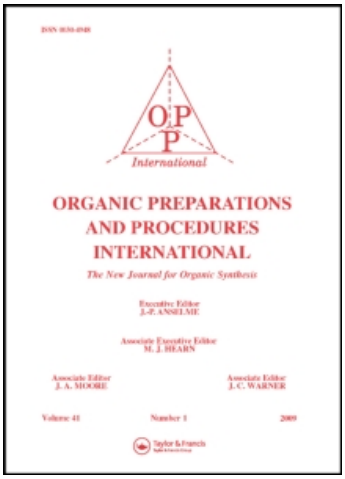


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# RECENT PROGRESS IN ISOLATION, BIOACTIVITY EVALUATION AND TOTAL SYNTHESIS OF DIARYLHEPTANOIDS

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# RECENT PROGRESS IN ISOLATION, BIOACTIVITY EVALUATION AND TOTAL SYNTHESIS OF DIARYLHEPTANOIDS

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## I. INTRODUCTION

Diarylheptanoids are a family of natural plant metabolites whose characteristic structural feature is the presence of two aromatic rings tethered by a linear seven carbon chain. They could be further divided into three subgroups, namely linear (I), [7,0] metacyclophane (II) with a biaryl bridge and *meta,para*-cyclophane with an endo aryl-aryl ether bond (*Fig. 1*).[1]

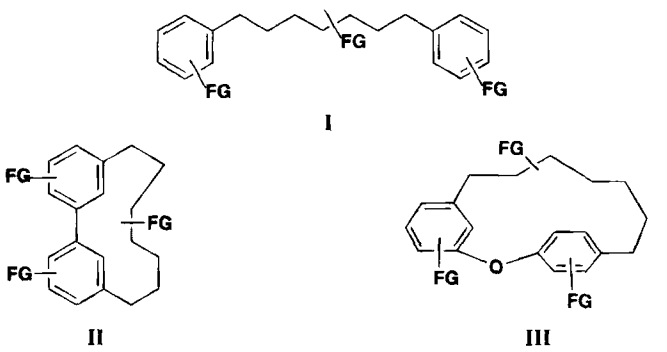



**Fig.1**

Diarylheptanoids have been isolated from number of plant species such as Aceraceae, Betulaceae, Zingiberaceae, Leguminosae and Juglandaceae, Myricaceae etc. The extract of these plants has been widely used in traditional medicine in Asia. For examples, the root of *Juglans mandshurica* Maximowicz (Juglandaceae) has been used as a folk medicine for treatment of cancer in Korea, while extract of *A. Blepharocalyx* (Zingiberaceae) has been used as a stomachic in south-west China. *Curcuma* species (Zingiberaceae) is certainly among the most studied plant of these series.[2] Indeed, the rhizome extract of *Curcuma long* L. has long been used in India and China against biliary disorders, anorexia, coryza, cough, diabetic wounds, heptatic disorders, rheumatism, sinusitis, abdominal pains, icterus etc. Certain *Curcuma* species were recommended as choleretic drugs in Europe

ethnomedicine. The curcumin (*Fig. 2*), the oldest member of diarylheptanoid family, has been demonstrated at least in part responsible for the biological activities of this plant.

As earlier work on the the isolation and synthetic work in this field has been summarized in Nógrádi's 1995 review,[1] the present article will emphasize the recent progress on this subject. Recently identified bioactivities of curcuminoids and the representative examples of diarylheptanoids isolated after 1994 will be briefly summarized followed by synthetic works. Overlap on the description of some classic synthetic methodologies will nevertheless be inevitable.

## II. BIOACTIVITY OF CURCUMINOIDS

The antioxidative and anti-inflammatory activities of curcuminoids are well-known.[3] Since tumor promotion is often associated with inflammatory reaction, substances with an anti-inflammatory activity are potential antitumor-promoting agents. It is thus not suprising that curcumin turns out to be a potent inhibitor of mutagenesis and chemically induced carcinogenesis. Topical application of curcumin strongly inhibited 7,12-dimethylbenz-[a]anthracene-induced tumor initiation[4], 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced tumor promotion in mouse skin and DNA/RNA synthesis ($IC_{50}$ = 1.5-1 μM).[5] Dietary curcumin significantly reduced the incidence and the multiplicity of colonic tumors as well as activities of cyclo-oxygenase and lipo-oxygenase in colonic mucosa.[6]



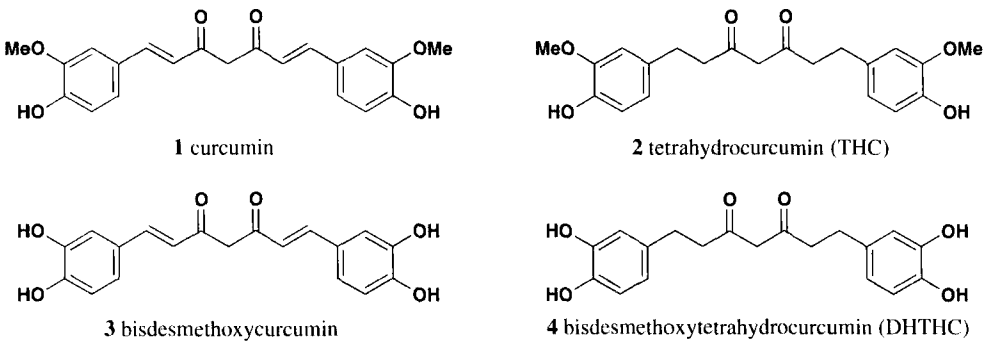



**Fig. 2**

Curcumin has recently been reported to be an inhibitor of superoxide generation in macrophages[7] and differentiated HL-60 cells (by 85% at 50 μM).[8] It suppresses TPA-induced stress both via interference with infiltration of leukocytes into the inflammatory regions and inhibition of their activation. Inhibition of $H_2O_2$ generation is thus proposed to be one of the important pathways of anti-tumor promotion by curcuminoids *in vivo*. In view of its relatively low toxicity to rodents, it appears that curcumin has practical cancer preventive potential. Indeed, the results of phase I chemopreventive clinical trial of curcumin in 25 high-risk cancer patients were encouraging.[9] A combination chemotherapy of curcumin with adriamycin was found to be beneficial to limit free radical-mediated

organ injury.[10] It has also been reported that curcumin antagonized acute cyclosporine-induced cholestasis.[9]

The bioactivity of synthetic analogues of curcumins has been evaluated simultaneously. The inhibitory effect of tetrahydrocurcumin (THC) on superoxide generation was weaker than that of curcumin, while bisdesmethoxytetrahydrocurcumin (DHTHC) having two *ortho* diphenol functions has activity comparable to the parent compound.[8a] THC was also less active than curcumin in inhibiting TPA-induced ornithine decarboxylase activity and tumor promotion in 7,12-dimethylbenz-[a]anthracene-initiated mouse skin carcinogenesis.[5] However, THC was shown to be more active than the parent compound in terms of inhibition of ACF development and cell propliferation,[8b] while bisdesmethoxycurcumin was more effective in treating cyclosporine-induced cholestasis.[9] Demethylation of *O*-methoxyphenol to *O*-dihydroxy compound has been shown to be, in general, an effective modification for preparing free radical scavengers to protect cells against $H_2O_2$-induced cytotoxity.[11] On the other hand, the 1,3-diketone moiety was proposed to be important for its metal-ion chelating ability in inhibiting metalloenzymes, while the conjugated double bonds of the curcumin may further potentiate its chelating property.[8]



## III. RECENTLY ISOLATED DIARYLHEPTANOIDS AND BIOLOGICAL ACTIVITY

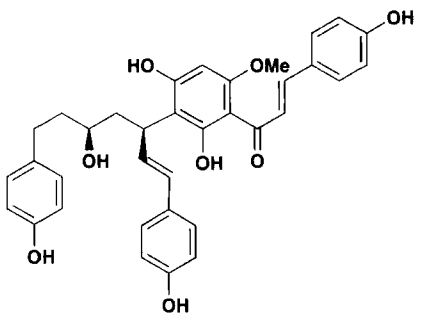
### 1. From Zingiberaceae

Zingiberaceae (ginger family), including ginger (*zingiber officinale*), tumeric (*curcuma longa*) and *alpinia blepharocalyx*, have been used for centuries as foods, spices, dyes, perfumes and in traditional oriental medicine. Research aimed at identifying active components has led to the isolation of number of biaryl heptanoids, among which, the curcumin is probably one of the most well known compound of this family. Continued interest in these plants has led to the isolation of some structurally more complex molecules in recent years.

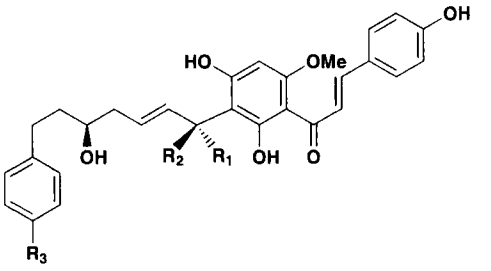
*a) Alpinia Blepharocalyx*

The seeds of *Apinia blepharocalyx* K SCHUM. are used in China for treatment of stomach disorders. Dozens of new diarylheptanoids have recently been isolated and identified resulting from a collaborative work between Japanese and Chinese chemists (*Figs 3 and 4*).[12,13] Calyxin A-H contain a chalcone or a flavone moiety, while blephacocalyxins have two diarylheptanoid units joined by a chalcone. Blephacocalyxin C-E are the first examples of dimeric diarylheptanoids wherein two diarylheptanoids are directly connected with a C-C bond between C-6 of one unit and C-5 or C-7 of the other. Calyxin A, B, C, D and blephacocalyxin A, B inhibited the nitric oxide (NO) production in endotoxin-activated murine macrophages and thus could potentially act as immunoregulator. Blephacocalyxin D and E exhibited an antiproliferative activity against colon 26-L5 carcinoma cells and HT-1080 fibrosarcoma cells, with an $ED_{50}$ value of 3.61 μM and 9.02 μM, respectively. It was noticed that the cytotoxicity of blephacocalyxin E against HT-1080 fibrosarcoma cells was identical with that of 5-fluorouracil ($ED_{50}$ = 8.0 μM) and falls within the range of a potent cytotoxic agent.

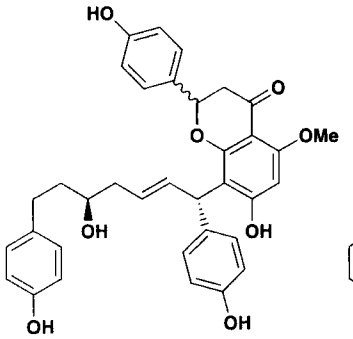
Calyxin A and B inhibited 3α-hydroxysteroid dehydrogenase (3α-HSD), while 1,7-bis(4-hydroxyphenyl)-3-hydroxy-1,3-heptadien-5-one (**5**) inhibited platelet aggregation induced by collagen ($IC_{50}$ = 14.7 μg/mL), arachidonic acid ($IC_{50}$ = 26.6 μg/mL) and adenosinediphosphate ($IC_{50}$ = 65.7 μg/mL).[12e]



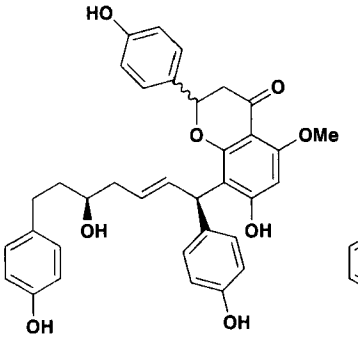

Calyxin A



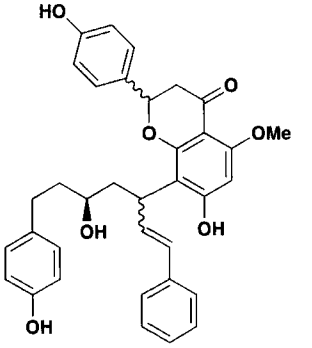

Calyxin B $R_1$ = 4-hydroxyphenyl, $R_2$ = H, $R_3$ = OH
Epi-calyxin B $R_1$ = H, $R_2$ = 4-hydroxyphenyl, $R_3$ = OH
Calyxin H $R_1$ = 4-hydroxyphenyl, $R_2$ = $R_3$ = H
Epi-calyxin H $R_1$ = $R_3$ = H, $R_2$ = 4-hydroxyphenyl



