DEVELOPMENT OF MODIFIED CHIRAL DIOXOLANE BISPHOSPHINE LIGANDS AND THEIR USE IN EFFICIENT ASYMMETRIC SYNTHESIS OF NATURALLY OCCURRING LIGNANS

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Abstract ----- This review deals with our recent works on the development of efficient chiral bisphisphine ligands, modified DIOPs, bearing a dioxolane framework and their application to the asymmetric total synthesis of naturally occurring lignans such as (+)-collinusin, (-)-deoxypodophyllotoxin, and (+)-neoisostegane using rhodium(I)-catalyzed asymmetric hydrogenation of itaconic acid derivatives as a key step. Related asymmetric total syntheses of lignans using an equimolar amount of chiral sources are also reviewed.

I. Introduction

To date, much efforts have been devoted to the syntheses of naturally occurring and/or biologically active compounds as optically pure forms[1] since most of the each enantioisomer shows different physiological activities.[2] One of the most effective methods for the synthesis of optically active compounds is a catalytic asymmetric synthesis from prochiral starting materials.[3] Among several types of catalytic asymmetric reactions,[1,3] catalytic asymmetric hydrogenations using the complexes of transition metals and chiral ligands have been developed to be practical methods for the syntheses of many optically active compounds, some of which are useful building blocks of naturally occurring compounds.

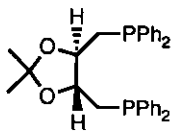
As one of the most important groups of naturally occurring compounds, lignans, which are widely distributed in plants, are known to have broard biological activities,[4] among of which anti-tumour activity has received much attention. In these days, some lignan derivatives such as etoposide and teniposide are utilized as anti-tumour drugs.[5] Although there have been many types of syntheses of racemic lignans,[6] only a few asymmetric total syntheses of these compounds have been reported (see Chapter III).

Recently, we have developed highly efficient chiral bisphosphine ligands, BCPMs,[7] BPPMs,[8] DIOCP,[9] DIOPs,[10-12] and some others[13] for rhodium(I)-catalyzed asymmetric hydrogenations of several functionalized ketones and olefins. In this review are described the development of modified DIOPs for efficient catalytic asymmetric hydrogenations and their use in asymmetric total synthesis of some optically pure lignans. In addition, related asymmetric total syntheses of naturally occurring lignans using an equimolar amount of chiral sources are also reviewed.

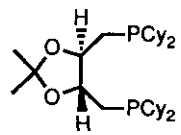
II. Development of Chiral Bisphosphine Ligands, Modified DIOPs, for Efficient Asymmetric Hydrogenations

1. Synthesis of DIOCP and Its Use in Rhodium(I)-catalyzed Asymmetric Hydrogenation of Ketopantolactone

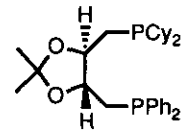
DIOP (**1**) having a dioxolane framework is one of the chiral bisphosphine ligands efficient for the asymmetric hydrogenations of prochiral olefins such as *N*-(acyl)-α-dehydroamino acids and enamides.[14] It can be easily prepared from tartaric acid[15] and is now commercially available. However, DIOP (**1**)-rhodium(I) catalyst did not show excellent enantioselectivity and high catalytic activity in the asymmetric hydrogenation of some other prochiral ketones and olefins. More recently, Cy-DIOP (**2**), a trialkyl-type of bisphosphine, was synthesized and used for catalytic symmetric hydrogenation of α-keto ester derivatives.[16] The neutral rhodium (I) complex of Cy-DIOP (**2**) showed excellent catalytic activity but the enantioselectivity was not much higher than the original DIOP (**1**)-rhodium(I) complex.



(4*R*,5*R*)-DIOP (**1**)



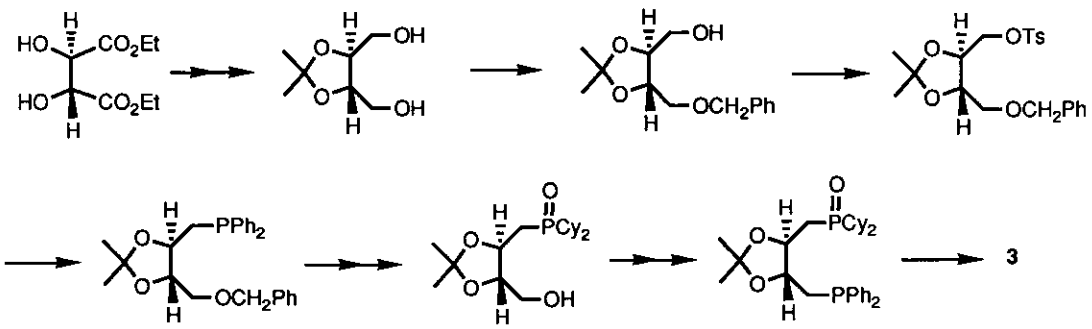
(4*R*,5*R*)-Cy-DIOP (**2**)



