# CONSTRUCTION OF HETEROCYCLIC LIGNANS IN NATURAL PRODUCT SYNTHESIS AND MEDICINAL CHEMISTRY

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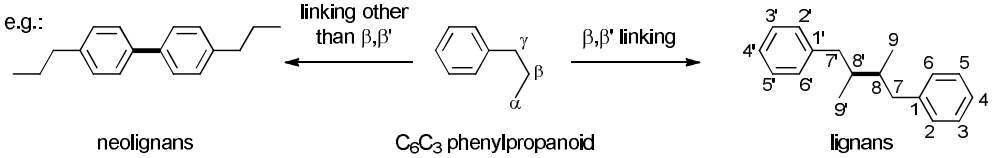
***Abstract.*** *Oxygen-containing heterocyclic lignans are chiral molecules for which a variety of preparative methods exist and which displays numerous biological activities. Hence, efforts towards their syntheses are highly important. Due to the diversity of this class of natural products, the usefulness of a given synthetic approach will depend strongly on the particular type of lignan that is aimed for. This chapter explains the classification of lignans and highlights examples of laboratory preparation, discussing the stereoselectivity and modularity of the synthetic routes for which a range of very different ideas are brought to bear. The motivation for work in this field often derives from the biological activity of these compounds, an aspect which is commented on as well.*

**Contents**



## 1. Introduction

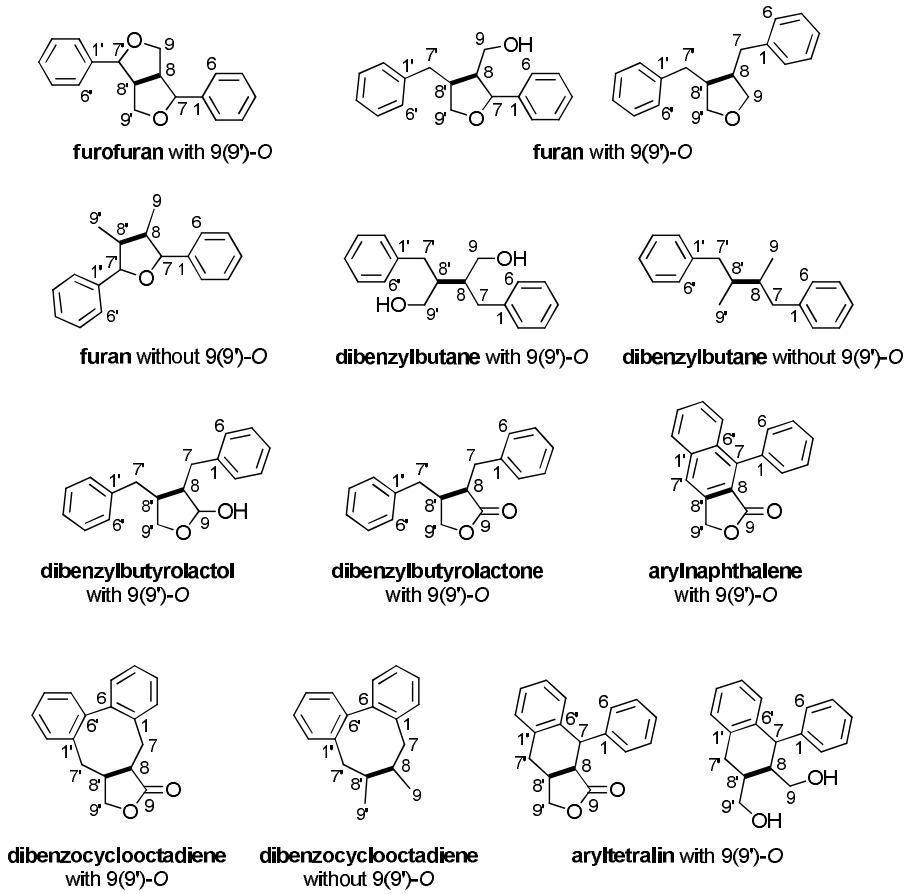
Lignans form a wide range of natural compounds which occur in both herbaceous plants (herbs) and woody plants (trees, shrubs and vines). They are secondary metabolites[1] consisting of at least two phenylpropanoid units ($C_6C_3$ building blocks).[2] The definition is often restricted to dimeric phenylpropanoids[1] because it is the most prominent form in which they are known to appear in Nature.[3] The structural diversity of these compounds has led to various nomenclature proposals to number the skeletal atoms, resulting in IUPAC recommendations for rational and consistent naming[3] which will be used for description throughout. Therein, a compound is considered a lignan if the two $C_6C_3$ units (in the dimeric case) are linked by a β-β' bond, subsequently termed the 8-8' bond, whereas if the units are combined in any other way (including linkages *via* the aryl moiety), the resulting structure is usually called a neolignan (Scheme 1).




**Scheme 1.** General coupling and atom numbering pattern of lignans. A bold bond is used to highlight the 8-8' linkage.

### 1.1. Classification of lignans

A classification approach for lignans based on their general structure has been used,[4] grouping them into eight different types: furan, furofuran, dibenzylbutane, dibenzylbutyrolactone, aryltetralin, arylnaphthalene, dibenzocyclooctadiene and dibenzylbutyrolactol lignans (Scheme 2 shows their skeletal structures).



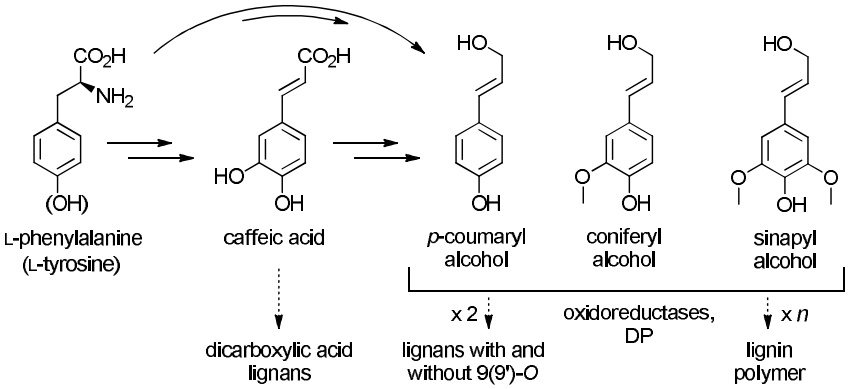

**Scheme 2.** Generic lignan skeletons. A bold bond is used to highlight the 8-8' linkage.

Moreover, these compounds also fall into one of three categories of oxygen appearance: lignans with oxygen at the 9(9')-carbon, lignans without oxygen at the 9(9')-carbon, and dicarboxylic acid lignans. Some lignan types appear in more than one category and/or there exist different cyclization patterns for a given type. For example, furan lignans occur with or without oxygen at the 9(9')-carbon, and the decoration of the tetrahydrofuran core can also vary.

Accordingly, this account seeks to draw attention to synthetic approaches toward those lignans which are heterocycles, with a particular focus on stereoselective synthesis. Due to their multiple pharmacological activities, their preparation reaches beyond natural product synthesis and is also important in areas such as medicinal chemistry and drug discovery.

### 1.2. Occurrence and relevance

Lignan biosynthesis in plants[4-5] starts with L-phenylalanine or, less frequently, L-tyrosine, proceeds through steps of ammonia elimination, arene hydroxylation, methylation and reduction to give arylallylic alcohols *p*-coumaryl, sinapyl and, most notably, coniferyl alcohol as the $C_6C_3$ building blocks for both lignans with and without 9(9')-oxygen as well as lignin polymer, whereas caffeic acid, an intermediate in this sequence, is the precursor of dicarboxylic acid lignans (Scheme 3).




**Scheme 3.** Simplified biosynthetic pathway of lignan formation in plants.

Certain oxidoreductase enzymes (including oxidases, peroxidases and laccases)[6-7] abstract both a proton and an electron from the free phenolic hydroxy group in *para* position of the phenylpropanoid, which leads to resonance-stabilized quinone radicals. Pairing of these radicals gives different oxidative coupling products and thus different types of lignans (or neolignans), depending on the recombination sites. Centrally involved therein is the dirigent protein (DP or DIR) which accounts for the diastereoselectivity of the reaction by *si*-*si* coupling and also ensures the optical purity of the resulting dimers.[6-7]

Phenylpropanoids in general protect plants in stress conditions like infections, wounding, exposure to UV radiation and ozone, pollutants and herbivores.[8] As for lignans specifically, various phytochemical roles have been demonstrated,[2] such as the protective function against pests and pathogens[9] or their negative allelopathy[10] (the ability to hinder the growth of other plants nearby which are competing for resources).

Lignans are the subject of current studies in pharmacognosy, pharmacology, and medicine because of their anti-viral, anti-cancer, anti-bacterial, anti-fungal, anti-oxidant, anti-inflammatory, parasiticidal, immunity-related, metabolic and cardiovascular effects (among others).[2, 11] High levels of lignans and their metabolites in humans have been shown to be inversely correlated with diseases such as cancer and cardiovascular disease,[12-14] in support of the common notion that vegetables and fruits constitute a healthy diet.