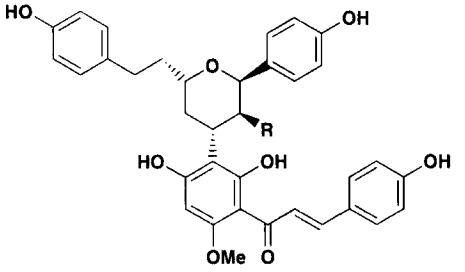

Calyxin C
Epicalyxin C



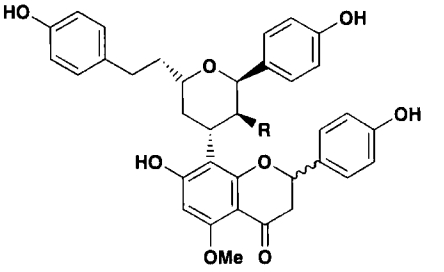

Calyxin D
Epicalyxin D




Calyxin E

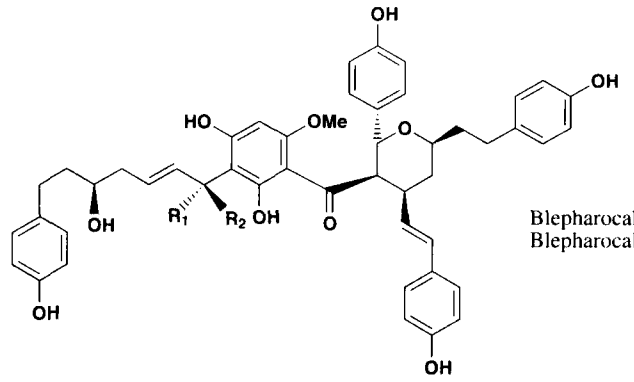



Calyxin F R = H
6-hydroxycalyxin F R = OH

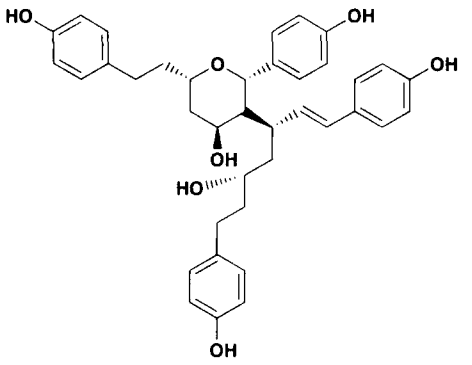



Calyxin G
Epicalyxin G

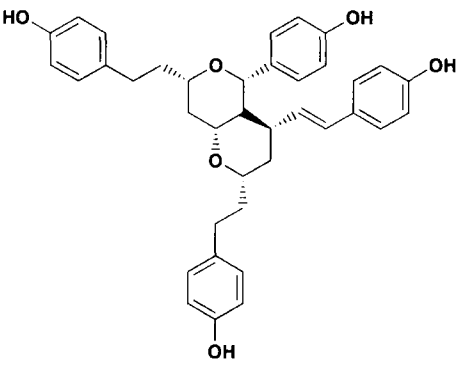
**Fig. 3**



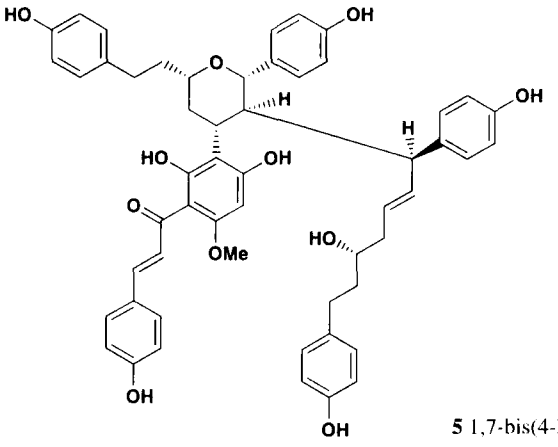
Blepharocalyxin A , $R_1$ = 4-hydroxypehnyl, $R_2$ = H
Blepharocalyxin B, $R_1$ = H, $R_2$ = 4-hydroxypehnyl



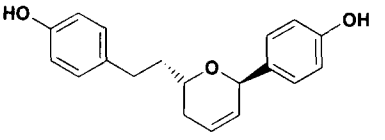
Blepharocalyxin C



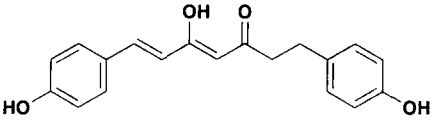
Blepharocalyxin D



Blepharocalyxin E



5,6-dehydro-4"-de-O-methylcentrolobin

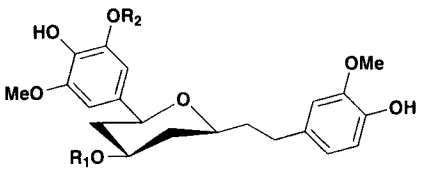


**5** 1,7-bis(4-hydroxyphenyl)-3-hydroxy-1,3-heptadien-5-one

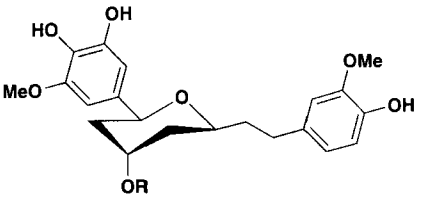
**Fig. 4**

b) *Zingiber Officinale*

Five new diarylheptanoids containing a tetrahydropyran unit were recently isolated (*Fig. 5*).[14] Related compound with a dihydropyranone unit has previously been isolated from *Curcuma, longa* L.[15] Biological activity has not been reported.




**6** $R_1$ = Ac, $R_2$ = H
**7** $R_1$ = $R_2$ = H
**8** $R_1$ = H, $R_2$ = Me




**9** R = Ac
**10** R = H

**Fig. 5**

## 2. From *Centrolobium Sclerophyllum* (Leguminosae)

A known compound: 2-[β-(p-hydroxy-phenyl)-ethyl]-6-(p-hydroxyphenyl)-tetrahedropyran[16] (De-O-methylcentrolobin[17]) has been isolated, although the stereochemistry remains unknown (*Fig. 6*). A good antileishmanial activity with the $LD_{50}$ = 77 nM was demonstrated during this study.

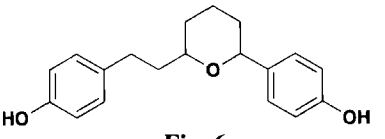
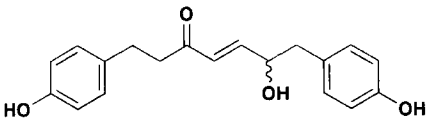



**Fig. 6**

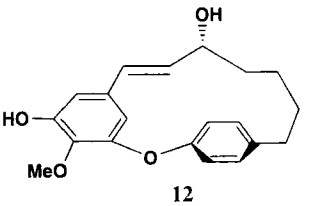
## 3. From Betulaceae

a) *Betula Species*

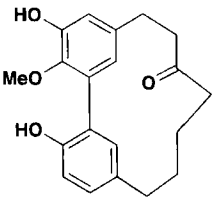
In a series of papers, Tanaka and coworkers have isolated several new diarylheptanoids from the *Betula* species in Japan (*Fig. 7*).[18]



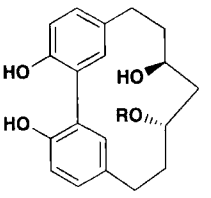

**11**



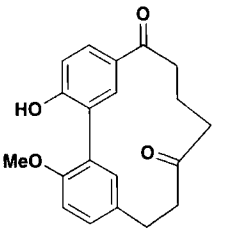

**12**



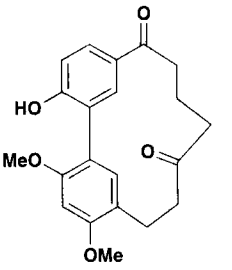

**13**




**14** R = β-D-glucosyl



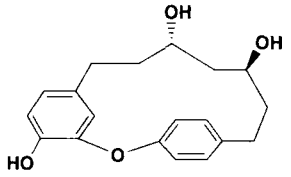

**15**



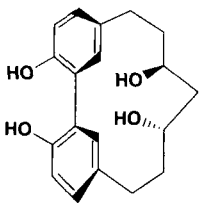

**16**

**Fig. 7**

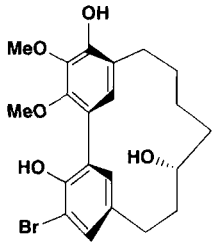
From the heartwood of *Betula maximowicziana*, maximowicziol A[19,20] and a known compound alnusdiol[21] were isolated (*Fig. 8*). The originality of this work is that the axial chirality of biaryl moiety of [7,0]-metacyclophane was mentioned and determined for the first time in this series. In 1970, the X-ray crystallographic analysis of 16-bromomyricanol was published and the absolute stereochemistry of secondary alcohol was determined to be (*R*) using heavy-atom method.[22] However, the atropisomerism of the molecule was not mentioned, although the *P* configuration of biphenyl axis could be clearly assigned from the X-ray structure. In the present work, Hanawa *et al.* have determined the relative stereochemitry of alnisdiol by X-ray analysis and then its absolute configuration (as shown in *Fig. 7*) by comparing its CD spectra with that of 16-bromomyricanol. The fact that most natural [7,0] diharylheptanoids gave only one set of peaks in NMR spectra leads to the conclusion that such atropisomerism might exist in most of them and that it remains an interesting issue worthy of studying.




(3*S*, 5*S*)-maximowicziol A




(*P*, 3*S*, 5*S*)-alnusdiol

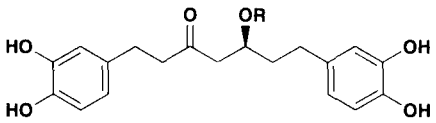



16-bromomyricanol

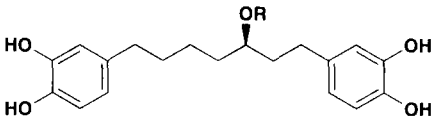
**Fig. 8**

*b) Alnus Species*

Three new glycosylated linear diarylheptanoids (**17**, **20**, **21**) have been isolated from *Alnus japonica* species,[23] while two acylated compounds **18**, **19** were obtained from *Alnus rubra*, Bong (*Fig. 9*).[24]




**17** R = 6-*O*-galloyl-β-D-glucopyranosyl
**18** R= β-D-glucose-6-OCOPh
**19** R = β-D-glucose-6-OCO-(3'-methoxy-4-hydroxy phenyl




**20** R = β-D-glucopyranosyl
**21** R = 6-*O*-β-D-apiosyl-β-D-glucopyranosyl
**22** R = H

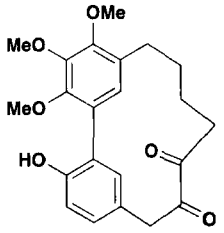
**Fig. 9**

Compound **20** and **22** have also been isolated, for the first time, from *Pinus* species (Pinaceae)[25] and their $IC_{50}$ values in the PKC (protein kinase C) assay were determined to be 1.6 μg/mL and 1.4 μg/mL, respectiviely.

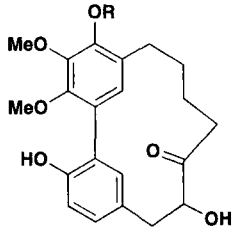
## 4. From Myricaceae

Several new macrocyclic diarylheptanoids have been identified from *Myrica gale* var .

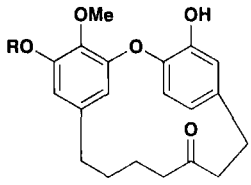
*tomentosa* (*Fig. 10*).[26] During this study, an enantiomer of previously known (-) galeon[27] was isolated and the configuration of planar chirality was determined to be (*P*) by X-ray crystallographic analysis of the corresponding 4-bromobenzoate **24**. No biological data were available.



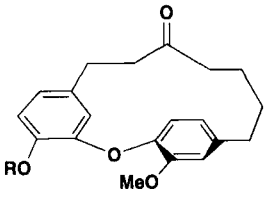

12-dehydro-porson



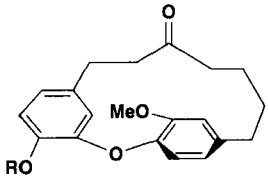

12-hydroxy-myricanone R = H
myricatomentoside II
R = β-glucopyranosyl



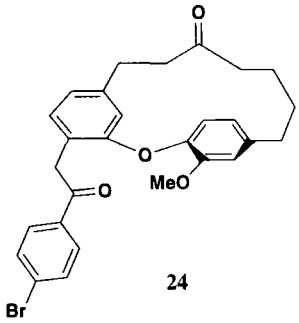

myricatomentoside I
R = β-glucopyranosyl




*P*-(+)-galeon




*M*-(-)-galeon

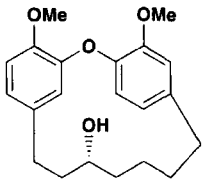



24

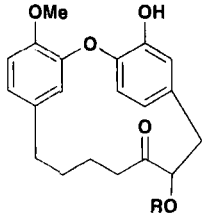
**Fig. 10**

## 5. From Juglandaceae

Two 16-membered *meta,para*-cyclophanes with an endo aryl-aryl ether bond have been identified from *Platycarya strobilacea* and *Juglans mandshurica*, respectively (*Fig. 11*).[28] Hindered rotation around the biaryl ether linkage together with the presence of *ortho*-methoxy group in the *para* substituted aromatic ring might create a planar chirality.[27] However, the atropisomerism was not specified in these two preliminary reports. The stereochemistry of secondary alcohol was determined to be *R* for platycarynol, while that of compound **23** remains unknown. Compound **23** was inactive against human colon carcinoma and human carcinoma cell lines.




Platycarynol




**23** R = β-D-glucopyranosyl

**Fig. 11**

### 6. From Aceraceae

The stem bark of *Acero nikoense* MAXIM (Aceraceae), a tree indigenous to Japan, has been used in folk medicine as a remedy for hepatic disorders and for eyewash. Number of diarylheptanoids have been identified and some recent examples are listed in Fig 12.[29] While the relative stereochemistry of 1,3-diols in acerogenin F—J was determined, the absolute configuration of these compounds remains unknown.

