CHAPTER - I

A Review on Lignan Lactones
A Review on Lignan lactones

1.1. Occurrence, nomenclature and classification

The term "Lignan" was introduced by Haworth for a family of optically active plant products formed by joining certain derivatives of n-propylbenzene residues at the β-carbon atoms of the side chains. The aromatic rings of all lignans are oxygenated and bear hydroxyl, methoxyl or methylene-dioxy groups. The side chains also exist in various states of oxidation, and in lignans reviewed here the side chains are existing in the form of cyclic esters i.e. in the form of Y-butyrolactones.

During 1930-1950, Haworth and co-workers elucidated the structures of many lignans, devised methods for lignan synthesis and investigated the stereochemical relationships of lignans. Lignans are of wide occurrence and have been obtained from root, heartwood, bark, foliage, fruit, seeds, leaves and resinous exudate of the plants. The presence of a given lignan is sometimes a characteristic of a certain botanical group and therefore of taxonomic interest.

Haworth classified lignans into five principal groups on the basis of different modes of combination of two units of n-propylbenzene. These types formal chemical names of the structures are presented in Chart 1.1.1. Another nomenclature was introduced by Freudenberg and Weinges based on partial structures (1-3). Here the numbering starts
on the benzene rings at the carbon chain linkage as shown (Chart 1.2). The structures 1 and 2 are the same but in certain lignans of furan type (see type 3a and 3c vs 3b and 4 in Chart 1.1) the two benzene rings are placed in somewhat different fashion.

These three main groups of structures are are further subdivided according to the nature of oxygen substitution in the benzene ring as pipero, guaiia and syringa (see Chart 1.2) lignans. But this subdivision of lignans is now inadequate because of the newer lignans containing different substituents in each ring.

This review is only on the naturally occurring lignan lactones. Naturally occurring lignan lactones belong to three groups A, B and C (see Chart 1.3). A and B are types 2 and 5b of Haworth's classification (Chart 1.1). The third group C viz. bisbenzocyclooctadiene lactones belong to a new series, the first examples in nature of which were discovered by Kupchan.13