(4*R*,5*R*)-DIOCP (**3**)

Previously, we have proposed a design concept, 'Respective Control Concept,' for developing highly efficient chiral bisphosphine ligands.[1a,9] On the basis of this concept, (4*R*,5*R*)-DIOCP (**3**), a modified DIOP bearing

both a dicyclohexylphosphino group and a diphenylphosphino group was designed and synthesized *via* 10 steps from L-(+)-diethyl tartarate as shown in Scheme 1.[9]



Scheme 1

Asymmetric hydrogenation of ketopantolactone was chosen as a model reaction for evaluation of the capability of DIOCP (**3**) for comparison with DIOP (**1**) and Cy-DIOP (**2**).[9] The results summarized in Table 1 indicate that the DIOCP (**2**)-Rh(I) complex shows higher catalytic activity than the DIOP (**1**)-Rh(I) complex and better enantioselectivity than the Cy-DIOP (**2**)-Rh(I) complex. These results may suggest that the dicyclohexylphosphino group and the diphenylphosphino group orient *trans* and *cis*, respectively, to the prochiral keto group in the rate determining and enantioselecting step. This was the first example that the 'Respective Control

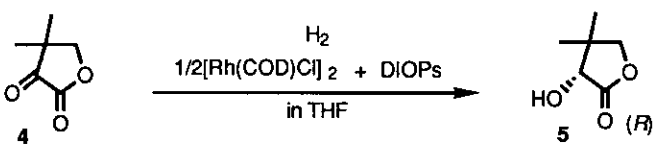


Table 1. Asymmetric Hydrogenation of Ketopantolactone(4)

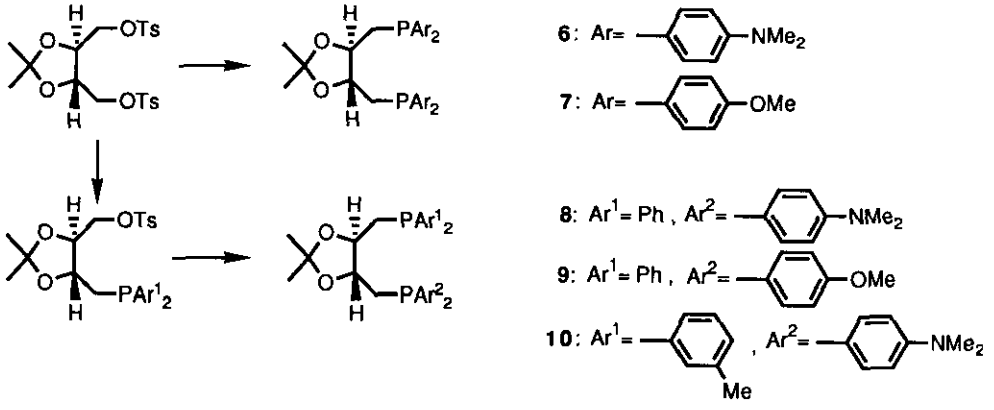
Ligand	[Rh]/[Subst.]	atm/°C/h	Convn/%	Opt. Yield/%e.e.[a] (Confign)
(4*R*,5*R*)-DIOCP(3)	10^{-3}	50/50/45	100	72(*R*)
	10^{-4}	50/50/45	67	57(*R*)
	10^{-3}	15/50/70	100	75(*R*)
(4*R*,5*R*)-DIOP(1)	10^{-2}	50/50/45	100	52(*R*)
	10^{-3}	50/50/45	45	37(*R*)
(4*R*,5*R*)-CyDIOP(2)[b]	2×10^{-3}	15/r.t./12	100	45(*R*)

a) Calculated by using the reported value $[\alpha]_D^{20}$ -50.7°(*c* 2.05, H_2O) for pure (*R*)-(-)-pantolactone.
b) K. Yamamoto *et al.*, *Chemistry Lett.*, 1984, 1603.

Concept' was shown to have the general utility for improving the C_2-symmetric bisphosphine ligands such as DIOP (**1**).

