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The Chemistry of Natural Diarylheptanoids

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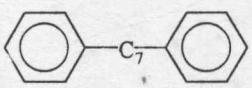
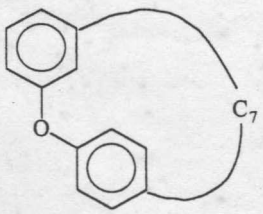
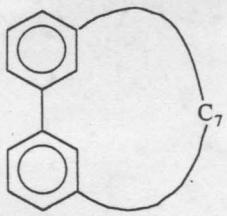
1. Introduction
2. Phytochemistry of diarylheptanoids
3. Biosynthesis of diarylheptanoids
4. Biological activity of diarylheptanoids
5. Synthesis of diarylheptanoids

1. INTRODUCTION

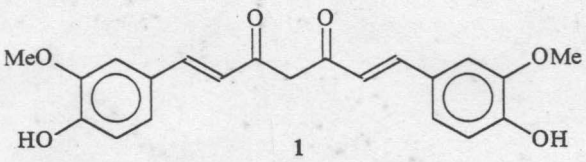
Diarylheptanoids constitute a distinct group of natural plant metabolites characterized by two aromatic rings linked by a linear seven-carbon aliphatic chain. They may be divided into two subgroups, i.e. open chain and macrocyclic diarylheptanoids. In the latter the aromatic rings are connected to form a diarylether or a biaryl moiety.







Curcumin (1), yellow dye of *Curcuma tinctoria* and other *Curcuma* species was first mentioned as early as in 1808 by Trommsdorff and isolated in 1815 by Vogel and Pelletier (1) was not only the first diarylheptanoid ever to be discovered, but also among the first natural organic compounds prepared in a more or less pure state.



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The constitution of this relatively simple and broadly used compound was established surprisingly late by Lampe and Milobedzka (2), first in 1910 by degradation followed in 1913 by a synthesis (3,4). Curcumin remained the only representative of the group as long as until 1964. In the following 30 years, however, about 70 linear and 35 macrocylic diarylheptanoids were isolated. In the present review we are dicussing their chemistry, phytochemistry, biosynthesis, biological activity, and synthesis.

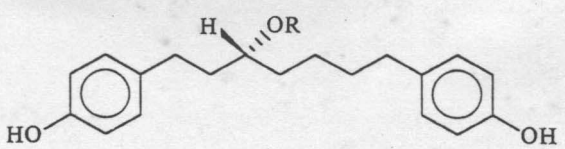
2. PHYTOCHEMISTRY OF DIARYLHEPTANOIDS

2.1 Open chain diarylheptanoids

Open chain diarylheptanoids were isolated from *Acer nicoense (Aceraceae)*, from *Alnus* and *Betula* species (*Betulaceae),* from *Alpinia, Curcuma* and *Zingiber* species belonging to the family of gingers (*Zingiberaceae*) and finally from certain *Centrolobium* species (*Leguminosae*). Individual compounds will be classified according to the plant families in which they occur.

2.1.1. *Aceraceae*

From the stem bark of *Acer nicoense* Maxim, indigeneous in Japan, Nagai and his coworkers isolated two new glycosides of already known (-)-centrolobol (2) (5) *i.e.* aceroside VII (3) and aceroside VII (4) (6)*.



2 R = H
3 R = β-D-Glcp
4 R = β-D-Apif-(1→6)-β-D-Glcp

* Glcp = glucopyranosyl, Apif = apiofuranosyl, Araf = arabofuranosyl

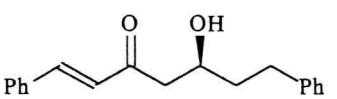
Originally an *S* configuration has been assigned to (-)-centrolobol by Albuquerque *et al.* (5), but NMR studies connected with the isolation of the glycosides indicated an *R* configuration for the aglycon (6).

2.1.2 *Betulaceae*

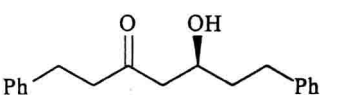
In the family of *Betulaceae* open chain diaryl-heptanoids were found in *Alnus* and *Betula* species.

2.1.2.1. *Alnus* species

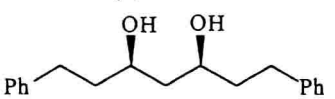
Two optically active compounds (**5** and **6**), for which the fancy names yashabushiketol and dihydro-yashabushiketol were coined, were isolated by Asakawa *et al.* from *A. firma* (7,8) and *A. sieboldiana* species (9), while from the former source Urarova and her coworkers isolated a levorotatory saturated diol **7** (10). Absolute configuration of (-)-**7** was established to be *S,S* by Asakawa *et al.* (11) by correlation with (*S*)-**6**. In *A. firma* Suga *et al.* discovered a dienone (**8**) (12) which could not be derived from diarylheptanoids isolated earlier.