All the above lignan lactones are listed along with their melting points and sources in Table 1. These lignan lactones occur in all parts of plants, but a majority of them have been isolated from the heartwood and bark. They bear typical oxygenated pattern both in benzene rings and contain two oxygenated carbon atoms existing in the form of a cyclic ester viz. a γ-lactone. The 4-carbon atom in many of the cyclolignans (group B, Chart 1.3) bears a oxygen function
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<tbody>
<tr>
<td>1</td>
<td>Hinokinin</td>
<td>$3,4,3',4'-(OCH_2O)_2$</td>
<td>64-65°</td>
<td>Chamaecyparis heartwood</td>
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<tr>
<td>2</td>
<td>Matairesionol</td>
<td>$3,3'-\text{(OMe)}_2$, $4,4'-\text{(OH)}_2$</td>
<td>119</td>
<td>Picea podocarpus, abies spicata heartwood</td>
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<td>Hydroxy Matairesinol</td>
<td>$3,3'-\text{(OMe)}_2$, $4,4',4''\text{(OH)}_3$</td>
<td>147</td>
<td>Picea abies heartwood</td>
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<td>4</td>
<td>Arctigenin</td>
<td>$3,3',4'-\text{(OMe)}_3$, $4'-\text{(OH)}$</td>
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<td>Picea abies heartwood</td>
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<td>Oxomatairesinol</td>
<td>$3,3'-\text{(OMe)}_2$, $4,4'-\text{(OH)}_2-7\text{-OXO}$</td>
<td>70-72</td>
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<td>6</td>
<td>Savinin</td>
<td>$3,4,3',4'-(OCH_2O)_2$, $7,8'\text{-dehydro}$</td>
<td>146</td>
<td>Taiwanine cryptomenioidus heartwood</td>
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<td>7</td>
<td>Taiwanin</td>
<td>$3,4,3',4'-(OCH_2O)_2$, $7,8,7',8'\text{-didehydro}$</td>
<td>-</td>
<td>Taiwanine cryptomenioidus heartwood</td>
<td>16</td>
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<td>8</td>
<td>Pinopolustrin</td>
<td>$3,3'-\text{(OMe)}_2$, $4,4',8'\text{-(OH)}_3$</td>
<td>-</td>
<td>Pinus palustrin heartwood</td>
<td>19</td>
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<tr>
<td>9</td>
<td>Thujaplicatin</td>
<td>3,3'-(OH)₂</td>
<td>-</td>
<td>Thujaplicata</td>
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<tr>
<td></td>
<td></td>
<td>4,4',5'-(OMe)₃</td>
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<tr>
<td>10</td>
<td>Thujaplicatin methyl ether</td>
<td>3,3',5'- (OMe)₃</td>
<td>167</td>
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<td>4,4'-(OH)₂</td>
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<td>128</td>
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<td>4,4',5'- (OH)₃</td>
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<td>12</td>
<td>Dihydroxy Thujaplicatin</td>
<td>3,3'-(OMe)₂</td>
<td>163</td>
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<td></td>
<td>4,5,7,4',7'- (OH)₅</td>
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<td>13</td>
<td>Dihydroxy Thujaplicatin methyl ether</td>
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<td>99-100°</td>
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<td>4,4',7,7'- (OH)₄</td>
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<tr>
<td>14</td>
<td>Pluviatolide</td>
<td>3',4'-(OCH₂O)</td>
<td>160</td>
<td>Zanthoxylum pluviatile heartwood</td>
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<tr>
<td></td>
<td></td>
<td>3-OMe, 4-OH</td>
<td></td>
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<td>15</td>
<td>Sventinin</td>
<td>3,4,3',4'- (OCH₂O)₂</td>
<td>-</td>
<td>Rutamicro carpa leaves</td>
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<td></td>
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<td>7'-OH</td>
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<tr>
<td>16</td>
<td>Halianthoidin</td>
<td>3,4-(OMe)₂</td>
<td>134°</td>
<td>Heliopsis scabre roots</td>
<td>22</td>
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<tr>
<td></td>
<td></td>
<td>3',4'-(OCH₂O)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>7-OCOCH=CHCH₃</td>
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<tr>
<td>17. Podorhizol</td>
<td>4,5-(OCH₂O)</td>
<td>125-26°</td>
<td>Podophyllum emodiwell</td>
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<tr>
<td></td>
<td>3',4',5'-(-OMe)₃7'-OH</td>
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**Group 'B' of Chart 1.1.3**

| 18. Plicatin | 3,3'-(OMe)₂ |   | Thujaplicata Dann heartwood |
|   | 4,8,4',5',8'-(-OH)₅ |   |   |

| 19. Cleistanthin | 3,4-(OCH₂O),3',4'-(-OMe)₂ | 135 | Cleistanthus collinus leaves |
|   | 7,8,7',9'-bis-dehydro-7'-oxylose |   |   |

| 20. Collinusin | 3,4-(OCH₂O),3',4'-(-OMe)₂ | 196 | Cleistanthus collinus leaves |
| 21. Justicidin A | 3,4,7'-(-OMe)₃ | 260° | Justicia Hayatai var decumbens |
|   | 3',4'-(-CH₂O₂) |   |   |
|   | 7,8,7',8'-bisdehydro |   |   |

| 22. Justicidin B | 3,4-(OCH₂O),3',4'-(-OMe)₂ | 240° | Cleistanthus collinus leaves and Justicia Hayatai var decumbens |
|   | 7,8,7',8'-bisdehydro |   |   |

| 23. Diphyllin | 3,4-(OCH₂O),7'-OH |   | Diphylleia grayi leaves and Cleistanthus collinus leaves |
|   | 3',4'-(-OMe)₂,7,8,7',8'-bisdehydro |   |   |