2. Synthesis of 4'-Substituted DIOPs and Their Use in Catalytic Asymmetric Hydrogenation of Ketopantolactone, Itaconic Acid, and Dimethyl Itaconate

Previously, modified DIOPs bearing substituents on the phenyl groups had been prepared and used for efficient Rh(I)-catalyzed asymmetric hydrogenation of α-(acetamido)acrylic acids.[17] Although symmetrical or unsymmetrical *para*-substituted DIOPs were reported to give less change of the enantioselectivity than *ortho*- or *meta*-substituted ones, the net role of the electronic effects of the phosphino groups on the enantioselectivity had not been clarified. Therefore, we prepared *para*-substituted DIOPs (**6-9**), which were sterically more C_2-symmetrical than DIOCP (**3**), for elucidating the electronic effect.[10]



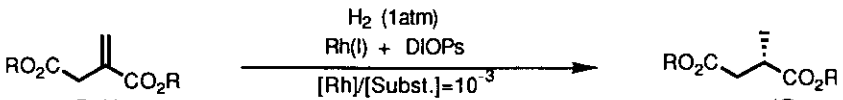
Scheme 2

The results of the asymmetric hydrogenation of ketopantolactone with their neutral rhodium(I)-complexes (summarized in Table 2) show that the ligands (**6-9**) bearing at least one phosphino group more electron-rich than a diphenylphsophino group exhibited higher catalytic activity and better enantioselectivity than original DIOP (**1**).

Asymmetric hydrogenations of itaconic acid (**11**) and dimethyl itaconate (**12**) as the representative substrates of functionalized electron-deficient olefins were carried out with their neutral and cationic rhodium(I) complexes. The results summarized in Table 3 show clearly the electronic effects on their catalytic activity and enantio-

Table 2. **Asymmetric Hydrogenation of Ketopantolactone(4)**

Ligand Ar^1	Ligand Ar^2	Convn/%	Opt. Yield/%e.e. (Confign)
Me_2N	Me_2N (**6**)	100	46 (*R*)
	Me_2N (**8**)	100	45 (*R*)
MeO	MeO (**7**)	100	55 (*R*)
	MeO (**9**)	92	53 (*R*)
Me	Me_2N (**10**)	100	53 (*R*)



11: R=H
12: R=Me

13: R=H (*S*)
14: R=Me

Table 3. **Asymmetric Hydrogenation of Itaconic Acid(11) and Dimethyl Itaconate(12)**

Ligand	[Rh][a]	Substrate: Itaconic acid (**11**) Convn/%	Itaconic acid (**11**) Opt. Yield/%e.e.[b]	Dimethyl itaconate (**12**) Convn/%	Dimethyl itaconate (**12**) Opt. Yield/%e.e.[c]
6	Rh^N	100	70 (*S*)	100	53 (*S*)
	Rh^+	100	66 (*S*)	98	50 (*S*)
8	Rh^N	100	67 (*S*)	100	42 (*S*)
	Rh^+	100	68 (*S*)	100	36 (*S*)
7	Rh^N	100	70 (*S*)	–	–
9	Rh^N	100	65 (*S*)	–	–
1	Rh^N	7	–	30	7 (*S*)
	Rh^+	88	62 (*S*)	44	9 (*S*)
(4*R*,5*R*)-MOD-DIOP (**15**)	Rh^N	100	86 (*S*)	100	41 (*S*)
	Rh^+	100	91 (*S*)	100	79 (*S*)
(4*R*,5*R*)-XYL-DIOP (**16**)	Rh^N	92	78 (*S*)	100	80 (*S*)
	Rh^+	95	84 (*S*)	100	84 (*S*)

a) Rh^N: 1/2[Rh(COD)Cl]$_2$ + Ligand, Rh^+: [Rh(COD)Ligand]$^+BF_4^-$.

b) Calculated on the basis of the maximum optical rotation value $[\alpha]_D^{20}$+16.88°(*c* 2.16, EtOH) for the pure (*R*)-(+)-methylsuccinic acid.

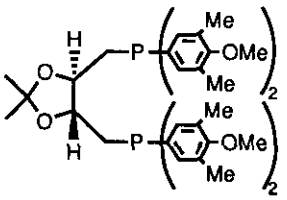
c) Calculated on the basis of the maximum optical rotation value $[\alpha]_D^{20}$-6.86°(neat) for dimethyl (*S*)-(-)-methylsuccinate determined by hplc analysis.

selectivity. The ligands bearing electron-donating groups on the phenyl groups exhibited much higher catalytic activity and enantioselectivity than DIOP (**1**).

