# Dendralenes: The Breakthrough

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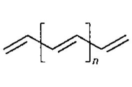
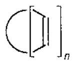
By connecting double and single bonds, formally five classes of hydrocarbons can be constructed which differ considerably from one another not only chemically and physically but also in terms of their practical significance:[1] linear polyenes **1**; annulenes **2**, which consist exclusively of endocyclic "double bonds"; radialenes **3**, polyolefins which are characterized by semicyclic double bonds; fulvenes **4**, hybrids consisting of endo- and semicyclic double bonds; and finally, dendralenes **5**,[2]which are acyclic cross-conjugated polyenes.



**1**



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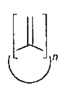

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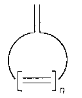

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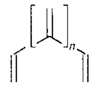
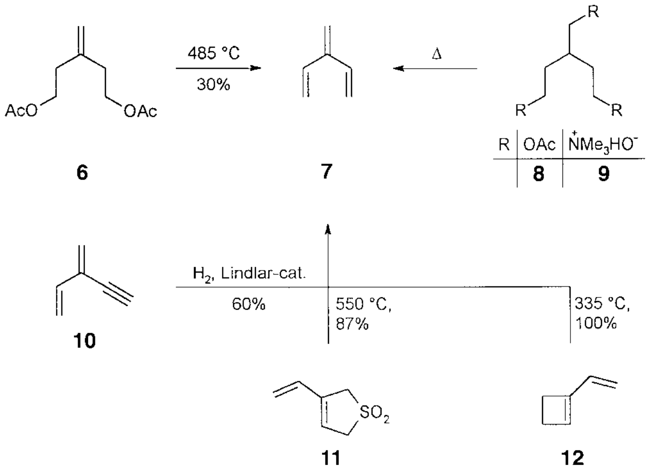


**5**

Of these π systems, the first two are by far the most thoroughly investigated and also play the greatest practical role, be it in the form of vital molecules such as β-carotene or as key substances in organic syntheses, such as benzene. Of the remaining three substance classes, which are all cross-conjugated, fulvenes and their derivatives have been studied most extensively; however, in the last few years radialenes have gradually come out of the shadows.[3, 4] Although von Auwers had obtained the first dendralene derivatives at the beginning of the twentieth century and this substance class was later studied by Staudinger, among others, who described them as "open fulvenes",[2] there have been no in depth studies of the chemistry of the parent dendralene systems. The reason for this is simple: Except for compounds **5** with $n = 1$ ([3]dendralene **7**, Scheme 1) and $n = 2$ ([4]dendralene **15**, Scheme 2), higher vinylogues were not known until the recent investigations by Sherburn et al., details of which are given below.

A considerable number of processes have been described for the preparation of the two simplest dendralenes; however, most of them are rather means of formation than efficient preparative methods. As Scheme 1 shows for [3]dendralene **7**, thermal methods of preparation predominate (eliminations and pericyclic processes); however, these methods do not always start from readily accessible precursors.[5] The most effective—and therefore suitable for subsequent reaction chemistry—is the cheletropic decomposition of **11** carried out by Cadogan and Gosney et al.,[6] although this sulfolene derivative first appears at the end of a reaction path with several steps. The situation was even more critical for [4]dendralene **15**,[2, 7] especially since the thermal decomposition reactions represented in the lower half of Scheme 2 have all been carried out in the course of mechanistic studies.



Scheme 1. Routes to [3]dendralene **7**.

Before the first general synthesis concept for the preparation of dendralenes is presented, it will be shown that these π systems, neglected until now, are interesting not only preparatively but also from a structural point of view. The application of dendralenes in Diels–Alder additions holds particular promise in synthetic chemistry. This is outlined in more detail in Scheme 3 for the two simplest dendralenes. The [2+4] cycloaddition of **7** with a dienophile **20**, not only leads to the expected 1:1 adduct **21** but also generates a conjugated diene system which is available for a second addition with **20** to give **22** (Scheme 3a). In principle, dienophiles containing a triple bond and heteroorganic addends are also suitable as dienophile components.

Tsuge and co-workers—building on work by Bailey and Blomquist[5]—have already made extensive use of the preparative potential of these types of diene transmissive Diels–Alder additions[8]. Clearly, the dienophile does not have to be identical in the two stages of the reaction, which increases the