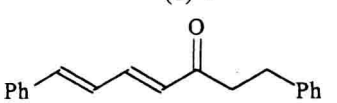
(*S*)-**5**



(*S*)-**6**



(*S,S*)-**7**



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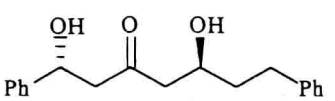
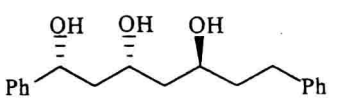
In the flowers of *A. sieboldiana* Asakawa *et al.* found a series of diols, triols, and ketodiols (13), namely the epimeric diols yashabushidiol A [(*R,S*)-**7**] and B [(*R,R*)-**7**], the epimeric ketodiols yashabushiketodiol A [(1*R,*5*S*)-**9**] and B [(1*S*,5*S*)-**9**)], as well as yashabushitriol (**10**). Configuration of all of them has been established by NMR spectroscopy and correlation with (*S*)-**6**.



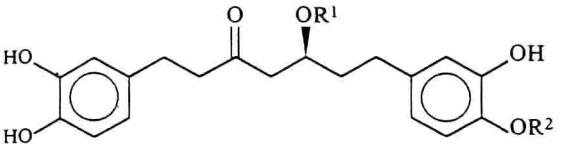
(1*R*,5*S*)-**9**



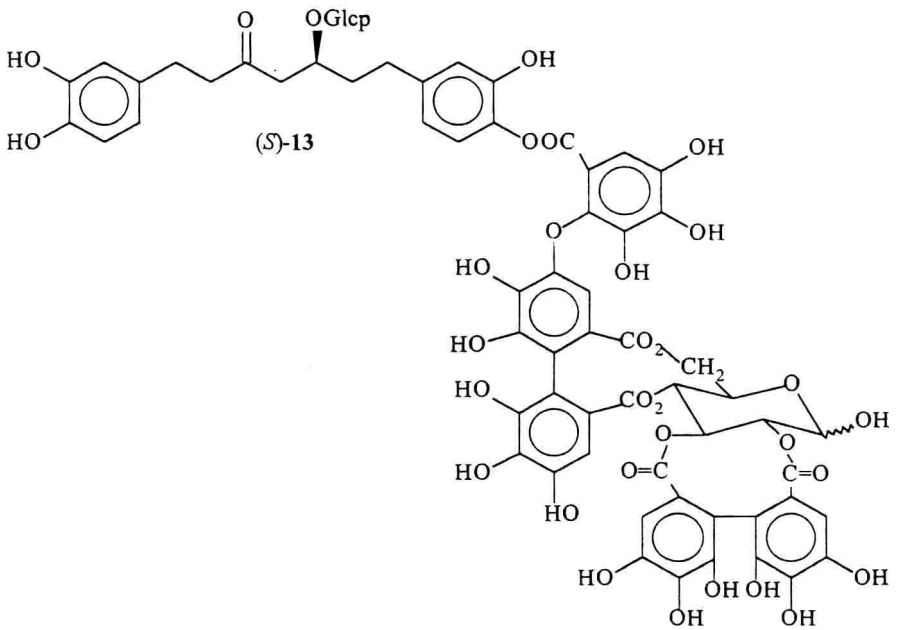
(1*R*,2*R*,5*S*)-**10**

Oregonin, an optically active ketol [(*S*)-**11**) is the diarylheptanoid component of several *Alnus* species and was first isolated as its xyloside in 1974 from *A. rubra* (14), but the absolute configuration of the aglycon remained unknown until it was also isolated from *A.*

serrulatoides and the problem settled by an X-ray analysis (15). Recently Lee and his coworkers isolated the glucoside of oregonin (**12**) (16) from *A. hirsuta* along with its interesting conjugate with ellagitannine (**13**, see on next page).

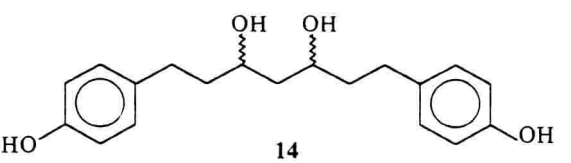


	R^1	R^2
(*S*)-**11**	H	H
(*S*)-**12**	β-D-Glcp	H



(*S*)-**13**

In a study on the colouring matters of *Alnus* species Nomura and his coworkers isolated a series of new open chain diarylheptanoids from *A. japonica* (17), such as hannokinol (**14**) (18), hannokinin (**15**) (19) both of undetermined stereochemistry, and the enone **16**, a dehydration product of **15**.



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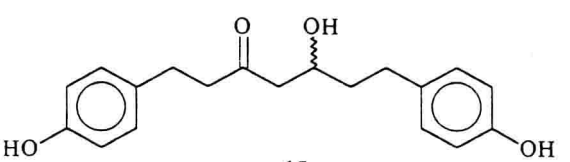

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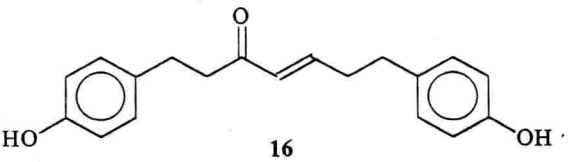

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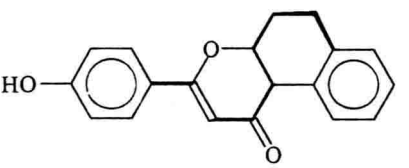
Whereas **14** and **15** could also be isolated from *A. hirsuta* and from *Betula platyphylla* (20), the occurrence of the enone in these plants was not reported and therefore **16** may be an artefact formed during isolation.