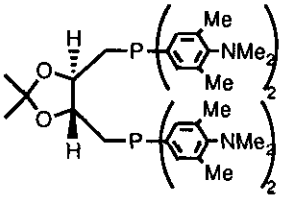
Further, we designed and prepared a modified DIOP (**10**) bearing a *meta*-methyl group and a *para*-dimethylamino group on each phenyl group.[10] Its rhodium(I) complex showed slightly better enantioselectivity than those of modified DIOPs (**6, 8**) bearing *para*-dimethylamino groups in the asymmetric hydrogenations of itaconic acid (**11**) and dimethyl itaconate (**12**).

3. Synthesis of MOD-DIOP and XYL-DIOP and Their Use in Efficient Asymmetric Hydrogenation of Itaconic Acid and Its Derivatives

On the basis of the facts that the electron-donating substituents of modified DIOPs (**6-10**) give higher catalytic activity and enantioselectivity and the *meta*-methyl substituent plays a role in higher enantioselection, we designed and prepared two new efficient modified DIOPs, MOD-DIOP (**15**)[11] and XYL-DIOP (**16**),[12] bearing 4'-methoxy and 3',4'-dimethyl groups and bearing 4'-dimethylamino and 3',4'-dimethyl groups, respectively.



(4*R*,5*R*)-MOD-DIOP (**15**)



(4*R*,5*R*)-XYL-DIOP (**16**)

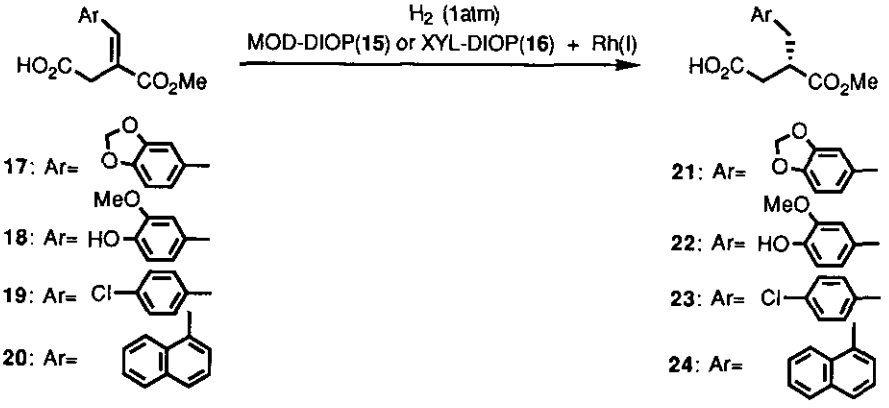


Table 4. **Asymmetric Hydrogenation of Itaconic Acid Derivatives (17 - 20)**

Substrate	Ligand	[Rh]	Convn/%	e.e./%[a)]	Confign
17	**15**	Rh^N	100	94	*S*
		Rh^+	100	90	*S*
	16	Rh^N	100	94	*S*
		Rh^+	100	90	*S*
18	**15**	Rh^+	100	91	*S*
19	**15**	Rh^+	100	94	*S*
20	**15**	Rh^+	100	78	*S*