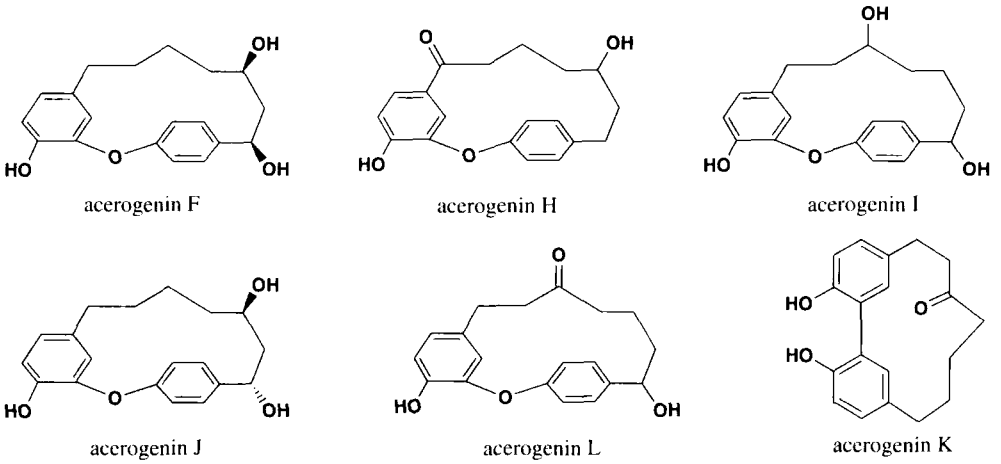



**Fig. 12**

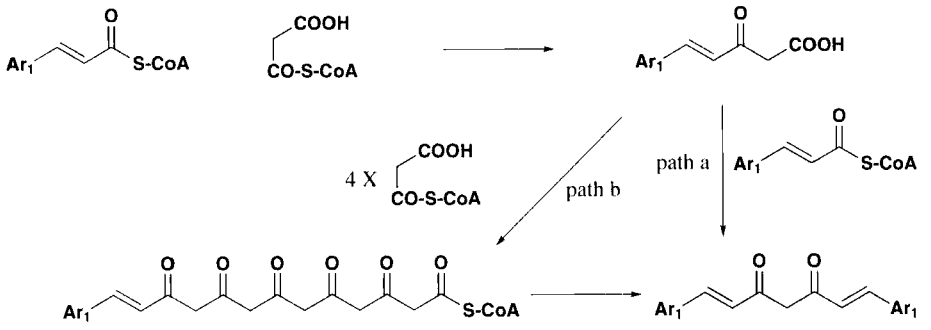


## III. SYNTHESIS OF LINEAR DIARYLHEPTANOIDS

### 1. Biosynthesis

In natural diarylheptanoid, at least one carbon of the tether chain was functionalized in the form of a secondary alcohol or a carbonyl group (C3/C5 position). This observation has led to a hypothesis that its biosynthesis involved two cinnamate units which were coupled to a central carbon provided by malonate (path a, *Scheme 1*).[30] Biogenesis of linear diarylheptanoids, with particular reference to curcumin, has been studied by Whiting and co-workers using *C. Longa* plant.[31] While the labelling experiments with [1-$^{14}$C] and [3-$^{14}$C] phenylalanines did support the phenylalanine-cinnamate pathway and the idea that cinnamate was involved as one of the biosynthesis starter, mechanisms concerning the chain elongation and the formation of the second aromatic ring remain to be clarified. In fact, results of feeding experiments with [1-$^{14}$C] and [3-$^{14}$C] sodium acetate, and [1-$^{14}$C] and [3-$^{14}$C] sodium malonate was inconsistent with path a by the fact that incorporation of [1-$^{14}$C] acetate and -malonate were as good as (or even better than) those of the corresponding 2-labelled acids. Whiting observed that the fractional activities of carbons along the heptane skeleton is similar to that obtained in polyketide biosynthesis and thus proposed an alternative chain elongation hypothesis (path b,

*Scheme 1*). Nevertheless, feeding experiments did not provided a clear-cut indications to distinguish between these two possible pathways. Later studies with different plant species indicated that the exact biosynthetic scheme may vary from plant to plant and that both paths a and b may operate *(vide infra)*.




**Scheme 1**

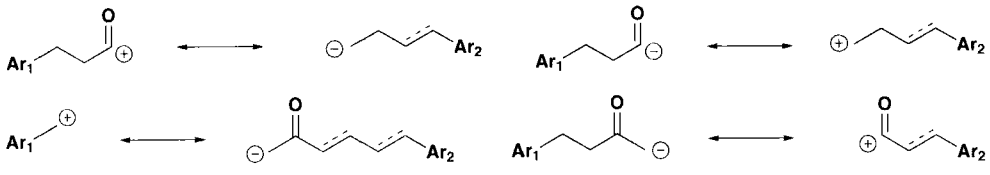


## 2. Synthesis

Linear diarylheptanoids are structurally simple compounds and are thus easily accessible by today's standards. In the following section, this family of natural product will be divided into three groups according to the oxygenation level of the tether chain. Brief descriptions of synthetic works will be presented accordingly.

*a) With One Oxygenation*

If there is only one oxygenation in the tether chain, then it is to be positioned on $C_3$ for biogenetic reason (*cf Scheme 1*). This type of diarylheptanoid can be further divided into several sub-groups according to the unsaturation of the seven carbon chain (table 1). Among various possible synthetic routes, four conventional disconnections were evident as shown in *Scheme 2*. Synthetically, each pair of synthons can be gathered by a) nucleophilic addition to an aldehyde, b) alkylation of a 1,3-dithiane (*umpolung* strategy), c) aldol condensation and its variants and d) Wittig-type reaction.




**Scheme 2**

**Table 1.**

| Generic Structure | Examples |
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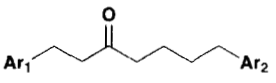
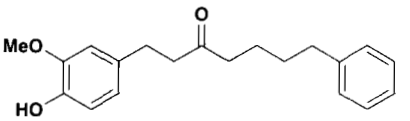
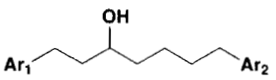
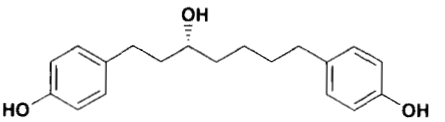
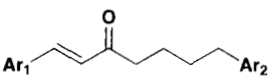
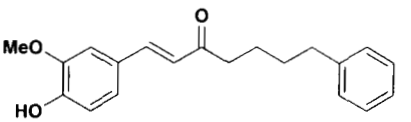
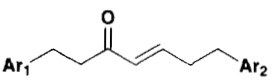
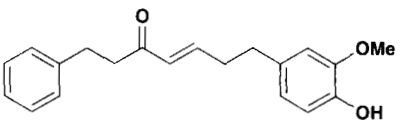
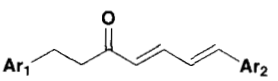
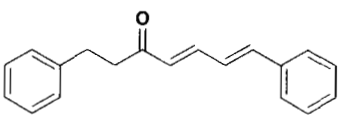
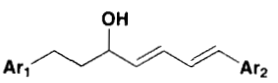
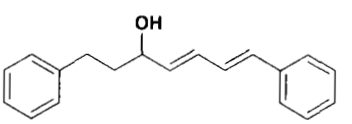
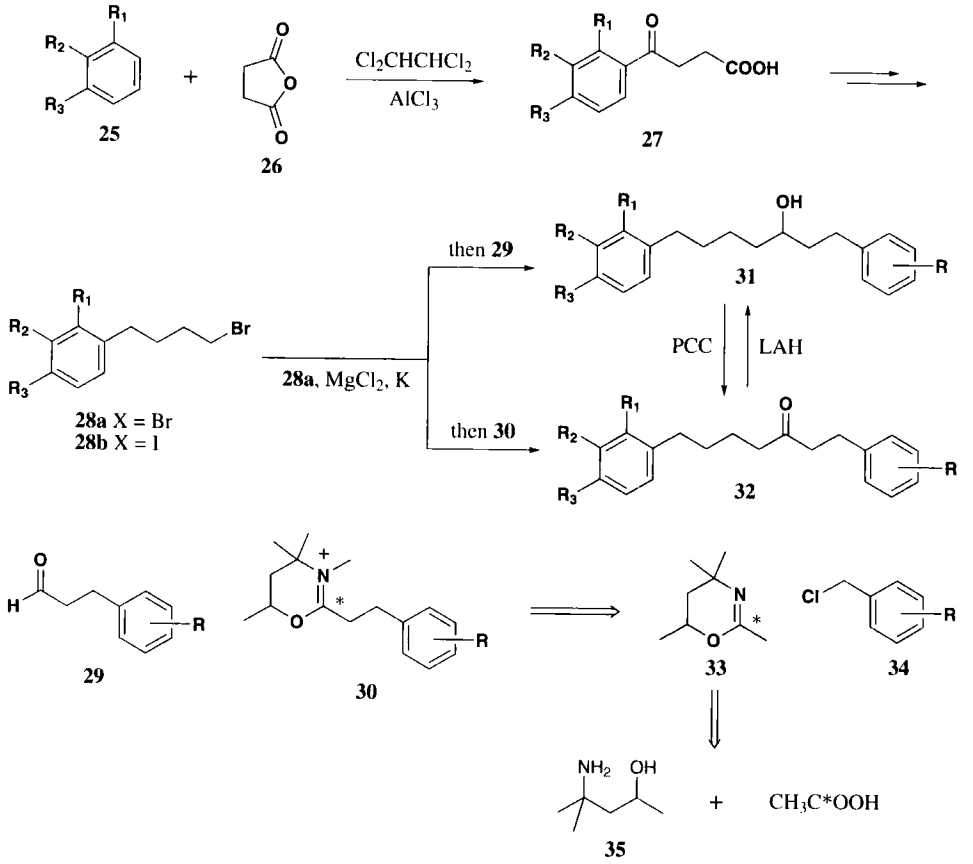
|  |  Yakuchinone A |
|  |  (-)-centrolobol |
|  |  Yakuchinone B |
|  |  |
|  |  |
|  |  |

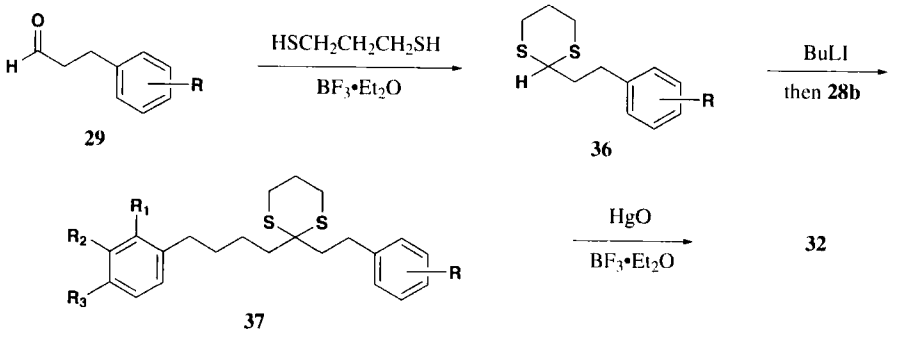
A general strategy involving addition of an organometallic reagent to an aldehyde for the synthesis of diarylheptan-3-one was described by Whiting *et al.* (*Scheme 3*).[32] Friedel-Crafts acylation of electron-rich aromatic rings with succinic anhydride in 1,1,2,2-tetrachloroethane in the presence of aluminium chloride gave the keto acid **27** which was then transformed into the bromide **28a** or iodide **28b** by standard synthetic operations. Transformation of **28a** into the corresponding Grignard reagent followed by reaction with 3-arylpropionaldehyde (**29**) and with dihydrooxazonium salt **30** gave the diarylheptanol-3 (**31**) and diarylheptan-3-one (**32**), respectively. This coupling reaction was accompanied by side-reactions such as proton-quenching, homo-coupling of organomagnesium and reduction of aldehyde. Consequently, the yield of this last step was only moderate at best (42% for **31** and 19% for **32**). The interconversion between compounds **31** and **32** is of course easily realized by a reduction-oxidation process. The merit of using dihydrooxazonium salt is that it offers the possibility to incoporate $^{14}C$ into the natural products. In fact, 1,3-oxazine **30** labelled at $C_2$ can be easily prepared

from [1-$^{14}$C]acetic acid. Weinreb's amide[33] and its variation unknown at that time, should be a variable substitute for the 1,3-oxazine, if direct access to heptan-3-one was sought following Whiting's route.



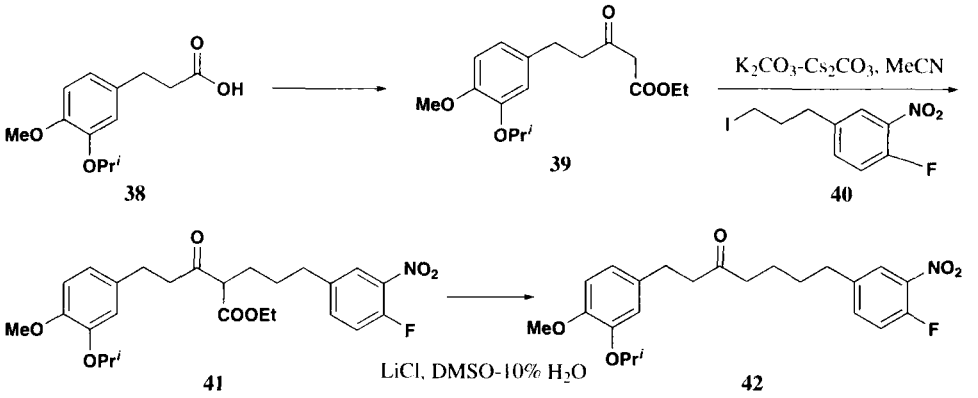

**Scheme 3**

The *umpolung* approach based on the dithiane chemistry was developed by the same group (*Scheme 4*). Alkylation of lithiated dithiane **36** by iodide **28b** gave **37** in 33% yield. Hydrolysis of the latter gave then the diarylheptanoid **32** in 73% yield.



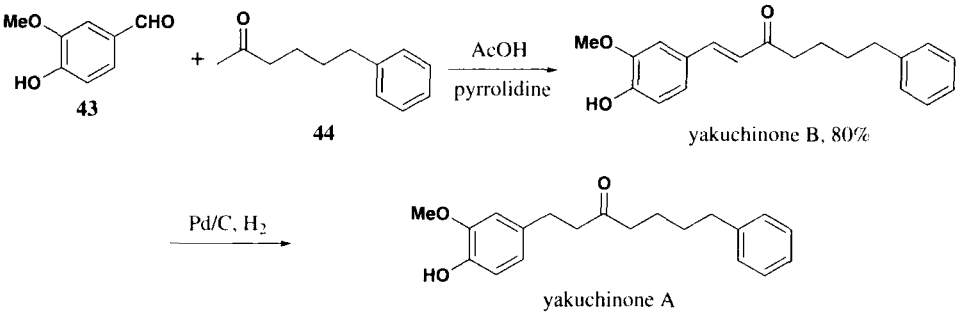

**Scheme 4**

Alternatively, acylation of malonate mono-anion followed by alkylation with a suitable electrophile provided an efficient access to diarylheptan-3-one (*Scheme 5*).[34] Thus, acylation of dihydrocinnamic acid derivative **38** with malonate gave the keto ester **39** which was in turn alkylated by iodide **40** to afford keto ester **41** in 83% yield. Decarboxylation under Krapcho conditions[35] then furnished compound **42** in 90% yield. The fluoro-nitro substituents present in the iodide **40** was to facilitate the subsequent intramolecular $S_NAr$ reaction, a methodology developed in our laboratory for the construction of biaryl ether containing macrocycles (*vide infra*).[36]



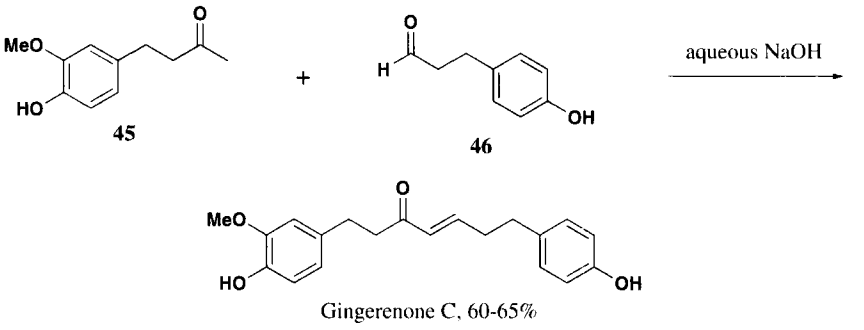

**Scheme 5**

Two pungent principles, yakuchinones A and B isolated from *Alpinia oxyphylla*,[37] were synthesized by the Claisen-Schmidt reaction (*Scheme 6*).[38] Thus, condensation of vanillin with 6-phenyl-2-hexanone gave in one step yakuchinone B in 80% yield. Hydrogenation then gave yakuchinone A. This synthetic scheme was quite general and has been applied to the preparation of a number of analogues. It was found that the presence of a phenolic hydroxyl group was indispensable for high pungency, while unsaturation tends to decrease the pungency. Sankawa *et al.* demonstrated that Yakuchinone A was a potent inhibitor of PG biosynthesis enzyme ($IC_{50}$ = 0.51 μM) and could be the main active component of *A. oxyphilla*.[39].