The dextrorotatory antipode of the widely distributed (-)-centrolobol (**2**) was first discovered by Sasaya in *A. hirsuta* (21) in the company of an interesting tetrahydronaphthopyrone derivative (**17**), being in evident biogenetic relationship to open chain diarylheptanoids.



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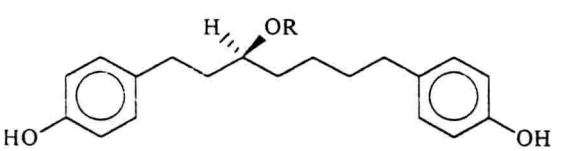
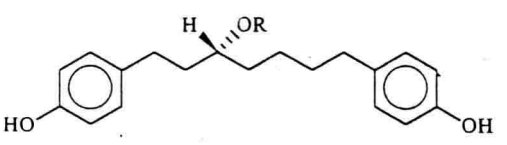
2.1.2.2. *Betula* species

The first diarylheptanoid from *B. platyphylla*, the glucoside platyphylloside (**18**) was isolated by M. Terazawa *et al.* (22). Configuration of the aglycon, *i.e.* platyphyllone (**15**) was determined by NMR studies by Ohta and his coworkers (23).



(*S*)-**18** R = β-D-Glcp
(*S*)-**19** R = β-D-Apif-(1→6)-β-D-Glcp
(*S*)-**20** R = β-D-Apif-(1→2)-β-D-Glcp

From *B. pendula* Šmite *et al.* isolated a two new apiose containing glycosides of (*S*)-**15,** namely **19** and **20** (24) along with two known (**3** and **4**) and one new glycosides (**21**) of (*R*)-centrolobol (**2**) (6).

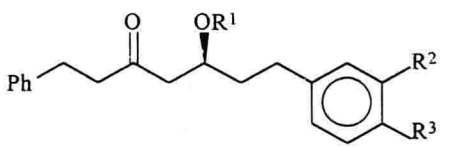


(*R*)-**21** R = β-D-Apif(1→2)-[β-D-Apif-(1→6)]-β-D-Glcp

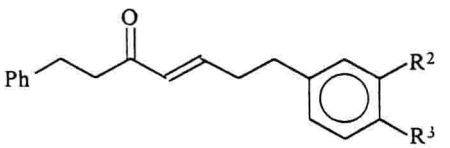
2.2.2. *Zingiberaceae*

2.2.2.1. *Alpinia* species

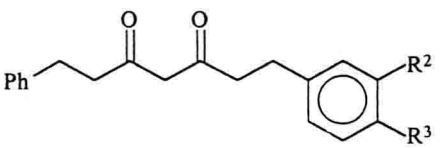
Examination of *A. officinarum* by Itokawa and his group provided besides the known compound **6** (8) and the ketol **22** (25) two new enones, **28** and **29** (26). Circular dichroism studies revealed the interesting fact that, in contrast to the known components of *Alnus firma* and *A. sieboldiana*, which contained (*S*)-**6** and (*S*)-**22**, in *Alpinia officinarum* the same alcohols were present as the *R* enantiomers. On further investigation the same plant also yielded a total of eight new achiral or racemic diarylheptanoids: **23**, **24**, **31** (27), **25**, **26**, and **30**, (28), **33** (29), **27** and **32** (30). Since the highly susceptible β-hydroxyketones can readily undergo dehydration and subsequent addition of methanol, the enones **28**, **29**, and **30**, as well as the β-methoxyketones **23**, **25**, and **26** may be artefacts. This assumption is also supported by the racemic nature of **23**, **25**, and **26**.



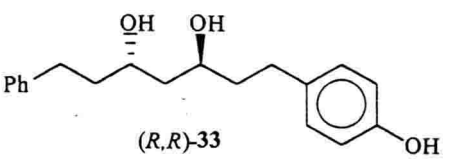
	R1	R2	R3
22	H	OMe	OH
23	Me	OMe	OH
24	H	H	OH
25	Me	H	H
26	Me	H	OH
27	H	OH	OH



	R1	R2
28	H	H
29	OMe	OH
30	H	OH

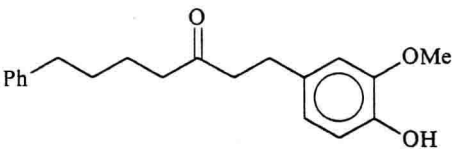


	R1	R2
31	OMe	OH
32	OMe	H



(*R*,*R*)-**33**

Itokawa and his coworkers isolated from *A. oxyphylla* the closely related ketones yakuchinone A and B (**34** and **35**) (31, 32), while *A. katsumadai* yielded, apart from the *Alnus* constituents **7** and **8**, four new compounds (**36-39**) (33).