Continued
| 24 | Podophylootoxin | 3,4,5-(OMe)₃ | 183 | Podophyllum peltatum resin and podophyllum emodi |
| 25 | Dimethyl dehydroxy podophyllootoxin | 3,5-(OMe)₂,4'-OH | 244° | Polygala paenea podophyllum emodi podophyllum peltatum |
| 26 | Demethyl podophyllootoxin | 3,5-(OMe)₂,3',4'-(CH₂O)₂ | 250-51° | Podophyllum emodi resin |
| 27 | Dehydropodophyllotoxin | 3,4,5-(OMe)₃,7'-OH | 268° | Podophyllum emodi resin |
| 28 | Dehydroxy podophyllootoxin | 3,4,5-(OMe)₃,3',4'-(CH₂O)₂ | 167-68° | Anthriscus sylvestris root and Juniperus silicicola |
| 29 | β-Peltatin | 3,4,5-(OMe)₃,2'-OH | 231-33° | Podophyllum peltatum resin |
| 30 | α-Peltatin | 3,4-(OMe)₂ | 220° | Podophyllum peltatum resin |
| 31 | Picropodophyllum | isomer of podophyllootoxin at C-7 | 231° | Podophyllum emodi resin |

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<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Structure</th>
<th>Boiling Point</th>
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<tr>
<td>32</td>
<td>Steganone</td>
<td>2,3-((\text{OCH}_2\text{O}))</td>
<td>155–56°</td>
<td>Steganotaenia</td>
<td>13</td>
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<tr>
<td></td>
<td></td>
<td>10,11,12-((\text{OMe}))_3</td>
<td></td>
<td>araliacea</td>
<td>Hochst</td>
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<tr>
<td></td>
<td></td>
<td>(R^1 = \text{OCH}_3), (R^2 = \text{CH}_3)</td>
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<tr>
<td>33</td>
<td>Steganacin</td>
<td>2,3-((\text{OCH}_2\text{O}))</td>
<td>142–43°</td>
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<td>araliacea</td>
<td>Hochst</td>
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<tr>
<td></td>
<td></td>
<td>(R^1 = \text{OCH}_3), (R^2 = \text{H})</td>
<td></td>
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<tr>
<td>34</td>
<td>Steganangin</td>
<td>2,3-((\text{OCH}_2\text{O}))</td>
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<td>Steganotaenia</td>
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<td>10,11,12-((\text{OMe}))_3</td>
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<td>araliacea</td>
<td>Hochst</td>
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<td></td>
<td></td>
<td>(R^1 = \text{OCH}_3), (R^2 = \text{H})</td>
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<tr>
<td>35</td>
<td>Steganol</td>
<td>2,3-((\text{OCH}_2\text{O}))</td>
<td></td>
<td>Steganotaenia</td>
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<td>10,11,12-((\text{OMe}))_3</td>
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<td>araliacea</td>
<td>Hochst</td>
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<td>(R^1 = \text{OH}), (R^2 = \text{H})</td>
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</table>
CHART - 1 1 2

1

2

3

PODOPHYLLOTOXIN
1D, 2L, 3D, 4D

GUAIA LIGNAN

GUAIA CYCLO LIGNAN
CHART - 1.1.3

2,3-DIBENZYL BUTYROLACTONE

A

1-ARYLTETRAHYDRONAPHTHALENE  2,3-LACTONE

B

BIS-BENZOCYCLOOCTADIENE LACTONE

C
such as alcohol acetyl, ketone etc. But the same oxygen function such as ketone, ester, acetyl and alcohol is placed at carbon number 6 in the lignans of group C (Chart 1.3) isolated by Kupchan.¹³

1.2 Isolation Methods

Various types of isolation methods have been adopted in separating lignans from different plant sources. All the lignan lactones represented here are isolated from the plant by solvent extraction method.

Hartwell,¹⁸ from podophyllum emodi resin, separated podophyllotoxin free of other contaminants. It was found that aqueous suspensions of the dried needles of certain Junipers caused haemorrhage and necrosis in the tumor. By successive fractionation with different solvents and by column chromatography, the crystals of podophyllotoxin and savanin were separated. Some lignans, like Taiwanin¹⁶ type, are isolated from the heartwood of the plant by extraction with acetone.

