), or molecular mechanics methods (MM2, MM+).[17a] As a starting point and reference, the angles α and β of *c,c,c,c*-[5.5.5.5]fenestrane have been calculated: they are both 113.8° (Figure 8a). Additional double bonds in bridgehead positions can contribute to the expansion of those angles, increasing both angles to 137.8° in the entirely unsaturated [5.5.5.5]fenestrene (Figure 8d).[17c,20]

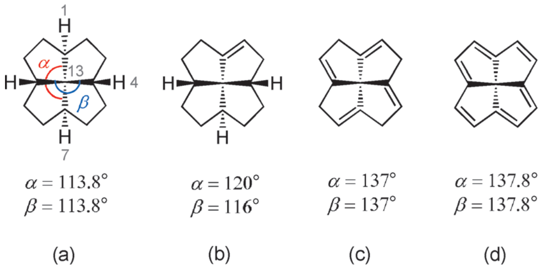


Figure 8. Influence of bridgehead double bonds on the angles (α and β) around the central carbon atom.

The reduction of the size of at least one cycle has also an effect on the central carbon atom and its bond angles. For *c,c,c,c*-[4.5.4.5]fenestrane, the values of both angles were calculated as 126° (Figure 9a). The influence of sterically demanding substituents in bridgehead positions is less evident, the 1,4,7,10-tetramethyl-*c,c,c,c*-[5.5.5.5]fenestrane for example has calculated angles of 120° (Figure 9b). On the other hand, *trans* isomers are more promising: the calculated angles α and β are 118° and 126°, respectively, for *t,c,c,c*-[5.5.5.5]fenestrane (Figure 9c), and 130° and 137°, respectively, for *c,t,c,t*-[5.5.5.5]fenestrane (Figure 9d).[17c,21] The [4.5.5.5]fenestr-8-ene has been designed by combining bridgehead double bonds, smaller cycles, and a *trans* relationship in the same compound; here α would be 138° and β 131° (Figure 10a).[17c] Sterically demanding substituents in the bridgehead positions, as in 1,6-dimethyl-[4.5.5.5]fenestr-8-ene (Figure 10b), slightly increase the calculated values. The opposite angles are indeed the largest calculated angles α and β up to date: 140° and 132°, respectively.[17a]

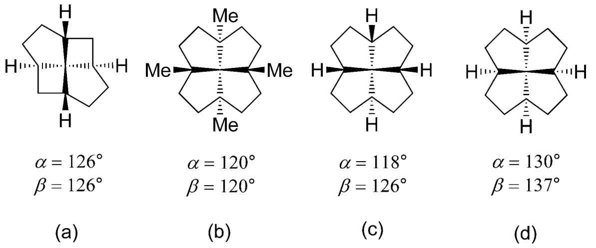


Figure 9. Influence of ring size (a), bridgehead substituents (b), and *trans* isomers (c and d).

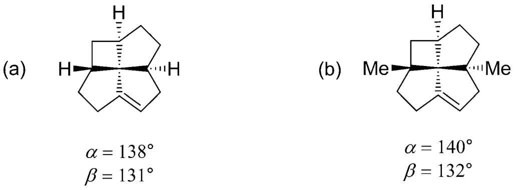


Figure 10. Predicted angles for two *c,t,c,c*-[4.5.5.5]fenestr-6-enes.

Because of their fascinating structure and their role in the search for ptCs, fenestranes are popular targets of synthetic chemists. The groups working on the synthesis of these scaffolds have often covered both aspects, synthesis and theory, thus enabling comparison and better understanding of their results. In the following sections, we will indicate the angles α and β from both X-ray analyses and in silico methods, if they were identified (X-ray: α, β; [calculation]: α, β).

3. Natural Products of the Fenestrane Family and Their Syntheses

3.1. All-Carbon Scaffold

In 1979, Corbett et al. worked with extracts from *Dacrydium cupressinum*, commonly known as rimu, a large endemic evergreen coniferous tree from the forests of New Zealand.[22] Among other compounds, they found a new diterpene, which made up about 12% of the total oil obtained by steam distillation of the leaves and terminal twigs. They proposed structure **1** (Figure 11)[23] for the compound and gave it the name laurenene or lauren-1-ene.

A series of reactions and modifications, which led to the derivatives **3**, allowed to correct the proposed structure and to

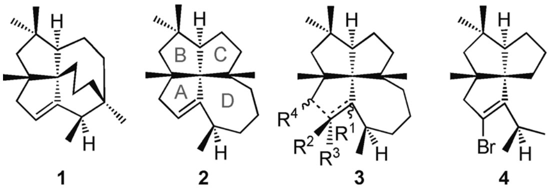


Figure 11. Laurenene (**2**) isolated by Corbett et al.,[22] and its derivatives, with R^1 to R^4 being a large number of combinations of H, OH, OAc, CO_2H, etc.

identify the new compound as the [5.5.5.7]fenestrene **2**. The structure was confirmed by X-ray analysis of the brominated derivative **4**, and the angles around the central carbon atom were determined to be 117.9° and 118.9°.[24] Laurenene (**2**) represents the first, and so far only, isolated natural product with an all-carbon fenestrane scaffold. Since its discovery, three total syntheses of laurenene have been completed: those of Crimmins and Gould[25] and Tsunoda et al.[26] were published nearly simultaneously in 1987, and the third one by Wender et al.[27] one year later.[28]

3.2. [m.n.p]Fenestranes

[*m.n.p*]Fenestrane scaffolds are much more abundant in both synthesis and natural products. Because of the large number of contributions in this area, it is not possible to offer a detailed account of these compounds, which would lead to a whole review on its own. Nevertheless, we wish to provide a rapid overview of this family of compounds, and possibly a starting point to a more detailed bibliographic survey for interested readers. Sesquiterpenes that have a tricyclo[6.3.0.0^{1,5}]undecane core (also called angular triquinanes), which is indeed a [5.5.5]fenestrane scaffold, are isolated particularly often (Figure 12).[29] They can be grouped into four subcategories, depending on the positions of the substituents: isocomanes,[30,31] silphinanes,[32] silphiperfolanes,[33] and pentalenanes.[34]

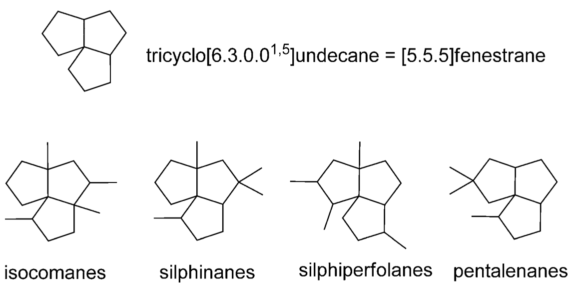


Figure 12. The angular triquinane scaffold, a [5.5.5]fenestrane, and families of natural products with triquinane scaffolds.

A member of the diterpenoid family, aflavinine (**5**), which was isolated from *Aspergillus flavus*, has a [6.6.6]fenestrane scaffold (Figure 13).[35] Later, the sesquiterpene **6** with a [4.5.6]fenestrane scaffold was isolated from the red algae *Laurencia obtusa*, and was shown to have a slight cytotoxic activity toward a series of cancer cell lines.[36] Some other examples of synthesized [*m.n.p*]fenestranes are: [3.5.3]fenestrane **7**, [3.5.4]fenestranes **8**,[37] and [4.4.4]fenestranes **9**.[38]

3.3. Fenestranes with Heteroatoms

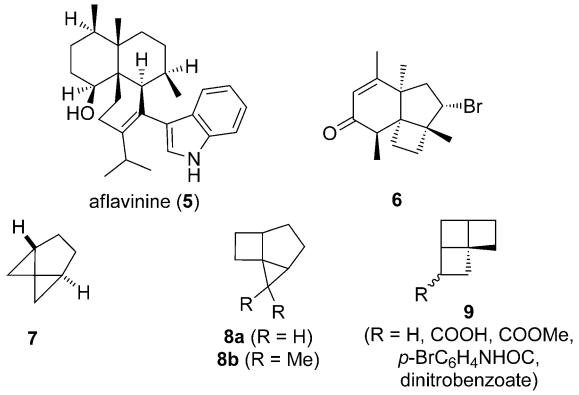


Figure 13. Natural (**5** and **6**) and synthetic (**7**–**9**) products with [*m.n.p*]fenestrane scaffolds.

