Pericyclic Key Reactions in Biological Systems and Biomimetic Syntheses

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1 Introduction

The pericyclic reactions of organic chemistry, in contrast to polar or radical structural transformations of molecules, are one-step processes proceeding through a cyclic transition-state structure.[1,2] Thus, they constitute reactions of the concerted type.[1] Pericyclic reactions are not only of particular interest because of their stereospecific course and their broad preparative significance in the chemistry of drugs and natural products but also for theoretical reasons. As was realized by Woodward and Hoffmann,[3] Zimmermann,[4] Dewar,[5] Fukui,[6a] and others, the stereochemical progress is determined by the symmetry of the molecular orbitals participating in the reaction (the so-called HOMO and LUMO according to the frontier molecular orbital concept[6]). Thus, with the help of, for example, Woodward and Hoffmann's concept on the 'principle of the control of orbital symmetry', the stereochemical route of a thermally or photochemically induced pericyclic reaction and thus the resultant product spectrum can be predicted.[1,2,6] Figure 1 shows a typical, thermally allowed pericyclic 6-electron reaction in hydrocarbon chemistry together with the appropriate Woodward–Hoffmann nomenclature.[2,3]

The transition-state structures derived from quantum chemical *ab initio* calculations[1] exhibit a great variety from strongly bonded, closed shell to weakly bonded, flexible forms with diradical character. Pericyclic reactions possess an extremely wide potential for application in organic synthesis since most of them can be realized according to stereochemically preplanned structural concepts. Creative successes have, in particular, been reported in the fields of the total synthesis of natural products and the development of drugs.[6b] In the field of the specific molecular designing of drugs, pericyclic synthesis concepts open the way to unimagined and in some cases fascinating possibilities ranging through to the asymmetric synthesis of physiologically active, enantiomerically pure substances. Pericyclic reactions also occur in natural biological systems; for example, in some biochemical processes and the biosynthesis of numerous secondary metabolites, especially in the plant kingdom. The stereospecific production of enantiomerically pure natural products points in many cases to a highly ordered, enzymatic catalysis. These naturally occurring, thermally or photochemically allowed rearrangements are of great interest for the *in situ* generation of pharmacologically or biologically relevant, reactive intermediates.[1] On the other hand, the pericyclic reactions confirmed in biological systems provide valuable chemical information for the conception of new natural product synthesis. The elucidation of biosynthetic mechanisms and the frequently associated biomimetic synthetic investigations (simulation of synthetic steps of biosynthesis) can be planned rather precisely when pericyclic reactions are involved.

In the present review, some examples of typical and outstanding pericyclic reactions taking place in biological systems are discussed and classified on the basis of the type of the reaction mechanism. In addition to natural processes, some biomimetic syntheses are also included. In many of the selected examples, the 'formal' pericyclic mode of formation of structurally clarified (and often enantiomerically pure) natural products can be predicted by means of the *retrosynthetic analysis* principle.

2 Reactions in Biological Systems and Biomimetic Syntheses

2.1 Electrocyclic Reactions

The formation of vitamin D_3 (cholecalciferol) in the outer skin regions proceeds from 7-dehydrocholesterol (1), a ubiquitous companion of cholesterol, under the influence of sun light (UV light, $\lambda = 275$—310 nm).[7] Photochemically induced *conrotatory cycloreversion* in the steroid ring B gives rise to precalciferol D_3 (2) which is ultimately transformed into vitamin D_3 by way of a both thermally and orbital-symmetry allowed *[1,7]-sigmatropic H-shift* from C-19 to C-9 [(I) represents the thermodynamically more stable conformer in the crystal] (Figure 2a).[7] Experimental evidence for the entire reaction process has been obtained

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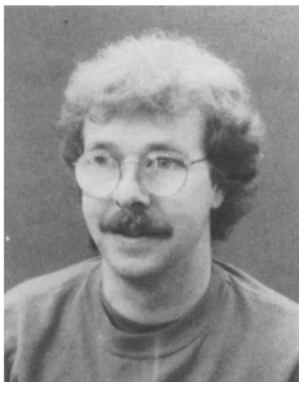


Ulf Pindur was born in Bad Darkau, Germany in 1943. He obtained his Diplom degree in pharmacy and food chemistry at the University of Marburg in 1971/1972. He earned his Dr. rer. nat. degree in synthetic organic chemistry in 1974 and his Habilitation in pharmaceutical chemistry in 1980 at the University of Marburg and was appointed Privat Dozent. From 1980 to 1985 he was Professor of Pharmaceutical Chemistry at the University of Würzburg and at the end of 1985 he was appointed to his present position, Professor of Pharmaceutical Chemistry at the University of Mainz where he has been head of the Institute for Pharmacy since 1990. His research interests include pericyclic reactions of heterocyclic systems to give natural products and biologically active compounds (DNA attacking molecules), applications of theoretical pharmaceutical chemistry for drug design, and analytical aspects of the mechanisms of colour reactions of drugs.