**Scheme 6**

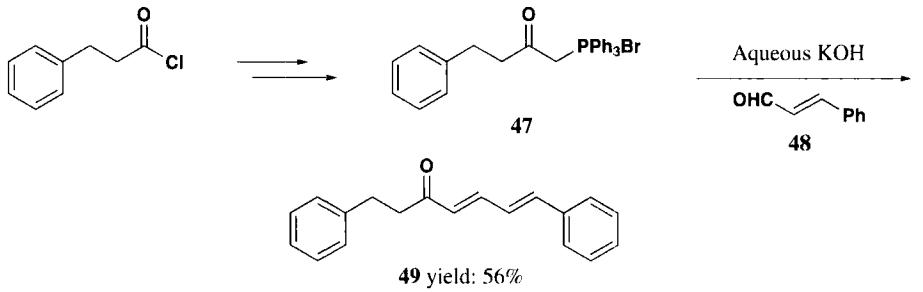
Employing the same Claisen-Schmidt reaction, Huang and Li[40] have recently synthesized Gingerenone C, one of the diarylheptanoids isolated from *Zingiber officinale*[41]




**Scheme 7**



Diarylheptanoids containing a dienone moiety have been synthesized by Wittig type reaction between phosphorane **47** and cinnamaldehyde **48** (*Scheme 8*).[42]




**Scheme 8**

*b) With Two Oxygenations*

Some representative natural linear 1,7-diarylheptanoids with two oxygenations on the tether chain were listed in Table 2. For construction of the 1,3-diketone unit, aldol type condensation of acetoacetate derivatives or β-keto ester with carbonyl electrophiles is the most obvious route, while nuclophilic addition of organometallic reagent to selectively protected keto-aldehyde and alkylation of β-keto-dithiane have been used for the construction of β-hydroxy ketone moiety.

**Table 2.**

| Generic Structure | Examples |
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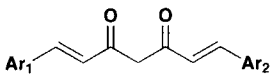
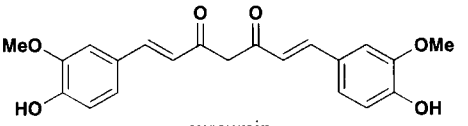
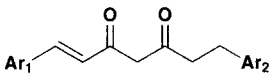
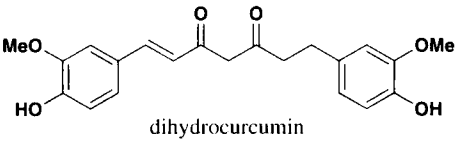
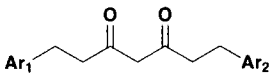
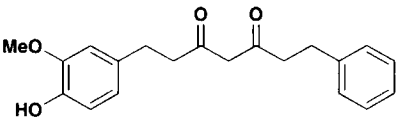
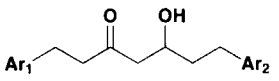
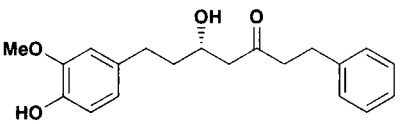
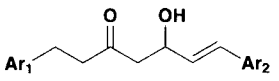
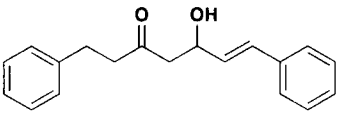
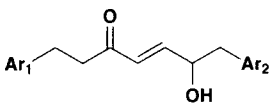
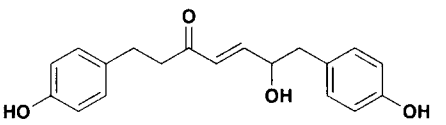
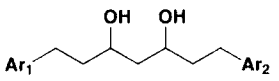
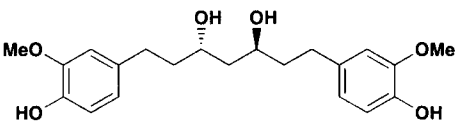
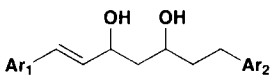
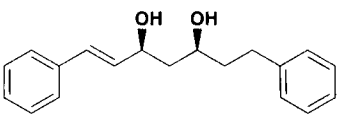
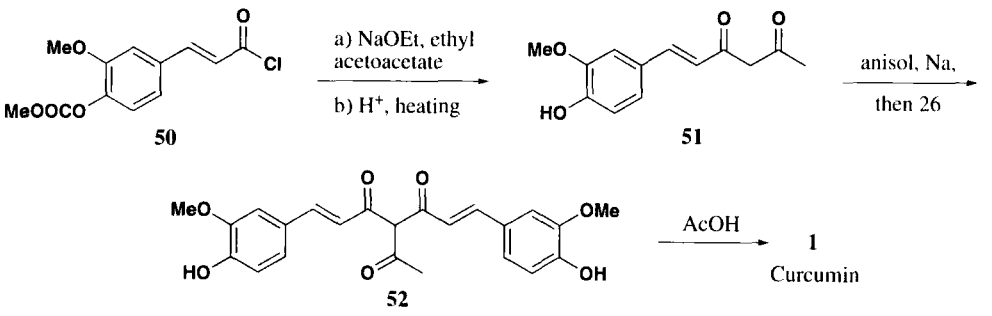
|  |  curcumin |
|  |  dihydrocurcumin |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

*Note: the 1,3-diketon existed in a enol form. It was nevertheless drawn in a keto form for the sake of comparison.*

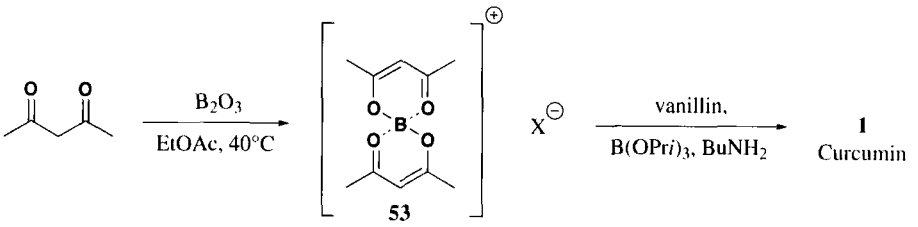
The first laboratory synthesis of diarylheptanoids was that of curcumin accomplished in 1918 (*Scheme 9*).[43] Acylation of acetoacetate by carbomethoxyferuloyl chloride **50** gave, after decar-

boxylation, diketone **51**. Repeating the acylation afforded the triketone **52** which upon acidic treatment gave curcumin.



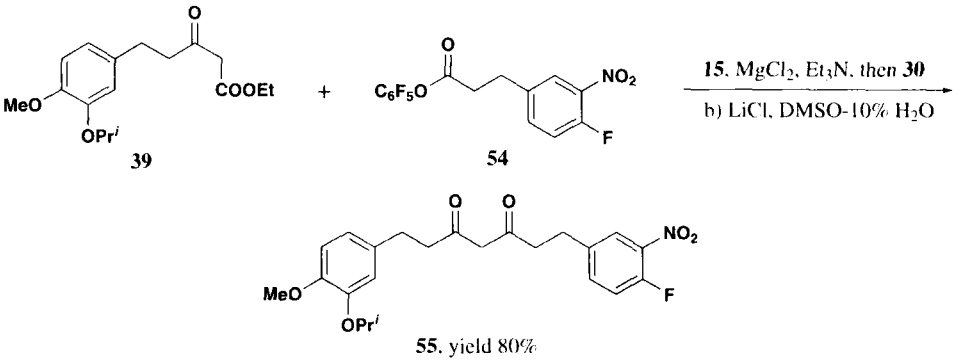

**Scheme 9**

The importance of curcumin as food aditives, dye and its recently demonstrated chemopreventive effect have called for the elaboration of a practical industrial synthesis. Such a synthesis, developped by Pavolini[44] and later improved by Pabon[45] is shown in *Scheme 10*. Reaction of vanillin with 2,4-pentanedione, pretreated with boric anhydride, in the presence of triisopropylborate and butylamine gave curcumin in 80% yield. To obtain high yield of curcumin, the C-3 of 2,4-pentanedione had to be protected in order to avoid the undesired Knoevenagel condensation. This was achieved by reaction of 2,4-pentanedione with boric anhydride to produce the presumed boron complex **53**. The method is quite general and has been applied to the synthesis of other symmetric natural and non-natural 1,7-diarylheptanoids[46] (*Scheme 10*).



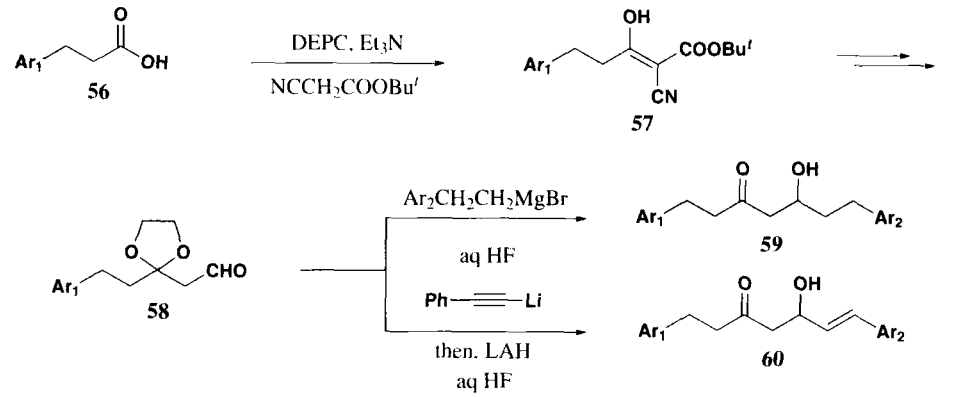

**Scheme 10**

In our synthesis of garuganine type macrocycles, Knoevenagel condensation has been exploited for the construction of 1,3-diketone unit (*Scheme 11*).[47] Formation of magesium enolate of keto ester **39** followed by addition of activated ester **54** afforded, after decarboxylation, compound **55** in 80% yield.



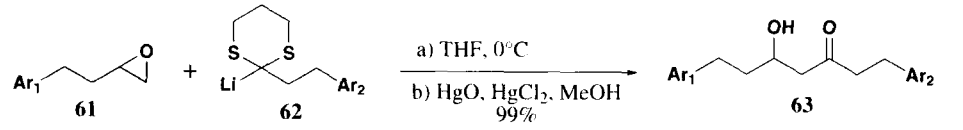

**Scheme 11**

Direct C-acylation of carboxylic acid followed by nucleophilic addition to the selectively protected keto-aldehyde were two key steps in Shioiri's synthesis of β-hydroxy ketone[48] (*Scheme 12*). The scheme can of course be extended to the synthesis of 1,3-diketone containing natural products by a simple oxidation step.




**Scheme 12**

Ring opening of epoxide by dithiane anion followed by hydrolysis constitutes another general route to β-hydroxy ketone developed by Semmelhack *et al.*[49] (*Scheme 13*).