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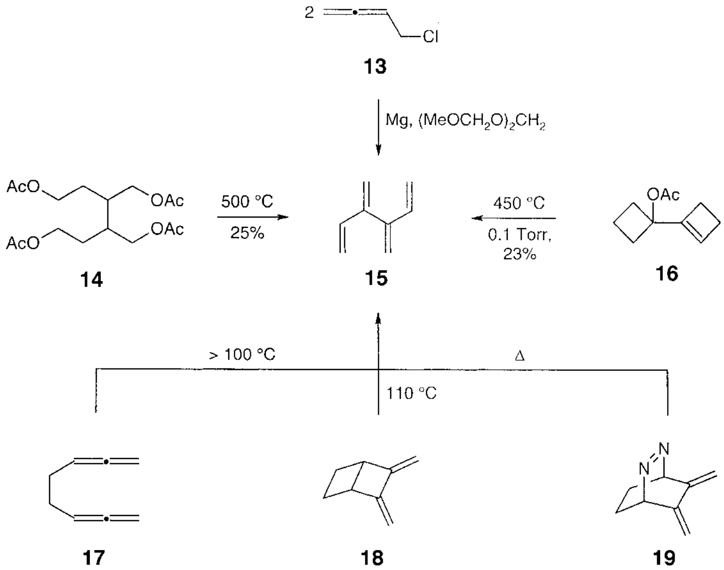
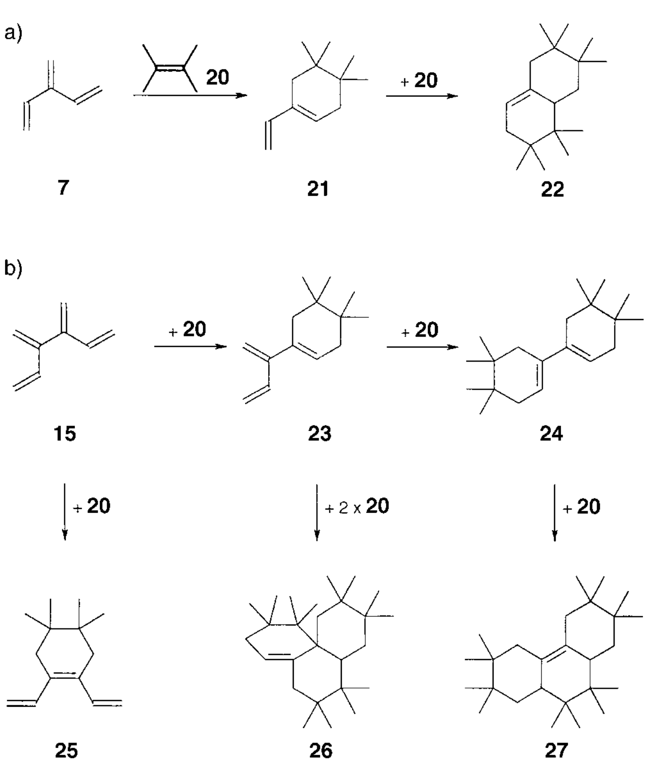


Scheme 2. Routes to [4]dendralene **15**.

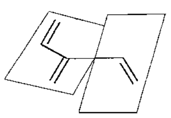


Scheme 3. Diene-transmissive Diels–Alder additions with **7** and **15**.

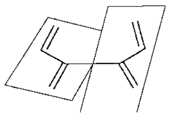
preparative potential of these double cycloadditions considerably. The adducts of type **22** can be further processed in various ways, for example by dehydrogenation to give 1,2,6,7-tetrasubstituted naphthalene derivatives. Consecutive reactions of this type with their excellent atom economy are of considerable interest particularly in view of the current efforts to increase the efficiency of organic transformations.

As expected, the possibilities for [4]dendralene **15**, which until now has only been used occasionally in diene-transmissive additions,[7c] to participate in [2+4] cycloadditions are much greater (Scheme 3b). Two possibilities arise for the first addition, depending on whether **20** adds to a terminal diene unit (formation of **23**) or to the central diene unit (formation of **25**). For **23**, two further alternatives are offered which could either lead via **24** to the 3:1 adduct **27** or—by consecutive additions of two equivalent dienophiles—to the tris-adduct **26** (notice the formation of a quaternary carbon atom in **26**). Depending on the type of dienophile, the adducts **27** could also be used again for aromatization experiments. New types of products are also expected in many other reactions of dendralenes (photochemistry, metal complexation, ionic additions).

As far as the structure of dendralenes is concerned the early work concentrated on the analysis of UV spectra—not surprising if one considers that the cross-conjugation motif occurs in many dyes (triphenylmethane dyes, indigo etc.). The electronic spectra show, for instance, that the dendralenes cannot exist in coplanar form. Their absorption maxima lie in the same region as in simple 1,3-dienes; they are not shifted to longer wavelengths as one would expect for an extended π-electron system. This is confirmed by detailed structural investigations accompanied by various calculation methods. According to electron diffraction measurements, **7** has the *anti, skew* conformation **28** with a dihedral angle of 40° between the planes of the *anti*-butadiene fragment and the remaining vinyl group.[9] In **15** this dihedral angle is 72° and again the *anti*-butadiene halves are practically planar (see structure **29**).[10]