Following the initial definition by Georgian and Saltzman, compounds that bear heteroatoms within the scaffold of four condensed cycles are in essence not fenestranes. However, they are no less interesting, and both natural products and synthetic examples are usually included in the fenestrane family. In 2006, Gloer and co-workers isolated a family of sesquiterpenes **10** from fungal extracts, *Penicillium griseofulvum* Dierckx (MYC-1728 = NRRL 35584). These sesquiterpenes have *c,c,c,c*-[5.5.5.6]dioxafenestrane structures and were named penifulvine A–E (Figure 14).[39] Penifulvine A has interesting antifungal and insecticidal activities.[40] In addition, a compound with a silphinane scaffold (compare with Figure 12) was also identified: [5.5.5]fenestrene **11**.

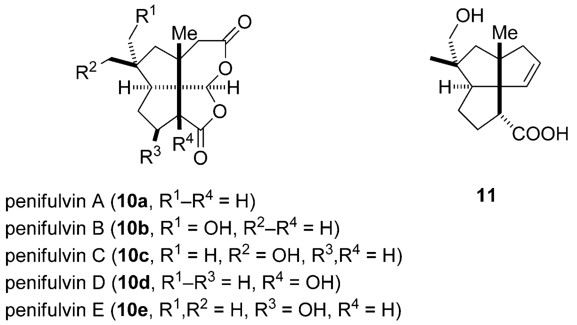
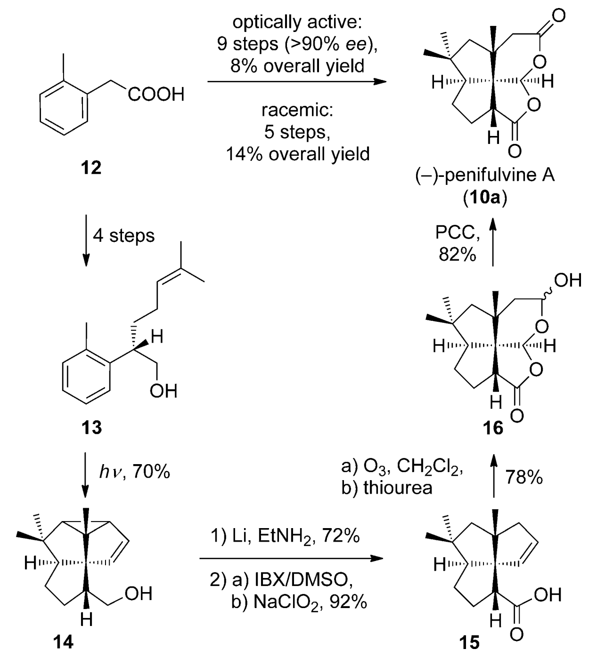


Figure 14. Penifulvines A–E and the related [5.5.5]fenestrene **11**.

In 2009, Gaich and Mulzer accomplished the total synthesis of penifulvine A (**10a**).[41] Their work is based on a [3+2] arene–olefin cycloaddition of **13** as the key step to form the tetracyclic compound **14**, then opening of the cyclopropane by reduction under Birch-like conditions, and oxidation to the carboxylic acid **15** (Scheme 1). This is followed by ozonolysis and spontaneous cyclization to **16**, and a final oxidation to obtain **10a**. In addition to the enantiopure (−)-penifulvine A (9 steps, total yield 8%), their method also gave access to the racemic form in even better yield (5 steps, total yield 14%). Moreover, the authors obtained the derivatives (−)-penifulvine B (**10b**) and (−)-penifulvine C (**10c**) by employing the same strategy.[42]

Most recently, another sesquiterpene was isolated from an extract of the marine fungus *Aspergillus aculeatus* (CRI323-04), harvested on Kho Phi Phi Island in Thailand.[43] The



Scheme 1. Synthesis of (−)-penifulvine A (**10a**). DMSO = dimethyl sulfoxide, IBX = *ortho*-iodoxybenzoic acid, PCC = pyridinium chlorochromate.

structure of this new compound differs from the penifulvanes only in the position of one carbon atom (Figure 15). The authors proposed the name aspergilanes for the scaffold, and consequently asperaculine A (**17**) for the isolated compound.

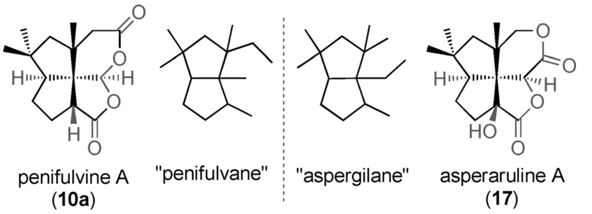
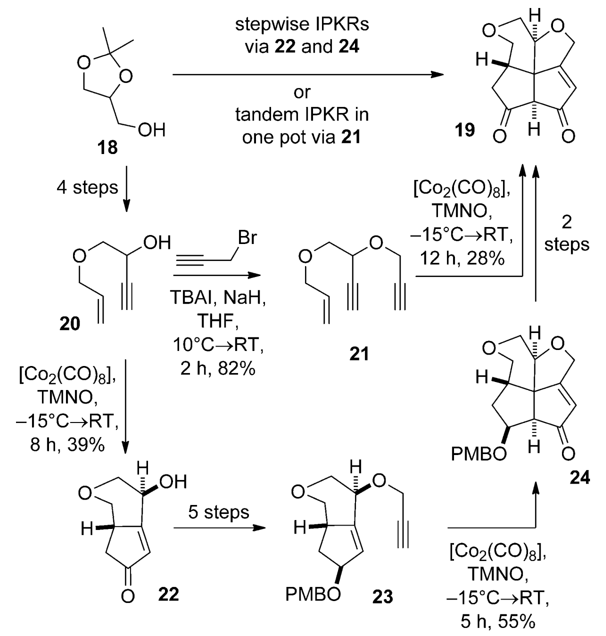


Figure 15. Compounds of the penifulvane and aspergilane families.

One year later, in the context of asperculine A synthesis, Mehta and Kahn studied the formation of the dioxa-fenestrane framework **19**, involving intramolecular Pauson–Khand reactions (IPKRs; Scheme 2).[44] Starting from glycerol-derived solketal **18**, they achieved the synthesis of **19** by a stepwise strategy involving a total of 13 steps, with two IPKRs as key steps via the intermediates **22** and **24**. A second strategy employed the tandem IPKR of enediyne **21** and successfully led to the same dioxa-fenestrane **19** in only six steps.

4. Recent Examples of Synthetic Fenestranes

Over the last five decades, synthetic efforts toward the fenestrane scaffold have been made by a number of very competent chemists. Various strategies have been employed, including enone–olefin photocycloadditions,[45,46] arene–olefin cycloadditions,[47,48] the Weiss reaction,[49] benzannellated fenestranes through cyclodehydration,[50] and Pauson–Khand reactions (PKRs),[51] to name just a few. In the following sections, only recent results (since 2006) will be described.[17] However, in some cases the citation of earlier contributions is necessary to clarify these recent results. For the compounds that are not discussed here, the interested reader can refer to the compilation given in the Supporting Information.



Scheme 2. Access to the aspergilane core through intramolecular Pauson–Khand reactions (IPKR). PMB = *para*-methoxybenzyl, TBAI = tetra-*n*-butylammonium iodide, TMNO = trimethylamine N-oxide.