## 2. Lignan synthesis

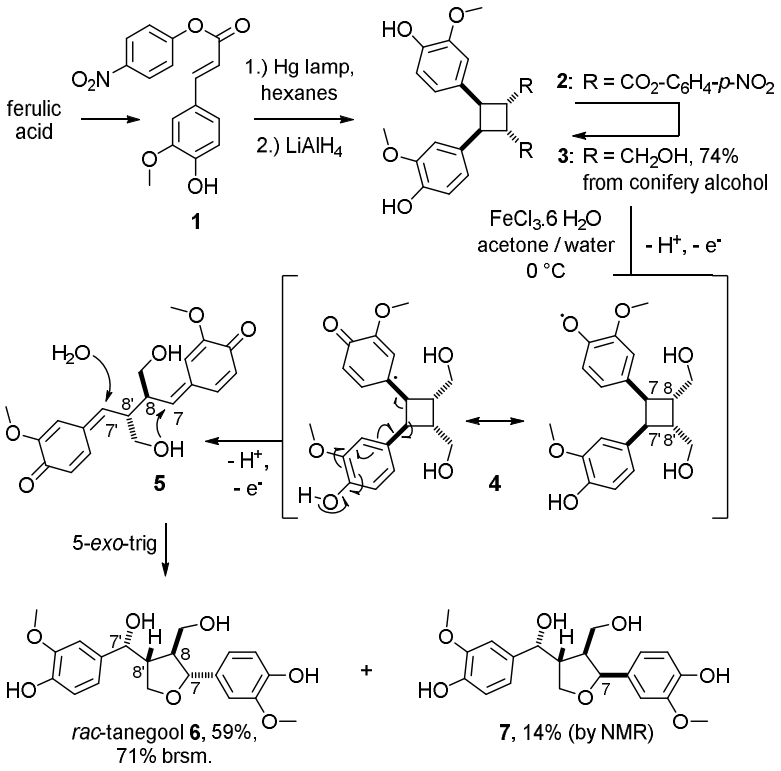
As a result of their physiological activity, lignans have been the subject of many studies to prepare them by chemical synthesis or means of biotechnology. It has been suggested[15-16] that an *in vitro* biotechnological approach developed in the mid-1990s that is based on the use of the aforementioned dirigent protein[7, 17] could be an alternative to chemical synthesis for certain types of lignans. Although still promising, this approach has not yet turned into a practical method for synthesizing them during the intervening two decades, likely due to issues of limited substrate scope (i.e. the phenylpropanoid monomers for oxidative coupling) and-even more important in applications such as natural compound-inspired drug discovery-a limited variety of products that can actually be obtained in this way (considering for example the problems one would encounter when trying to selectively heterodimerize two different phenylpropanoids). Therefore, the need to procure new lignan compounds to explore their physiological properties still calls for a chemical way of preparing them, at least for the foreseeable future.

The following subsections deal with examples of the above mentioned lignan types. Important steps in the synthesis are highlighted, focusing on the key ideas relevant to the methodology used for the particular example at hand.

### 2.1. Synthesis of furan-type lignans

Biosynthesis can actually serve as a blueprint for chemical synthetic plans as well. Moreover, individual reaction steps and the order of events can be changed, which is the case in very recent work by Lumb and Albertson.[18] As mentioned above, regio- and stereochemistry is important in the attempt to dimerize two molecules of precursor to a lignan compound. It would be helpful if these precursor molecules could be brought together by a regio- and stereoselective process, even if the immediate reaction product is not a substituted tetrahydrofuran but some other cyclic structure. Therefore, a suspension of *p*-nitrocinnamyl ferulate **1** in hexanes (thereby avoiding issues with olefin isomerization which happens predominantly in the solution phase)[19] was cyclized in a [2+2] head-to-head-photodimerization to cyclobutane **2**, representing such a cyclic compound (Scheme 4). This was subsequently reduced to bishydroxymethyl compound **3**. The most efficient oxidant for ring expansion then appeared to be $FeCl_3.6\,H_2O$ in water/acetone, affording predominantly the furan-type *rac*-tanegool **6** (59%, 71% based on recovered starting material), separable from mixtures of starting material and 7-epimer **7**. The mechanism was proposed to occur in a radical or radical cation fashion (the radical variant *via* **4** and then bis-*p*-quinone methide **5** is shown in the scheme), and the resulting diastereoselectivity was likely to arise from steric repulsion in the open-chain intermediate **5**. The link to lignan biosynthesis and the idea of changing the order of events here is that the cyclization of **5** to **6** is akin to the one which occurs in plants as well, but the (relative) configurations at C8 and C8' are

already set up during the orbital-controlled photochemical reaction. Consequently, the 8-8' bond remains untouched thereafter.

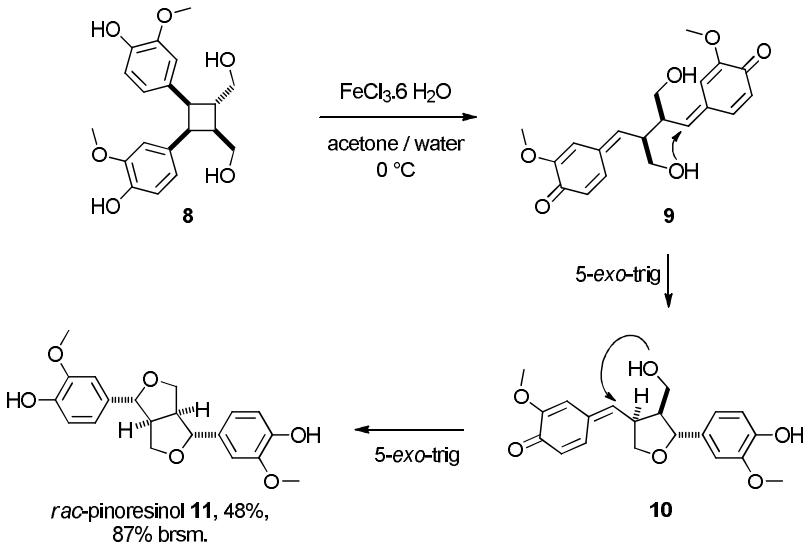



**Scheme 4.** Synthesis of *rac*-tanegool **6** *via* photocyclization, $FeCl_3$-mediated oxidation and *in situ* 5-*exo*-trig cyclization.

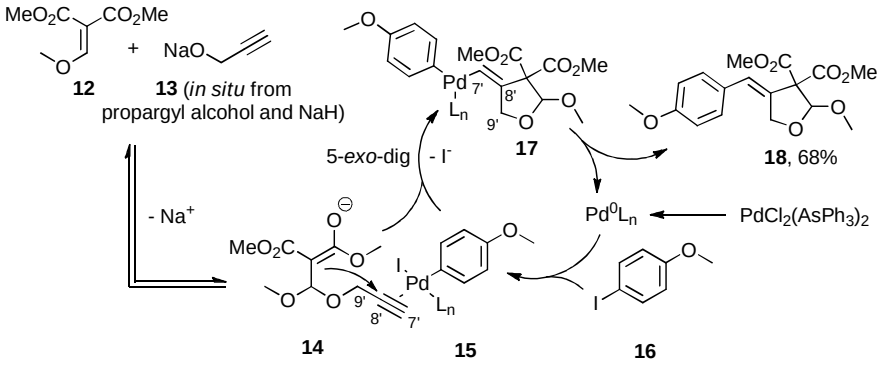
Notably, when the hydroxymethyl substituents in intermediate **3** were switched into *trans* configuration (compound **8**, Scheme 5), the 5-*exo*-trig cyclization occurred twice, with the second hydroxy group taking the role of a water molecule in intermediate **10** when compared to the above case, giving rise to *rac*-pinoresinol **11** (48%, 87% based on recovered starting material; *vide infra* for a more detailed discussion of the synthesis of such bicyclic, furofuran-type lignans). In the communication, the authors also announced on-going exploration of asymmetric variants to this route; note that $C_s$-symmetric cyclobutane **3** is a *meso* compound and presumed intermediates **5** and **9** do not contain chiral information at C7 and C7' any more, thus opening the possibility to generate optically active furan and furofuran products from precursors **3** and **8** if the 5-*exo*-trig reaction can be rendered enantioselective (bearing some resemblance to the natural, DP-mediated process).

Bouyssi, Balme and co-workers developed a route[20-21] to trisubstituted furan lignans partly based on their previous work on multicomponent reactions.[22-23] The method makes extensive use of transition metal catalysis, beginning with a three-component cyclization which had been at work in a previous formal

synthesis of a disubstituted furan lignan as well.[24] Therein, sodium propargyloxide **13** first adds to Michael acceptor **12** (Scheme 6). Next, intramolecular nucleophilic attack of the resulting enolate **14** to the triple bond, activated by organopalladium complex **15** (which originates from the oxidative addition of aryl halide **16** to palladium(0)) takes place, according to the mechanistic rationale.[22-23] This 5-*exo*-dig cyclization results in intermediate **17**, and reductive elimination gives compound **18**, thereby accomplishing both the formation of the core furan-type system as well as the incorporation of one aryl moiety.



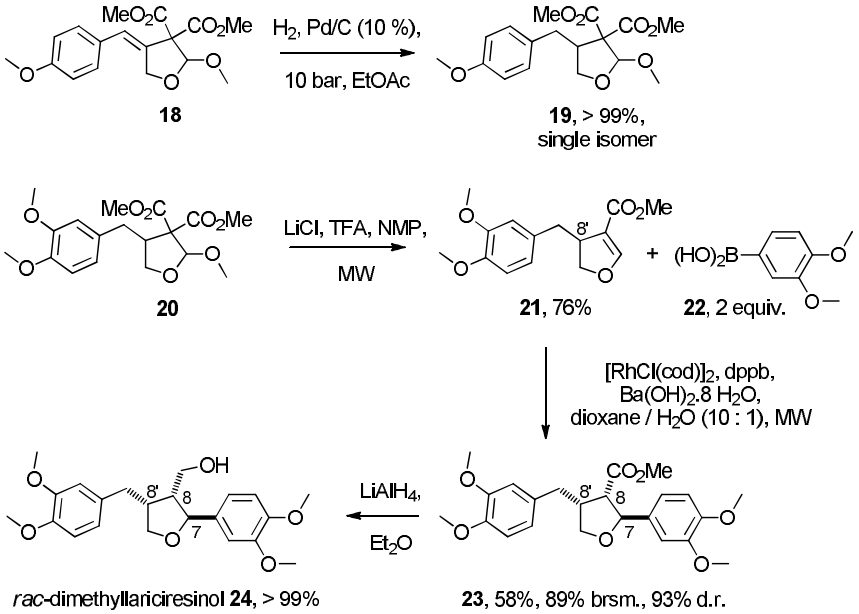

**Scheme 5.** Bioinspired synthesis of *rac*-pinoresinol **11** involving double 5-*exo*-trig cyclization.




**Scheme 6.** Palladium-catalyzed three-component reaction (shown for a particular example).

Catalytic hydrogenation then removes the double bond in **18** and gives **19** as a single, but unidentified, diastereoisomer (Scheme 7). Tandem decarboxylation-elimination of a similar diester **20** under microwave conditions affords dihydrofuran **21**. The authors then chose to employ a rhodium(I)-catalyzed Hayashi-Miyaura reaction[25] with aryl boronic acid **22** to incorporate the second aryl moiety in a 1,4-addition,

occurring at the side of **21** which is less hindered by the 8' substituent. Accordingly, this yielded intermediate **23** in 58%, with the aryl and benzylic moieties pointing away from each other. Moreover, the 7,8-relationship in compound **23** was predominantly *trans*-configured (93% d.r.), and final reduction of the methyl ester gave the naturally occurring *rac*-dimethyllariciresinol **24** in excellent yield as the last step of the sequence.