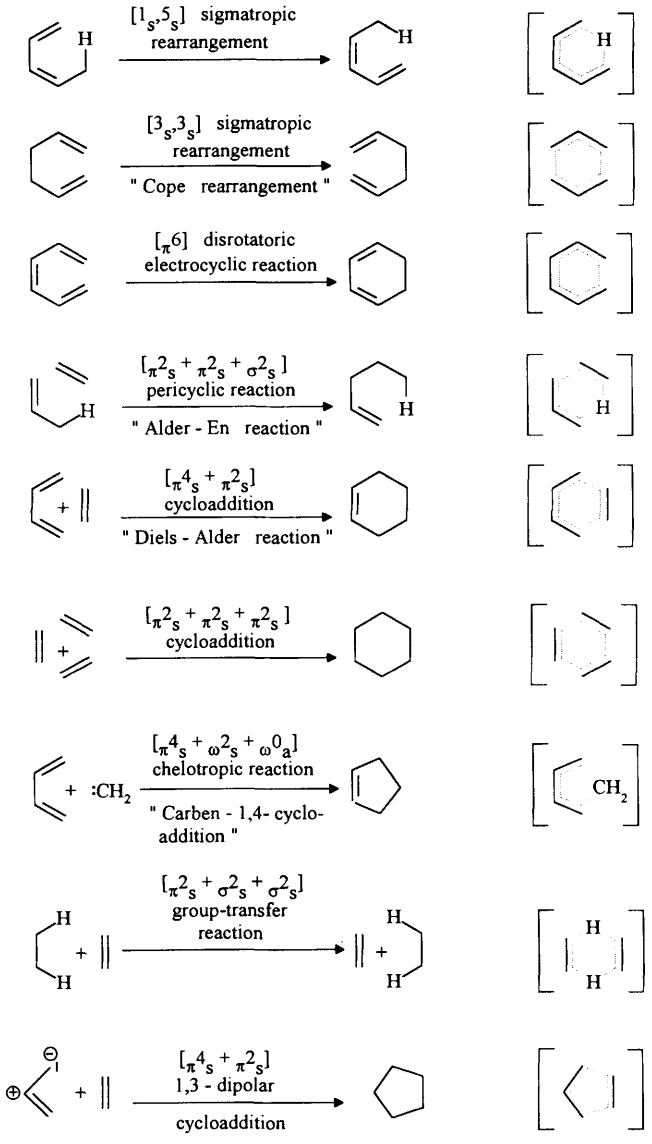


Figure 1 Examples of the simple basic structures in *hydrocarbon chemistry* for the usual, thermally allowed pericyclic reactions in which six electrons participate. The respective transition state structures are shown on the right in square brackets. The carbon atoms in the reaction partners may individually be exchanged for heteroatoms (*e.g.* O, S, N) (hetero-Diels–Alder reaction, hetero-Cope rearrangement, 1,3-dipolar cycloaddition with heterodipoles, *etc.*).

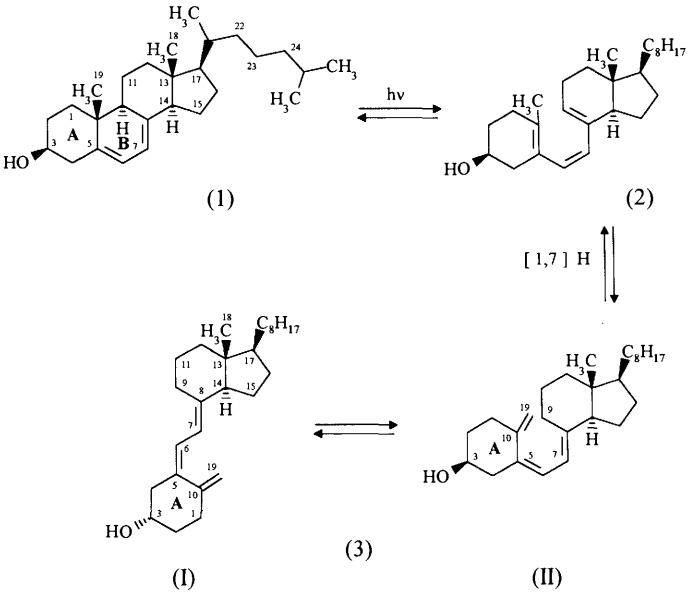


Figure 2 Photochemically initiated biosynthesis of vitamin D_3 (3) from 7-dehydrocholesterol (1). The technical production of vitamin D_2 from ergosterol is based upon an analogous (biomimetic) concept.

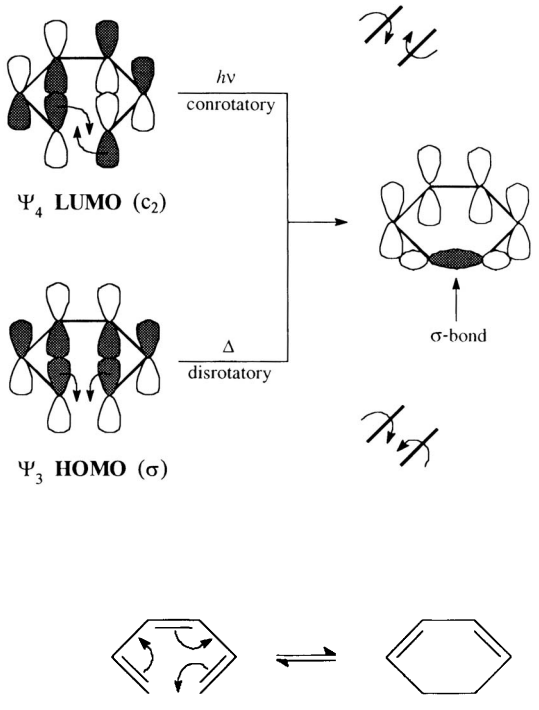


Figure 2b Qualitative frontier orbital model according to the Woodward–Hoffmann principle of retention of orbital symmetry for the 1,6-electrocyclization of 1,3,5-hexatriene to 1,3-cyclohexadiene. In the biosynthesis of vitamin D_3 the symmetry of the LUMO in ring B has a decisive role in the control of the reaction (orbital control).