4.1. Cycloadditions, Including Arene–Olefin Cycloadditions

The first synthetic approach to aza-fenestranes was developed in 2002 by Denmark et al., who used tandem [4+2] and tandem [3+2] cycloadditions. Starting with vinylic ether **25** and nitroalkene **27**, they obtained the desired *c,c,c,c*-[5.5.5.5]-1-azafenestrane (Figure 16),[52] which led to **29**·BH_3 after complexation with BH_3 (X-ray: 116.1°, 116.6°; DFT: 114.5°, 117.5°). Subsequently, by employing steric effects, the alternative vinylic ether **26** and nitroalkene **28** gave the corresponding *c,c,c,c*-[4.5.5.5]-1-azafenestrane **30**·BH_3. Yet, the X-ray crystallographic analysis could only be performed

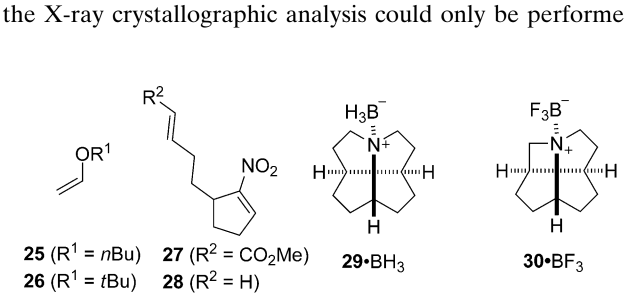
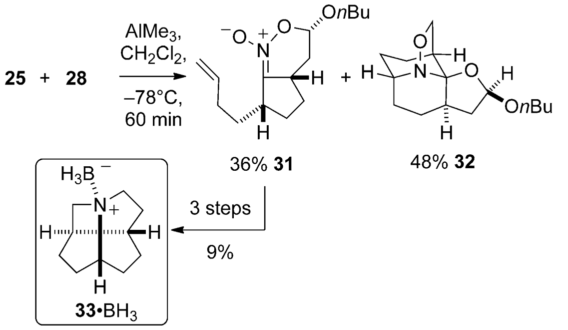


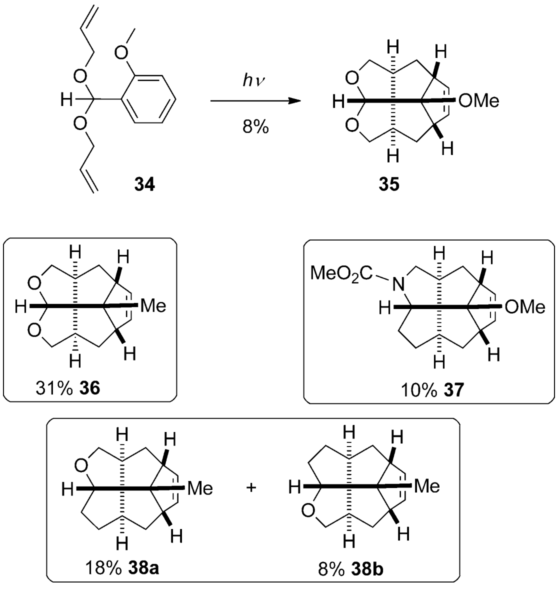
Figure 16. Aza-fenestranes **29**·BH_3 and **30**·BF_3 and their precursors.

with the adduct **30**·BF_3 (X-ray: 120.3°, 121.3°; DFT: 118.2°, 123.2°). More recently, the nitroso-acetal **31** could also be obtained from vinylic ether **25** and nitroalkene **28** (Scheme 3).[53] Ring contraction, reduction, and treatment with BH_3·THF then led to the *c,c,c,t*-[4.5.5.5]-1-azafenestrane **33**·BH_3 (X-ray: 126.3°, 120.7°; DFT: 126.7°, 123.1°). In this manner, Denmark et al. could show that contracting one cycle of the fenestrane or introducing a *trans* configuration has an influence on the bond angles: the flattening of the central carbon atom indeed increases from *c,c,c,c*-[5.5.5.5] **29**·BH_3 over *c,c,c,c*-[4.5.5.5] **30**·BH_3 to *c,c,c,t*-[4.5.5.5] **33**·BH_3.

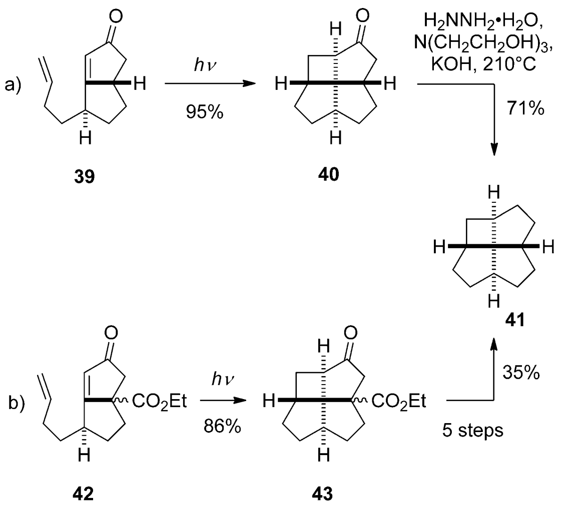


Scheme 3. Access to the *c,c,c,t*-[4.5.5.5]-1-aza-fenestrane **33**.

In 2010, a photoinduced double [3+2] arene–olefin cycloaddition was used as a key step for the synthesis of the *c,c,c,c*-[5.5.5.5]-dioxa-fenestrane **35** (Scheme 4, X-ray: 120.2°, 128.5°).[54] The yield of the isolated product (8%) is low, the method can however be validated in view of the number of bonds obtained stereoselectively and in only one step. The authors later used the same strategy to access more examples, obtaining the heterofenestranes **36**, **37**, and **38**.[55]



Scheme 4. Access to heterofenestranes through double arene–olefin cycloaddition.

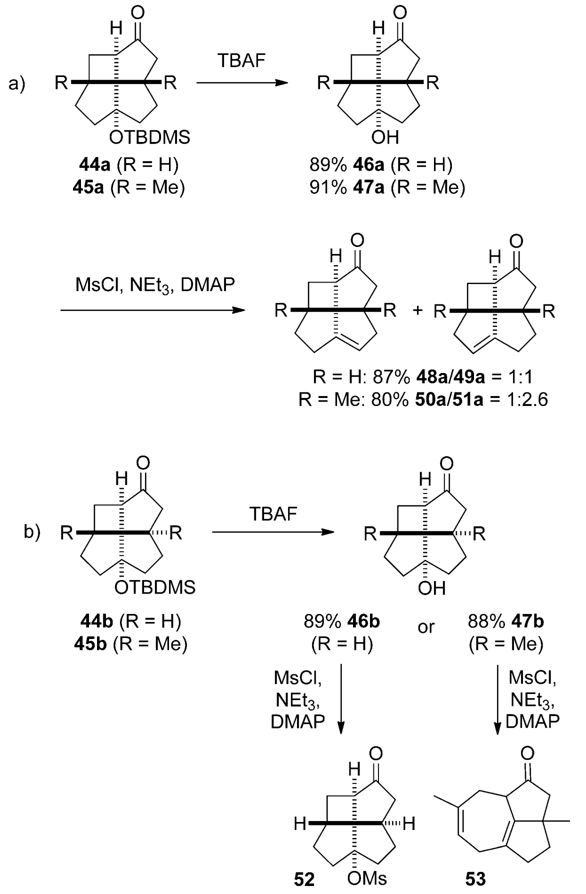


Scheme 5. Syntheses of fenestrane **41** by a) Dauben and Walker in 1982,[46a] and b) Keese and co-workers in 2013.[56,57]

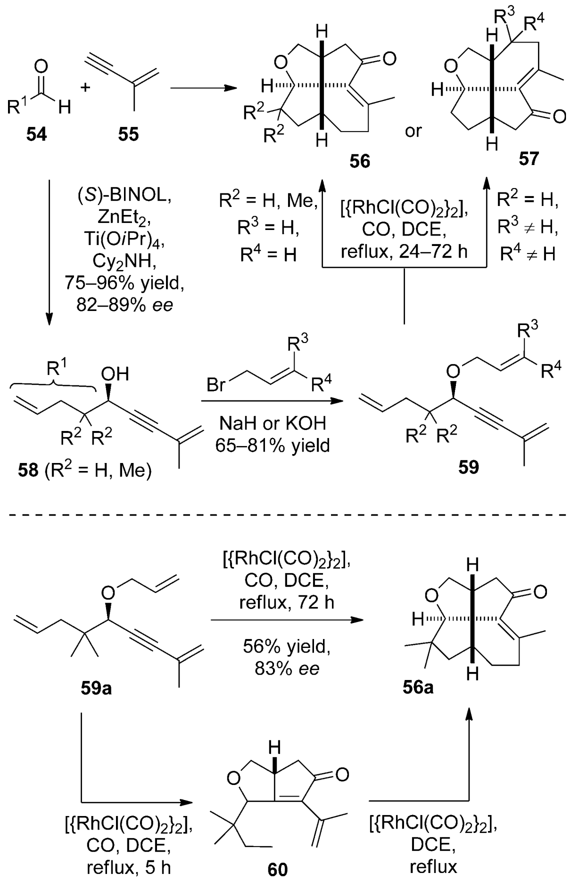
Most recently, Keese and co-workers published a new synthesis of *c,c,c,c*-[4.5.5.5]fenestrane **41**.[56] In 1982, the same compound was already accessed by Dauben and Walker through cycloaddition to obtain the all-*cis*-[4.5.5.5]fenestrane **40**, followed by Wolff–Kishner reduction (Scheme 5a).[46a] On the other hand, Keese and co-workers used their earlier developed route to [4.5.5.5]fenestranes of type **43**,[57] and then transformed the mixture in five steps to compound **41** (Scheme 5b). They also performed DFT and MP2 calculations for the opposite bond angles α and β for a series of compounds, with the results for **41** being quite similar for both methods (DFT: $\alpha = 121.4°$, $\beta = 122.3°$; MP2: $\alpha = 122.0°$, $\beta = 121.6°$).