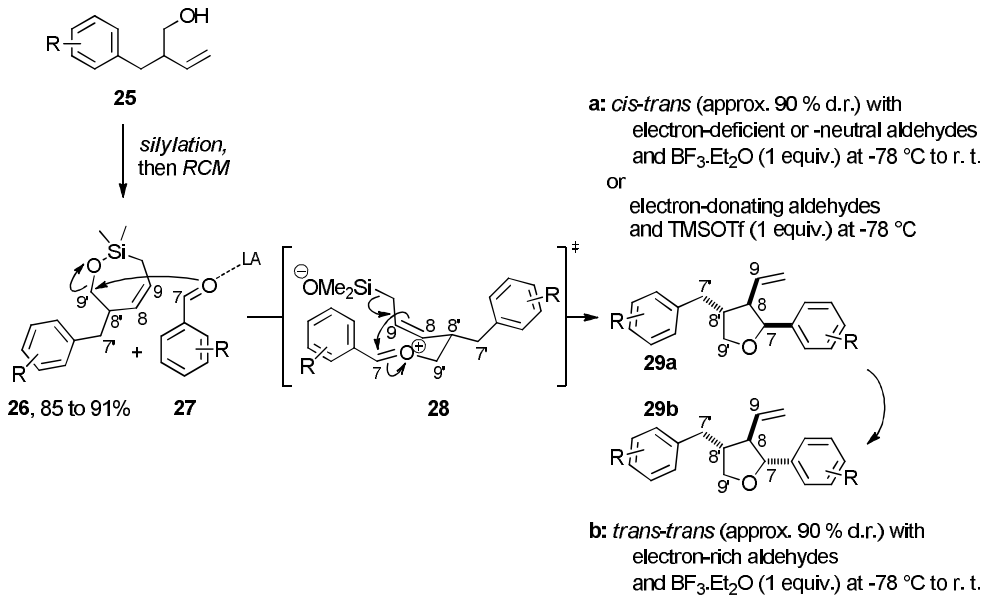



**Scheme 7.** Synthesis of furan lignans. In the relevant literature, details for the steps to diester **20** are not given, nor are those beyond **19** (as far as the synthesis of lignans like *rac*-dimethyllariciresinol **24** is concerned). Therefore, the scheme is discontinuous at **19**/**20**.

Since this route is also divergent, it would be possible to use intermediates like **21** for swift variation of the substituent at C7. The furan-type lignans are racemic in this synthesis, but success at obtaining optically active final products in high enantiomeric excess would (only) hinge on efforts to achieve reagent-controlled and selective hydrogenation of cyclization products such as **18**, overriding the bias exerted by the later-eliminated methoxy group at C7. With this assumption, compounds like **19** or **20** would then be a pair of diastereoisomers (because the configuration at C8' would then be determined), chiral information at C7 would be lost during decarboxylation-elimination (although this process might not be equally efficient for both of these diastereoisomers), and the remainder of the synthesis would be substrate-controlled, as in the racemic case above. The use of transition metal-based strategies toward lignans and similar compounds was also reviewed by authors from this research group.[26]

In the above example, dimethyllariciresinol **24** is *trans*-configured between C7 and C8, while it is *cis*-configured between C8 and C8'. Given its three contiguous chiral centers, there exist four pairs of enantiomers (all-*cis*, all-*trans*, *cis*-*trans*, *trans*-*cis*). The synthesis of all eight stereoisomers was indeed

completed for the closely related lariciresinol[27] (which has hydroxy in place of methoxy groups at both *para* positions) by making use of Evans' oxazolidinone as a chiral auxiliary.[28] From the viewpoint of medicinal chemistry and the synthesis of a structurally diverse library of lignan-like compounds, it would be elegant if one could switch, at least to some extent, between different stereoconfigurations during a particular transformation-preferably by reagent control. An interesting approach in this direction was demonstrated by Marsden and co-workers.[29] Therein, oxasilacycloheptenes **26** were prepared in excellent yields by silylation of homoallylic alcohols **25**, followed by ring-closing metathesis with Grubbs' second-generation catalyst (Scheme 8). Intermediates **26** were then susceptible to Lewis acid-promoted ring cleavage, contracting to tetrahydrofurans **29** in the presence of aldehydes **27**. Following previous work by both the Marsden[30] and the Cossy[31] research groups in this area, the authors realized that the stereochemical result depended on the electronic properties of the aldehyde and the Lewis acid that was used during transformation of **26**. An electron-deficient benzaldehyde and -neutral hexanal, in the presence of boron trifluoride, mainly gave *cis-trans*-configured products **29a** (yields around 70%), while various electron-rich aldehydes mainly afforded *trans-trans* products **29b** (yields around 55%) under otherwise identical conditions (approximately 90% d.r. in both cases).

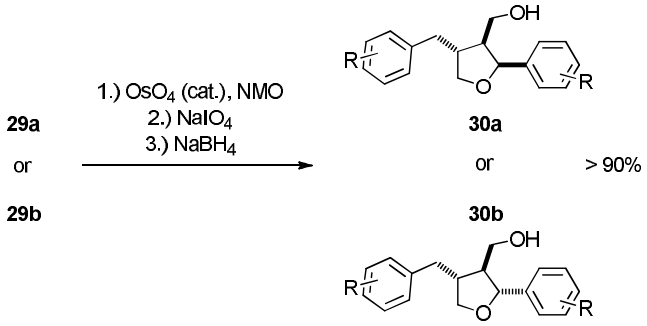



**Scheme 8.** Mechanistic rationale accounting for the stereoselectivity of tetrahydrofuran formation.

This was rationalized by assuming that the reaction, upon ring-opening, actually proceeds to the *cis-trans* product in both cases through a chair-like transition state **28** with the aryl and benzylic substituents equatorially disposed. While the reaction is then trapped in the 7,8-*cis* arrangement of the five-membered ring with electron-deficient and -neutral aryl substituents at C7, subsequent Lewis acid-base interaction between boron trifluoride and the tetrahydrofuran oxygen results in C7-O bond cleavage in the case of

electron-donating aryls, and re-formation of the bond gives the 7,8-*trans* product. That is to say, the initial *cis*-configuration is the kinetic product of the reaction, epimerizing to the thermodynamic *trans* product where the C7-C8 bond is allowed to rotate. When the Lewis acid was changed to trimethylsilyl triflate, the temperature could be kept at -78 °C throughout the reaction, such that epimerization did not take place (according to this model). Therefore, use of electron-donating piperonal also resulted in the formation of mainly *cis-trans* product (also around 90% d.r. and approximately 75% yield), thus switching the selectivity entirely with reagent control.

Compounds **29** were then subjected to osmium tetroxide/ NMO dihydroxylation, cleavage with sodium periodate and sodium borohydride reduction to afford furan-type lignans **30** in exceptional (> 90%) yield over these last three steps (Scheme 9).



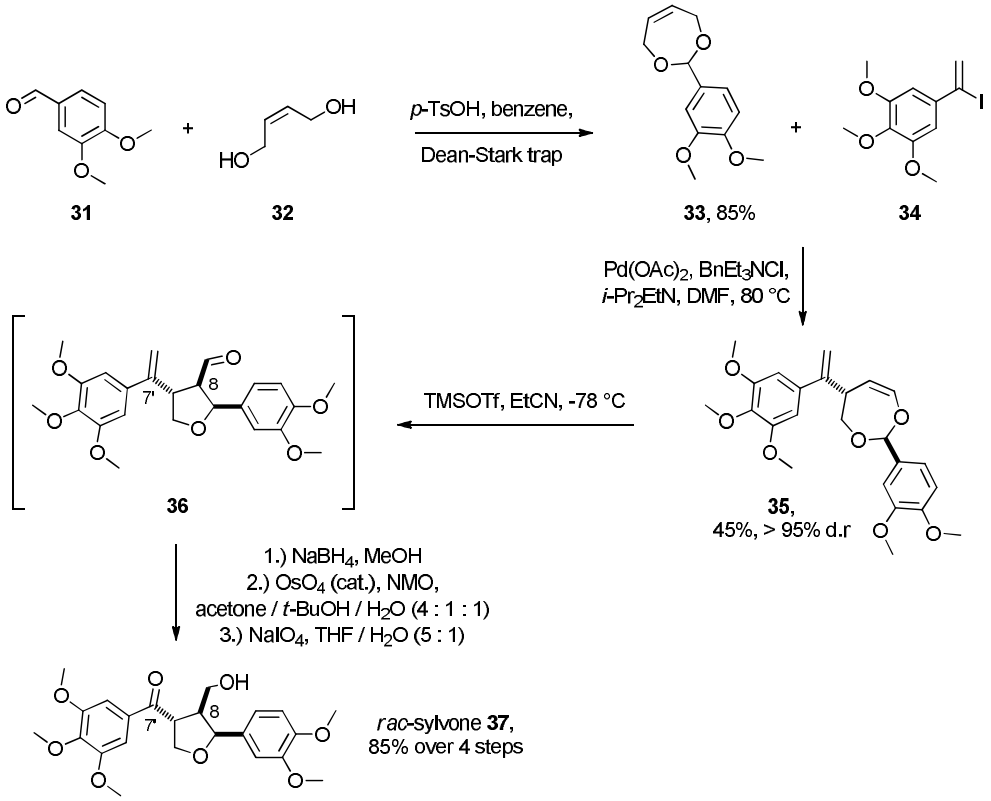

**Scheme 9.** Final steps to afford the furan-type lignans.

This is also a case of rapid lignan construction and where asymmetry in the targeted compounds **30** might very well be introduced by preparing homoallylic alcohols **25** enantioselectively, for instance *via* kinetic resolution.