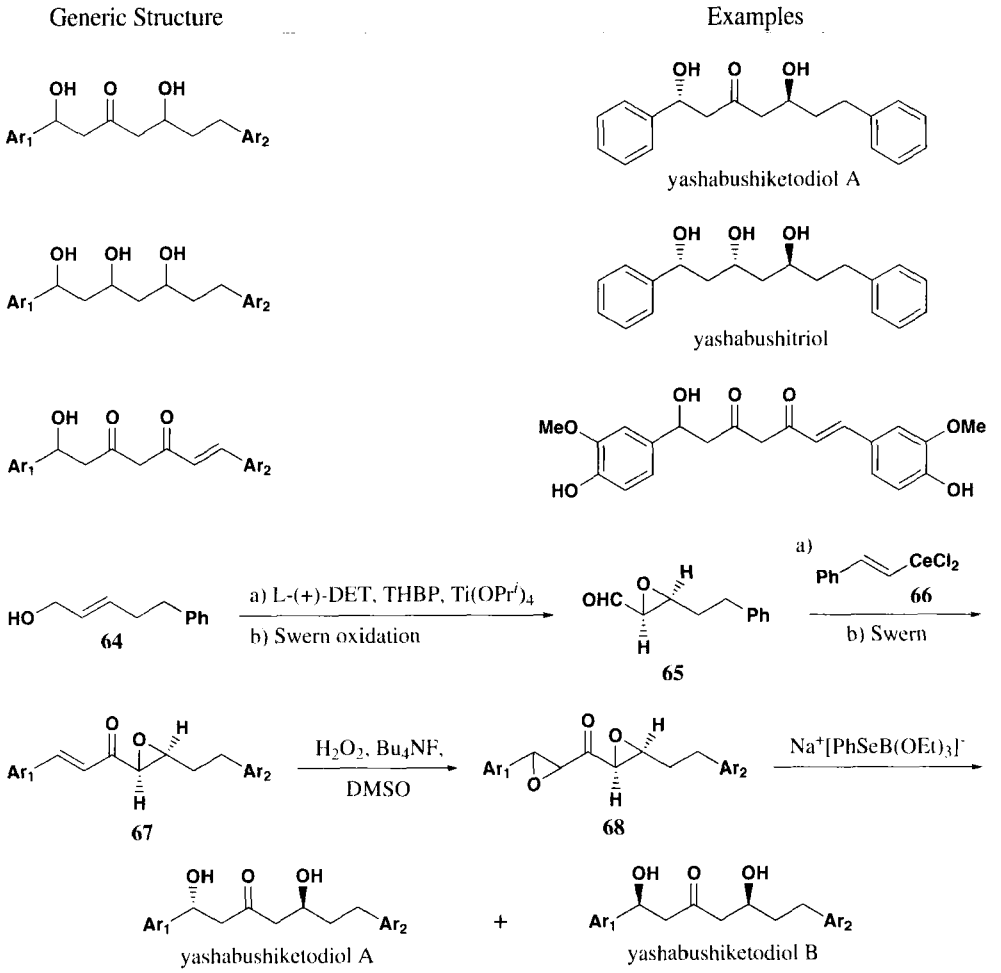



**Scheme 13**

*c) With Three Oxygenations*

Linear diarylheptanoids containing three oxygenations are relatively rare. Some examples are listed in table 3. Yashabushiketodiol A and yashabushitriol containing such functionalities have been isolated from *Alnus sieboldiana*, which are used as an erosion-control plant.[50] An enantioselective synthesis of these compounds reported by Yoshikoshi *et al.* is shown in *Scheme 14*.[51]

**Table 3.**




**Scheme 14**

Sharpless asymmetric epoxidation[52] of allyl alcohol **64** followed by Swern oxidation[53] of primary alcohol gave (2*S*,3*S*)-epoxyaldehyde **65** (94% ee) in 85% yield. 1,2-addition of β-styryl-cerium **66** to the aldehyde **65** gave, after oxidation, the enone **67**. Epoxidation of enone (30% $H_2O_2$, $Bu_4NF$ in DMSO) afforded a diastereomeric mixture of bis-epoxy ketone **68** in a 1 to 1 ratio (75%). Organoselenium-mediated regioselective reduction of **68** gave, after purification, diastereomerically pure yashabushiketodiol A and yashabushiketodiol B in 42% and 41% yields, respectively.

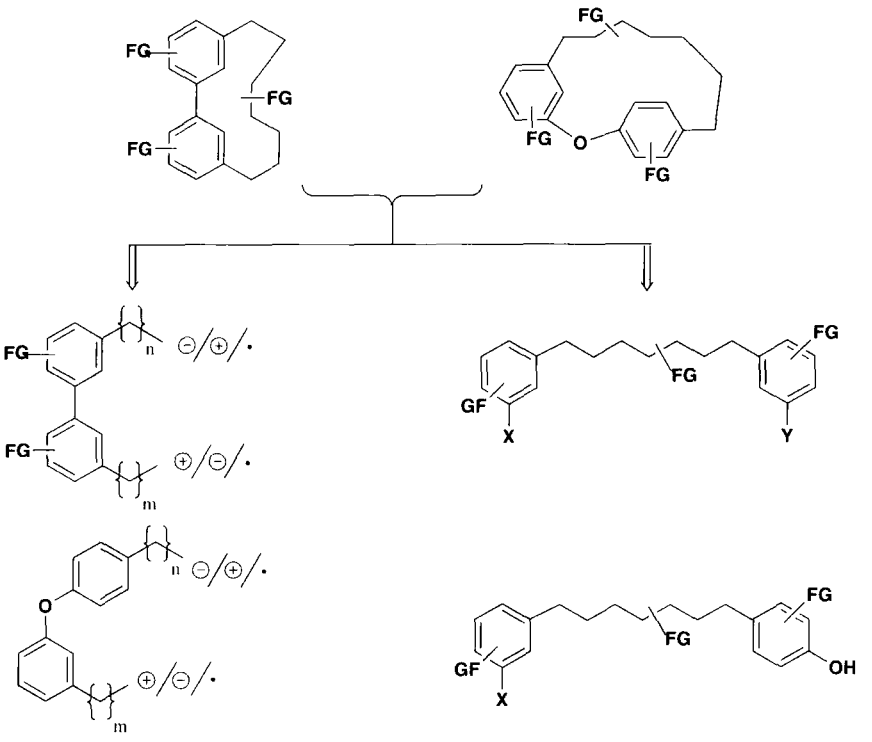
Yashabushitriol can be obtained by reduction of yashabushiketodiol A with sodium borohydride.[50]

## IV. SYNTHESIS OF CYCLIC DIARYLHEPTANOIDS

Macrocyclic compound, by virture of its outstanding pharmaceutical activity and the inherent challenges associated with its construction, has attracted much attentions among synthetic chemists.[54] Not suprisingly, synthetic activities in such a field are numerous and, at the same time rewarding. Ring closure reactions would certainly be a central issue in planning a synthesis of a macrocyclic compound. The outcome of such a reaction depends on both the choice of strategic bond and the reaction selected for its construction in a forward sense. In addition to the well-adopted macrolactamization and macrolactonization reactions,[55] the intramolecular ring closure metathesis (RCM),[56] intramolecular Wittig type reactions,[57] intramolecular oxidative coupling[58], intramolecular nucleophilic aromatic substitution reaction (SNAr)[36] and transition metal catalyzed reactions,[59] among others, have recently been developed and proved to be powerful new ring closure methods

Due to the ring strain, rotation of the aryl-aryl and the aryl-aryl ether bond may be hindered in certain macrocycles. Consequently, the synthesis of such molecules became even more challenging as one has to not only find the right way to perform the cyclization but also to control the atropisomerism.

As far as the synthesis of cyclic diarylheptanoids is concerned, two obvious yet strategic bond disconnections are shown in *Scheme 15*. One involves the formation of a carbon-carbon bond at

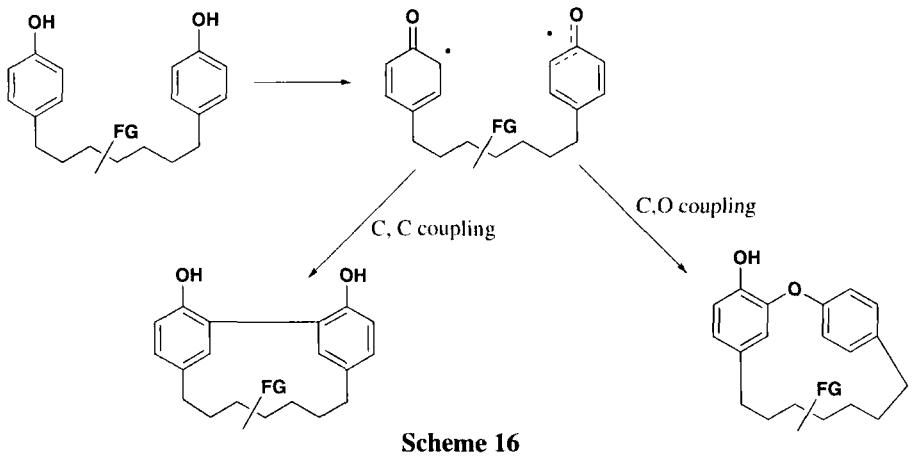



**Scheme 15**

the tether chain, while the other calls for the macrocyclization via formation of an aryl-aryl or an aryl-aryl ether bond, respectively. Both strategies have indeeded been reduced to practice and will be summarized in the following sections.

## 1. Biosynthesis

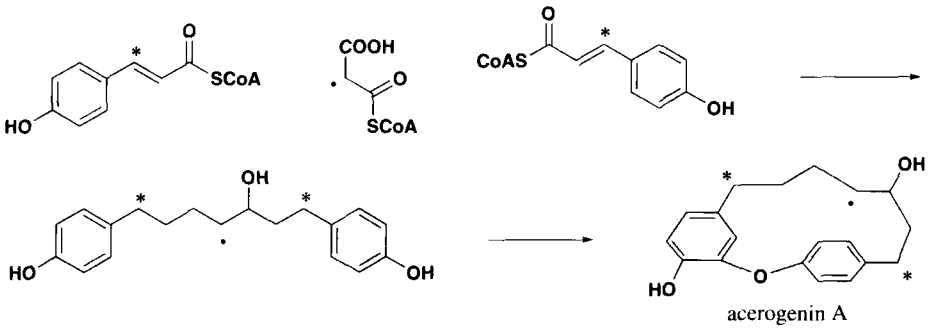
The co-occurrence of cyclized diarylheptanoids with their corresponding acyclic counterpart in plant such as *A. japonica*,[60] and *Acer Nikoense* [29,61] etc provided indication of their biosynthetic relationship. Intramolecular phenolic oxidative coupling of linear diarylheptanoids,[62] shown in *Scheme 16*, would predict that biphenylcyclophane will be *meta, meta* bridged in nature, while diphenylether type cyclophane be *meta, para* bridged. Such a structural pattern were indeed found in natural products.




**Scheme 16**

Biosynthesis of macrocyclic diarylheptanoids (acerogenin A) was investigated by Fujita *et al.*[63] by feeding various labelled compounds to the young shoots of *Acer nicoense*. When DL-[3-$^{14}$C] phenylalanine and [3-$^{14}$C] cinnamic acid was fed to the young shoots of *Acer nicoense*, about 95% of the radioactivity of acerogenine remained on the C1/C7, but in the case of L-[1-$^{14}$C] phenylalanine, only about 5% of the radioactivity was incoporated at the positions C1/C7 of acerogenine A. These results indicated the entire incorporation of a cinnamate unit and are in accord with previous hypothesis that cinnamate is the biosynthesis starter of diarylheptanoids. Interestingly, a different picture emerged when feeding experiments were performed with [2-$^{14}$C] sodium acetate, [2-$^{14}$C] malonic acid, and [1-$^{14}$C] sodium acetate. In contrast to the labelling experiment with *Curcuma Longa*, Fujita found that [2-$^{14}$C] sodium acetate and [2-$^{14}$C] malonic acid were efficiently incorporated into the acerogenine, but not [1-$^{14}$C] sodium acetate. Based on these observations, they proposed the following biosynthetic route of acerogenine A (*Scheme 16*). Thus, acerogenin A was proposed to be biosynthe-

sized by intramolecular oxidative coupling of its linear precursor which was, in turn, obtained by unifying two units of cinnamate and one malonate. It was concluded that different plants may use different chain elongation mechanism to produce the linear diarylheptanoids.




**Scheme 17**

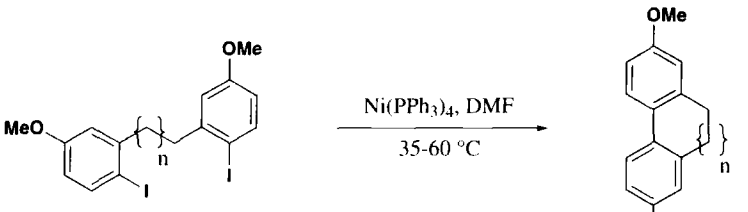


## 2. Total Synthesis of Bridged Biphenyl Macrocycles

*a) Ring Closure via Aryl-Aryl Bond Formation*

i) Nickel (0) Promoted Intramolecular Reductive Coupling of Arylhalide.

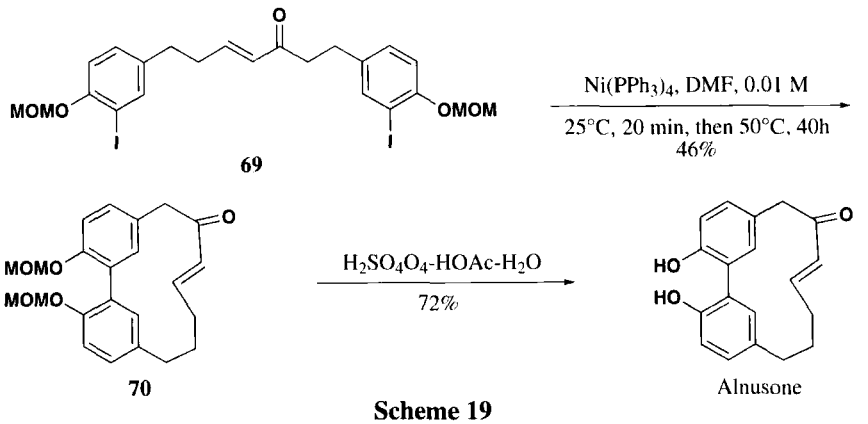
Transition metal catalyzed cross-coupling reactions (Suzuki, Stille, Negishi etc) are among the most powerful methods for the construction of biaryl unit.[64] However, the principle of metal promoted coupling of two aryl halides such as Ullmann reaction (copper catalyzed) are generally synthetically less efficient for the construction of structurally complex molecules due to the drastic conditions required.[65] Thus, the zerovalent nickel promoted intramolecular coupling of aryl halide developed by Semmelhack provides a significant contribution to the field (*Scheme 18*).[49] A limitation of this cyclization technology is that it fails with sterically hindered *ortho*-disubstituted substrates.