4.2. Pauson–Khand Reaction

Early examples of the synthesis of all-*cis*-[4.5.5.5]fenestrane **44a** and its *c,c,t,c*-isomer **44b** (Scheme 6, X-ray **44b**: 131.1°, 120.2°) were achieved by Keese and co-workers, who combined a PKR with a photochemical cycloaddition.[58] In order to enhance the flattening of the central carbon atom, they recently planned to add double bonds in bridgehead positions to obtain [4.5.5.5]fenestrenes.[59] They used fenestranes **44a** and **44b** as starting materials for further transformations, and for both compounds the cleavage of the TBDMS group was achieved in good yields. For the all-*cis* derivative **46a**, the activation of the hydroxy group as mesylate and then elimination led to a mixture of the two regioisomers **48a** and **49a** (Scheme 6a). For the *trans* compound **46b**, the same efforts did not lead to the corresponding fenestrene, but only to compound **52**, which still possesses the OMs group (Scheme 6b). Moreover, the developed strategy of PKR and photochemical cycloaddition led to the dimethyl-*c,c,c,c*-[4.5.5.5]fenestrane **45a** and the dimethyl-*c,c,t,c*-[4.5.5.5]fenestrane **45b** (X-ray: 128.9°, 122.8°, DFT: 129.8°, 123.8°).[60] Analogous to the related compounds without methyl groups, deprotection provided **47a** and **47b**. Starting



Scheme 6. Addition of bridgehead double bonds starting from fenestranes **44** and **45**. DMAP = 4-dimethylaminopyridine, Ms = methanesulfonyl, TBAF = tetra-*n*-butylammonium fluoride, TBDMS = *tert*-butyldimethylsilyl.



Scheme 7. Access to oxa-fenestranes **56** and **57** through Rh^I-catalyzed stereoselective tandem PKR/[4+2] cycloaddition. BINOL = 2,2′-dihydroxy-1,1′-binaphthyl, Cy = cyclohexyl, DCE = 1,2-dichloroethane.

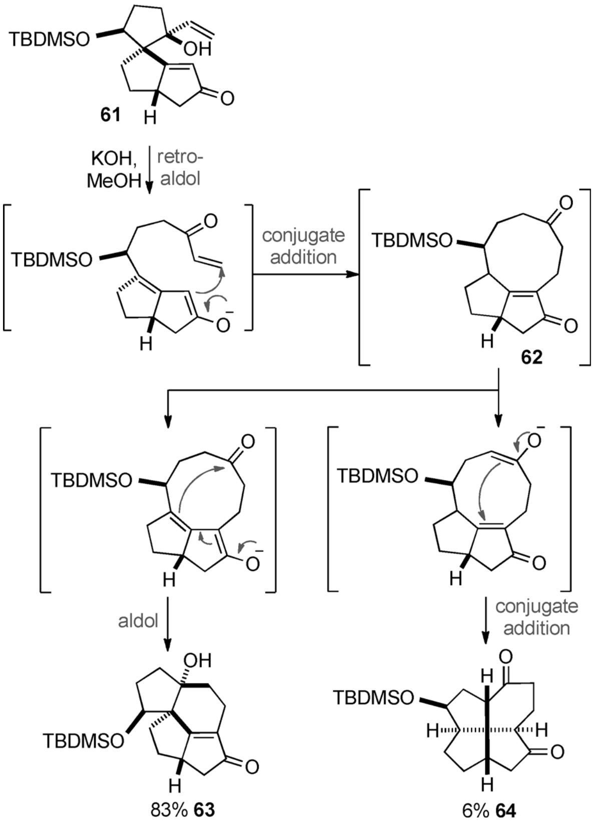
from **47a**, a mixture of the two all-*cis*-fenestrenes **50a** and **51a** was obtained by mesylation and elimination (Scheme 6a). Once more, the reaction of the *trans* compound **47b** did not give the desired fenestrene, but compounds **53** and related structures instead (Scheme 6b).

Chen et al. studied the asymmetric synthesis of polyquinanes that contain a quaternary chiral carbon center and recently reported their three-step procedure, which includes a Rh^I-catalyzed stereoselective tandem PKR/[4+2] cycloaddition.[61] The first step is a catalytic asymmetric addition of 1,3-enynes to aliphatic aldehydes (Scheme 7, top). These are followed by substitution reactions of allyl bromides, leading to the optically active trienynes **59**. Finally, in the presence of a catalytic amount of [{RhCl(CO)$_2$}$_2$] and 1 atm of CO, these trienynes undergo a highly stereoselective tandem PKR/[4+2] cycloaddition to generate optically active polycyclic products. The product that is obtained depends on the structure of the starting trienyne **59**, leading either to **56** or **57**. Mechanistically, the Rh-catalyzed PKR is assumed to take place first, followed by a [4+2] cycloaddition (through an *exo*-Diels–Alder reaction), which is also metal-catalyzed. This assumption is supported by the observation that after a short reaction time of five hours, intermediate **60** can be isolated from the reaction starting from trienyne **59a** (R^2 = Me, R^3,R^4 = H; Scheme 7, bottom). Upon heating in 1,2-dichloroethane only, this intermediate did not react, whereas the addition of [{RhCl(CO)$_2$}$_2$] and heating to reflux in 1,2-dichloroethane led to **56a**. The same oxa-fenestrane **56a** was obtained when trienyne **59a** was heated to reflux with the catalyst for 72 hours, thus confirming the proposed mechanism.

4.3. Other Strategies

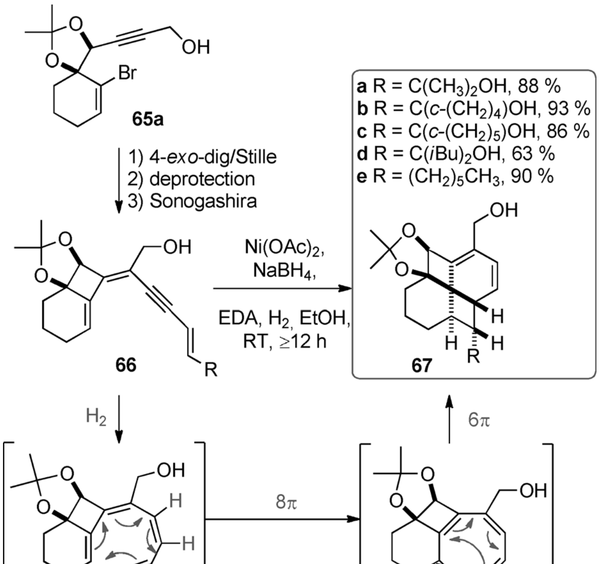
During an attempt to access the skeleton of aquariane through a ring-expanding Cope rearrangement as the key step, Thornton and Burnell observed the formation of a [5.5.5.6]fenestrane as side product.[62] The precursor **61** did not react as desired in a concerted anionic oxy-Cope rearrangement, but with a retro-aldol ring opening followed by conjugate addition (Scheme 8). The intermediate **62** was not stable under basic conditions, but reacted further to give two enols, leading either to **63** by aldol reaction or to the fenestrane **64** by another conjugate addition.