A somewhat similar strategy[32] to the 7'-oxo furan lignan *rac*-sylvone **37** was developed later on by Rovis and Nasveschuk, based on the ring contraction of 1,3-dioxepine **35** (Scheme 10). To this end, veratraldehyde **31** and *cis*-1,4-butenediol **32** were condensed to intermediate **33**, which underwent Heck reaction affording key intermediate **35** with high diastereoselectivity (>95%) and acceptable yield (45%), given the brevity of the synthesis. The use of propionitrile (in place of the more common but higher melting acetonitrile) allowed running the reaction to **36** at -78 °C, necessary to achieve good d.r. (90%) in this ring contraction step with trimethylsilyl triflate which established the third stereocenter at C8. Due to its sensitivity to acid, aldehyde **36** itself was used without purification, as were the remaining intermediates. Therefore, target lignan **37** was obtained in 85% yield over the last four steps from **35**.

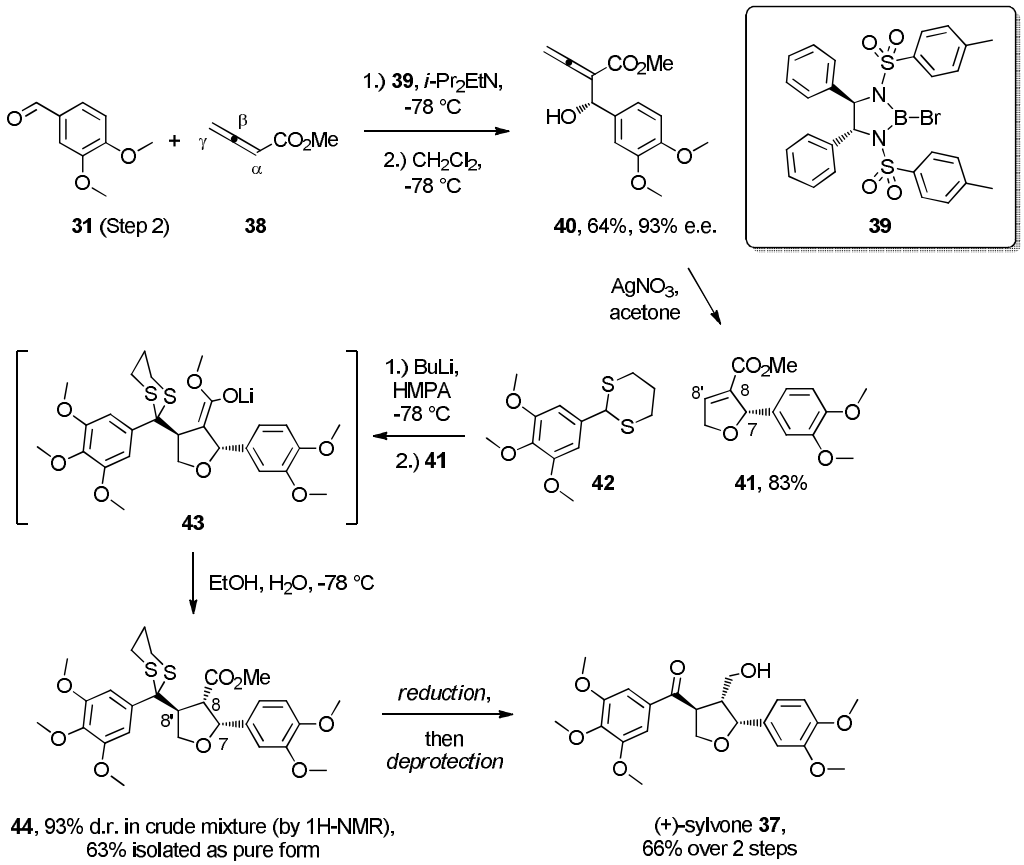
An asymmetric approach to (+)-sylvone was implemented in very recent work by Yu and co-workers.[33] Based on the authors' previous work,[34] the synthesis started by the organocatalytic, enantioselective addition of methyl allenoate **38** to veratraldehyde **31** (Scheme 11). Allenes may be considered dehydrated carbonyl compounds, and α-allenoates display strong electrophilic behavior at the central β position, while they are nucleophiles in disguise at the α and γ positions.[35] As such, the preparation

of intermediate **40** under basic conditions and assisted by chiral **39** would correspond to an asymmetric aldol addition, and furnished the desired **40** in good yield and enantiomeric excess.



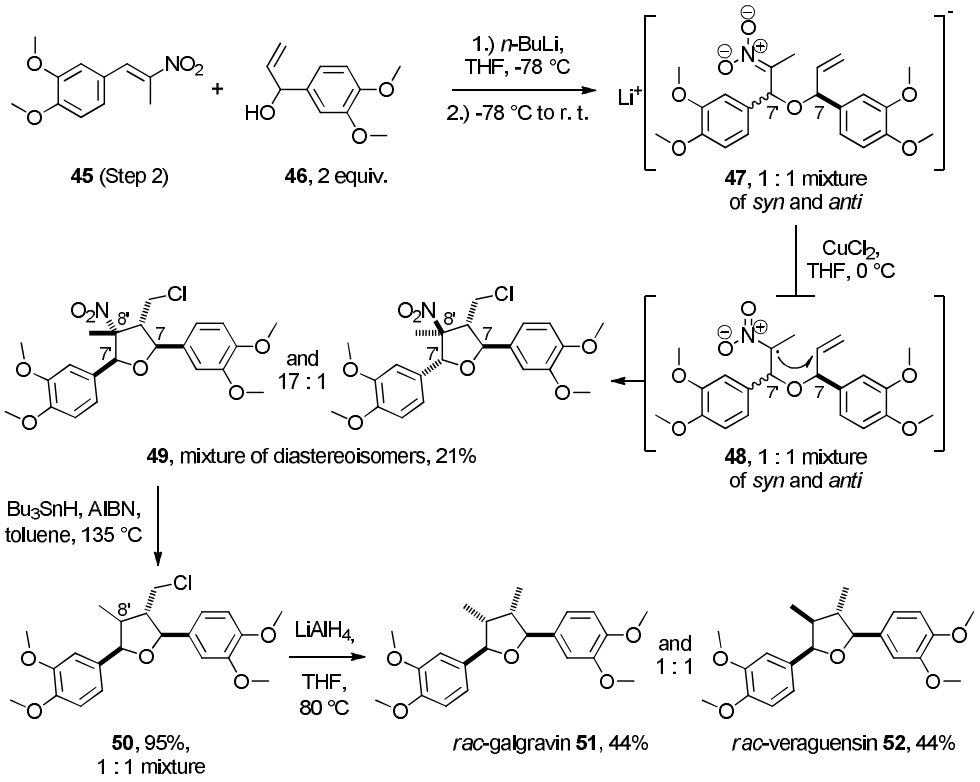

**Scheme 10.** Preparation of *rac*-sylvone **37**.

Then, after some experimentation with various metal catalysts, the authors found that 20 mol% silver nitrate in acetone smoothly oxacyclized **40** to dihydrofuran **41**. The last strategic step comprised the conjugate addition of lithiated 1,3-dithiane **42** to the less shielded face of **41**, which required HMPA as an additive for this reaction to proceed. Moreover, reaction times were crucial, too, and under optimized conditions the Michael acceptor **41** was added dropwise to a mixture of **42**, butyllithium and 5 equivalents of HMPA at -78 °C, and the reaction quenched with aqueous ethanol after 30 min to avoid decomposition of unstable **43**. This quench protonated **43** at C8 such that the methoxycarbonyl group would favor pointing away from the bulky dithiane, resulting in the 7,8-*cis* and 8,8'-*trans* configuration. Following this transformation which created two new chiral centers at C8 and C8', a d.r. of 93% was observed (with a second unidentified diastereoisomer present in the reaction mixture), and pure **44** was obtained after chromatography in 63% isolated yield. Finally, ester reduction and deprotection to free the ketone gave (+)-sylvone **37** (Scheme 11).




**Scheme 11.** Asymmetric preparation of (+)-sylvone **37** *via* addition of an allenoate to an aldehyde, oxacyclization and diastereoselective conjugate addition of a dithiane derivative.

Creating a new short lignan synthesis is rather challenging because, as was pointed out, it is necessary to gain control over the stereochemistry of the reaction, and this difficulty is aggravated with highly substituted tetrahydrofurans. For example, all diastereoisomers of the tetrasubstituted furan-type lignan skeleton without 9(9')-oxygen (Scheme 2) appear as known natural products,[36] and any methodology toward them is faced with the problem of establishing a target with four contiguous stereocenters, preferably as a single enantiomer. Jahn and Rudakov investigated the possibility of preparing such compounds *via* a tandem alkoxide conjugate addition-radical 5-*exo* cyclization procedure (Scheme 12),[37] shown in the synthesis of the furan lignans galgravin **51** and veraguensin **52**. This would be a very attractive approach because it is a very concise synthetic plan, and the starting nitroalkene **45**[38] and vinylbenzyl alcohol **46**[39] are readily accessible in good to excellent yields by Henry reaction and Grignard addition, respectively. Moreover, starting material **46** can be obtained in high optical purity by a number of methods,[40-42] which would render the synthesis asymmetric if diastereocontrol over the remaining chiral centers could be established.




**Scheme 12.** Furolignans *rac*-galgravin **51** and *rac*-veraguensin **52** *via* a tandem alkoxide conjugate addition-radical 5-*exo* cyclization sequence.