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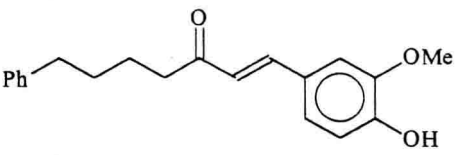

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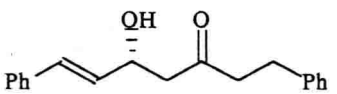

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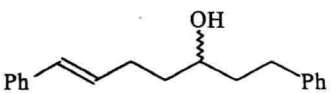

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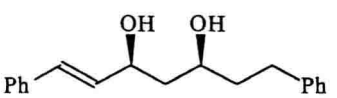

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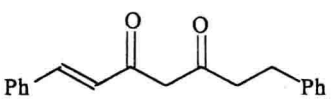

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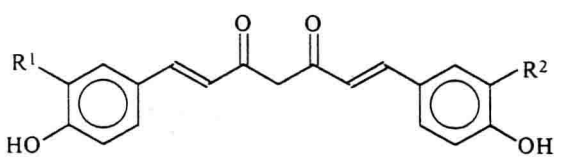
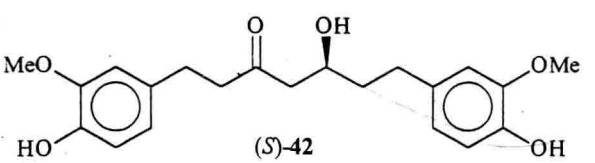
2.2.2.2 *Curcuma* species

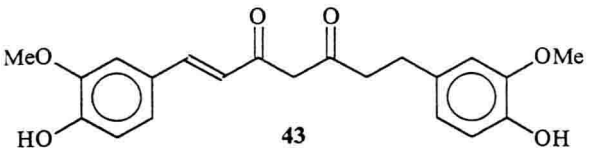
As we have mentioned in the introduction the first diarylheptanoid, curcumin (**1**) was isolated in 1815 by Vogel and Pelletier from *C. longa* (1). Following the elucidation of its constitution and its synthesis (2-4) it was also submitted to X-ray analysis (34). Prompted by its colouring properties, its extended use in spices and later also by its promising biological actitvities *C. longa* extracts were the subject of several studies. Thus Srivanasan reported in 1953 the isolation of two minor components, demethoxycurcumin (**40**) and bis-demethoxy-curcumin (**41**) (35), their constitution was determined by Whiting *et al.* (36). The first saturated curcumin derivative, hexahydrocurcumin *(S)*-(**42**), was discovered by Murata and his coworkers (37). Its enantiomer was later found in *Alpinia officinarum* and based on its CD spectrum an *R* configuration was assigned to this compound. Structural variation in the curcumin family was enriched by the discovery of dihydrocurcumin (**43**) by Ravindranath (38), and by Kiuchi, who isolated the first cyclic derivative, cyclocurcumin (**44**) (39).



	R^1	R^2
40	H	OMe
41	H	H



(S)-**42**



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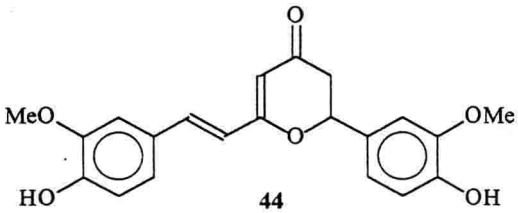

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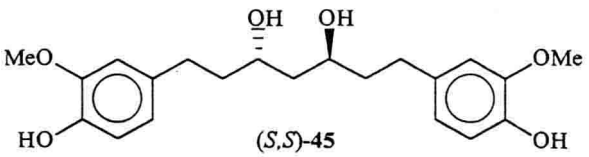
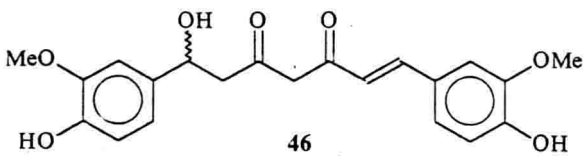
Curcumin, as well as compounds **40-43** were also isolated from *C. xanthorrhiza* by Uehara *et al.*(29), who obtained from this source also two new compounds, the optically active diol (*S,S*)-**45** and the racemic diketoalcohol **46**. While formation of **45** can be envisaged by reduction of hexahydrocurcumin, racemic **46** might have been the result of addition of water onto the double bond of curcumin. Masuda and his coworkers reported in 1992 the isolation of an unsymmetrical curcumin derivative, 5-methoxycurcumin (**47**) from *C. xanthorrhiza* (40).



(*S,S*)-**45**



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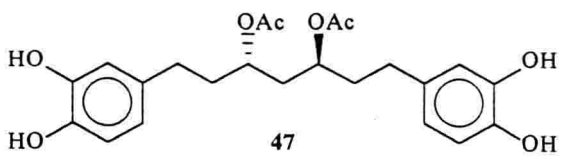
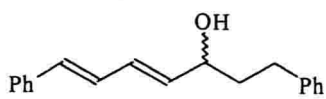


47

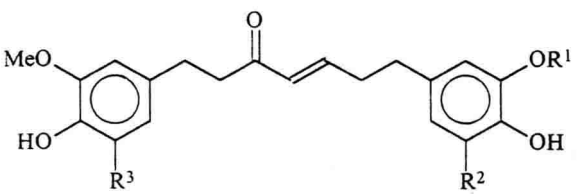
It is interesting that compound **8** isolated previously from *Alnus firma* (Betulaceae) and its reduced from (**48**) are also present in *C. xanthorrhiza* (*Zingiberaceae*) (41).