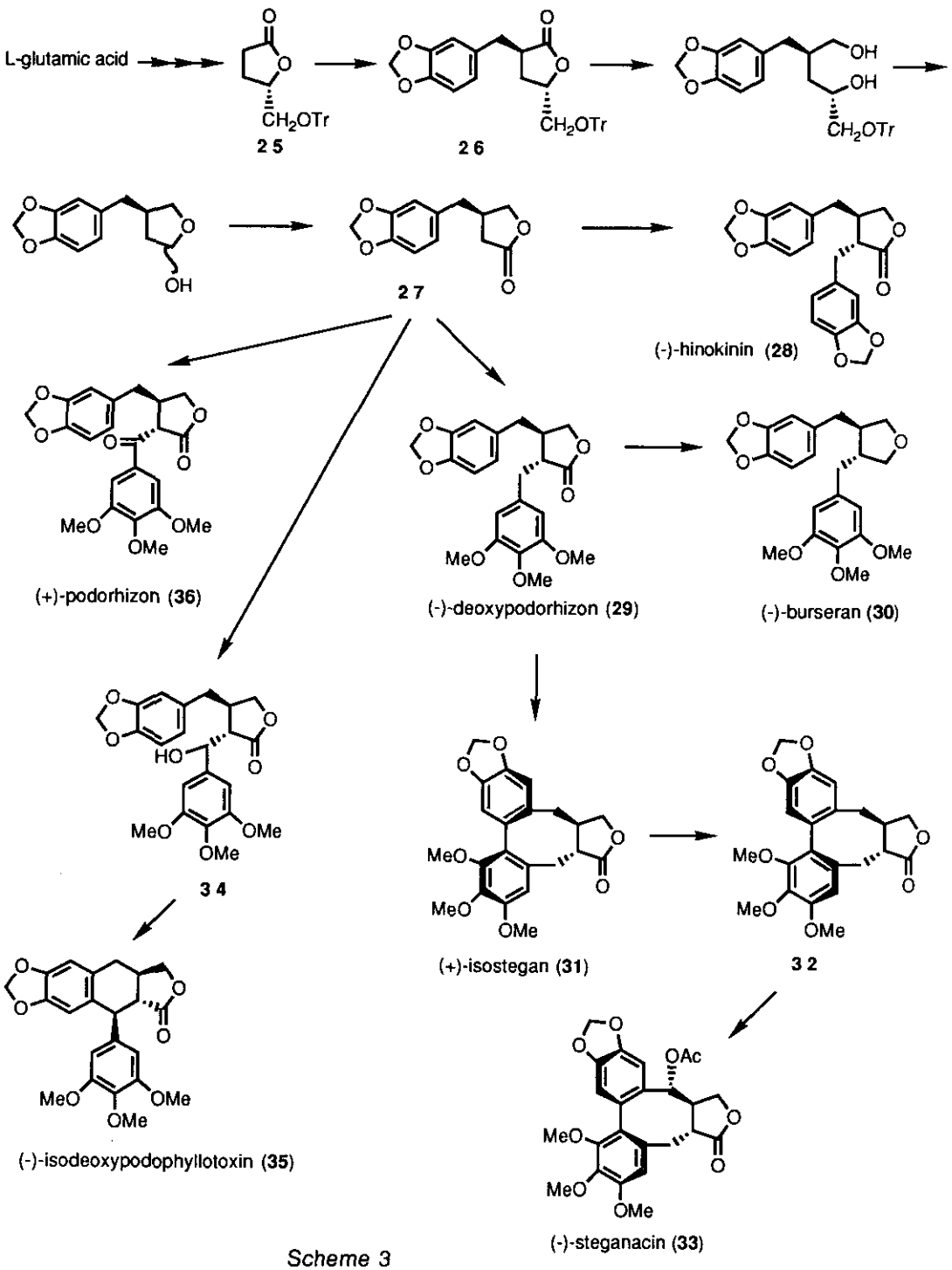
a) Determined by hplc analysis of its morpholino derivative, O⌒NCOCH$_2$CH(CH$_2$Ar)CO$_2$Me on Chiralcel OC (Daicel).

Asymmetric hydrogenations of itaconic acid (**11**) and its ester (**12**) were carried out with their rhodium (I) complex catalysts (molar ratio: substrate to the catalyst = 1000) under an atmospheric hydrogen pressure. The results summarized in Table 3 show that these modified DIOPs (**15, 16**) are highly efficient ligands for asymmetric hydrogenations of itaconic acid (**11**) and its ester (**12**). So far only a few chiral bisphosphine ligands have been developed effective for asymmetric hydrogenations of itaconic acids and their derivatives.[18] The analogues (**17-20**) of itaconic acid bearing β-aryl groups were also hydrogenated in high enantioselectivity under the similar conditions (Table 4). These results provided useful methodology for developing highly efficient chiral bisphosphine ligands other than ones bearing diphenylphosphino groups so far reported.

III. Traditional Methods for the Synthesis of Optically Active Lignans Using an Equimolar Amount of Chiral Sources

Lignans possessing many varied types of structures have attracted much interest on account of their widespread occurrence and broad range of biological activity, and several lignans are known to exhibit anti-tumor activity.[4] Many elegant syntheses of racemic lignans have been reported[6] over the years using phenolic oxidative coupling of cinnamic acid derivatives, non-phenolic oxidative coupling, Diels-Alder reaction, conjugated addition of dithioacetal carbanion to butenolide, alkylation of γ-butyrolactone, and some other reactions.