In 2008, Suffert and co-workers demonstrated their access to [4.6.4.6]fenestradienes using cascade reactions. The precursor trienyne **66** was obtained in nine steps from cyclohexenone, including a tandem 4-*exo*-dig cyclocarbopallada-

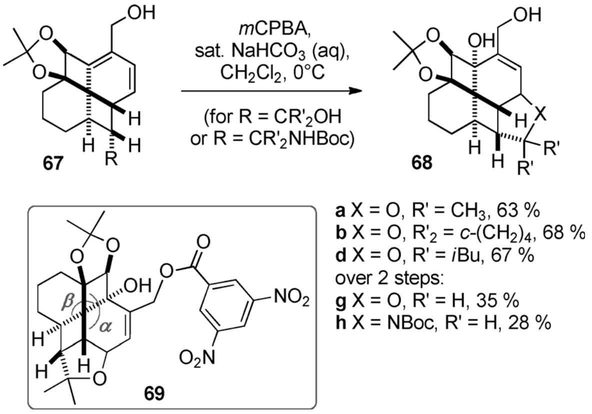


Scheme 8. Isolation of the [5.5.5.6]fenestrane **64** as side product.

tion/Stille coupling of propargylic alcohol **65**. In the presence of the catalyst P-2 Ni, formed in situ from $Ni(OAc)_2$ and $NaBH_4$ at room temperature (Scheme 9), trienyne **66** undergoes a cascade reaction: a semi-hydrogenation, then a 8π electrocyclization, followed by a 6π electrocyclization, leading to [4.6.4.6]fenestradienes **67** in a one-pot process.[63,64] In addition, fenestradienes **67** could be stabilized by epoxidation and rearrangement with *m*-CPBA, giving the [4.6.4.6]fenestrenes **68** (Scheme 10). The free hydroxy group of compound **68a** was esterified and the 3,5-dinitrobenzoate **69** provided crystals for X-ray analysis. The angles α and β were 118° and 124°, respectively (in silico: 120.6° and 119.3°).

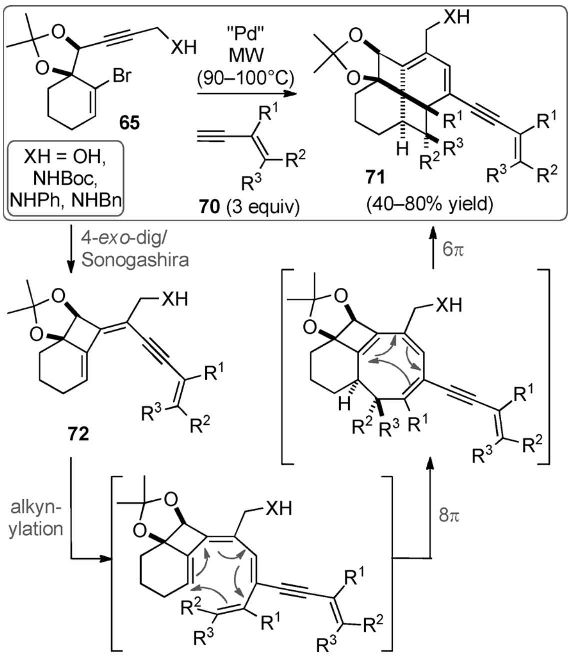


Scheme 9. Synthesis of [4.6.4.6]fenestradienes **67**. EDA = ethylenediamine.



Scheme 10. Epoxidation and rearrangement of **67**, and crystalline compound **69**. Boc = *tert*-butoxycarbonyl, *m*CPBA = *meta*-chloroperoxybenzoic acid.

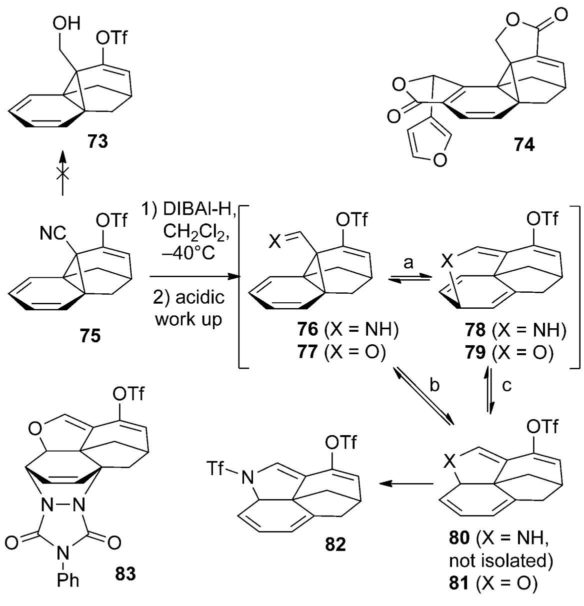
More recently, the group studied another approach to the fenestrane scaffold directly from the propargylic alcohols or propargylic amines **65**, with a new five-step cascade reaction (Scheme 11).[65] Upon irradiation at 90–100 °C, the trienyne **72** is first formed by 4-*exo*-dig cyclocarbopalladation and Sono-



Scheme 11. One-pot synthesis of fenestradienes **71** starting from propargylic alcohols or amines **65** ("Pd" = $Pd(OAc)_2$, PPh_3, CuI, iPr_2NH); R^1 = H, Me; R^2 = H, CH_2NHBoc, CH_2OH, $CH_2OTBDMS$, CH_2CH_2Ph, $Cc\text{-}(CH_2)_4OH$, $Cc\text{-}(CH_2)_5OH$; R^3 = H, $CH_2OTBDMS$. Bn = benzyl, MW = microwave.

gashira coupling.[66] The addition of another equivalent of enyne **70** to the triple bond, formally an alkynylation, leads to a tetraene intermediate, which spontaneously reacts in an 8π electrocyclization, followed by a 6π electrocyclization, leading to [4.6.4.6]fenestradiene **71** as the major product. As for the previous series, one of the fenestradienes **71** was transformed into a 3,5-dinitrobenzoate and the X-ray analysis showed indeed an increased deformation of the central carbon atom, probably because of the new bridgehead double bond ($\alpha = 126°$, $\beta = 122°$).

Working on the synthesis of the [5.3.1]propellane-containing and biologically active neoclerodane salvileucalin B (**74**), Banwell and co-workers found an access to aza- and oxa-[5.6.5.6]fenestratetraenes **80–83** through sigmatropic rearrangements (Scheme 12).[67]



Scheme 12. Rearrangements leading to [5.6.5.6]fenestratetraenes **81** and **82**. a) [3,3]-Sigmatropic rearrangement. b) [3,5]-Sigmatropic rearrangement. c) 1,3 Shift. DIBAL-H = diisobutylaluminum hydride, Tf = trifluoromethanesulfonyl.

The attempted conversion of **75** to **73** by treatment with DIBAl-H did not give the desired product, but both [5.6.5.6]fenestratetraenes **81** and **82** instead. Mechanistic considerations lead to a pathway that involves sigmatropic and allylic rearrangements as well as cleavage of the cyclopropane ring. X-ray analysis of **82** and **83** showed enlarged bond angles for both compounds (X-ray **82**: 112.7°, 121.2°; X-ray **83**: 113.5°, 126.0°).

Without going into details, it is noteworthy that other fenestranes with more than one heteroatom have been studied and synthesized (Figure 17). These compounds have either a scaffold that is not very rigid, such as in the tetra-aza compound **84**,[68] or don't have a central carbon atom, as the silicon compound **86**.[69] In consequence, they are not suitable for the study of ptCs. However, they are interesting synthetic targets; one extreme example is the "inorganic fenestrane" **85**,[70] which has a scaffold without carbon atoms as part of the four condensed cycles.

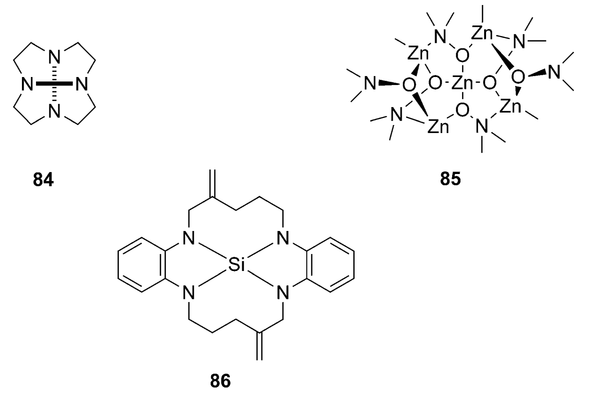


Figure 17. Further examples of heterofenestranes.