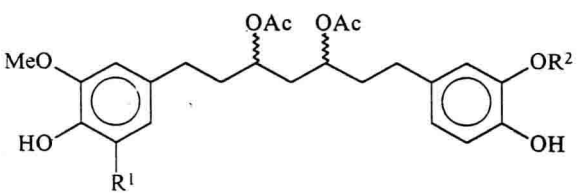
(**48**)

2.2.2.3. Zingiber species

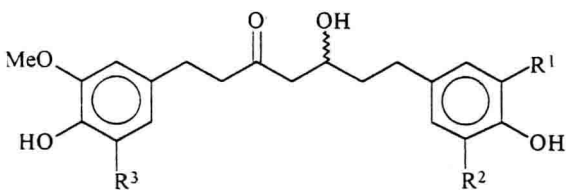
Diarylheptanoids from *Zinziber officinale*, the common ginger, the gingerones A, B, and C (**49-51**), as well as isogingerone B (**52**) were isolated by Endo and his coworkers in 1990 (42). Later Kikuzaki *et al.* isolated additional components, such as **53**, the demethyl derivative of **49**, further (*S*)-hexahydrocurcumin (**42**), from which **49** can be derived by dehydration (43). It is noteworthy that apart from the diastereomeric diols (*S,S*)-**45** and (*R,S*)-**45**, arising from the reduction of **42**, the corresponding acetates, **54** and **55**, could also be isolated (44). The same authors later described two more diarylheptanoid acetates (**56, 60**) and a series of racemic β-hydroxyketones (**57-59**) (45). Considering that β-hydroxyketones readily eliminate water, it cannot be excluded that the enones **49-53** are artefacts.



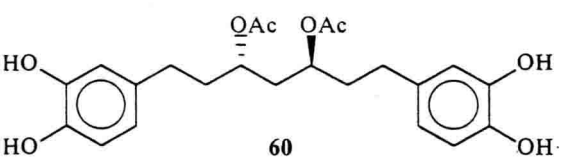
	R^1	R^2	R^3
49	OMe	H	H
50	OMe	OMe	H
51	H	H	
52	OMe	H	OMe
53	OH	H	H



	R^1	R^2
54	H	H
meso-**55**	H	Me
56	OMe	H



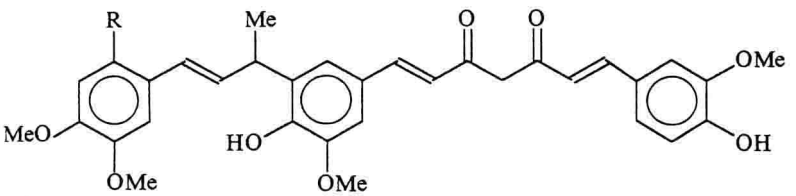
	R^1	R^2	R^3
57	H	H	H
58	OMe	H	OMe
59	H	OMe	OMe



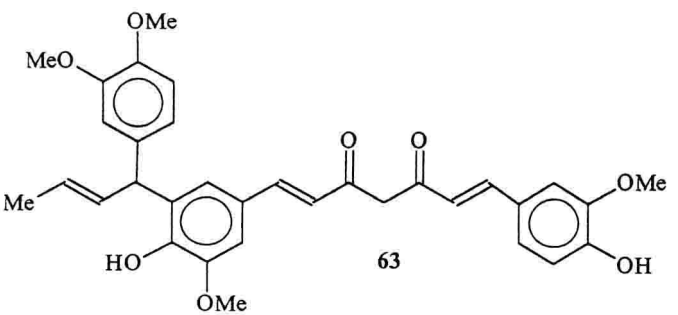
60

Recently another species of the same family *Z. cassumar* was investigated by Masuda *et al.* who isolated from this plant three novel diarylheptanoids, the cassumins A, B, and C (**61-63**) (46), in which the diarylheptanoid sceleton was extended by an arylbutenyl unit.

Three more compounds of presumably similar biogenetic origin, cassumunarin A, B, and C (**64-66**) were found in the same plant by Jitoe and his associates (46).