However, only a few methods have been developed for the asymmetric synthesis of lignans. The methods reported for the synthesis of optically active lignans involve diastereoselective alkylation,[19-23] diastereoselective conjugated addition,[24-26,31-33] diastereoselective reduction,[27] diastereoselective cycloaddition,[28-30] and optical resolution.[34-40]

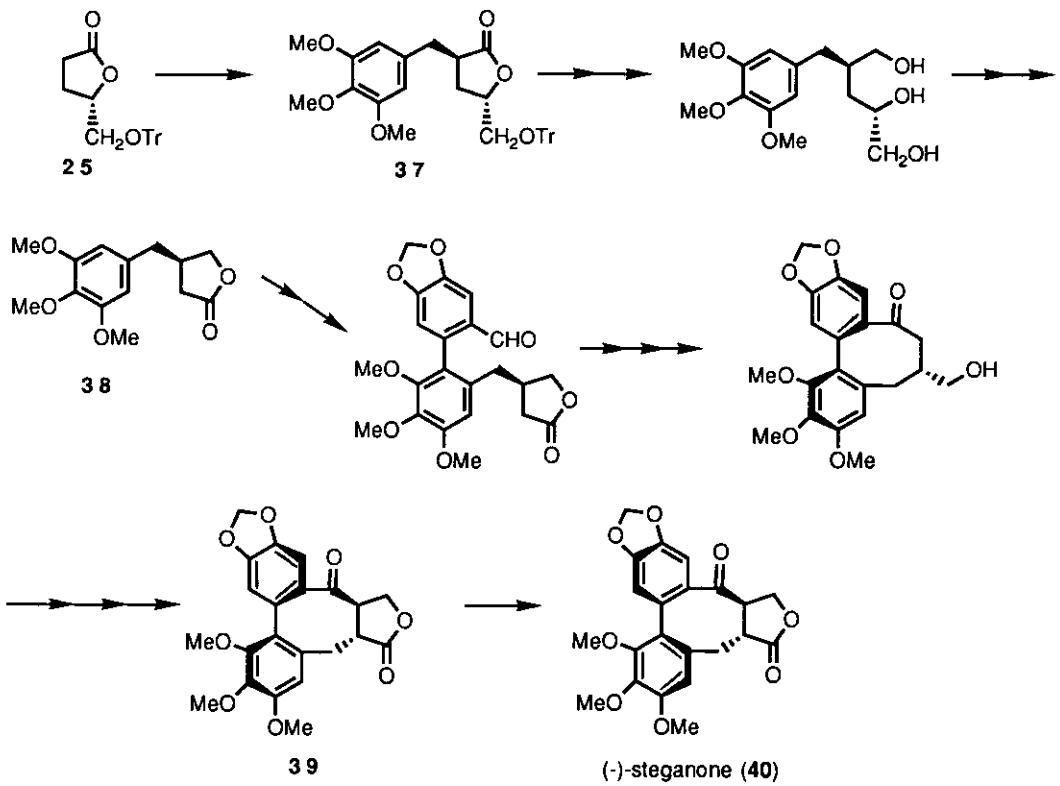

L-glutamic acid
CH2OTr
25
26
OH
OH
CH2OTr
OH
27
(-)-hinokinin (28)
MeO
OMe
OMe
(+)-podorhizon (36)
(-)-deoxypodorhizon (29)
(-)-burseran (30)
HO
34
(+)-isostegan (31)
32
OAc
(-)-isodeoxypodophyllotoxin (35)
(-)-steganacin (33)

Scheme 3

1. Synthesis of Optically Active Lignans Involving Diastereoselective α-Alkylation of Optically Active γ-Butyrolactone

Koga and Tomioka synthesized natural antipodes of optically active lignans, (-)-hinokinin (**28**),[19] (-)-deoxypodorhizon (**29**),[19] (-)-burseran (**30**),[20] (-)-steganacin (**33**),[21] (-)-isodeoxypodophyllotoxin (**35**),[19] and (+)-podorhizon (**36**)[22] by using diastereoselective α-alkylation of an optically active γ-butyrolactone (**25**) obtained *via* a multistep sequence from L-glutamic acid (Scheme 3).