n = 1, yield 81%
n = 4, yield 85%
n = 5, yield 38%

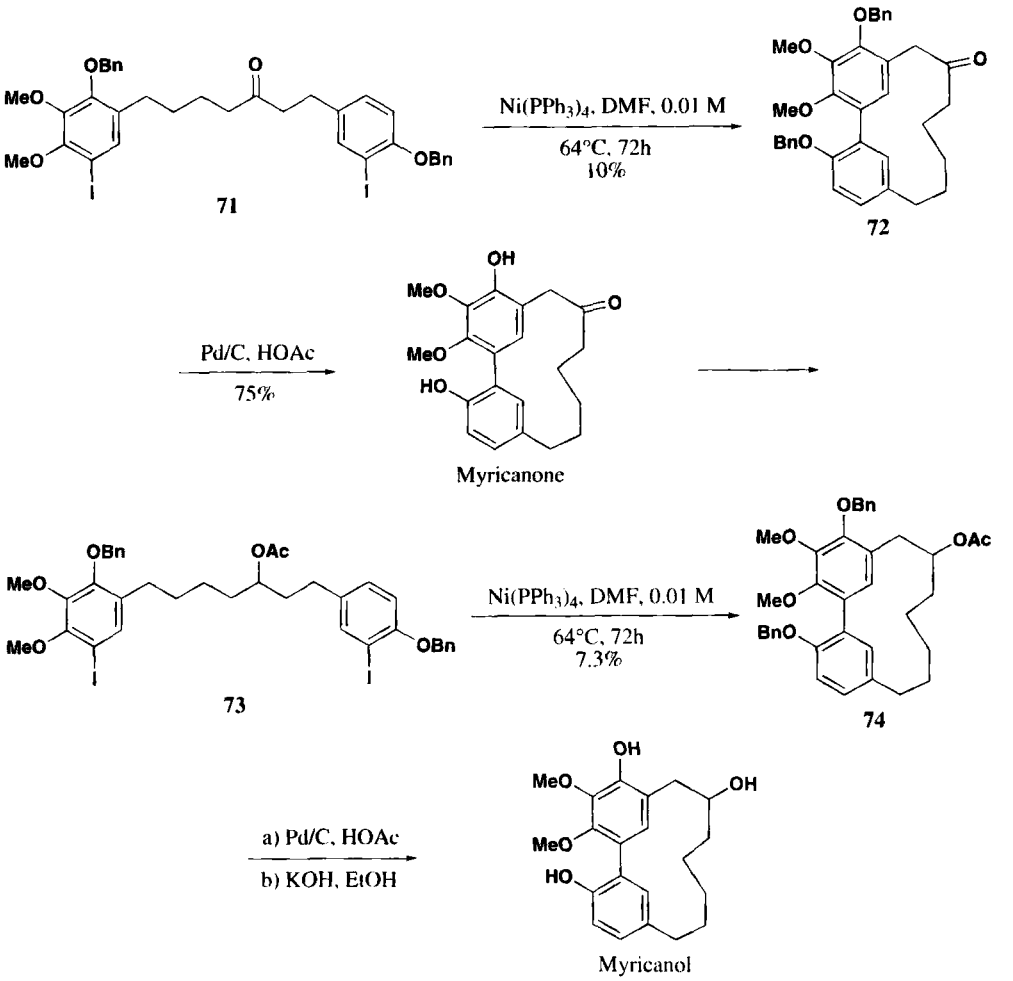
**Scheme 18**

Based on this chemistry, the same group developed a total synthesis of alnusone (*Scheme 19*).[49] Heating a solution of diiodide **69** in DMF in the presence of tetrakis(triphenylphosphine)nickel afforded the 13-membered *meta,meta*-bridged biphenylmacrocycle in 46% yield. Deprotection of MOM ether under acidic conditions gave then the natural alnusone in 72% yield. It is worth noting that high dilution technique is not required in this case.




**Scheme 19**

Employing the same strategy, Whiting *et al* synthesized myricanone and myricanol as shown in *Scheme 20*.[66] The cyclization of diiodide **71** gave the desired dibenzylmyricanone (**72**) albeit in only 10% yield, the major side reaction being hydrodeiodination. Hydrogenolysis gave then the myricanone, identical with the natural product in all respects. Myricanol has also been synthesized starting from diiodide **73** with similar low efficiency in the cyclization step. Both angle strain and van der Waals hydrogen interactions inside the alnusone may be less important than in myricanone due to the presence of an extra double bond in the former molecule. This fact together with the difference in steric hindrance around the aryl iodide precursors may explain the different efficiency in nickel promoted cyclization of **69** and **71**.

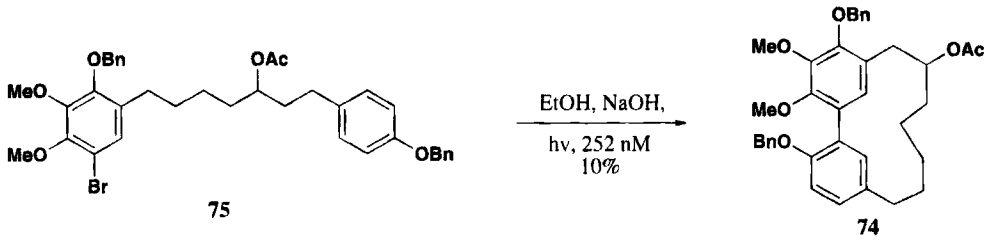



**Scheme 20**

Synthetic dibenzylmyricanol (**74**), possessing both an asymmetric carbon center and a chiral axis, should in principle be obtained as a mixture of two pairs of diastereoisomers. However, this point was not discussed and it seems that only one atropisomer was obtained (7.3%). The NMR spectra data were not described in the original paper.

ii) Photochemical Aryl-Aryl Bond Formation

Photocyclization of the appropriate aryl halide constitutes a valuable technique for the construction of aryl-aryl bond.[65] This photolytically induced radical cyclization has been applied by Whiting for the synthesis of myricanol (*Scheme 21*).[66] Thus irradiation of the bromide **75** in ethanolic sodium hydroxide with 252 nM light in a Rayonet reactor for 30 min afforded the dibenzylmyricanol in about 10% yield.

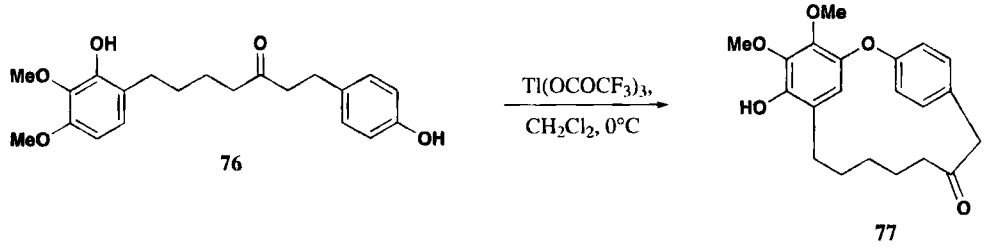



**Scheme 21**

iii) Intramolecular Oxidative Coupling

Biomimetic oxidation of linear diarylheptanoids **76** has also been examined.[66] Direct oxidation of **76** with potassium hexacyanoferrate (III), silver oxide (I), mangnese oxide (IV), and vanadium oxychloride (V) gave only tars, whereas thallium tris(trifluoroacetate) induced intramolecular C-O coupling afforded the 15-membered *m,p*-cyclophane of acerogenine type (*Scheme 22*). No further developement has been reported from this group in spite of its great potential in the synthesis of natural products with an endo aryl-aryl ether bond in general and cyclic diarylheptanoids in particular.



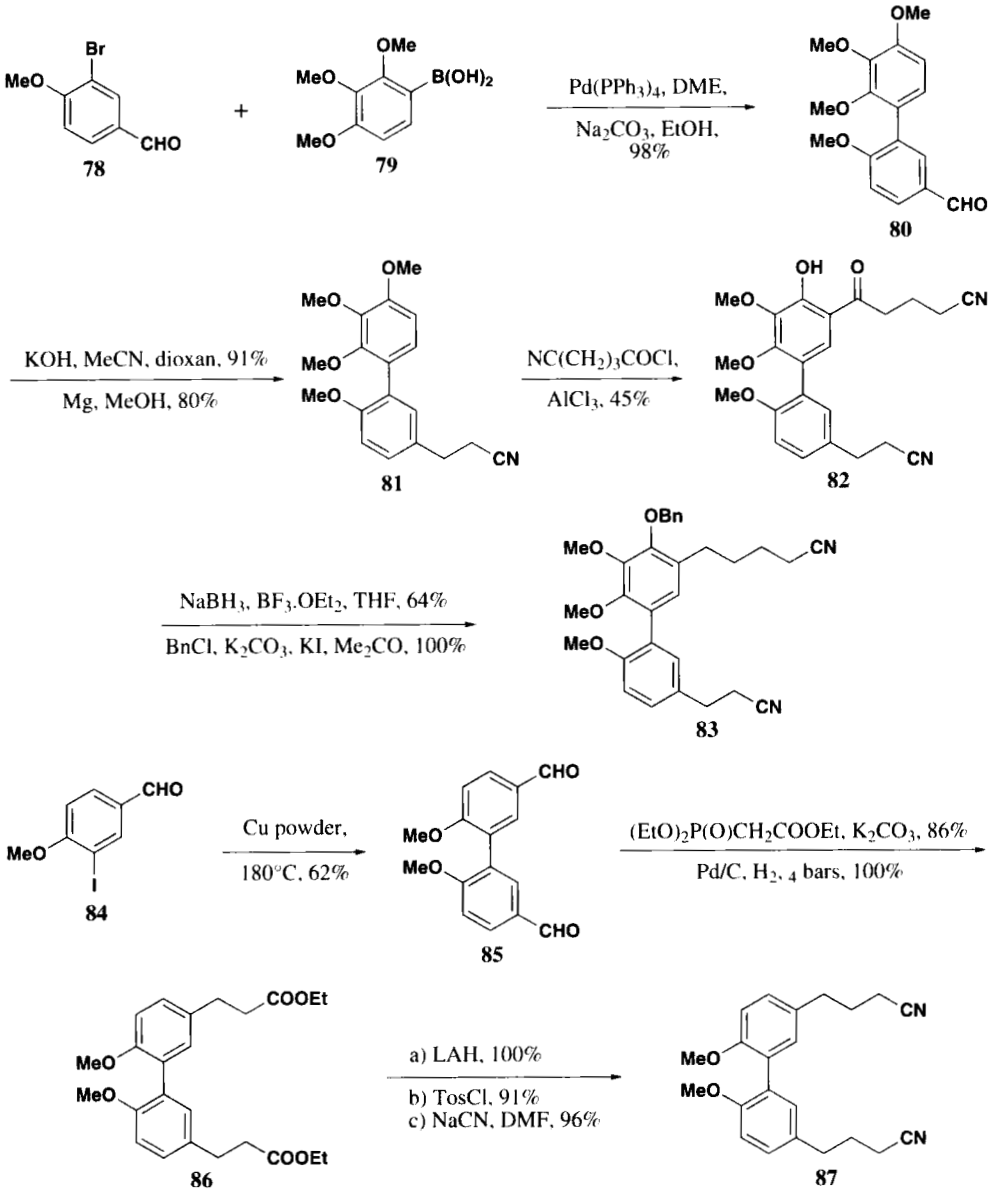



**Scheme 22**

By using thallium trinitrate as oxidant and tetrahalogenated biaryl containing substrates, Yamamura and Nishiyama[58] have discovered an elegant methodology for the formation of biaryl ether bond with concommittant formation of macrocycle.

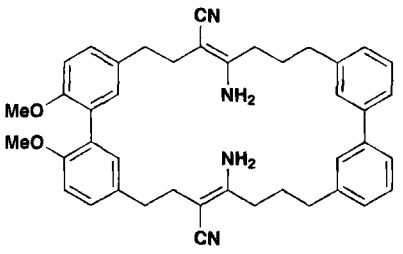
*b) Attempted Ring Formation via Thorpe-Ziegler Reaction*

Formation of an appropriately functionalized biaryl followed by an intramolecular Thorpe-Ziegler reaction have been investigated by the group of Brown.[67] The precursors for their cyclization studies were synthesized as shown in *Scheme 23*. The Suzuki reaction was used for the construction of unsymmetric biaryl **80**, while the Ullmann reaction was employed for the preparation of symmetric biaryl **85**.

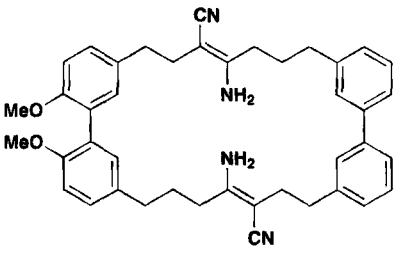



**Scheme 23**

Treatment of unsymmetric biaryl dinitrile **83** with sodium methylphenylamide in high dilution conditions (THF) led to the formation of a mixture of unidentified products. On the other hand, a mixture of two regioisomeric cyclodimers **88** and **89** was produced under the same conditions starting from symmetric biaryl **87** (*Fig 13*). No desired macrocycle was idendified from the reaction mixture.




**88**




**89**

**Fig. 13**



## 3. Total Synthesis of *m,p*-Cyclophanes

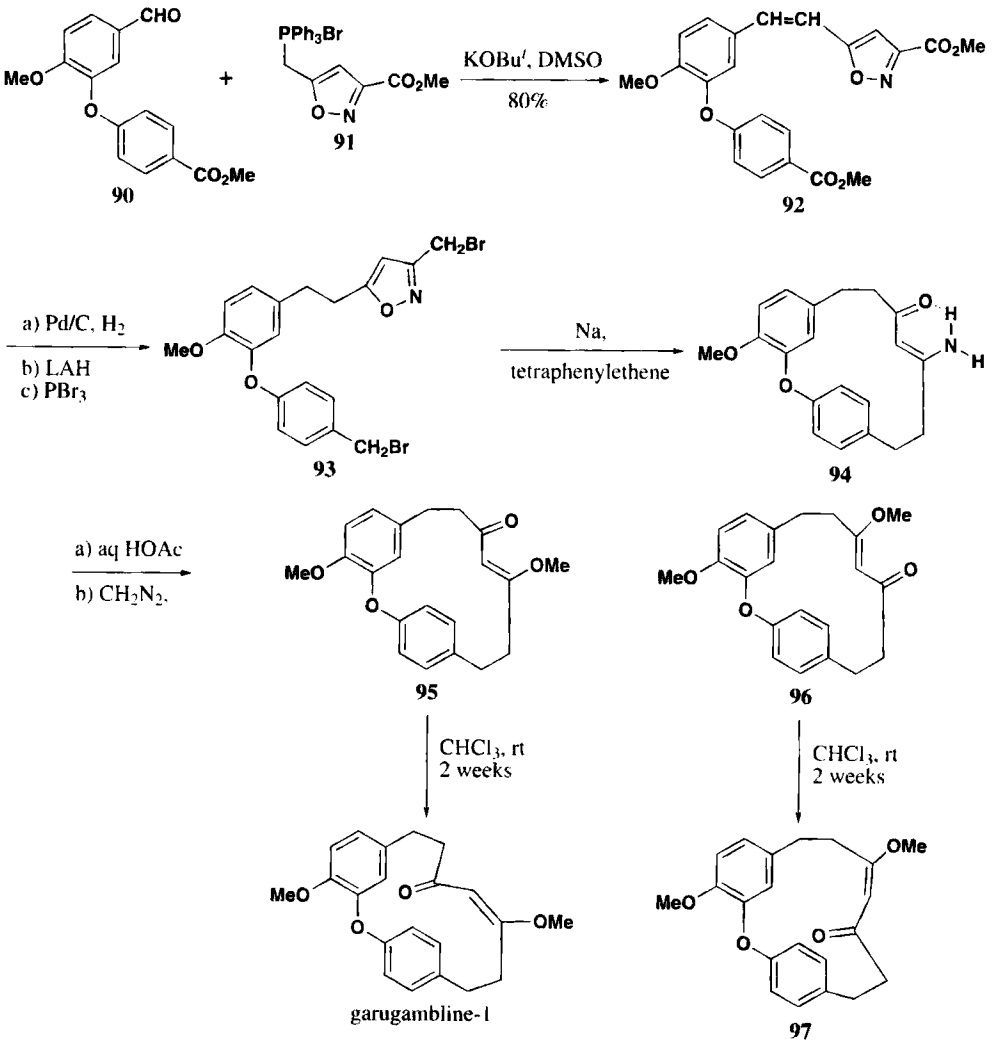
Synthesis of diaryl ethers with sensitive functionalities has been a long-standing problem. Until recently, the classical Ullmann ether synthesis using copper or copper salts required harsh conditions as a result of the poor nucleophilicity of the phenoxide and the low reactivity of the aryl halides involved. The desire to accomplish the total synthesis of structurally complex vancomycin which has two biaryl ether containing macrocycles and very epimerization prone-amino acids has led to the development of a number of powerful new synthetic technologies.[68] As expected, intensive research work in the glycopeptide field has brought fruit to the synthesis of other families of biaryl ether containing natural products. The accidental formation of diarylether containing macrocycles by thallium tris(trifluoroacetate) mediated oxidative coupling of linear diarylheptanoid has been summarized in previous section (*Scheme 22*).[66]