through isotopic labelling, kinetic measurements, and determination of the quantum yield. In reality, however, more complex equilibrium systems are involved.[8] The frontier orbitals (HOMO and LUMO) of the parent structure 1,3,5-hexatriene [π system of (2)] according to the Woodward–Hoffmann rules are displayed qualitatively in Figure 2b. For the course of the cyclization, referred to the 1,3,5-hexatriene/1,3-cyclohexadiene equilibrium, the HOMO of the triene is relevant in the case of thermal excitation and the corresponding LUMO in the case of photochemical excitation (disrotatory or conrotatory process, respectively). In the case of the formation of vitamin D_3 in the organism, ring B of 7-dehydrocholesterol (1) corresponds to the 1,3-cyclohexadiene structure in Figure 2b.

The transformation of chorismine to prephenic acid [(4) → (5)] which occurs in plants and microorganisms in the synthesis of aromatic amino-acids (phenylalanine, tyrosine) is a stereospecific *Claisen rearrangement* of the hetero-Cope type, *i.e.* a *[3,3]-sigmatropic process* (see Figure 1).[9,10] This process is catalysed by the genuine enzyme chorismate mutase – a key enzyme of the shikimate pathway – through degradation of the transition state structure (I) (Figure 3).[10b] This reaction can also be accelerated by the action of so-called catalytic antibodies.[10a] Catalytic antibodies have increasingly gained importance in recent years as enzyme equivalents in organic and bioorganic chemistry.[19b] In order to obtain specific antibodies for the catalysis of the (4)/(5)-rearrangement, the compounds (6a, 6b) are used as haptenes for simulation (as mimeticum) of the Claisen transition state I.[10a]

The enediyne cytostatic/antibiotic agents constitute a class of new natural compounds of bacterial origin now undergoing rapid development. These DNA-cleaving natural products,

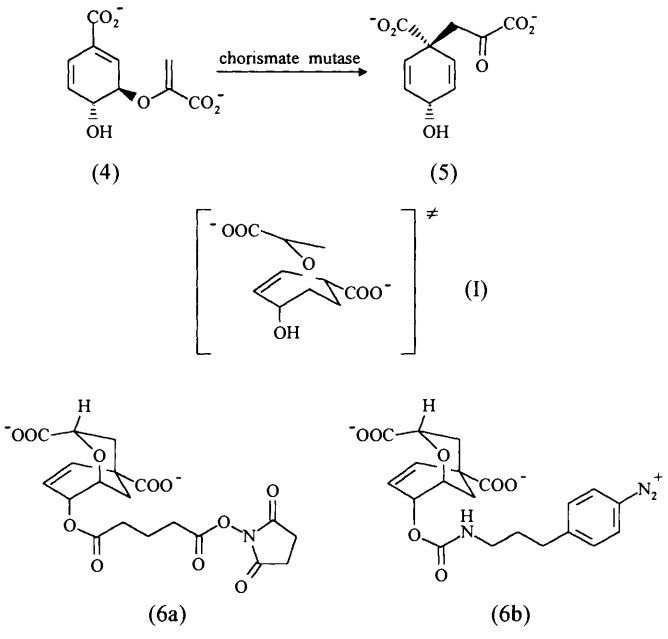


Figure 3 Enzyme-catalysed [3,3]-sigmatropic rearrangement of chorismine to prephenic acid (chorismate–prephenate rearrangement).[9,10a] The hapten molecules (6) are used to generate catalytic antibodies as an enzyme equivalent.[10a]

which combine an unusual molecular structure with practically unbelievable biological activities and fascinating modes of action, now occupy a central position as novel lead structures in medicinal chemistry.[11] Members of this substance groups are, for example, calicheamicins (Table 1) isolated from *Micromonospora echinospora* ssp. *calichensis*.[11a] They are active against Gram-positive and Gram-negative bacteria. Most important, however, is their extraordinary activity against P338 mouse tumour, leukaemia L1210 cell lines, and those of neoplasms such as colon 26 and B-16 melanoma at optimal doses of 0.15 to 5 μg/kg body weight. The biological activities are attributed to sequence-specific DNA damage; thus, for example, calicheamicin γ_1^I (7f) binds specifically to TCCT, CTCT, and TTTT sequences in the minor groove of B-DNA. Here, the oligosaccharide part, essential for the molecular recognition, is oriented towards the 3′ end of the DNA fragment (Figures 4 and 5). It is currently assumed that the oligosaccharide unit constitutes the