**28**

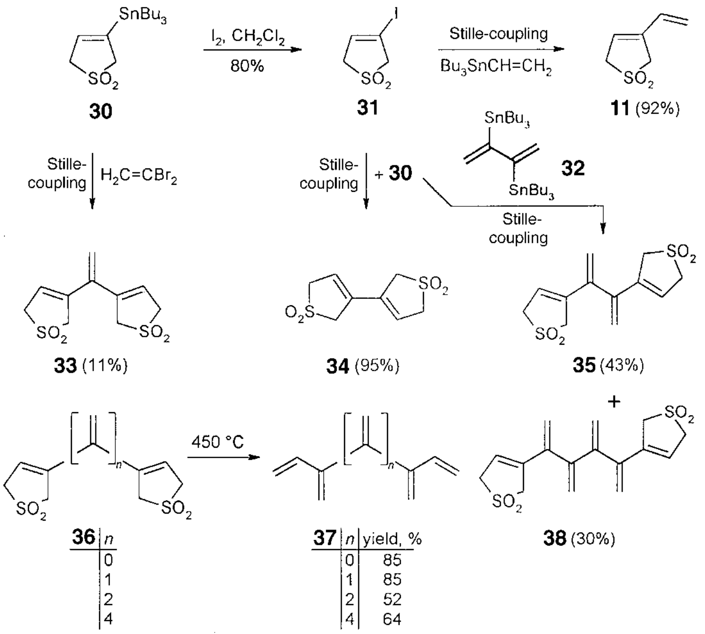


**29**

The unsatisfactory situation that promising substance class could not be developed further has recently been rectified by the groups of Fielder, Rowan, and Sherburn in Australia/New Zealand who have achieved a general route to dendralenes.[11] In planning the corresponding sequence, the well known instability and tendency to polymerize of dendralenes **7** and **15** were taken into consideration from the very beginning, in that a synthetic route was designed in which the dendralene π system is not released until the very end. In particular the butadiene fragment was transported in capped form as a sulfolene ring to the end of the synthesis, as Cadogan and Gosney et al.[6] had done for the simplest dendralene **7**.

As Scheme 4 shows, the synthesis developed by Sherburn et al. begins with the vinyl stannane **30**, which is initially converted by iodolysis to the vinyl iodide **31**. The actual "construction" then followed through Stille cross-couplings; the mild reaction conditions used prevented the premature release of the sulfur dioxide from the masked dendralene intermediates. The sulfolenes **11**, **33**, and **34** were obtained readily in the presence of $[PdCl_2(CH_3CN)_2]$ in DMF under argon at temperatures up to 40 °C. The coupling of **31** with the bis-stannane **32**, not only gave the bis-sulfolene **35**, but also the [8]dendralene precursor **38**.

The masked dendralenes **36** are crystalline compounds, stable at room temperature from which, as hoped, the



Scheme 4. General dendralene synthesis according to Sherburn et al.

hydrocarbons **37** are released on demand in good yields by high-temperature pyrolysis. As no solvent is required in these cheletropic reactions, the workup is clearly made easier. The dendralenes **37** obtained, up to [8]dendralene ($n = 6$), have been completely characterized by the usual spectroscopic and analytical methods and can, although they have a tendency to polymerize, be manipulated—the deciding prerequisite for the study of their reactivity.

[1] Overview: H. Hopf, *Classics in Hydrocarbon Chemistry*, Wiley-VCH, Weinheim, **2000**, Chap. 2, pp. 5–18.

[2] At present only one review article exists on dendralenes: H. Hopf, *Angew. Chem.* **1984**, *96*, 947–958; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 947–959; see also ref. [1], Chap. 11, pp. 251–300.

[3] Review: H. Hopf, G. Maas, *Angew. Chem.* **1992**, *104*, 953–977; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 931–954.

[4] H. Hopf, G. Maas in *The Chemistry of Dienes and Polyenes, Vol. I* (Ed.: Z. Rappoport), Wiley, Chichester, **1997**, Chap. 21, pp. 927–977.

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# The First Cadmium-Specific Enzyme

## Henry Strasdeit*

*Is the Biochemistry of Cadmium More Similar to That of Zinc or Mercury?*

From a biological point of view, group 12 of the periodic table is remarkable. Its lightest element, zinc, occurs as an essential constituent in numerous proteins. However, the situation is entirely different for the heaviest group homologue, mercury. This is considered one of the most toxic nonradioactive elements. Also in the case of cadmium, which is the middle element of the group, toxicity and carcinogenicity have been nearly exclusively in the foreground so far. Positive biological effects, for example, on the growth of a fungus species,[1] have been described only sporadically and remain biochemically unexplained. The recently published discovery of the first cadmium enzyme can therefore rank as a landmark in the biological chemistry of cadmium.[2]

Cadmium quite clearly differs chemically from mercury. This is true for many aspects of the toxicity as well. For example, the alkyl species $MR_2$ and $RM^+$ are only slowly degraded in the case of mercury and therefore show a characteristic symptomology of poisoning,[3] while in the case of cadmium the species are not of any special toxicological importance because of their fast hydrolysis to $Cd^{2+}$. On the other hand it has been known for a long time that, in its compounds, cadmium often resembles zinc. Against this background it should thus not be too surprising that cadmium can also have a defined function in organisms. However, nothing of that became visible in the biological career of this element during the first 140 years after its discovery (Table 1).

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