61 R = H
62 R = OMe



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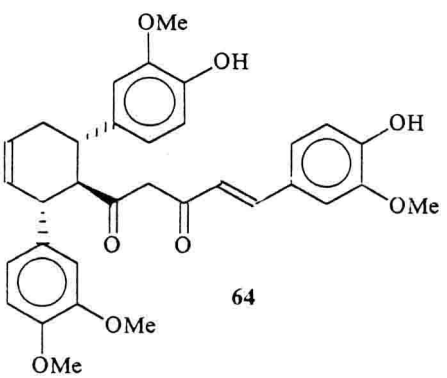
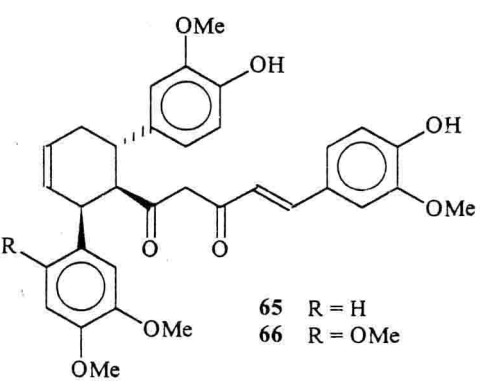


64



65 R = H
66 R = OMe

2.2.3. Leguminosae

Among leguminous *Centrolobium* species diarylheptanoids were first isolated from *C. robustum* in 1964 (5). It contains (-)-(*R*)-centrolobol (**2**), found later in several other plants too (*Acer nicoense* (*Aceraceae*) (6), *Betula pendula* (*Betulaceae*) (24)) as well as two cyclic components, (3*R*,7*S*)-centrolobin (**67**) and (3*R*,7*S*)-de-*O*-methylcentrolobin (**68**) (47). First

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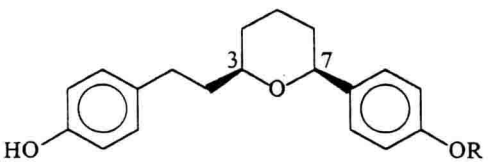
an *S* configuration was assigned to (-)-**2** (5), but this was corrected later to *R* (6). Stereochemistry of the cyclic components **67** and **68** were cleared as late as in 1984 by Jurd and his coworkers (48). A systematic study by Gottlieb *et al.* established the surprising fact that, in contrast to *C. robustum*, *C. paraense* and *C. sclerophyllum* contains centrolobol and de-*O*-methylcentrolobin in the antipodal form [(*S*)-**2**, (3*S*,7*R*)-**68**] (49), while (3*S*,7*R*)-centrolobin (**67**) was only identified in *C. tomentosum*.



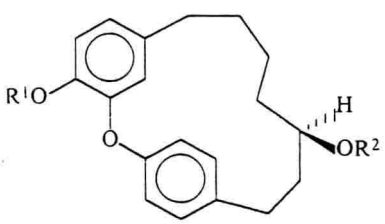
67 R = H
68 R = Me

2.2. Macrocyclic diarylheptanoids

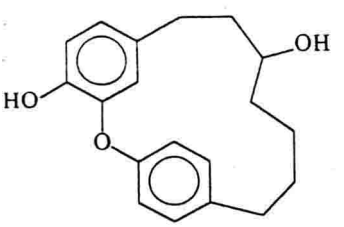
Macrocyclic diarylheptanoids can be derived from their open chain congeners by oxidative phenol coupling resulting in macrocyclic biaryls or biaryl ethers. Usually they were named after the plant source and can be conveniently classified according to the plant families in which they occur.

2.2.1. *Aceraceae*

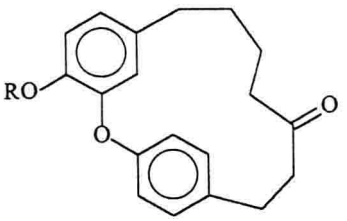
From *Acer nicoense*, a maple indigeneous in Japana series of macrocyclic diarylethers, mainly in form of their glycosides were isolated predominantly by Inoue, Nagai and his coworkers. Thus acerogenin A (**72**) (50) is the common aglycon of acerosides I (**69**) (50), III (**70**) (51), and VI (**71**) (51). On further study of *A. nicoense* Kubo and his group discovered a second aglycon, acerogenin B (**73**) (52) but none of its glycosides. Aceroside IV (**74**) and its aglycon acerogenin C (**75**) (53), as well as aceroside V (**76**) and its aglycon acerogenin D (**77**) isolated 10 years later, are also diarylether type macrocyclic diarylheptanoids.



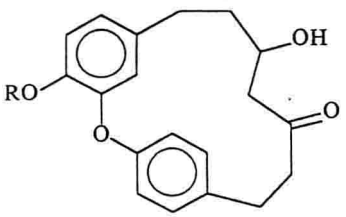
	R^1	R^2
69	β-D-Glcp	H
70	H	β-D-Apif-(1→6)-β-D-Glcp
71	H	β-D-Glcp
72	H	H

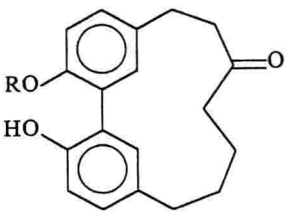


73



74 R = β-D-Glcp
75 R = H





76 R = β-D-Glcp
77 R = H

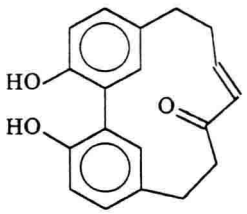
78 R = β-D-Glcp
79 R.= H

From *Acer nicoense* the first biaryl type macrocycle, aceroside XI (**78**) and its aglycon acerogenin E (**79**) was isolated by Nagumo *et al.* in 1993 (54). Although in other plants several diaryl type macrocyclic diarylheptanoids have been isolated, the cooccurrence of **79** and its ether type analogues confirmed the hypothesis about their biogenesis by oxidative phenol coupling.