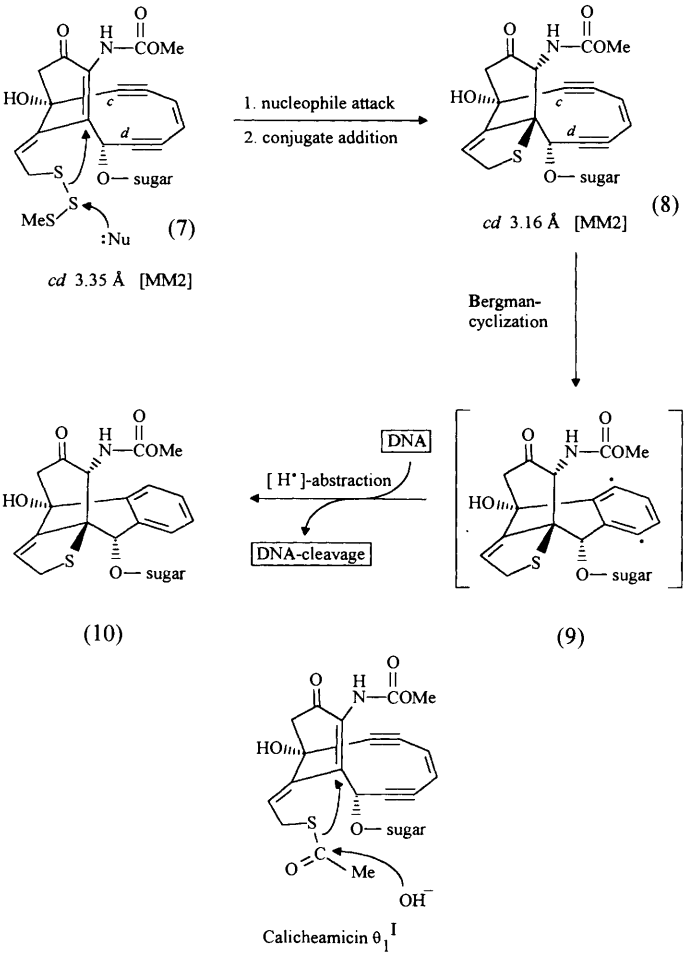
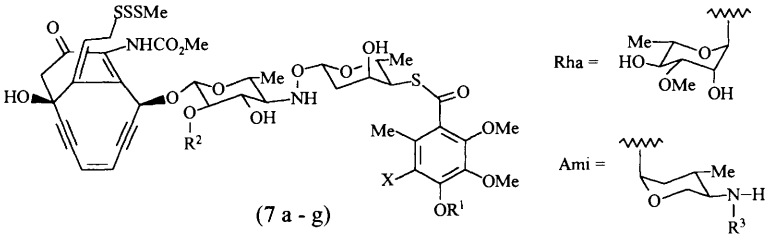


Figure 4 Mechanism for the cleavage of DNA by calicheamicin γ_1^I (7f). According to MM2 force-field calculations,[11a] the distance *dc* in (7f) is shortened by 0.19 Å on transformation to (8).

Table 1 The calicheamicin family



(7a—g)	X	R^1	R^2	R^3
(a) Calicheamicin β_1^{Br}	Br	Rha	Ami	$CHMe_2$
(b) Calicheamicin γ_1^{Br}	Br	Rha	Ami	Et
(c) Calicheamicin α_2^I	I	H	Ami	Et
(d) Calicheamicin α_3^I	I	Rha	H	—
(e) Calicheamicin β_1^I	I	Rha	Ami	$CHMe_2$
(f) Calicheamicin γ_1^I	I	Rha	Ami	Et
(g) Calicheamicin δ_1^I	I	Rha	Ami	Me