5. Summary and Outlook

During the last 40 years, a large number of fenestranes were synthesized by employing various key steps, typically photoinduced [2+2] cycloadditions or [3+2] arene–olefin cycloadditions, the PKR and cyclodehydrations. In order to study the deformation around the central carbon atom, the angles were calculated for most of the envisioned and obtained compounds, and in addition measured by X-ray analysis of the crystalline compounds. In general, the measured angles are in agreement with the predicted values, and it was established that the deformation can be enhanced with the following modifications: using sterically demanding bridgehead substituents, introducing bridgehead double bonds, including smaller cycles in the scaffold, and favoring *trans*-connected bridgehead substituents. Nevertheless, the synthesis of fenestranes is not uncomplicated, and up to date, no fenestrane with both angles larger than 130° was obtained. The examples with the largest angles are shown in Figure 18: the *c,c,t,c*-[4.5.5.5]fenestrane **87** (X-ray: 132.4°, 119.5°),[57b] the

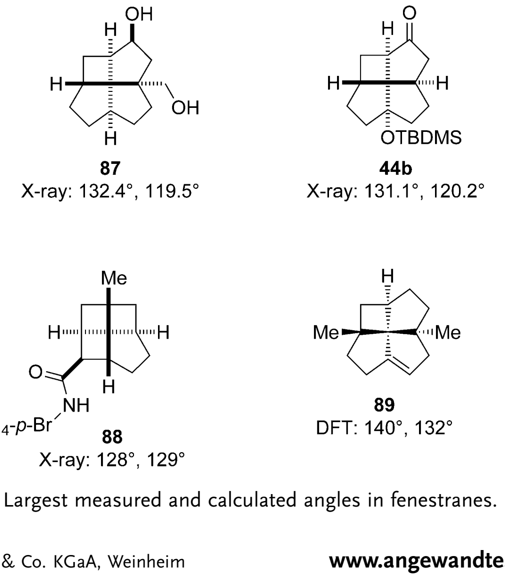


Figure 18. Largest measured and calculated angles in fenestranes.

c,*c*,*t*,*c*-[4.5.5.5]fenestrane **44b** (X-ray: 131.1°, 120.2),[58a] and the *c*,*c*,*c*,*c*-[4.4.4.5]fenestrane **88** (X-ray: 128°, 129°).[71] The compound that unifies the four factors leading to planarization, the 1,7-dimethyl-*c*,*c*,*t*,*c*-[4.5.5.5]fenestr-9-ene **89**, should have the largest angles (DFT: 140°, 132°).[17a] However, it has never been synthesized and the challenge of its synthesis is still open. As shown in the introduction of this Minireview, total planarization in the form of a ptC was achieved with other scaffolds, for example CAl$_3$Si or several organometallic compounds. Based on in silico studies, fenestranes that bear a ptC are not likely to be synthesized; other cage structures are more likely to be obtained, such as the dimethanospiro-[2.2]octaplane (Figure 1c) with a calculated perfect planar configuration for the central carbon atom. Nevertheless, fenestranes remain fascinating synthetic targets that easily capture the attention of curious chemists. In view of the newly found natural products, penifulvanes and aspergilanes, a study of the biosynthesis of such scaffolds could also be intriguing. It seems likely that penifulvin A (**10a**) is biogenetically related to the silphinenes,[40] and thus biosynthesized from a silphinene-type intermediate, oxidative cleavage of an analogue of silphinene, and subsequent bislactonization. But why does the plant form such complex scaffolds? This question is all the more intriguing for laurenene (**2**), for which, to our knowledge, no biological function or activity has been found. In general, studies about biological or even medicinal activities of fenestranes are rare, especially for the synthetic compounds. Exceptions are the study by Suffert and co-workers on proapoptotic activities toward human TRAIL-resistant metastatic cell lines,[72] or the antifungal and insecticidal activity of penifulvin A (**10a**). Hence, with their rigid scaffold, functionalized fenestranes could be ideal and selective ligands for biological targets. Another issue should also be addressed, not only in view of potential applications in medicinal chemistry: no enantioselective synthesis of a fenestrane possessing a full-carbon framework has been undertaken; in all the achieved syntheses, a racemic mixture was isolated.

We thank the CNRS and the MENRT for financial support to M.C., Prestwick Chemical-Illkirch France for a grant to A.B. (CIFRE), and the referees for valuable criticism that substantially improved the quality of this Minireview.

Received: May 27, 2013
Revised: June 18, 2013

---

[1] a) J. H. van't Hoff, *Arch. Neerl. Sci. Exactes Nat.* **1874**, *9*, 44; b) J. A. Le Bel, *Bull. Soc. Chim. Fr.* **1874**, *22*, 337.

[2] R. Hoffmann, R. W. Alder, C. F. Wilcox, Jr., *J. Am. Chem. Soc.* **1970**, *92*, 4992–4993.

[3] a) K. B. Wiberg, G. B. Ellison, *Tetrahedron* **1974**, *30*, 1573–1578; b) J. B. Collins, J. D. Dill, E. D. Jemmis, Y. Apeloig, P. von R. Schleyer, R. Seeger, J. A. Pople, *J. Am. Chem. Soc.* **1976**, *98*, 5419–5427; c) W. Siebert, A. Gunuale, *Chem. Soc. Rev.* **1999**, *28*, 367–371; d) V. I. Minkin, R. M. Minyaev, R. Hoffmann, *Russ. Chem. Rev.* **2002**, *71*, 869–892.

[4] K. Sorger, P. von R. Schleyer, *J. Mol. Struct. THEOCHEM* **1995**, *338*, 317–346.

[5] For other examples of predicted structures, see: a) P. von R. Schleyer, A. I. Boldyrev, *J. Chem. Soc. Chem. Commun.* **1991**, 1536–1538; b) L. S. Wang, A. I. Boldyrev, X. Li, J. Simons, *J. Am. Chem. Soc.* **2000**, *122*, 7681–7687; c) X. Li, H.-J. Zhai, L.-S. Wang, *Chem. Phys. Lett.* **2002**, *357*, 415–419; d) R. M. Minyaev, T. N. Gribanova, V. I. Minkin, A. G. Starikov, R. Hoffmann, *J. Org. Chem.* **2005**, *70*, 6693–6704; e) T. N. Gribanova, R. M. Minyaev, V. I. Minkin, *Russ. J. Gen. Chem.* **2008**, *78*, 750–768; and references cited therein.

[6] For predicted planar C$_5^{2-}$ dianions, see: a) R. W. Weber, J. M. Cook, *Can. J. Chem.* **1978**, *56*, 189–192; b) G. Merino, M. A. Mendez-Rojas, A. Vela, *J. Am. Chem. Soc.* **2003**, *125*, 6026–6027; c) A. J. Pihko, A. M. P. Koskinen, *Tetrahedron* **2005**, *61*, 8769–8807; d) G. Merino, M. A. Mendez-Rojas, A. Vela, T. Heine, *J. Comput. Chem.* **2007**, *28*, 362–372.

[7] S. L. Buchwald, E. A. Lucas, W. M. Davis, *J. Am. Chem. Soc.* **1989**, *111*, 397–398.

[8] For other organometallic compounds, see Ref. [3c] and: a) R. Choukroun, P. Cassoux, *Acc. Chem. Res.* **1999**, *32*, 494–502; b) G. Erker, *Chem. Soc. Rev.* **1999**, *28*, 307–314; c) M. Su, *Inorg. Chem.* **2005**, *44*, 4829–4833; d) D. Roy, C. Corminboeuf, C. S. Wannere, R. B. King, P. von R. Schleyer, *Inorg. Chem.* **2006**, *45*, 8902–8906; and references cited therein.

[9] For caged hydrocarbon species, see: a) J. F. Liebman, A. Greenberg, *Chem. Rev.* **1976**, *76*, 311–365; b) P. E. Eaton, B. D. Leipzig, *J. Am. Chem. Soc.* **1983**, *105*, 1656–1658; c) K. B. Wiberg, *Chem. Rev.* **1989**, *89*, 975–983; d) M. P. McGrath, L. Radom, H. F. Schaefer III, *J. Org. Chem.* **1992**, *57*, 4847–4850; e) H. Dodziuk, J. Leszczyriski, K. S. Nowirinski, *J. Org. Chem.* **1995**, *60*, 6860–6863; and references cited therein.