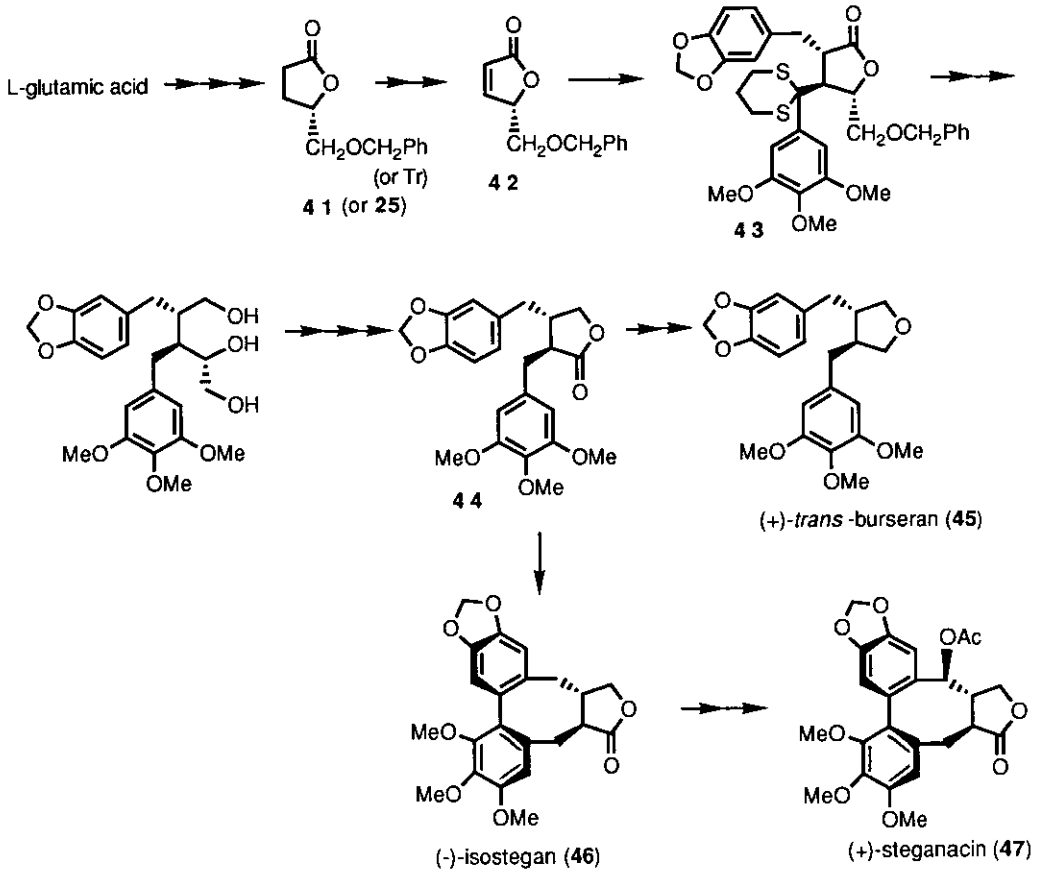
Another route *via* α-arylmethylation of the same γ-butyrolactone (**25**) was used by Brown *et al.* for the synthesis of (-)-steganone (**40**) (Scheme 4).[23]



Scheme 4

2. Synthesis of Optically Active Lignans Involving Diastereoselective Conjugated Addition to Optically Active Butenolides

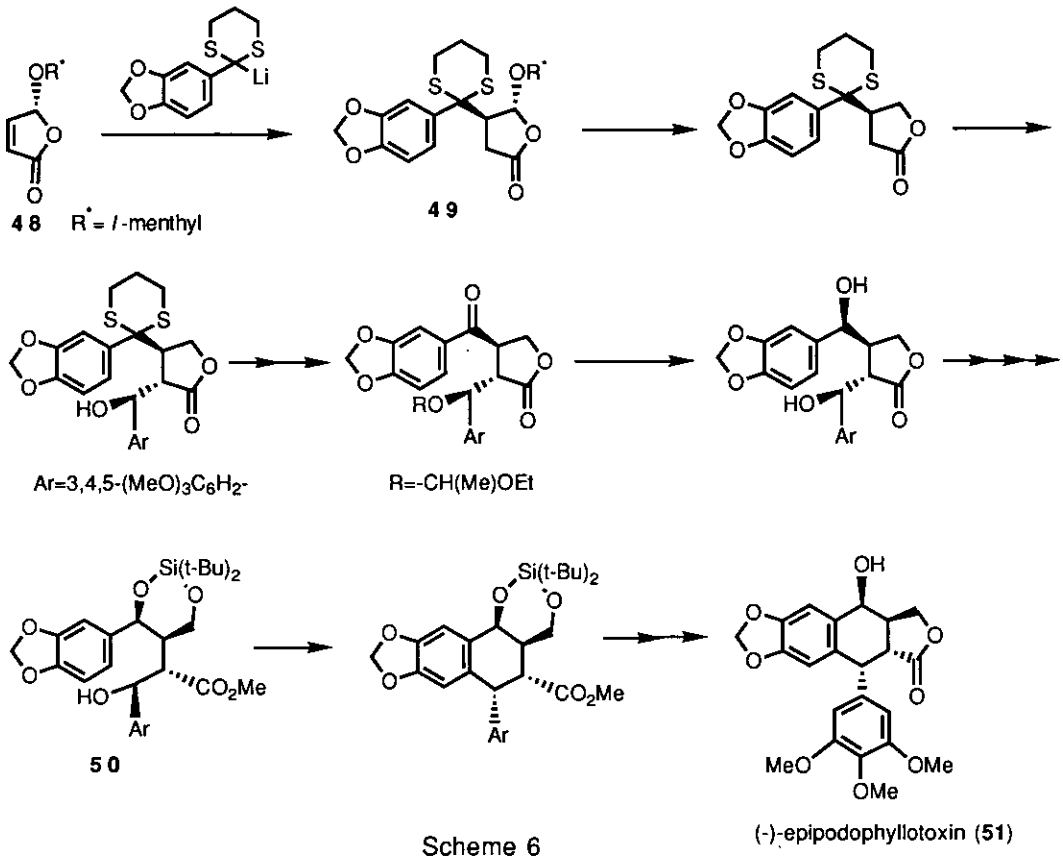
Koga and co-workers synthesized unnatural antipodes, (+)-*trans*-burseran (**45**),[24] (-)-isostegan (**46**),[24] and(+)-steganacin (**47**)[25] by using conjugated addition of dithioacetal carbanion to optically active butenolide (**42**) derived from L-glutamic acid (Scheme 5).