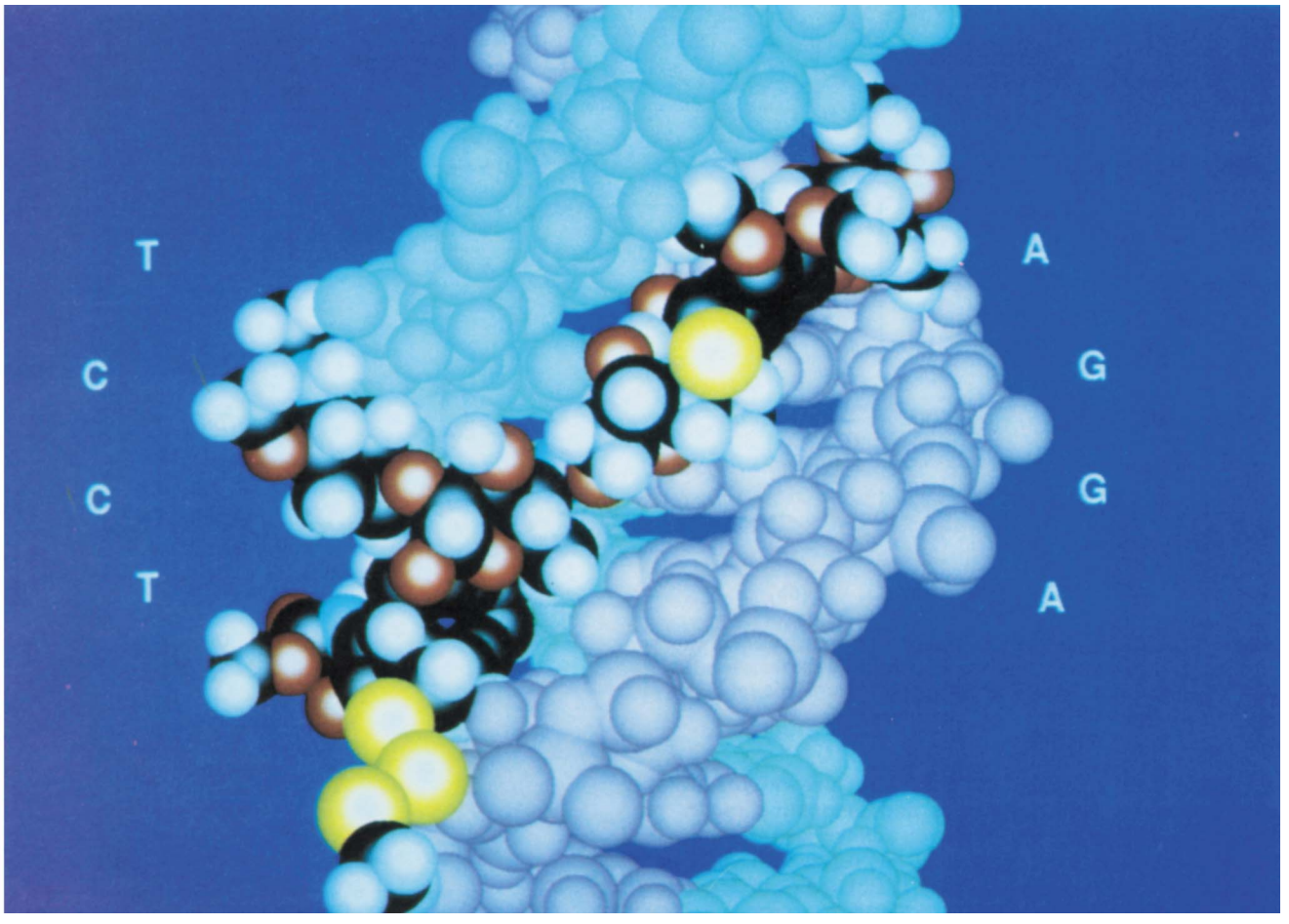


Figure 5 Computer-generated molecular model showing the minor groove binding of calicheamicin Θ_1^I (11) to double-stranded DNA along the TCCT site [11d]
(Reproduced with permission from *Chemistry & Biology* [11d])

most important part of the molecule for recognition and binding. Then a nucleophile (*e.g.* glutathione), possibly activated intramolecularly by a basic nitrogen atom, attacks the central sulfur atom of the unusual trisulfide linkage with formation of a thiolate (bioreduction process, see Figure 4). On account of the geometry of the allylic double bond, the thiolate moiety is in an ideal position to attack intramolecularly the α,β-unsaturated ketone incorporated in the neighbouring six-membered ring to furnish compound (8). This reaction, in which the sp^2 carbon atom at the site of attack changes its hydridization to sp^3, is an indispensable prerequisite for the subsequent Bergman cyclization (*6-electron electrocyclization* to a 1,4-sigma diradical) to furnish the benzoid-type, highly strained diradical (9) (= cycloaromatization *via* a benzoid 1,4-diradical). The reactive diradical is then in the correct position to extract two hydrogen radicals from the DNA, one from the C5′ position of desoxycytidine (C) and the other from a ribose of the opposite strand. The resulting DNA radicals then react with molecular oxygen *via* cleavage of the double strand.[11a]

In the mean time, several synthetic studies on the molecular design of calicheamicin as a lead structure with the aim of developing highly selective anti-tumour agents have been reported.[11a–11c] One result of this work was the design of calicheamicin Θ_1^I (11) based on the known mechanism of the biological action of calicheamicin γ_1^I (7f).[11b] In place of the trisulfide unit of the original, this novel derivative possesses a thioacetyl group as the reactive, electrophilic centre. Calicheamicin Θ_1^I (11) also reacts differently to its natural analogue: it is activated under neutral or mild basic conditions, *e.g.*, by hydroxide ions. The 1,4-phenylene diradicals derived from (11) also induce cleavage of the double-stranded B-DNA effectively and selectively at TCCT, CTCT, and TTTT sequences (concentration for biological activity: $< 10^{-9}$ M).

2.2 Diels–Alder Reactions

In the past few years there has been an explosion of reports about numerous inter- and intramolecular Diels–Alder reactions (or formal Diels–Alder reactions) occurring in plants and microorganisms.[12] Although definitive and experimentally confirmed evidence on the actual mechanisms is not available in all cases, highly feasible results, especially in the field of phytotoxins, have been presented on the basis of biosynthetic experiments (feeding experiments with cell cultures, use of labelled compounds, selective treatment with enzymes, and biomimetic syntheses). In some cases, in particular those involving enantiomerically pure target molecules, an enzymatic catalysis of the $[_4\pi_s + _2\pi_s]$-cycloaddition by an apparently genuinely existing 'Diels–Alderase' has been discussed.[13]

The biosyntheses of alkaloids of the *Iboga* and *Aspidosperma* types [*e.g.* catharanthine (14) or tabersonine (15)] are assumed to start from stemmadenine (12) (Figure 6). Heterolytic ring opening with elimination of water then leads to the postulated dehydrosecodine (13) which can undergo cyclization from two different orientations to furnish ultimately catharanthine (14) or tabersonine (15), respectively (Figure 6).[14–16] An isomeric dehydrosecodine of the type (13) has also been proposed as the biogenetic precursor of the *Aspidosperma* alkaloid pseudotabersonine.[15] Several biomimetic syntheses of *Iboga* and *Aspidosperma* alkaloids on the basis of this intramolecular enamine–acrylate reaction (Figure 6) have been described in detail.[16–18] The more stable dihydropyridone (16), an oxosecodine deriva-