[10] a) L. Radom, D. R. Rasmussen, *Pure Appl. Chem.* **1998**, *70*, 1977–1984; b) D. R. Rasmussen, L. Radom, *Angew. Chem.* **1999**, *111*, 3051–3054; *Angew. Chem. Int. Ed.* **1999**, *38*, 2875–2878.

[11] For other alkaplanes, see: a) M. P. McGrath, L. Radom, *J. Am. Chem. Soc.* **1993**, *115*, 3320–3321; b) D. R. Rasmussen, L. Radom, *Chem. Eur. J.* **2000**, *6*, 2470–2483.

[12] Z.-X. Wang, P. von R. Schleyer, *J. Am. Chem. Soc.* **2001**, *123*, 994–995.

[13] For planar species with higher coordination numbers, see: a) K. Exner, P. von R. Schleyer, *Science* **2000**, *290*, 1937–1940; b) Y. Pei, X. C. Zeng, *J. Am. Chem. Soc.* **2008**, *130*, 2580–2592; c) J. O. C. Jimenez-Halla, Y. B. Wu, Z. X. Wang, R. Islas, T. Heine, G. Merino, *Chem. Commun.* **2010**, *46*, 8776–8778; d) T. Heine, G. Merino, *Angew. Chem.* **2012**, *124*, 4349–4350; *Angew. Chem. Int. Ed.* **2012**, *51*, 4275–4276.

[14] T. R. Galeev, C. Romanescu, W. L. Li, L. S. Wang, A. I. Boldyrev, *Angew. Chem.* **2012**, *124*, 2143–2147; *Angew. Chem. Int. Ed.* **2012**, *51*, 2101–2105.

[15] V. Georgian, M. Saltzman, *Tetrahedron Lett.* **1972**, *13*, 4315–4317.

[16] R. Hoffmann, H. Hopf, *Angew. Chem.* **2008**, *120*, 4548–4556; *Angew. Chem. Int. Ed.* **2008**, *47*, 4474–4481.

[17] Earlier contributions are resumed in the following reviews: a) B. R. Venepalli, W. C. Agosta, *Chem. Rev.* **1987**, *87*, 399–410; b) M. Thommen, R. Keese, *Synlett* **1997**, 231–240; c) R. Keese, *Chem. Rev.* **2006**, *106*, 4787–4808.

[18] J. F. Liebman, A. Greenberg, *Chem. Rev.* **1976**, *76*, 311–365.

[19] W. Luef, R. Keese, *J. Mol. Struct. THEOCHEM* **1992**, *257*, 353–366.

[20] A. K. Gupta, X. Fu, J. P. Snyder, J. M. Cook, *Tetrahedron* **1991**, *47*, 3665–3710.

[21] D. Hirschi, W. Luef, P. Gerber, R. Keese, *Helv. Chim. Acta* **1992**, *75*, 1897–1908.

[22] R. E. Corbett, D. R. Lauren, R. T. Weavers, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1774–1790.

[23] D. R. Lauren, Ph.D. Thesis, University of Otago, **1971**.

[24] a) R. E. Corbett, C. M. Couldwell, D. R. Lauren, R. T. Weavers, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1791 – 1794; b) R. T. Weavers, *J. Org. Chem.* **2001**, *66*, 6453 – 6461.

[25] M. T. Crimmins, L. D. Gould, *J. Am. Chem. Soc.* **1987**, *109*, 6199 – 6200.

[26] T. Tsunoda, M. Amaike, U. S. F. Tambunan, Y. Fujise, S. Ito, M. Kodama, *Tetrahedron Lett.* **1987**, *28*, 2537 – 2540.

[27] P. A. Wender, T. W. Von Geldern, B. H. Levine, *J. Am. Chem. Soc.* **1988**, *110*, 4858 – 4860.

[28] For an alternative approach, see: a) L. A. Paquette, M. E. Okazaki, J.-C. Caille, *J. Org. Chem.* **1988**, *53*, 477 – 481; b) G. Mehta, K. S. Rao, *J. Org. Chem.* **1988**, *53*, 425 – 427.

[29] For reviews about angular triquinane natural products and their synthesis, see: a) G. Mehta, A. Srikrishna, *Chem. Rev.* **1997**, *97*, 671 – 719; b) L. A. Paquette, *Top. Curr. Chem.* **1979**, *79*, 41 – 165, particularly pages 108 – 133; c) L. A. Paquette, *Top. Curr. Chem.* **1984**, *119*, 1 – 163; d) L. A. Paquette, A. M. Doherty, *Polyquinane Chemistry*, *Synthesis and Reactions*, Springer, Berlin, **1987**.

[30] L. H. Zalkow, R. N. Harris III, N. I. Burke, *J. Nat. Prod.* **1979**, *42*, 96 – 102.

[31] For recent syntheses of isocomenes, see: a) Y. Iura, T. Sugahara, K. Ogasawara, *Org. Lett.* **2001**, *3*, 291 – 293; b) A. W. Schmidt, T. Olpp, E. Baum, T. Stiffel, H.-J. Knölker, *Synlett* **2007**, *15*, 2371 – 2374; c) A. W. Schmidt, T. Olpp, E. Baum, T. Stiffel, H.-J. Knölker, *Org. Biomol. Chem.* **2010**, *8*, 4562 – 4568.

[32] For syntheses of silphinanes, see: a) F. Bohlmann, L. N. Misra, J. Javupovic, H. Robinson, R. M. King, *J. Nat. Prod.* **1984**, *47*, 658 – 662; b) M. T. Crimmins, S. W. Mascarella, *J. Am. Chem. Soc.* **1986**, *108*, 3435 – 3438; c) Y. K. Rao, M. Nagarajan, *J. Org. Chem.* **1989**, *54*, 5678 – 5683; d) N. T. Tzvetkov, T. Arndt, J. Mattay, *Tetrahedron* **2007**, *63*, 10497 – 10510; and references cited therein.

[33] For syntheses of silphiperfolanes, see: a) A. S. Feliciano, J. M. M. Del Corral, E. Caballero, A. Alvarez, M. Medarde, *J. Nat. Prod.* **1986**, *49*, 845 – 853; b) A. B. Trendafilova-Savkovaa, M. N. Todorovaa, C. V. Gussev, *Z. Naturforsch. C* **2003**, *58*, 817 – 819; c) A. Srikrishna, G. Nagaraju, V. M. Sheth, *Tetrahedron* **2012**, *68*, 2650 – 2656; and references cited therein.

[34] For syntheses of pentalenanes, see: a) H. Seto, H. Yonehara, *J. Antibiot.* **1980**, *33*, 92 – 93; b) G. Mehta, K. S. Rao, *J. Am. Chem. Soc.* **1986**, *108*, 8015 – 8021; c) N. E. Schore, E. G. Rowley, *J. Am. Chem. Soc.* **1988**, *110*, 5224 – 5225; d) N. M. Harrington-Frost, G. Pattenden, *Tetrahedron Lett.* **2000**, *41*, 403 – 405; e) M. K. Pallerla, J. M. Fox, *Org. Lett.* **2007**, *9*, 5625 – 5628; and references cited therein.

[35] J. B. Gloer, M. R. TePaske, J. S. Sima, *J. Org. Chem.* **1988**, *53*, 5457 – 5460 and references cited therein. For a synthesis of aflavine, see: S. Danishefsky, S. Chackalamannil, P. Harrison, M. Silvestri, P. Cole, *J. Am. Chem. Soc.* **1985**, *107*, 2474 – 2484.

[36] M. Kladi, H. Xenaki, C. Vagias, P. Papazafiri, V. Roussis, *Tetrahedron* **2006**, *62*, 182 – 189.

[37] U. H. Brinker, T. Schrievers, L. Xu, *J. Am. Chem. Soc.* **1990**, *112*, 8609 – 8611.

[38] a) For an overview of syntheses of [*m.n.p*]fenestranes, see: Ref. [17a], pages 403–404; b) for a recent example, see: J. Deschamp, T. Hermant, O. Riant, *Tetrahedron* **2012**, *68*, 3457 – 3467.

[39] S. H. Shim, J. B. Gloer, D. T. Wicklow, *J. Nat. Prod.* **2006**, *69*, 1601 – 1605.