Lignans with catechyl, guaiacyl and syringyl groups can be located on chromatogram by chromatographic spraying reagents. Ferric chloride-Ferricyanide reagent which form prussian blue with all phenols can be used for these substances. Simple phenols couple with diazonium salts in alkaline solution to form azodyes, and this classical method has also been used for the location of lignans. Other
spraying reagents used for chromatogram are phosphomolybdic acid and sulfuric acid-methanol mixture.

Kupchan recently isolated four lignans, of a new type, from the dried plant, Steganotaenia araliacea Hochst, using ethanol as extraction solvent. The ethanol extract was further fractionated by extraction with different solvents and finally the material was chromatographed on silica gel column using benzene and ether as elution solvents.

1.3 Chemical reactions of lignans

Classically, the wood-constituent which on oxidation by heating with nitrobenzene in alkaline solution at 160°C, gives aromatic aldehydes are termed lignans. Coniferous woods on such oxidation with nitrobenzene give vanillin, deciduous woods give vanillin and syringaldehyde and monocotyledons give vanillin, syringaldehyde and p-hydroxybenzaldehyde. Another characteristic reaction of lignin is the typical ethanolation on refluxing in ethanol with catalytic amount of hydrochloric acid. Coniferous woods give \( \alpha \)-ethoxy propioguaicione, \( \beta \)-anilloyl and \( \beta \)-aniloxy methyl ketone. In the case of deciduous woods, the above products are formed along with the corresponding syringyl derivatives. This ethanolation is a specific reaction for lignans by virtue of their having a \( \beta \)-aryloxy-d-guaiacyl glycerol structure.
Since the physical methods (IR, UV, NMR, Mass etc.) are very much informative and give an exact idea about the nature of the carbon skeleton and type of the lignan, in recent years, chemical degradation methods and correlation studies are rarely used. The latter method is however very useful to know the stereochemistry of lignans. Degradation studies were restricted to a limited experiments such as selenium dehydrogenation, oxidation with potassium permanganate, hydrogenation with Pd/C and reduction with lithium aluminium hydride or sodium borohydride. The yields of the selenium degradation experiments are very poor (nearly 2-4%). Almost all lignans give dehydroguaiaretic acid on selenium dehydrogenation. Lignans on oxidation with KMnO₄ give substituted benzoic acid. Lignans having identical substituents in both the benzene rings give more than 50% substituted benzoic acid. Lignans of phenyltetralin type on oxidation with KMnO₄ give benzoyl benzoic acid. When lignan lactones are reduced with lithium aluminum hydride diols are produced.

1.4 Biological activity of lignan

Many biological properties are attributed to different classes of lignans. Among them the abortifacient and antitumor activity of some lignan lactones are of more interest and reported in literature extensively.
The nature of abortifacient activity of podophyllotoxin and podophyllin has been studied by Hartwell\textsuperscript{35}. Schrecker\textsuperscript{36} studied the tumor-damaging property of podophyllotoxin and showed that the potency of the activity is related to stereochemistry. Friedkin\textsuperscript{37} found that podophyllotoxin inhibited strongly binding of colchicine in vivo and in vitro and that they are useful in inhibiting cell division. Some of the podophyllin derivatives like podophyllic acid ethylhydrazide (designated as SPI) and podophyllotoxin-\(\beta\)-D-benzylidene glucoside (designated as SRG) were also studied extensively for their anticancer properties. SRG was used on the hypertriploid strain of \textit{Ehrlich ascites} carcinoma and a remarkable antimitotic effect was observed by Jose\textsuperscript{38}. Neiger\textsuperscript{39} studied the use of SRG and SPI in some cases of ENT carcinoma where for various reasons treatment by conventional methods such as radiotherapy and surgical section was not possible. He observed that in some cases there was complete disappearance of localised tumor deposits with SPI. Oral administration of SPI and SRG as anticancer agents showed high degree of tolerance and both subjective and objective improvements in some cases studied by Sarkar and coworkers\textsuperscript{40}. Podophyllic acid was also shown to be similarly effective by Sakamoto\textsuperscript{41}. Trepel\textsuperscript{42} observed in guinea pigs a marked diminution of tuberculin hypersensitivity which followed immunisation by BCG, by podophyllic acid. Reversible
inhibition of cilia regeneration of *S. coeruleus* was observed by Makrides\(^{43}\), using substantial doses of podophyllotoxin.