To this end, deprotonation with n-BuLi and conjugate addition of **46** to **45** furnished nitronate **47** which was shown to be a 1:1 mixture of *syn* and *anti* isomers with regard to the aryl substituents in positions 7 and 7' (relevant bonds emphasized in the scheme). However, subjecting this mixture immediately to an oxidant gave intermediate radicals **48**, where *syn*-**48** cyclized more efficiently to **49**, whereas *anti*-**48** was mainly trapped as an acyclic halonitroether (not shown) under certain conditions. In the case of copper(II) chloride as the oxidant and THF as the solvent at 0 °C, the cyclization proceeded with low yield (21% based on starting nitroalkene **45**) but high stereoselectivity (17:1 ratio in favor of the isomer as shown) to product **49**. Unfortunately, when removing the nitro group, the configuration at C8' could not be retained in **50** under radical reduction conditions, eventually furnishing a separable 1:1 mixture of *rac*-galgravin **51** and *rac*-veraguensin **52**.

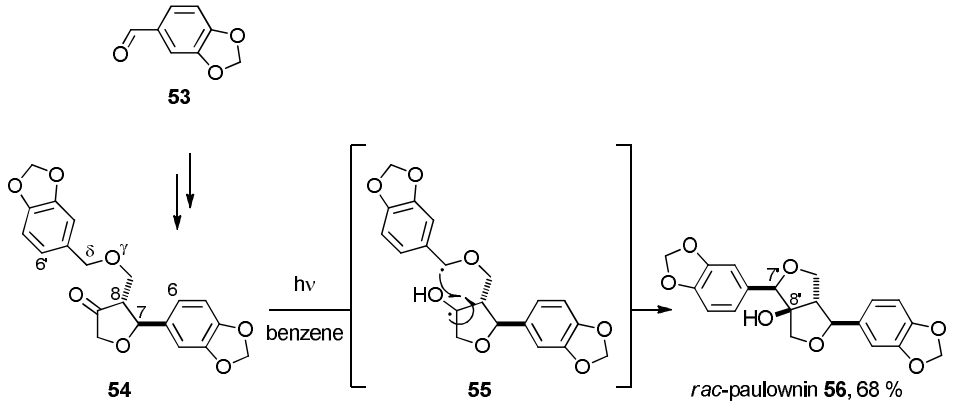
### 2.2. Synthesis of furofuran-type lignans

The furan lignans can be thought of as originating from a cyclization process that was halted half way through to the bicyclic furofuran structure. Indeed, as was shown in the example of monocyclic tanegool **6** above, a furan synthesis can switch the cyclization mode to give a bicyclic structure instead (pinoresinol **11**

in the mentioned case) if the geometry of the reacting molecule makes this a favorable reaction product. Compounds like pinoresinol are a more frequent variant of furofuran lignans, yet this subsection shall now deal with methods to specifically obtain some less common furofuran or non-natural lignans.

Kraus and Chen developed a strategy for the furofuro lignan *rac*-paulownin **56**,[43] in which piperonal **53** was elaborated to cyclic ketone **54** (Scheme 13) and where the aryl and piperonyloyxmethyl substituents (C7 and C8) were in *trans* configuration. The key step was then a Norrish-Yang cyclization to **56** in deoxygenated solvent with 68% yield (based on recovered **54** and approximately 90% completion of the reaction). The classic Norrish-Yang cyclization leads to 4-membered ring systems (cyclobutanes, oxetanes and azetidines) by γ-hydrogen abstraction of a photoexcited carbonyl group *via* a 1,4-diradical.[44]

Where this is not possible, δ-hydrogen abstraction as in **55** can occur, forming the 5-membered product as shown. While the authors reported complete kinetic stereoselectivity with the substituents in 7',8'-*cis* configuration as the sole product, later studies by Ishibashi and co-workers (conducted with optically active **54** and using rose bengal as a photosensitizer under modified illumination conditions) found that the 7'-epimer was also present in ratios of 9:1.[45] The diastereoselectivity of the cyclization also eroded drastically (down to about 3:2) when methoxy substituents were placed at the 6 or 6' position of the piperonyl moiety.

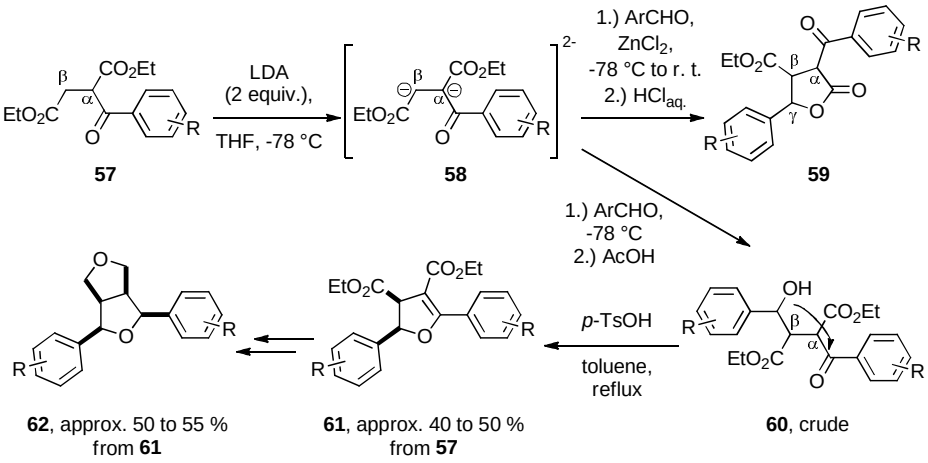



**Scheme 13.** Synthesis of *rac*-paulownin **56** using the photochemical Norrish-Yang cyclization.

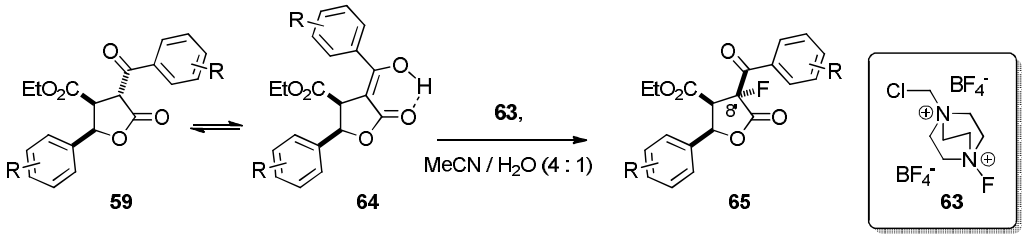
Pohmakotr and co-workers reported on the synthesis of substituted γ-aroyl-δ-butyrolactones **59** (Scheme 14) from γ-aroylsuccinic esters **57**.[46]

More recently, this group also published the synthesis of derivatives of furofuran lignans possessing fluorine substitution at C8', making this position a quaternary carbon atom.[48] Fluorination is typically considered during attempts to modify the behavior of pharmacologically active compounds. Given the biological activity of lignans in general, this represents a possibility to discover non-natural analogs with enhanced activity profile. The authors used intermediates of structure **59**, the synthesis of which had been established previously,[46, 49] and exposed them to the electrophilic fluorination agent Selectfluor® **63** in a mixture of acetonitrile and water at room temperature to obtain the corresponding lactones **65**, being fluorinated at their most acidic position (Scheme 15). Compounds **65** were obtained as single isomers with the configuration at the reacting carbon as shown because the products originated from the enol form **64**,

meaning that attack to the electrophilic fluorine occurred from the less hindered face of **64**. Yields of the examples presented were in excess of 70%. Unfortunately though, electron-rich substrates with 3,4-dimethoxy and 3,4-methylenedioxy-substituted arenes (i.e. typical substitution patterns that occur in lignans)-while actually giving the expected products at first-rapidly decomposed before they could be purified.



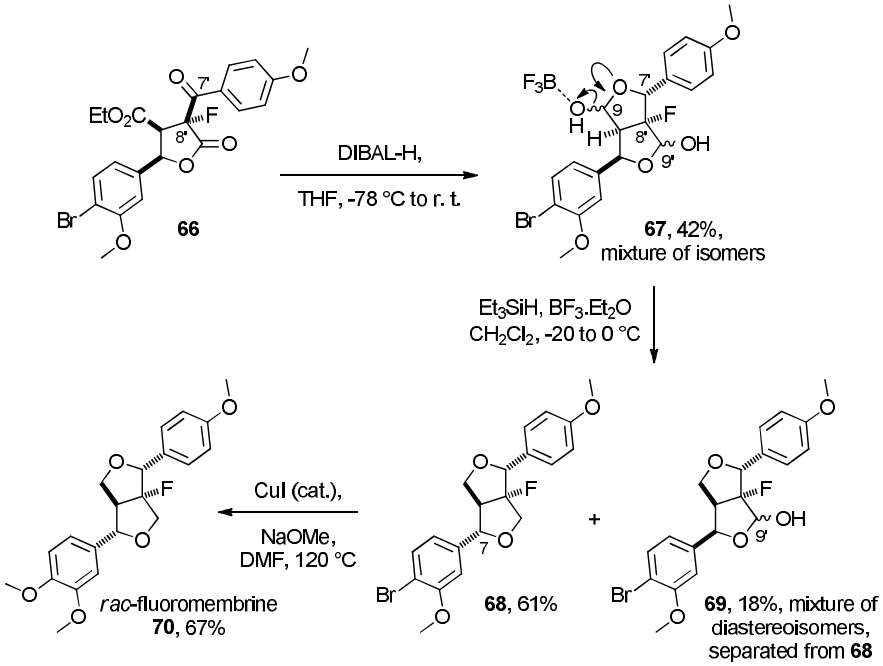

**Scheme 14.** Furofuran-type lignans *via* vicinal dianions.




**Scheme 15.** Fluorination of intermediates **59**.

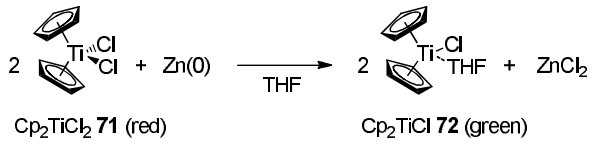
Part of the follow-up chemistry that was investigated comprised the elaboration of compounds **65** to fluorinated furofuran lignans. Especially, the fluorinated derivative **70** of the naturally occurring membrine[50] (called 1-fluoromembrine by the authors) was prepared in this way (Scheme 16). As such a fluoromembrine would require the unfeasible, electron-rich substitution pattern of three methoxy groups if prepared directly from a correspondingly substituted intermediate **65**, an indirect route was chosen instead. Brominated compound **66**, a particular instance of generic structure **65**, proved to be stable and was therefore converted to **67** by global reduction with diisobutylaluminium hydride. This lowered the oxidation state of all oxo functionalities by 2 units, and immediate intramolecular attack of the so-formed secondary alcohol at C7' afforded the bislactol in moderate yield. Then, treatment with boron trifluoride under triethylsilane-reductive conditions preferentially led to **69** at first. This is because, under the influence of the Lewis acid, the hydroxy group at C9 is more easily eliminated than the one at C9', owing to the presence of the fluorine atom at C8',

which inhibits development of a positive charge in its vicinity. Instead, the oxonium ion is formed as shown, and hydride donation by triethylsilane gives reaction intermediate **69**. The subsequent second elimination-reduction at C9' of **69** also proceeds in the same way, thus carrying the reaction on toward **68**, but it is slower than the first, and **69** also remains as a side product under the carefully balanced reaction conditions. However, the configuration at C7 in **68** is actually inverted when compared to **67** (or **69**). In essence, this is rationalized in the same way as is the epimerization of **29a** to **29b** in Scheme 8: boron trifluoride coordinates to the tetrahydrofuran oxygen and promotes reversible C7-O bond cleavage, such that the thermodynamically more stable, zig-zag-shaped **68** is obtained. Eventually, the aromatic bromine is replaced by sodium methoxide under copper(I) catalysis, producing the fluorinated membrine **70** in 67% yield as the last step.