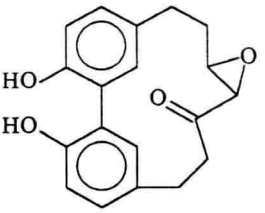
2.2.2. *Betulaceae*

2.2.2.1. *Alnus* species

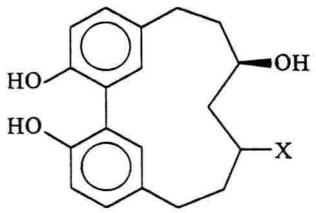
From *Alnus* species i.e. varieties of alder, containing also a large variety of open chain diarylheptanoids (7-21), some biaryl type macrocyclic compounds have also been isolated. In *Alnus japonica* Steud. indigeneous in Japan Nomura *et al.* found four diphenols of this kind. The constitution of alnuson (**80**) and alnusoxide (**81**) was elucidated in 1975 (20), while alnusdiol (**82**) and its oxidation product, alnusonol (**83**) were characterized in 1981 (17). It was observed that **81** could only be isolated from the dried plant and may be therefore an artefact. Alnusdiol was optically active and therefore a *trans*-diol but its absolute configuration remained unknown.
From *A. hirsuta* only the enone **82** and the ketol **83** could be isolated (21) also suggesting that the oxide **81** may be an artefact.



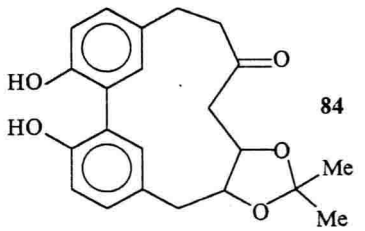
80



81



82 X = *trans*-OH
83 X = =O



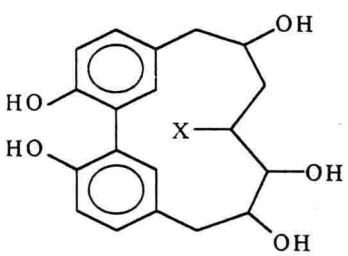
84

2.2.2.2. *Carpinus* species

Compounds **80** and **93** were reisolated by Sawa and his coworkers from *C. cordata* along with a new biaryl type macrocyclic diarylheptanoid (**84**) containing an unusual diol acetonide function.

2.2.2.3. *Ostrya* species

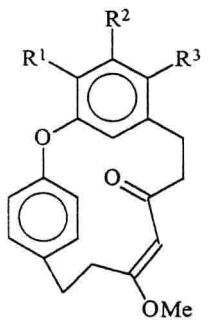
As the first known representative of macrocyclic diarylheptanoids the ketotriol asadanin (**85**) as well as the epimeric tetrols, asadanin I (**86**) and II (**87**) derived by reduction of the keto group were isolated from *O. japonica* by Yasne *et al.* in 1965 (56). The complete stereostructure of asadanins is still unknown, but interestingly it has been established that in the tetrols configuration at C-4 is the same, but different at C-2. Therefore it can be assumed that asadanin itself may occur in Nature in two epimeric forms.



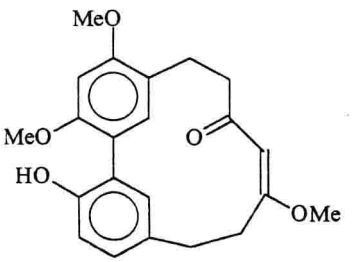
85 X = =O
86 X = OH
87 X = *epi*-OH

2.2.3. *Burseraceae*

Garuga pinata Roxb. and *Garuga gamblei* King, are indigeneous in India and are widely used for the preparation of traditional medicines. Garuganins and garugamblins are constituents of these plants and both biaryl and diaryl ether type macrocyclic compounds can be found among them. Of diaryl ether type are garuganin I (**88**) (57), III (**95**) (58), IV (**89**) and VI (**93**) (59), further garugamblin 1 (**90**) and 2 (**91**) (60-61), while in garuganin II (**92**) and its isomer, garuganin V (**94**) (59) the aromatic rings are linked by a C-C bond.



	R^1	R^2	R^3
88	OMe	H	OMe
89	H	OMe	H
90	OMe	H	H
91	OCH_2O		



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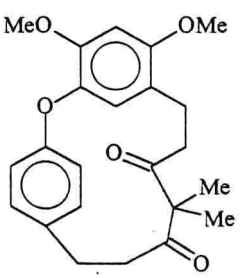

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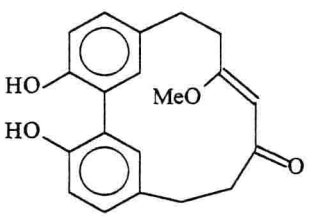
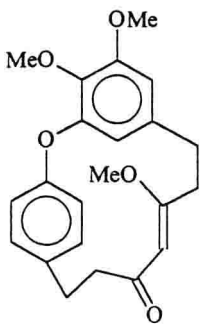
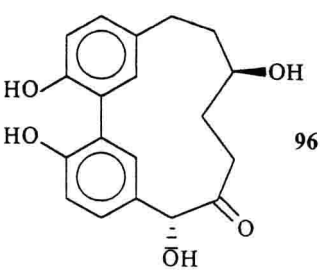


94

The constitution of **88** (62), **91**, **92** (63) and **93** (64) has been confirmed also by X-ray crystallography. Based only on NMR evidence to garuganin III Mishra *et al.* assigned structure **89**, but a total synthesis of this compound and its isomers by Keserű *et al.* (65) proved that the correct constitution of garuganin III was in fact **95**.