The active principles of *Justica Hayatal var decumbens*, viz. Justicidines have been used as fish poisons for hundreds of years\(^{25a,b,c}\).

The steganone and derivatives isolated by Kupchan\(^{13}\) in 1973 from *Steganotaenia araliacea Hochst*, are lignan lactones similar to podophyllotoxin structure. These also have shown interesting antileukaemic properties and have instigated efforts in total synthesis of the compounds for further biological studies.

1.5 **Stereochemistry**

The stereochemistry of many lignan derivatives and the absolute configuration of the different asymmetric centres are determined by correlation with \((-\) guaiaretic acid and lignin interconversions.

Guaiaretic acid, a simple lignan isolated from guaiacum resin\(^{44}\) by ether extraction, has one asymmetric centre. The absolute configuration of guaiaretic acid is determined by direct and indirect chemical correlation with D-phenylalanine and L-3,4-dihydroxyphenylalanine.

D-phenylalanine (VI) (Scheme\(^{45.1}\)) was chemically converted\(^{45a,b}\) to \((+)-\alpha\)-methylphenethylamine (V) (Scheme\(^{45.1}\)) by conventional methods which involved transformation of a
SCHEME - 1.5.1

D (-) GUAIARETIC ACID
DIMETHYL ETHER

I

II b D-SERIES

III b D-SERIES

II a L-SERIES

III a L-SERIES

IDENTICAL SIGN AND ROTATION

V L-SERIES

VI L-SERIES

D-PHENYLALANINE (+) α-Me-PHENETHYLAMINE α-Me-HYDROCINNAMIC ACID

Ar = 3,4 (MeO)₂ C₆H₃⁻
carboxyl to methyl group (Scheme 5.1). By virtue of the chemical transformation of the groups involved (V) should belong to the L-series. Dextrorotatory α-methylhydrocinnamic acid (IV) (Scheme 5.1) also gave the identical α-methylphenethylamine (V) by Curtius rearrangement. Hence (IV) also should belong to the L-series; (IV) had identical sign and rotation (+270) as its dimethoxy analogue (IIIA), (IIIa) and the derived ketone (IIa) should then also be L in configuration. The corresponding ketone obtained from guaiaretic acid dimethylether (I) (Scheme 5.1) had opposite rotation showing this ketone was the antipode of IIa viz IIb. Hence IIb and therefore I should belong to the D-series (Scheme 1.1). Ketone IIb was obtained directly from the antipode of α-methyl dihydrocinnamic acid (IIIA), viz. (IIIb), the D(-)3,4-dimethoxy-α-methyl dihydrocinnamic acid.

For a more rigorous proof of the absolute configuration of IIIb, it was correlated chemically46 with L-3,4-dihydroxy phenylalanine (VII) (Scheme 5.2) a natural amino acid of established configuration47a,b. Both IIIb and VII were chemically correlated, as shown, to N-tosyl 3,4-dimethoxy α-methyl-phenethylamine (VIII). Conversion of (VII) (L) to (VIII) involved reduction of carboxyl to methyl. Hence (VIII) should belong to the D-series. Since identical material is obtained from IIIb by Curtius rearrangement and tosylation,
SCHEME 1.5.2

II b

D (-) ACID

OPTICAL ANTIPODE OF
L (+) α-Me-HYDROCINNAMIC ACID

CURTIUS REARRANGENT

NH₂

H — C— CH₃
CH₂ Ar

D - SERIES

TsCl

CH₃

TSHN — C— H
CH₂ Ar

D - SERIES

VII

L-3,4-DIHYDROXYPHENYLALANINE

1) HCO₂H, Ac₂O
2) Me₂SO₄
3) MeOH / HCl
4) NaO Ме

COOCH₃

H₂N — C— H
CH₂ Ar

L - SERIES

VIII

Ar = 3, 4 (MeO)₂ C₆H₃−
(IIIb) and hence guaiaretic acid (I), with which it is related via the ketone IIb, should also belong to the D-series.