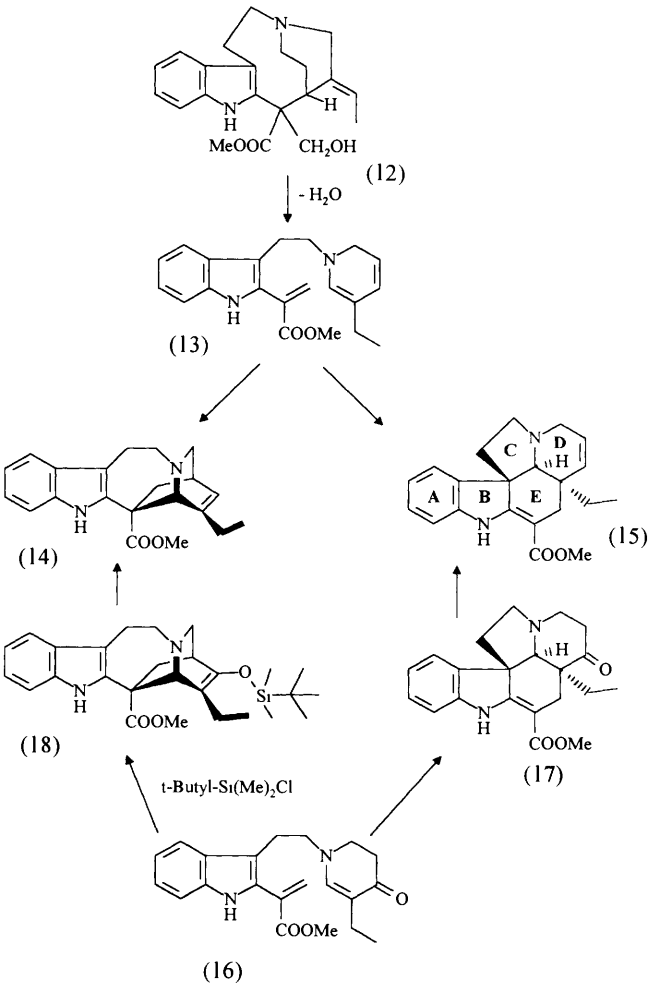


Figure 6 Possible biosyntheses of *Iboga* and *Aspidosperma* alkaloids and biomimetic synthetic strategies *via* 15-oxovincadifformine (17) and the 15-siloxycatharanthine (18) [16]

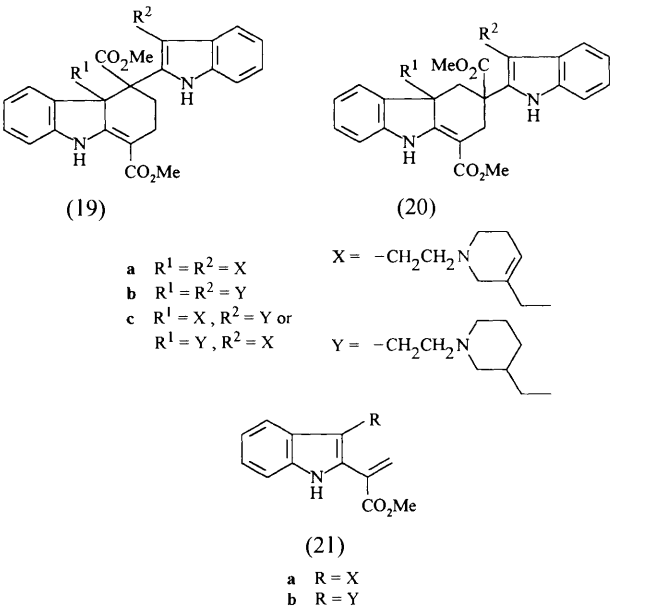
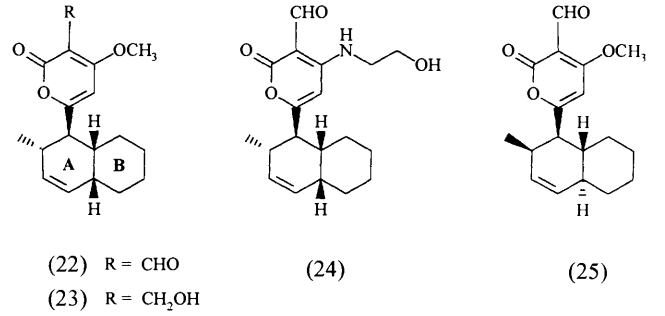


Figure 7 The dimeric indole alkaloids presecamines (19) and (20) and their putative biogenetic precursors (21a) and (21b)



tive, was used in some of the regio-controlled cycloadditions as an equivalent for dehydrosecodine [16]

By means of a related reaction, it should be possible to synthesize the dimeric indole alkaloids presecamines (19) and (20), isolated from the leaves or roots of *Rhazya* species, from Diels–Alder reactions of the secodines (21a) and (21b) which also possess the 2-vinylindole π-system (Figure 7) [19]

Parasitic lower fungi such as *Alternaria solani* (Fungi imperfecti) growing on Solanaceae species produce the solanopyrones A (22), B (23), C (24), and D (25) originating from the polyketide metabolism (Figure 8) [20 21] These constituent substances could be responsible for the hazardous potato disease known as potato blight in North America Biomimetic investigations[20 21] with the appropriate diene-dienophile precursor (26) (Figure 8) strongly support the genuine production of these analogues of the naturally occurring hydroxymethylglutaryl-coenzyme A reductase inhibitors (*e g* lovastatin from *Aspergillus terreus*) Since optically pure compounds are formed, an enzymatic catalysis has been discussed [12]