**Scheme 16.** Synthesis of *rac*-fluoromembrine.

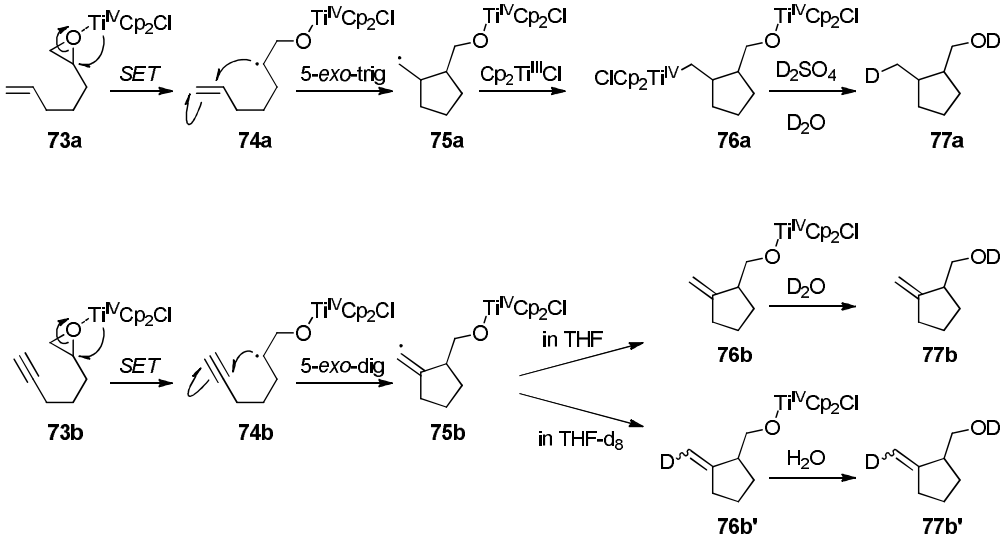
A synthetic strategy for lignans employing a titanium(III)-mediated radical cyclization method was presented by Roy and co-workers,[51-56] based on work by Nugent and RajanBabu.[57] Key to the method is bis(cyclopentadienyl)titanium(III) **72**, which reacts with epoxides in a homolytic C-O cleavage (Scheme 17).




**Scheme 17**. Preparation of $Cp_2TiCl$ **72** for *in situ* use (regarded as a monomer herein).

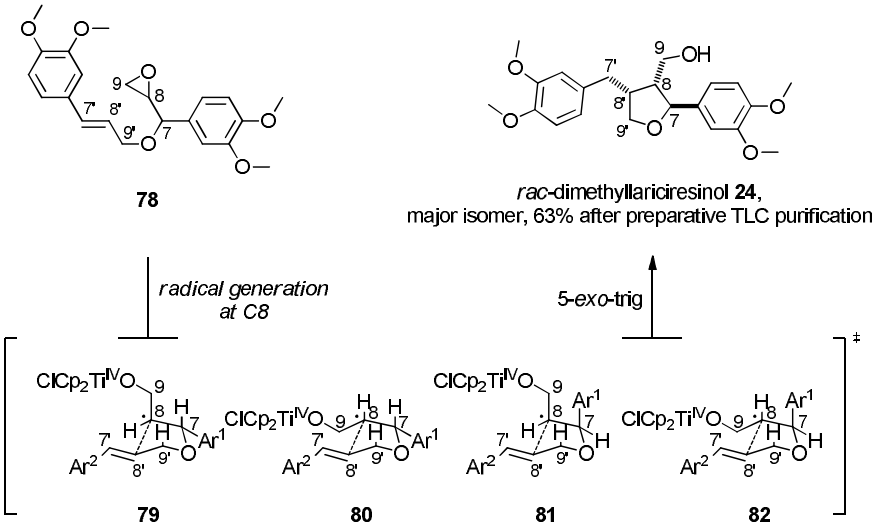
This compound exists as a chloride-bridged dimer in the solid state, but dissociates in the presence of electron donor solvents such as THF, in which it is readily soluble, to give a lime-green solution caused by titanium(III). It can thus be prepared as a solution in THF by quantitatively reducing commercially available bis(cyclopentadienyl)titanium(IV) **71** with metallic zinc at room temperature and then used directly because co-produced, THF-soluble $ZnCl_2$ (a Lewis acid) does not seem to affect its reactions.

Radicals generated from exposing epoxides to $Cp_2TiCl$ results in their deoxygenation to olefins or, in the presence of hydrogen donors such as 1,4-cyclohexadiene, reduction to alcohols. These radicals can also add intermolecularly to electron-deficient olefins, e.g. methacrylates, but most relevant here is that intramolecular radical addition to unactivated double and triple bonds can take place as well. Nugent and RajanBabu showed that, in the first step, the titanium(III) reagent probably needs to coordinate to the oxygen of epoxide **73a** or **73b**, respectively (Scheme 18). Single electron transfer (SET) from titanium(III) then results in the regioselective homolysis of the C-O bond of the epoxide at the carbon which affords the more highly substituted, and therefore more stable, radical **74**. In the investigated substrates, the multiple bond was spaced by three atoms from the radical position, and rapid *5-exo* attack led to ring-closed intermediates **75**. Notably, the reaction mechanism then takes two different paths depending on the type of the initial π system: in the case of a double bond, a methyl radical **75a** is formed which is stable enough to be eventually intercepted by a second molecule of $Cp_2TiCl$. This gives intermediate **76a** that can be isolated, and the Ti-C bond is only cleaved upon hydrolysis as was demonstrated by quenching the reaction mixture with 10% $D_2SO_4$ in $D_2O$ (**77a**) By contrast, deuterolysis of the experiment with triple bond-containing compound **73b** as the starting material produced **77b** which did not contain any deuterium at the methylene group, suggesting that the highly reactive vinyl radical **75b** abstracts hydrogen from the THF solvent before it can encounter another titanium(III) species. In fact, using THF-$d_8$ as the solvent and quenching the reaction with $H_2O$, deuterium is incorporated into the final product (**77b'**).




**Scheme 18.** Mechanism of titanium(III)-promoted radical and reductive cyclization.

While this method of forming five-membered rings may evidently be used for furan-type lignan synthesis, investigations into the stereochemical outcome of this cyclization with more elaborate substrates would be required. To this end, Roy and co-workers used the process in the synthesis of furan lignans from ethers such as **85** (a mixture of all four possible isomers) to give *rac*-dimethyllariciresinol **24** as shown, and a minor isomer thereof, in a ratio of 5:1 (Scheme 19).[52] An important consequence of the formation of a trigonal-planar radical center upon epoxide cleavage is that no chiral information at this carbon is retained, which means that the reaction is stereoconvergent with respect to C8. The 7,8 configuration in the major isomer **24** was obtained *trans*, while the configuration between C8 and C8' was *cis*. As the aforementioned minor isomer could not be isolated in pure form, its stereochemistry could not be assigned. The result was rationalized by invoking four possible conformers of the transition state during radical attack at the double bond, i.e. by assuming that the stereochemistry is governed entirely by steric interaction.

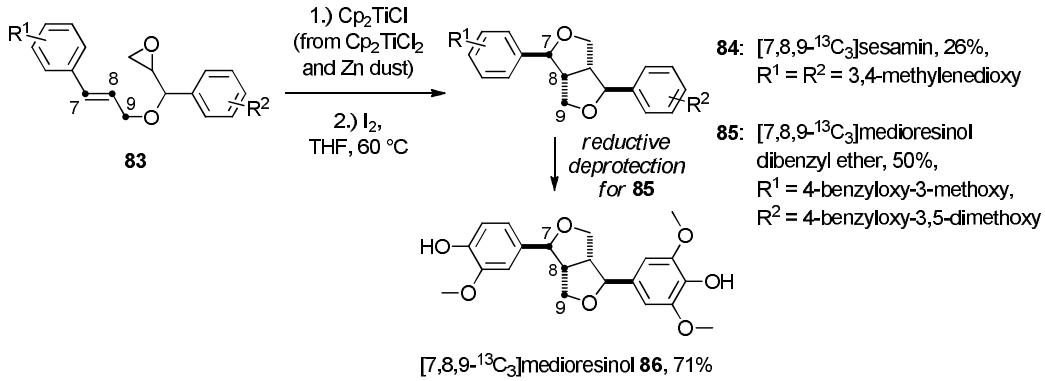



**Scheme 19.** The radical cyclization of **78** is presumed to proceed mainly *via* transition state **79**, affording *rac*-dimethyllariciresinol (and similar lignans of the same relative configuration) as the major product.