*a) Formation of Macrocycle via Formation of Aliphatic C-C Bond*

Ring closure *via* aliphatic C-C bond formation by the Wurtz and Wittig reactions have been developed by Nógrádi *et al.* for the synthesis of garugamblin-1, garugamblin-2 and garuganin III.

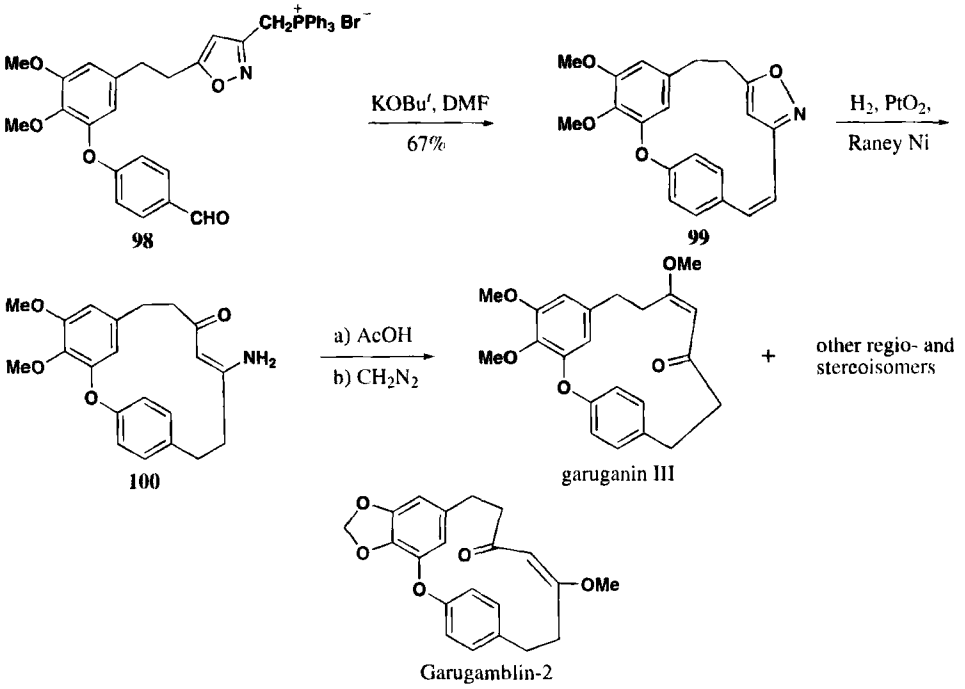
The synthesis of garugamblin-1 is summarized in *Scheme 24*.[69] Wittig reaction of biaryl aldehyde **90** with isoxazole **91** under basic conditions gave compound **92** which was transformed into the dibromide by a three-step sequence. Radical anion induced intramolecular Wurtz reaction with comcommittant cleavage of isoxazole gave the enaminoketone **94** in 16% yield, existing exclusively in a Z-form due to probably the intramolecular H-bonding effect. Acidic hydrolysis followed by *O*-

methylation of enol with diazomethane gave two regioisomeric Z-enol ether **95** and **96**. Compound **95** can be isomerized to natural garugambelin-1 by simply standing in a chloroform solution for two weeks.



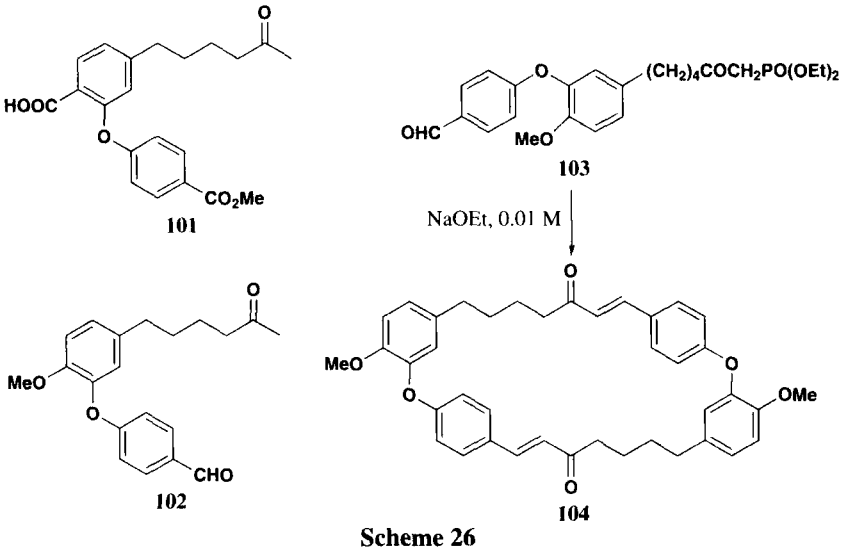

**Scheme 24**

The synthesis of garuganin III featuring a key intramolecular Wittig reaction is highlighted in *Scheme 25*.[70] Addition of potassium tert-butoxide to a dilute solution of **98** in DMF produced macrocycle **99** in 67% yield. Hydrogenation over platinum oxide doped with Raney nickel reduced simultaneously the olefin and the N-O bond leading to the enaminoketone **100**. Garuganin III was isolated from three other regio- and stereoisomers after acidic hydrolysis and methylation of 1,3-diketone. Garugamblin-2 was synthesized by the same group following exactly the same synthetic operations.[71]



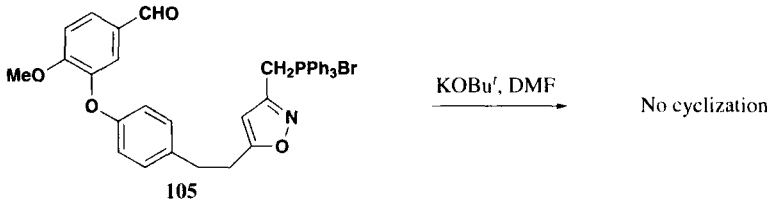

**Scheme 25**

While the isoxazole was cleverly devised as a protected 1,3-diketone surrogate, its role may far exceed what had originally been expected. The presence of isoxazole may help the preorganization of the linear precursor such that the intramolecular reaction was less entropically disfavored. Indeed, attempted intramolecular Claisen condensation of keto ester **101** and intramolecular Aldol reaction of keto aldehyde **102** gave only intractable mixture, while the Wittig-Horner reaction of aldehyde-phosphonate **103** gave the cyclodimer **104** in 13% yield (*Scheme 26*).[72]




**Scheme 26**

It is appropriate to note that this isoxazole strategy is very sensitive to the structural features of the cyclization precursor and thus limited in scope. For example, treatment of compound **105** under Wittig conditions failed to gave any monocyclic compound in spite of its structural similarity with compound **98** (*Scheme 27*).[72]



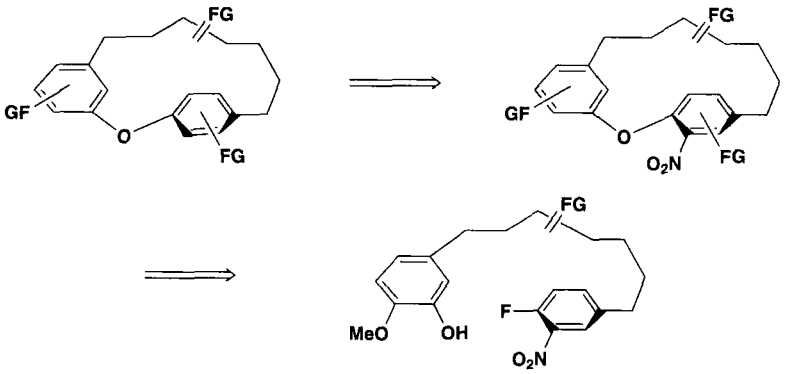

**Scheme 27**

*b) Ring Formation via Aryl-Aryl Ether Bond Formation*

i) Intramolecular $S_NAr$ Reaction.

Intrigued by difficulties associated with the synthesis of vancomycin type glycopeptide antibiotics, our group have developed a new cycloetherification reaction based on an intramolecular nucleophilic aromatic substitution reaction ($S_NAr$)[36] and has applied it in the construction of *polypeptide macrocycles* with endo *aryl–aryl* and *aryl–alkyl ether* bond(s).[73] We have attributed the success of this remarkable cycloetherification to an intramolecular recognition phenomenon. Several structural elements found in our previously studied substrates could indeed help the preorganization in such

a way that a folded conformation was a predominant low energy one, favoring thus the desired cyclization. To evaluate the influence of intramolecular H-bonding on the outcome of cyclization and to further expand the generality of this methodology, we were interested in investigating the cyclization of a linear compound wherein the two reactive sites are linked by *an aliphatic hydrocarbon chain*. The natural diarylheptanoids appeared to be appropriate synthetic targets for this purpose. The successful implementation of this strategy led to the discovery of an efficient and unified synthesis of *m,p*-cyclophane according to the general synthetic plane shown in *Scheme 28*.

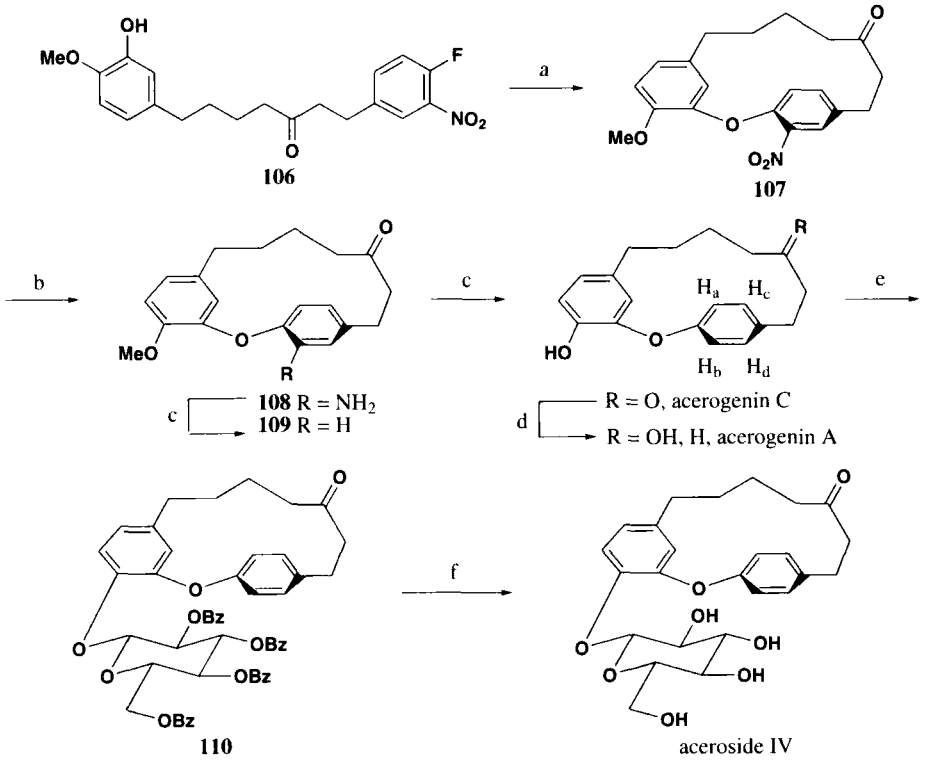



**Scheme 28**

*Scheme 29* highlights key steps on the way to the total synthesis of acerogenin A, acerogenin C and aceroside IV.[34] Cyclization of **106** occurred smoothly in DMF (0.01 M, CsF, room temperature, 5 h) providing the desired 15-membered macrocycle **107** in almost quantitative yield based on the $^1H$ NMR spectrum of the crude product. Potassium carbonate was also effective in promoting this cyclization, though a relatively longer time (10 h) was required. The cycloetherification rate could be accelerated by heating the reaction mixture at 60° without diminishing the yield of cyclophane **107**. To examine the effect of concentration on the outcome of the cyclization, compound **106** was treated with CsF in DMF at 0.01, 0.05, 0.1 and 1M. It was observed that even at high concentration (1 M of **106** in DMF), the analytically pure macrocycle **107** could still be obtained in 45-50% isolated yield. This provides experimental evidence that the intramolecular reaction of compound **106** is indeed facile and highly competitive with the alternative intermolecular process.