Hypotensive chalcones and the dimerization product kuwanone J have been isolated from the bark of the mulberry tree *Morus alba* L [22] Biogenetic experiments with *Morus alba* cell cultures involving feeding with the *O*-methylated genuine chalcone (29) revealed that the formation of the di-*O*-methylated kuwanone J (32) proceeds *via* an enzyme-catalysed, formal Diels–Alder reaction between the enone unit in (30) and the 2-methyl-1,3-butadiene component in the dehydro derivative (31) (Figure 9) [22]

In addition to a series of sesquiterpene lactones, several novel

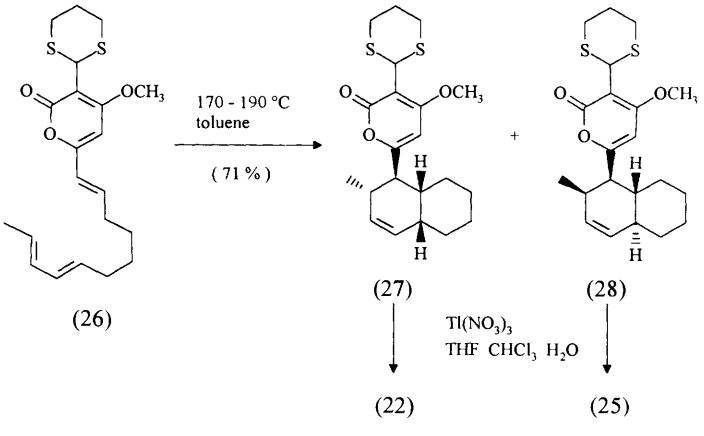


Figure 8 Phytotoxin lactones, (22)—(25), produced by the secondary metabolism of *Alternaria solani* and a biomimetic synthesis concept for the total synthesis of (22) and (25) involving an intramolecular Diels Alder reaction of (26) which leads primarily to the optically pure diastereomers (27) and (28)

bis-sesquiterpene lactones (33)—(37), have been isolated from *Helenium autumnale* L and their structures elucidated (Figure 10) [23 25] From this series, for example, the natural product (33) can be considered as a formal [4 + 2]-cycloadduct of isoalantolactone (38) and zingiberene (39) where the semicyclic double bond of the α-methylene-γ-butyrolactone acts as the dienophile

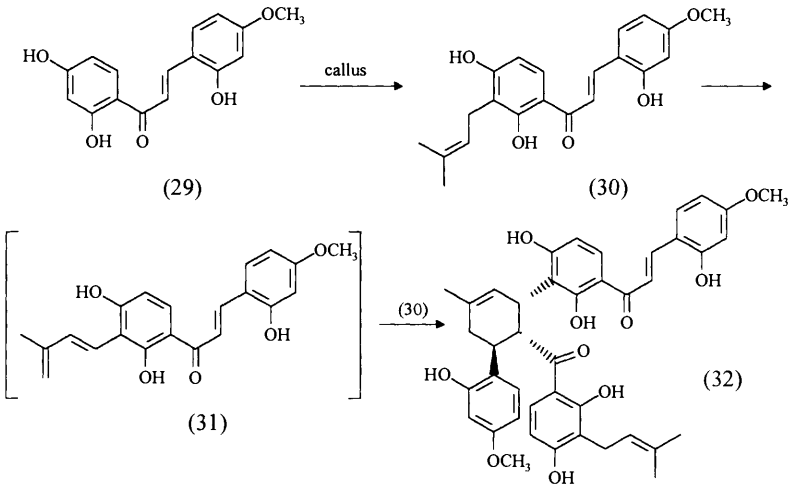


Figure 9 Biogenesis of the dimerization product (32) by asymmetrical Diels–Alder reaction of (31) and (30) in cell cultures of *Morus alba* L [22]

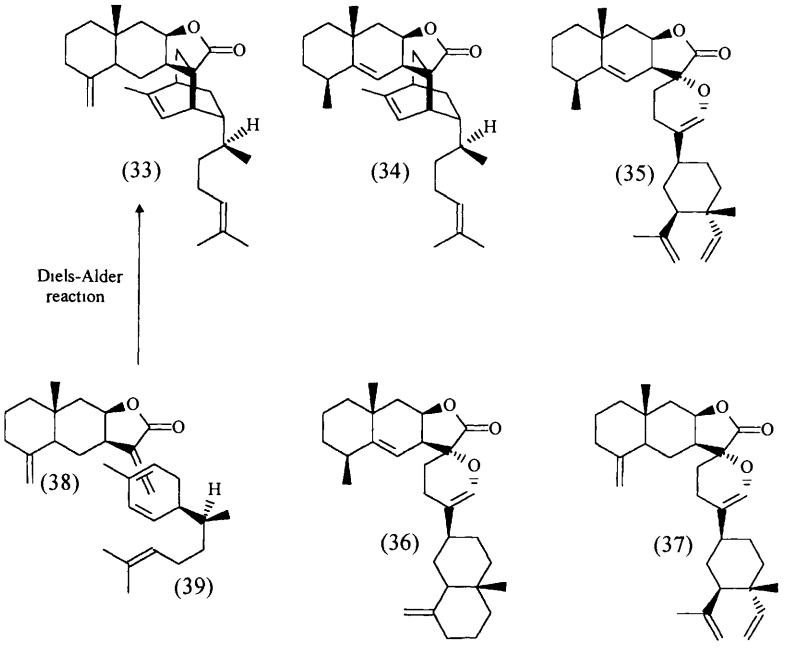


Figure 10 Novel bis-sesquiterpene lactones from *Helenium autumnale* L and their formal biosynthesis *via* a Diels–Alder reaction [23 25]

component and the cyclohexadiene ring of zingiberene (39) as the diene component For this transformation, a thermal Diels–Alder reaction has also been realized on a preparative scale [24] The biosynthetic key step to (35)—(37) can be constructed analogously, but in these cases a formal hetero-Diels–Alder reaction could lead to the target compounds (35)—(37)