In order to rationalize the formation of **24** as the major product, it is reasonable to assume that the arylvinyl group will be oriented as shown in all four cases because rotating the C8'-C9' bond by 180 degrees would create additional torsional strain. Stating this is important because the configuration in the final product at C8' is determined (according to this model) by the orientation of the arylvinyl group as shown in the scheme. First, conformation **81** is eliminated from consideration for it is likely the most unfavorable alignment of all four (the substituents at C7 and C8 are both pseudoaxial and in a *cis* relationship). Then, assuming that the pseudoequatorial *cis* arrangement of C7 and C8 (**80**) is the next-repulsive one leaves conformations **79** and **82**, with the C7 substituent pseudoequatorial and the C8 substituent pseudoaxial (**79**) or *vice versa* (**82**). Since the aryl group at C7 should exert more steric demand (more 1,2-torsional and 1,3-diaxial strain) than the titanyloxymethyl group at C8 (where the attached titanium complex is large but also

two bonds further away, allowing it to be rotated out of the way more easily), one would obtain transition state **79** as the lowest one in energy, in agreement with the configuration of product **24**. Importantly, if the cyclization precursor **78** is prepared asymmetrically, the ensuing **24** will be optically active as well, and its enantiomeric excess will only depend on the degree to which the absolute configuration at the C7 center can be established. In fact, this feature was exploited in a later synthesis to furnish lignans of this type enantioselectively.[55]

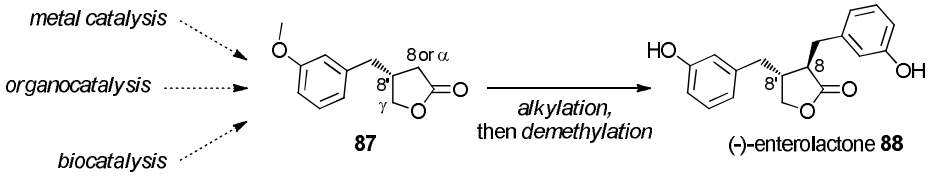
The above-mentioned explanation served to understand how the three contiguous chiral centers C7, C8 and C8' are obtained *via* this radical synthesis, but at this point, the final product **24** is still (only) a furan-type lignan. However, Roy and co-workers also showed that addition of iodine subsequent to initiation of cyclization by $Cp_2TiCl$ afforded the corresponding furofuran-type lignans in one pot.[52] This method was later also put to use by Botting and Haajanen who needed to synthesize such lignan derivatives that contained three $^{13}C$ atoms, to be used as internal standards in an LC-MS-based method that quantifies lignans in human plasma. [7,8,9-$^{13}C_3$]Sesamin **84** and [7,8,9-$^{13}C_3$]medioresinol **86** (the latter *via* its dibenzyl ether **85**) were thus prepared in this fashion from appropriate intermediate materials **83** (Scheme 20),[58] although the high yields of the Roy group (around 90% for the furofuran lignans) could not be reproduced.




**Scheme 20.** Formation of $^{13}C$-isotopically labeled furofuran lignans. The blobs at positions 7, 8 and 9 indicate $^{13}C$ atoms (omitting the primes compared to Scheme 19 is appropriate in this case of furofurans).

### 2.3. Synthesis of other lignan types

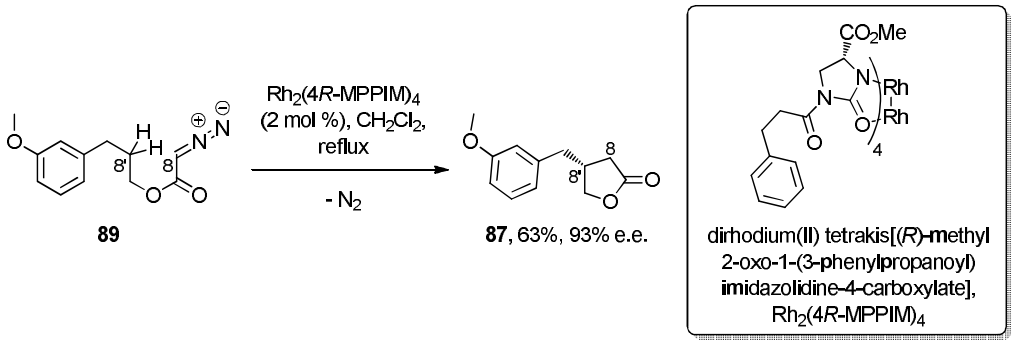
Despite their close association to plants, lignans are produced or metabolized to other lignan compounds by organisms outside the kingdom Plantae as well (Scheme 21).




**Scheme 21.** Different approaches to (-)-enterolactone **88** *via* intermediate **87**. Regarding the stereochemistry of the biocatalytic approach, compare the text below.

For example, pinoresinol and lariciresinol in food sources are metabolized by the mammalian intestinal microflora, with enterolactone **88**[12] as the predominant end-product.[13] In the case of **88**, an interesting comparison is possible between metal-, organo-, and biocatalytic methodologies. Valuable precursors for such 8,8'-*trans*-dibenzylbutyrolactone-type lignans in general are 8'-substituted γ-butyrolactones (intermediate **87** in the case of (-)-enterolactone), since base-mediated alkylation of the α-position proceeds diastereoselectively under good substrate control (>95:5 *trans* selectivity).[59-60]

In a metal-catalyzed approach[59, 61] to **87**, Doyle and co-workers prepared diazoacetate **89** from the corresponding alcohol, diketene and mesyl azide. In a screening of dirhodium(II) catalysts, chiral complex $Rh_2(4R\text{-MPPIM})_4$ proved to be the catalyst of choice for it afforded good yield (63%) and high enantioselectivity (93% ee) in a C-H activation-ring closure. In the model for this reaction,[62] the dirhodium complex displaces dinitrogen from C8 to give a carbene complex, and with concomitant dirhodium dissociation, one hydrogen migrates from the 8' to the 8 position while the C8-C8' bond is formed and the catalyst is released (Scheme 22). The N-acylimidazolidinone ligand was synthesized from D-asparagine and then converted to $Rh_2(4R\text{-MPPIM})_4$ with $Rh_2(OAc)_4$, therefore the method makes both enantiomers of enterolactone-like lignans accessible with proper choice of ligand starting material.

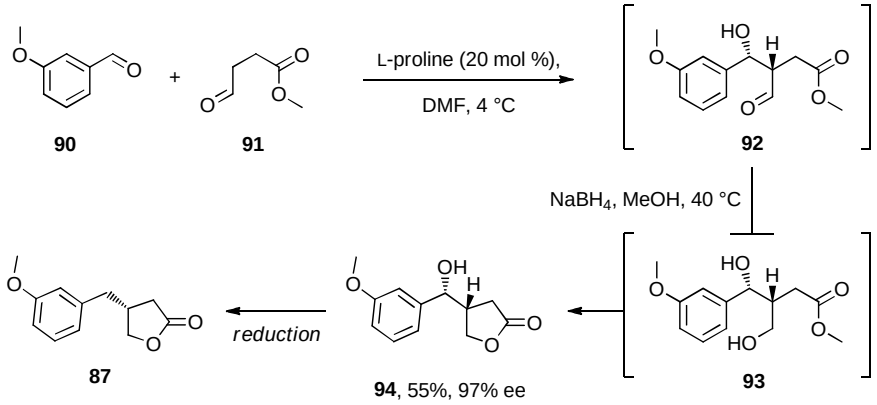



**Scheme 22.** Rhodium-catalyzed enantio- and regioselective ring closure to chiral intermediate **87**.

Amino acids and derivatives thereof can also perform enantioselective catalysis directly. L-Proline was used in the organocatalytic synthesis[60, 63] of **87** by Hajra and co-workers. Slow addition of oxobutyrate **91** to aldehyde **90** in the presence of 20% organocatalyst gave aldol adduct **92**, which was reduced immediately thereafter to **93** with sodium borohydride. This resulted in spontaneous lactonization to **94** in 55% yield and 97% e.e. (Scheme 23). Pd/C reduction of the benzylic hydroxy group then afforded intermediate **87**. With both antipodes of proline readily available, this method will also allow both enantiomers of enterolactone-like lignans to be prepared.

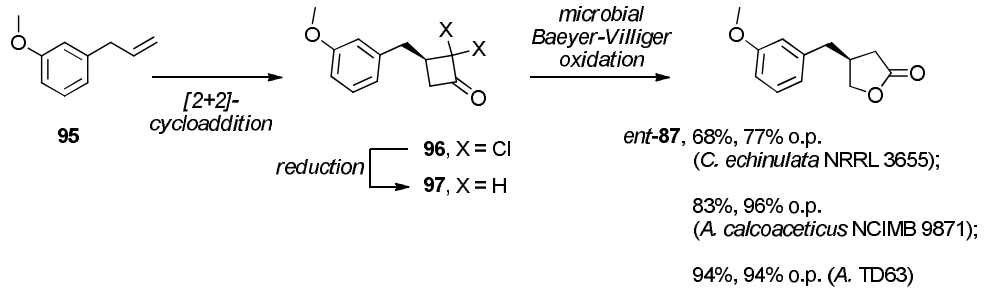
The Baeyer-Villiger oxidation of cyclic prochiral ketones gives rapid access to optically active lactones for which, unlike with methods based on non-dynamic kinetic resolution of racemic substrates, the theoretical yield is 100% (representing a desymmetrization process). The asymmetric insertion of oxygen into the ketone may be carried out with *e.g.* binol-derived phosphoric acids and hydrogen peroxide[64] or

scandium-(*N*,*N*′-dioxide) complexes with *m*-chloroperbenzoic acid[65] as the oxidant. Alternatively, enzymatic oxidations have been intensively studied, too.[66-68]




**Scheme 23.** Organocatalyzed enantioselective aldol addition to chiral intermediate **87.**

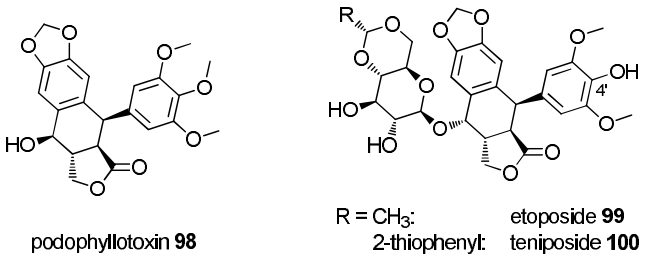
Furstoss and co-workers described the use of whole-cell systems such as of the fungus *Cunninghamella echinulata* and Gram-negative *Acinetobacter* strains expressing flavin-dependent Baeyer-Villiger monooxygenases (BVMOs) for preparative biocatalytic transformation.[69-70] Cyclobutanone **96**, which can be obtained from allylbenzene **95** by [2+2]-cycloaddition with trichloroacetyl chloride, was reduced to **97** with Cu-Zn couple.[65] This was then converted to *ent*-**87** in buffer at pH 7 (Scheme 24). Both yields and enantioselectivities were high, yet this example points to a common issue in biocatalysis: the configuration of the reaction products (and the stereopreference for the reactants in the case of chiral substrates) is determined by the chiral environment in the active site of the enzyme which is not readily mutated to equally active and selective catalysts to give the optical antipodes.