Based on the absolute configuration of guaiaretic acid, the absolute configuration of podophyllotoxin was determined by Schrecker and others\textsuperscript{36,45}. In podophyllotoxin (see Chart 1.2) the trans (1:2)-trans (2:3)-cis (3:4) arrangement of groups on carbon atom 1 to 4 was already established by chemical evidence\textsuperscript{48,49}. Also the configurational identity of C-3 with D (-) guaiaretic acid was also known\textsuperscript{44}. If C-3 is D, the absolute configuration of podophyllotoxin would then be 1D, 2L, 3D, 4D. Since podophyllotoxin was chemically correlated with other lignans this paved the way for establishing the absolute configuration of other lignans as well.

Absolute configuration of dihydroguaiaretic acid\textsuperscript{49} is also known as its dimethyl ether is obtained by the catalytic hydrogenation of D(-) guaiaretic acid dimethyl ether. Knowing the trans geometry of (--) hinokinin and (--) metairesinol and since the latter as its dimethyl ether (42) can be correlated with dihydroguaiaretic acid dimethyl ether, the absolute stereochemistry of (--) hinokinin and metairesinol and lignans chemically related to them\textsuperscript{46,49,51-54} (Scheme 5) like cubebin, sesamin, asarinin, lарiciresinol can all be determined.
SCHEME - 153

HINOKININ (1)  
CUBEBIN (38)  
ASARININ (41)

DIOL - DIHYDROCUBE BIN (39)  
SESAMIN (40)

DIMETHYLEETHER OF MATAIRE SINOL (42)  
DIMETHYLEETHER OF SECO-ISOLARICRESINOL (43)  
DIMETHYLEETHER OF LARICRESINOL (44)

DIMETHYLEETHER OF DEHYDROGUAIARE TIC ACID (37)  
DIMETHYLEETHER OF GUAIARE TIC ACID (36)

\[ Ar = \begin{array}{c} \text{O} \\ \text{O} \end{array}, \quad Ar' = \begin{array}{c} \text{MeO} \\ \text{MeO} \end{array} \]
NMR spectra was also used to study the structure and stereochemistry of a number of lignans\textsuperscript{55,56}. Most of the lignans contain methoxy and methylenedioxy substituents in the benzene rings. Methylenedioxy group generally gives a sharp singlet at the region 4.0 to 4.2 (\textit{J}). Aromatic methoxyls appear in the region 6.0 - 6.3 (\textit{J}). The aromatic protons whose chemical environments are more or less identical, show up as an unresolved multiplet in their NMR, crowded in the region 2.7 - 3.2 (\textit{J}).

Ayres and Chater\textsuperscript{57} applied gas chromatography for the separation of lignans. They have studied the retention time (t\textsubscript{R}) for a variety of lignans. They found that in case of galbulin type lignans the cis configuration has a lower t\textsubscript{R} value than the trans one. Similarly cyclic lignans with lactone show considerable increase in t\textsubscript{R} values.

1.6 Uses of lignans

Relatively few lignans have gained commercial importance. Guaiaretic acid derivatives are used to protect vegetable and animal fats. Some of them are used widely in dairy products to reduce spoilage of milk by oxidation. Studies regarding the potential use in cancer chemotherapy of podophyllotoxin, \textalpha{}-peltatin and \textbeta{}-peltatin have been carried out and they were found to produce severe damage to tumor. The activity of podophyllotoxin and \textalpha{}-peltatin are
apparently associated with tetrahydronaphthalene nucleus and the lactone ring. Demethyl podophyllotoxin, desoxy-podophyllotoxin are also active. The steric configuration is also important in the tumor-damaging activity since some picropodophyllotoxin derivatives are entirely inactive.
REFERENCES

44. G. Schroeter, L. Lichtenstadt and D. Ireneu, Ber., 51, 1587 (1918); CA 13, 990 (1919).