The phenylphenalenone derivative lachananthocarpone (41a) is the major pigment found in *Lachnanthes tinctoria* Ell (Haemodoraceae) (Figure 11) [26] The biosynthetic pathway to (41a) and its analogues (41b) and (41c) was proposed from the results of feeding the plants with [2-^{14}C]tyrosine and [1-^{13}C]phenylalanine, respectively The formation of a diarylheptanoid (40) as diene–dienophile system and its subsequent Diels–Alder reaction should represent the basic principle of the biosynthetic key step (Figure 11)

Furthermore, in addition to providing a new and presumably general synthetic approach to 2-hydroxyphenalenones, the synthesis of (41a) from (42) (Figure 12) reveals that the 9-phenylphenalenone system present in the pigments of plants of the Haemodoraceae family can indeed be constructed from suitably substituted 1,7-diarylheptanoid *ortho*-quinones In this respect, the synthesis may be considered as further substantiation of the hypothesis shown in Figure 11 [26]

Heliocide H_2 (48), an insecticidal sesterterpenoid, was isolated from cotton (*Gossypium hirsutum* L) [27] On the basis of *in vitro* Diels–Alder synthetic studies at room temperature, its biogenetic formation is presumed to be the result of a stereospecific [4 + 2] process between hemigossypolone (46) and myrcene (47) (Figure 13), probably *via* a highly ordered *endo*-transition state Myrcene will encounter less steric interaction by approaching the quinone ring in such a way that the myrcene alkenyl side-chain and the quinone isopropyl group are as far apart as possible This would result in the construction of the side-chain at C-18

Many further pericyclic reactions certainly still remain to be detected in biological processes and a particular challenge will be the isolation and characterization of the responsible enzymes – leading, we predict, to a renewed boom in preparative, pericyclic synthesis of active principles according to the concept of 'enzymatic organic synthesis'

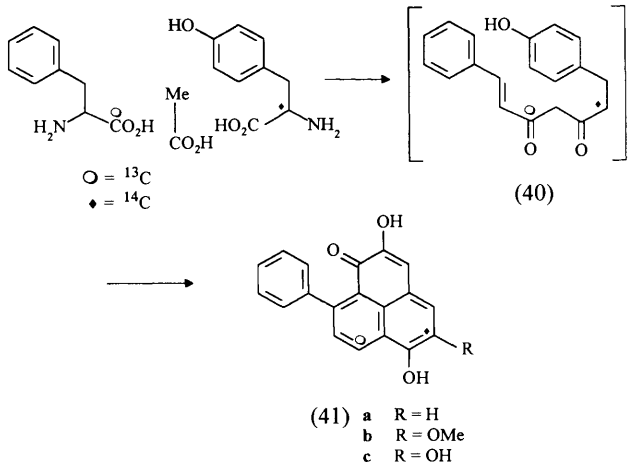


Figure 11 Biogenetic pathway to naturally occurring phenylphenalenones as plant pigments *via* an intramolecular Diels–Alder step [26]

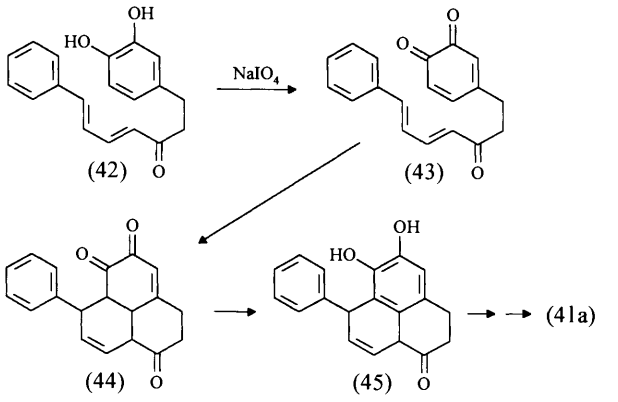


Figure 12 Biomimetic synthesis of (41a) from an appropriate diene–dienophile precursor (43) [26]

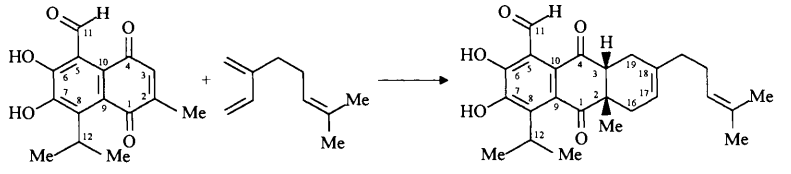


Figure 13 Possible biogenetic process leading to heliocide H_2 (48) *via* Diels–Alder reactions [27]

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