**Scheme 24.** Biocatalytic enantioselective Baeyer-Villiger oxidation to *ent*-**87**; o.p.: optical purity.

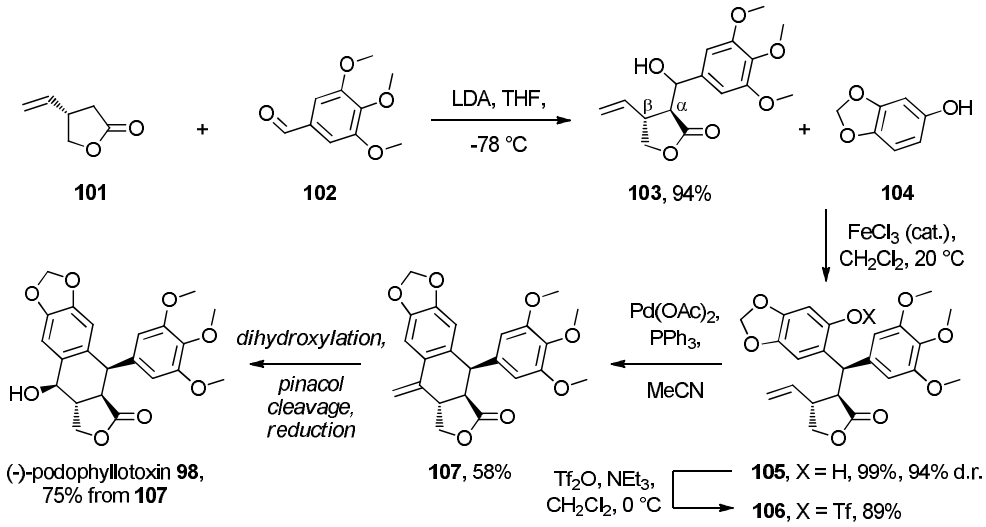
The aryltetralin-type lactone podophyllotoxin **98** (also discovered to be produced by the fungal endophyte *Trametes hirsuta*, normally residing inside its host plant *Podophyllum hexandrum*,[71] thereby being another example of a lignan that is biosynthesized by an organism other than a plant) has been the

subject of intensive study for its anti-viral and anti-tumor activity,[72-73] and semisynthetically-derived glycoconjugates thereof, such as etoposide **99** and teniposide **100**, are used in oncology (Scheme 25).[74]




**Scheme 25.** Aryltetralin lignan podophyllotoxin **98** and the semisynthetic 4'-*O*-demethylepipodophyllotoxin derivatives etoposide **99** and teniposide **100**, used clinically.

Among the numerous racemic and asymmetric syntheses of **98**, relatively new work[75] by Bach and Stadler deals with the preparation of the target compound in optically active form *via* an iron(III)-catalyzed Friedel-Crafts alkylation and an intramolecular Heck reaction as key steps (Scheme 26). Therein, the pivotal starting point is (*S*)-Taniguchi lactone **101**, a small but precious chiral building block for which a multi-kilogram scale manufacturing process, devoid of chromatography, has been established only recently.[76]

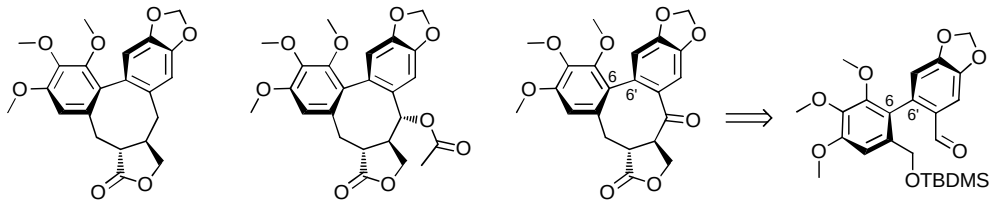



**Scheme 26. S**ynthesis of (-)-podophyllotoxin **98**.

Thus, aldol reaction of **101** to aldehyde **102** gave addition product **103** *trans*-diastereoselectively (note the similarity of compound **101** in structure and role to central intermediate **87**, as mentioned earlier in Scheme 21). Practically no stereoselectivity for the hydroxy group-bearing carbon was observed (52:48

ratio), but this was inconsequential because in the next step, an $S_N1$-type alkylation of sesamol **104**, involving a carbenium ion at this position in **103**, was carried out. After some experimentation, the authors found that iron(III) chloride as the Lewis acid was the catalyst of choice that afforded the highest d.r. (94%) and essentially quantitative yield of intermediate **105**. With this being accomplished, triflate formation **106** primed the molecule for intramolecular Heck reaction **107**, and a sequence of olefin dihydroxylation with osmium tetroxide/NMO, periodate cleavage and (entirely substrate controlled) diastereoselective reduction with lithium tri-*tert*-butoxy aluminium hydride provided (-)-podophyllotoxin **98**. This protective group-free route therefore highlights the usefulness of lactone **101**, for it does not need to employ any other chiral starting materials or reagents.

Preparative approaches toward dibenzocyclooctadiene-type lignans were reviewed not long ago.[77] Subsequent to that, Colobert, Leroux and co-workers focused on the formal synthesis of (-)-steganone **110**, a compound belonging to this class, known for the tubulin polymerization-inhibitory activity of some of its congeners (Scheme 27) and therefore the subject of several studies related to its synthesis since its discovery in 1973.[78] A particular property of these structures is that they display axial chirality due to the hindered rotation along the 6-6' bond. As compound **111** was an intermediate in previous syntheses of (-)-steganone,[79-80] atropodiastereoselective formation of this bond in an aryl-aryl cross-coupling reaction would therefore represent a formal total synthesis of the target molecule.



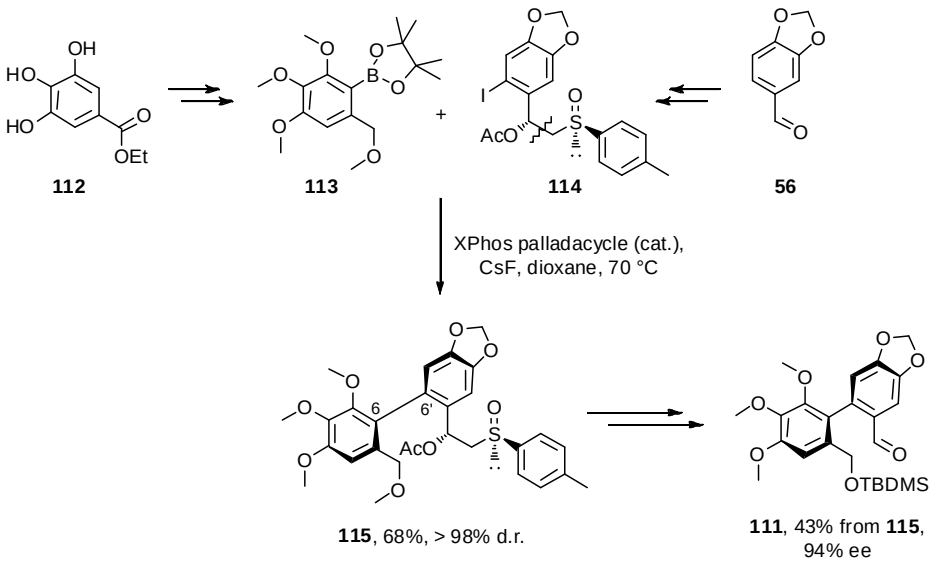

(-)-stegane **108** (-)-steganacin **109** (-)-steganone **110** **111**

**Scheme 27.** (-)-Steganone **110** and related compounds with **111** as key intermediate.

Boronic ester **113** was prepared from commercially available ethyl gallate **112**, while coupling partner **114**, containing a chiral sulfoxide subunit, came from piperonal **56**. The border to the auxiliary part in **114** is shown by a wavy line in Scheme 28. The introduction of (+)-($R_S$)-methyl *p*-tolyl sulfoxide as a chiral auxiliary is possible due to the acidic position adjacent to the sulfur atom, exploiting it for chemical reactivity. Suzuki-Miyaura coupling of **113** and **114** then afforded biaryl **115** in good yield and excellent diastereoselectivity, establishing the crucial 6-6' bond. Cleavage of the auxiliary and subsequent conversion to known intermediate **111** did not entail significant erosion of enantiomeric excess, thus completing a formal total synthesis of (-)-steganone.

## 3. Conclusions

The examples presented in this chapter highlight some preparative efforts to obtain lignan compounds using a range of methods, including radical and photochemistry as well as transition metal, organo- and biocatalysis.




**Scheme 28.** Atroposelective formation of intermediate **111** in the (-)-steganone synthesis.

While not all of them provide the targeted compounds in optically active form, the racemic approaches may be adapted accordingly, and it is an explicit objective of this chapter to raise awareness in this regard. Lignans are not as complicated and more quickly assembled than many other molecules from the realm of natural products. Therefore, this class of compounds is an excellent playfield to develop new synthetic methods and test their robustness by preparing lignans of different configuration and substituent decoration patterns. Combined with the biological activity of many lignans, fruitful results may be obtained with regard to both synthetic methodology and medicinal chemistry when embarking on a project that aims at preparing this sort of heterocyclic compounds.

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