[40] S. H. Shim, D. C. Swenson, J. B. Gloer, P. F. Dowd, D. T. Wicklow, *Org. Lett.* **2006**, *8*, 1225 – 1228.

[41] T. Gaich, J. Mulzer, *J. Am. Chem. Soc.* **2009**, *131*, 452 – 453.

[42] T. Gaich, J. Mulzer, *Org. Lett.* **2010**, *12*, 272 – 275.

[43] N. Ingavat, C. Mahidol, S. Ruchirawat, P. Kittakoop, *J. Nat. Prod.* **2011**, *74*, 1650 – 1652.

[44] G. Mehta, T. B. Khan, *Tetrahedron Lett.* **2012**, *53*, 4558 – 4561.

[45] For a review of enone – olefin photocycloadditions, including syntheses of [*m.n.p.q*]fenestranes and [*m.n.p*]fenestranes, see: M. T. Crimmins, *Chem. Rev.* **1988**, *88*, 1453 – 1473.

[46] For some examples for syntheses of fenestranes through enone–olefin photocycloadditions, see the following publications and references cited therein: a) W. G. Dauben, D. M. Walker, *Tetrahedron Lett.* **1982**, *23*, 711 – 714; b) S. Wolff, B. R. Venepalli, C. F. George, W. C. Agosta, *J. Am. Chem. Soc.* **1988**, *110*, 6785 – 6790; c) P. Gerber, R. Keese, *Tetrahedron Lett.* **1992**, *33*, 3987 – 3988.

[47] For a general review on the *meta* (or [3+2]) photocycloaddition of arenes to alkenes, see: J. Cornelisse, *Chem. Rev.* **1993**, *93*, 615 – 669.

[48] For some examples for syntheses of fenestranes through arene–olefin cycloadditions, see the following publications and references cited therein: a) J. Mani, S. Schuettel, C. Zhang, P. Bigler, C. Mueller, R. Keese, *Helv. Chim. Acta* **1989**, *72*, 487 – 495; b) P. A. Wender, M. A. DeLong, F. C. Wireko, *Acta Crystallogr. Sect C* **1997**, *53*, 954 – 956.

[49] For some examples for syntheses of fenestranes through Weiss reactions, see: X. Fu, G. Kubiak, W. Zhang, W. Han, A. K. Gupta, J. M. Cook, *Tetrahedron* **1993**, *49*, 1511 – 1524 and references cited therein.

[50] For reviews by Kuck and co-workers on benzannelated fenestranes or other multiple fused cyclopentane and indane units, based on cyclodehydration and including fenestranes, see: a) D. Kuck, *Synlett* **1996**, 949 – 965; b) D. Kuck in *Advances in Theoretically Interesting Molecules*, *Vol. 4* (Ed.: R. P. Thummel), JAI, Greenwich, London, **1998**, p. 81 – 155; c) D. Kuck, *Chem. Rev.* **2006**, *106*, 4885 – 4925.

[51] For some examples for syntheses of fenestranes through PKRs, see the following publications and references cited therein: a) W. A. Smit, S. M. Bukhanyuk, S. O. Simonyan, A. S. Shashkov, Y. T. Struchkov, A. I. Yanovskii, R. Caple, A. S. Gybin, L. G. Anderson, J. A. Whiteford, *Tetrahedron Lett.* **1991**, *32*, 2105 – 2108; b) A. Van der Waals, R. Keese, *J. Chem. Soc. Chem. Commun.* **1992**, 570 – 571; c) J. Wang, R. Guidetti-Grept, R. Keese, H. Stoeckli-Evans, *Helv. Chim. Acta* **1997**, *80*, 1169 – 1175; d) S. U. Son, K. H. Park, Y. K. Chung, *J. Am. Chem. Soc.* **2002**, *124*, 6838 – 6839.

[52] a) S. E. Denmark, L. A. Kramps, J. I. Montgomery, *Angew. Chem.* **2002**, *114*, 4296 – 4299; *Angew. Chem. Int. Ed.* **2002**, *41*, 4122 – 4125; b) S. E. Denmark, J. I. Montgomery, *Angew. Chem.* **2005**, *117*, 3798 – 3802; *Angew. Chem. Int. Ed.* **2005**, *44*, 3732 – 3736; c) mechanistic study: R. L. Davis, D. J. Tantillo, *J. Org. Chem.* **2010**, *75*, 1693 – 1700.

[53] S. E. Denmark, J. I. Montgomery, L. A. Kramps, *J. Am. Chem. Soc.* **2006**, *128*, 11620 – 11630.

[54] C. S. Penkett, J. A. Woolford, I. J. Day, M. P. Coles, *J. Am. Chem. Soc.* **2010**, *132*, 4 – 5.

[55] C. S. Penkett, J. A. Woolford, T. W. Read, R. J. Kahan, *J. Org. Chem.* **2011**, *76*, 1295 – 1304.

[56] P. Macchi, W. Jing, R. Guidetti-Grept, R. Keese, *Tetrahedron* **2013**, *69*, 2479 – 2483.

[57] a) R. Keese, *Angew. Chem.* **1992**, *104*, 307 – 309; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 344 – 345; b) D. Hirschi, W. Luef, P. Gerber, R. Keese, *Helv. Chim. Acta* **1992**, *75*, 1897 – 1908.

[58] a) M. Thommen, M. Frötsch, R. Keese, *Acta Crystallogr. Sect. C* **1996**, *52*, 2051 – 2053; b) M. Thommen, R. Keese, *Synlett* **1997**, 231 – 240.

[59] M. Thommen, L. Prevot, M. K. Eberle, P. Bigler, R. Keese, *Tetrahedron* **2011**, *67*, 3868 – 3873.

[60] a) P. Weyermann, R. Keese, *Tetrahedron* **2011**, *67*, 3874 – 3880; b) P. Weyermann, R. Keese, H. Stoeckli-Evans, *Acta Crystallogr. Sect. E* **2010**, *66*, o340.

[61] W. Chen, J.-H. Tay, J. Ying, X.-Q. Yu, L. Pu, *J. Org. Chem.* **2013**, *78*, 2256 – 2265.

[62] P. D. Thornton, D. J. Burnell, *Org. Lett.* **2006**, *8*, 3195 – 3198.
[63] C. Hulot, G. Blond, J. Suffert, *J. Am. Chem. Soc.* **2008**, *130*, 5046 – 5047.
[64] For the in silico study of the kinetics of these compounds, see: C. Hulot, S. Amiri, G. Blond, P. R. Schreiner, J. Suffert, *J. Am. Chem. Soc.* **2009**, *131*, 13387 – 13398.
[65] M. Charpenay, A. Boudhar, G. Blond, J. Suffert, *Angew. Chem.* **2012**, *124*, 4455 – 4458; *Angew. Chem. Int. Ed.* **2012**, *51*, 4379 – 4382.
[66] For the study of a tandem reaction with 4-*exo*-dig cyclocarbopalladation and Sonogashira coupling, see: M. Charpenay, A. Boudhar, A. Siby, S. Schigand, G. Blond, J. Suffert, *Adv. Synth. Catal.* **2011**, *353*, 3151 – 3156.
[67] N. Heinrich, A. C. Willis, I. A. Cade, J. Ho, M. L. Coote, M. G. Banwell, *Chem. Eur. J.* **2012**, *18*, 13585 – 13588.
[68] a) J. E. Richman, H. E. Simmons, *Tetrahedron* **1974**, *30*, 1769 – 1774; b) V. Galasso, D. Jones, J. E. Richman, *J. Mol. Struct. THEOCHEM* **1998**, *429*, 247 – 253.
[69] B. Ding, R. Keese, H. Stoeckli-Evans, *Angew. Chem.* **1999**, *111*, 387 – 388; *Angew. Chem. Int. Ed.* **1999**, *38*, 375 – 376.
[70] M. Ullrich, R. J. F. Berger, C. Lustig, R. Froehlich, N. W. Mitzel, *Eur. J. Inorg. Chem.* **2006**, 4219 – 4224.
[71] B. R. Venepalli, C. F. George, S. Wolff, W. C. Agosta, *J. Am. Chem. Soc.* **1985**, *107*, 5732 – 5739.
[72] C. Hulot, J. Peluso, G. Blond, C. D. Muller, J. Suffert, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6836 – 6839.