The transformation of 15-membered macrocycle **107** into the natural acerogenin A and C was straightforward. Reduction of the nitro group of **107** was carried out by hydrogenolysis under conventional conditions (Pd/C, MeOH, 1 atm) to afford the amino compound **108**, which was converted into compound **109** (90% overall yield) employing Doyle's one-step deamination procedure.[74] The *O*-demethylation of **109** was realized with $AlCl_3$ in refluxing $CH_2Cl_2$, to afford acerogenin C. Reduction of keto function with $NaBH_4$ gave then the racemic acerogenin A in excellent yield. The physical data of these two synthetic substances were identical in all respects to those of the natural products.

The synthesis of aceroside IV was realized using a two-phase glycosidation methodology.[75] Thus, 2,3,4,6-α-D-tetrabenzoylglucopyranosyl bromide was allowed to react with acerogenin C in the presence of tetrabutylammonium bromide ($CH_2Cl_2$–aqueous NaOH) to afford stereoselectively the β-aryl glucoside **110** in 93% yield. The anchimeric participation of the neighboring ester function may be responsible for the high stereoselectivity observed during the glucosidation process. Subsequent saponification (MeOH–$H_2O$, NaOH) of the benzoyl groups gave the aceroside IV in 95% isolated yield. The spectral data of our synthetic material were identical with those of the natural product.

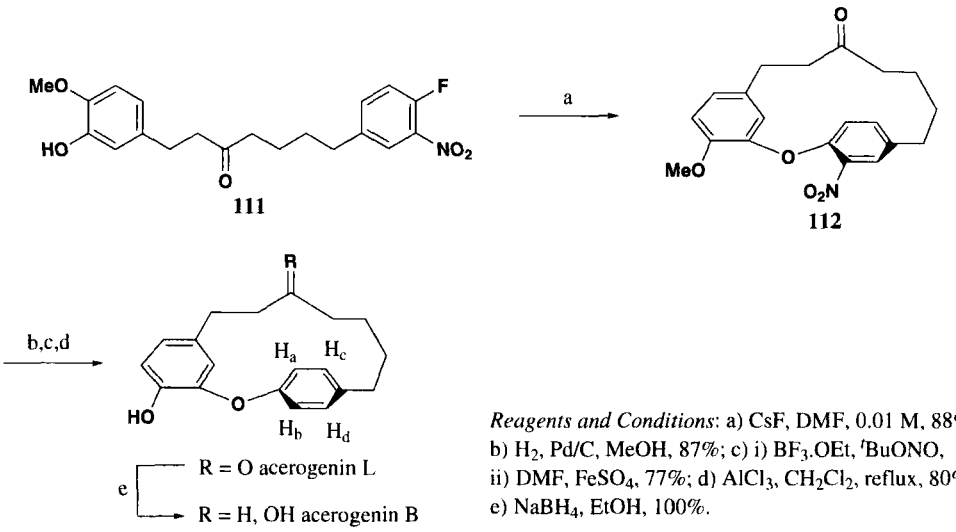



a) CsF, DMF, 0.05 M, 95%; b) $H_2$, Pd/C, MeOH; c) $^t$BuONO, DMF, 90%; d) $AlCl_3$, $CH_2Cl_2$, 88%; d) $NaBH_4$, EtOH, 100%, e) 2,3,4,6-tetrabenzoylglucopyranosyl bromide, $CH_2Cl_2$-NaOH, $Bu_4NBr$, 93%; f) MeOH-$H_2O$, NaOH, 95%.

**Scheme 29**

Acerogenin B and L are structurally very similar to acerogenin A and C. They differ from each other only by the position of carbonyl or hydroxy group in the carbon chain. Their synthesis based on the same strategy is summarized in *Scheme 30*. Macrocylization (CsF, DMF, 0.01M) of **111** gave the 15-membered (*m,p*)-cyclophane **112** in 88% yield. TBAF (DMF, 0.01M) was also effective

in promoting this cyclization to afford **112** in excellent yield. Reduction of nitro group to amine followed by hydro-deamination and cleavage of methyl ether gave then the acerogenin L in good overall yield. Acerogenin B was readily obtained in quantitative yield by reduction of acerogenine L with $NaBH_4$ under standard conditions.

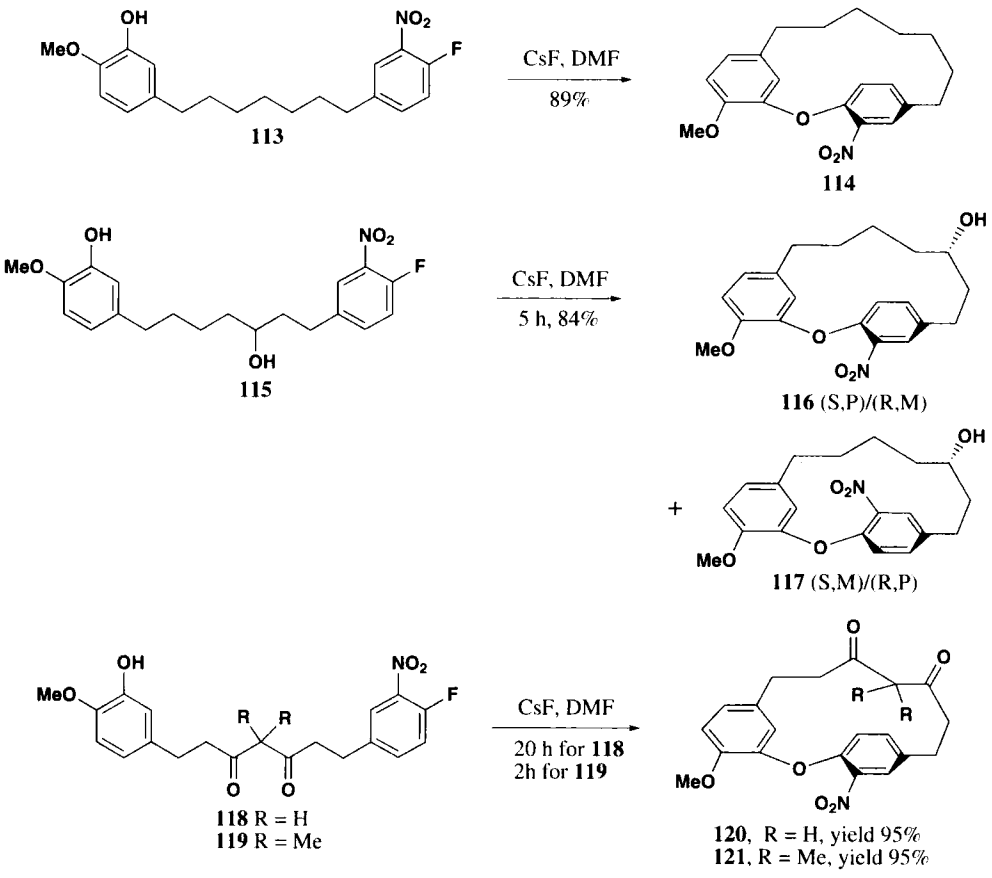



*Reagents and Conditions*: a) CsF, DMF, 0.01 M, 88%; b) $H_2$, Pd/C, MeOH, 87%; c) i) $BF_3$.OEt, $^t$BuONO, ii) DMF, $FeSO_4$, 77%; d) $AlCl_3$, $CH_2Cl_2$, reflux, 80%; e) $NaBH_4$, EtOH, 100%.

**Scheme 30**

The splitting pattern of the *para* disubstituted aromatic protons ($H_a$, $H_b$, $H_c$ and $H_d$) of acerogenin A and C in $^1$H NMR spectra are considerably different. Thus, only two signals were found for these protons which appeared as an AB quartet ($J$ = 8.3 Hz) in the spectrum of acerogenin C, while four signals, each being a doublet of doublet, were observed for these same protons in the spectrum of acerogenin A. This observation indicated that the rotational barrier around the biaryl ether bond of acerogenin C is lower than that of acerogenin A. Since the bond angle of an $sp^2$ carbon is larger than that of an $sp^3$ carbon, we speculated that the presence of a $sp^2$ carbon (carbonyl group) in the heptyl chain tether of acerogenin C reduced both angle strain and H-H steric interactions inside the ring of acerogenin C leading to a more flexible ring system than that of acerogenin A. It is interesting to note that once acerogenin C was glucosylated to give aceroside IV, the four protons ($H_a$, $H_b$, $H_c$ and $H_d$) became chemically and magnetically nonequivalent. The rotation of biaryl ether bond may be hindered in the case of aceroside IV because of the presence of buttressed *ortho* function adjacent to the aryl ether linkage. The same difference in splitting pattern of four protons ($H_a$, $H_b$, $H_c$ and $H_d$) was also observed in the $^1$H NMR spectra of acerogenin B and L.

The generality of this synthetic scheme was further demonstrated by the cyclization reactions listed in *Scheme 31*.




**Scheme 31**

Cycloetherification of **113** without any functionality in the tether chain under standard conditions (CsF, DMF, 0.01 M, 5 h) gave the macrocycle **114** in 89% yield, while compound **115** with a secondary alcohol function gave two pairs of diastereomers in 84% overall yield due to the presence of an asymmetric carbon center and a planar chirality. Precursors containing a 1,3-diketone function **118** and **119** can also be cyclized leading to **120** and **121** in excellent yield. A rate accelerating gem-dimethyl effect was observed in the course of this study.[76] Compound **120** is the precursor of garagamblin-1, while **121** has been transfered into the deoxy-garuganine VI.[47] These results indicated that the cyclization outcome was insensitive to the functionality present in the tethered chain and should thus find wide applications in the synthesis of related natural or non-natural cyclophanes.

The efficiency of macrocyclization was further illustrated by two additional control experiments wherein the intermolecular processes were statistically favored by addition of an external nucleophile or an electrophile (*Fig. 14*). When equimolar amounts of compounds **106** and 4-methoxyphenol (**121**) (DMF, 0.01 M) were treated with CsF at room temperature, a clean spot to spot transformation was observed and the cyclophane **107** was the only new product formed. Neither dimerization

(oligomerization) nor cross-coupled prouct **122** were observed in the crude $^1$H NMR spectrum. Similarly, the presence of an external electrophilic partner such as 4-fluoro-3-nitrotoluene (**123**) did not interfere with the reaction pathway of **106** and no trace of cross coupled product **124** was detected when a mixture of **106** and **123** was treated with CsF in DMF (0.01 M).

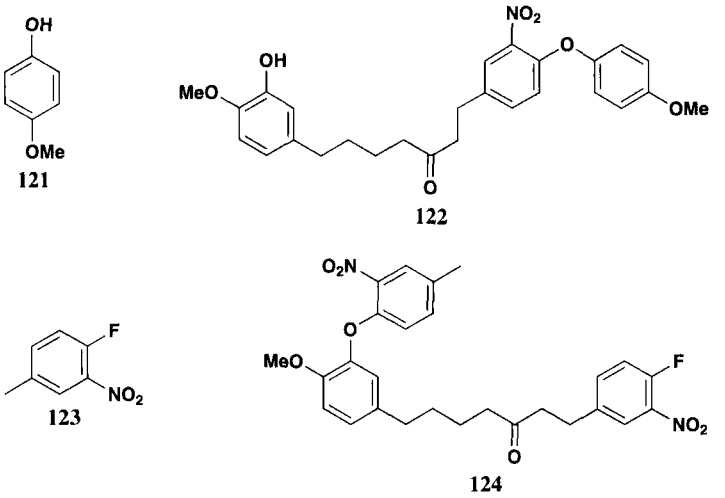
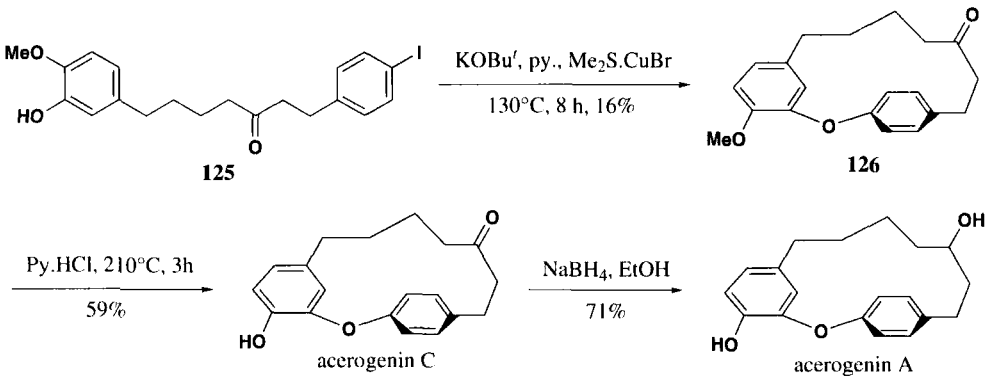



**Fig. 14**

ii) Intramolecular Ullmann Ether Synthesis

Parallel to our work, Nógrádi et al have developed a synthesis of acerogenin A and C by implementation of an intramolecular Ullmann ether synthesis (*Scheme 32*).[77]




**Scheme 32**

Heating a solution of linear diarylheptanoid **125** in pyridine to 130° in the presence of KO'Bu and $Me_2S.CuBr$ afforded the *O*-methyl acerogenin C in 16% yield, which was then transfered into natural product by treatment with pyridine hydrochloride. The latter was converted into acerogenine A by its reduction with $NaBH_4$ in EtOH.

## V. CONCLUSION

Curcumin, one of the first natural substances to be isolated in more or less pure state in the history of organic chemistry, continues to attract the attention of scientists from both academia and industry. Recent years have also witnessed the steady progress in the chemistry and biology of diarylheptanoids. Indeed, new structure and new bioactivity profile have been identified.

Progress towards the synthesis of the macrocyclic diarylheptanoids has been slow and synthetic challenges persist in spite of their simple structure. Thus, enantioseletive synthesis of (*P,3S,5S*)-alnusdiol (*Fig. 8*) and *P*-(+)-galeon, *M*-(-)-galeon (*Fig. 10*) remains elusive even in today's standards. Since the chiral axis and chiral plane in these molecules were created only upon cyclization (rotation was hindered due to the ring strain), the development of an *enantioselective macro-cyclization* became a prerequisite for realizing this goal. However, to the best of our knowledge, such a process was unavailable to date.

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