95



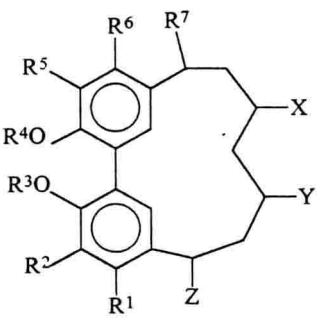
96

2.2.4. *Casuarianaceae*

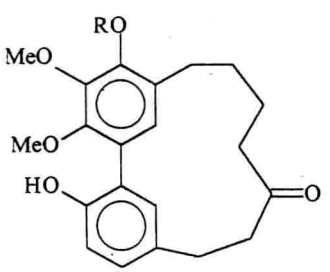
From *C. junghuhniana* Aoki and his coworkers isolated besides alnusoxide (**81**) another macrocyclic compound casuareinondiol (**96**) (66).

2.2.5. *Myricaceae*

From *Myrica nagi* Whiting and his coworkers isolated in 1970 two biaryl type diarylheptanoids, myricanon (**97**) and myricanol (**101**), as well as the glucoside of the latter (**104**) (67). Malterud *et al.* studied *M. gale* L. a species growing in Scandinavia and found three closely related compounds, porson (**98**), galeon (**99**) and hydroxygaleon (**100**) (69). Porson was later reisolated from *M. rubra* by Takeda *et al.* (70) in which also five myricanol glycosides (**104-108**) all from *M. rubra* (71, 72) and 5-deoxymyricanon (**102**) (70) were found. 13-Oxomyricanol (**103**), a constituent of *M. nagi* (73) is the most highly oxygenated compound in this series.

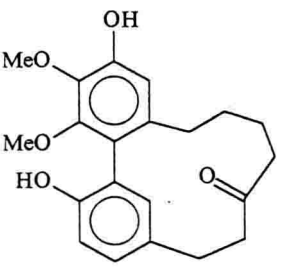


	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X	Y	Z
97	H	H	H	Me	OMe	OH	H	H	=O	H
98	OMe	OMe	Me	H	H	H	OH	H	=O	H
99	H	H	Me	H	H	H	H	=O	H	H
100	H	H	Me	H	H	H	OH	=O	H	H
101	H	H	H	Me	OMe	H	H	H	=O	H
102	H	H	H	Me	OMe	OH	H	H	OH	=O

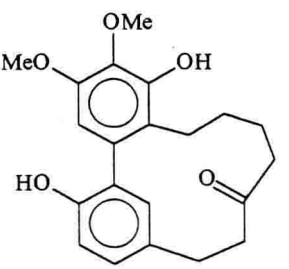


103 R = H
104 R = β-D-Glcp
105 R = β-D-Glcp-OCC_6H_2-3,4,5-$(OH)_3$
106 R = β-D-Glcp-(1→6)-β-D-Glcp
107 R = β-D-Glcp-(1→3)-β-D-Glcp
108 R = β-D-Glcp-(1→6)-α-L-Araf

Whiting and his coworkers observed that myricanon (**97**) rearranged under the action of Lewis acids giving isomyricanon (72). Based on NMR spectra the structure suggested for isomyricanon by Whiting *et al.* (**109**) has been later revised by Sakurai *et al.* to **110** (72).



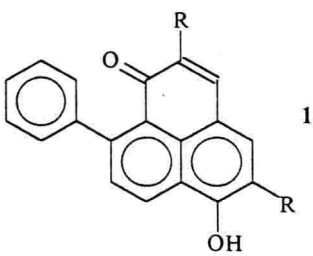
109



110

2.3. 9-Phenylphenalenones

At first sight the title compounds characterized by the general formula **111**, are rather unrelated to diarylheptanoids. At closer look, however, the two classes of compounds can be linked by a very plausible biosynthetic hypothesis first forwarded by Thomas (80) and shown in the following scheme below. 9-Phenylphenalenones were isolated from *Haemodorum* (74), *Lachnates* (75, 76), *Xiphidium* (77), *Wachendorfia* (78), and *Anigozanthos* (79) *(Haemodoraceae) species.*



111

A diarylheptanoid dienone (**112**) biosythesized from tyrosine and phenylalanine which, according to Bazan *et al.* (81), undergoes oxidation to form from the oxygenated aromatic ring an *ortho*-quinone (**113**). The latter, being an active dienophile, undergoes intramolecular Diels-Alder cycloaddition. Aromatization of the adduct finally gives a 9-phenyl-phenalenone. In fact periodate oxidation of **112** gave lachnanthocarpone (**114**), a typical 9-phenylphenalenone (82).

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