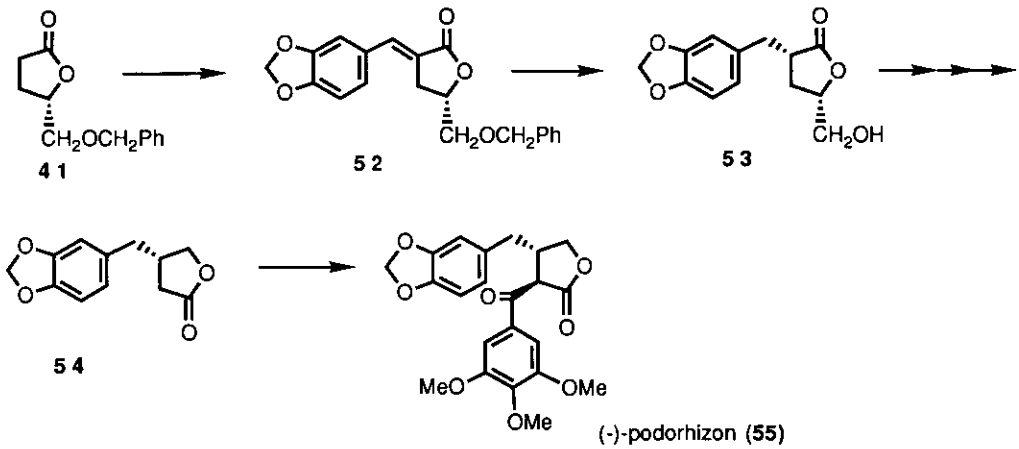
Scheme 5

Recently, Vandewalle and co-workers[26] achieved enantioselective total synthesis of (-)-epipodophyllotoxin (**51**) involving as key steps conjugated addition on chiral butenolide (**48**) and a stereoselective ring closure of **50** (Scheme 6).

(-)-Podorhizon (**55**) was obtained *via* diastereoselective reduction of optically active α-arylmethylene-γ-butyrolactone(**52**) (Scheme 7).[27]



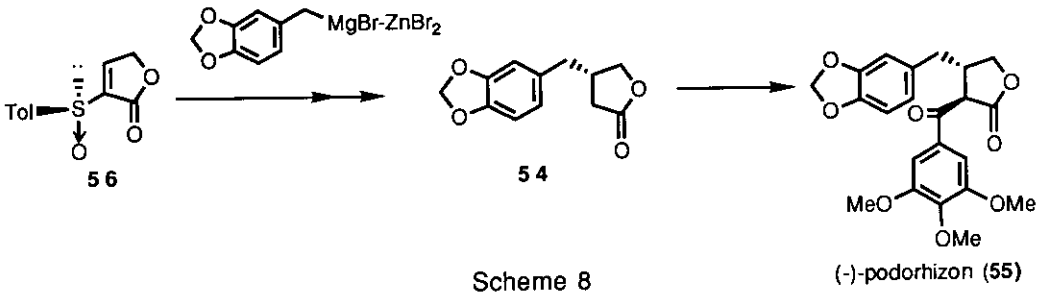
Scheme 6



Scheme 7

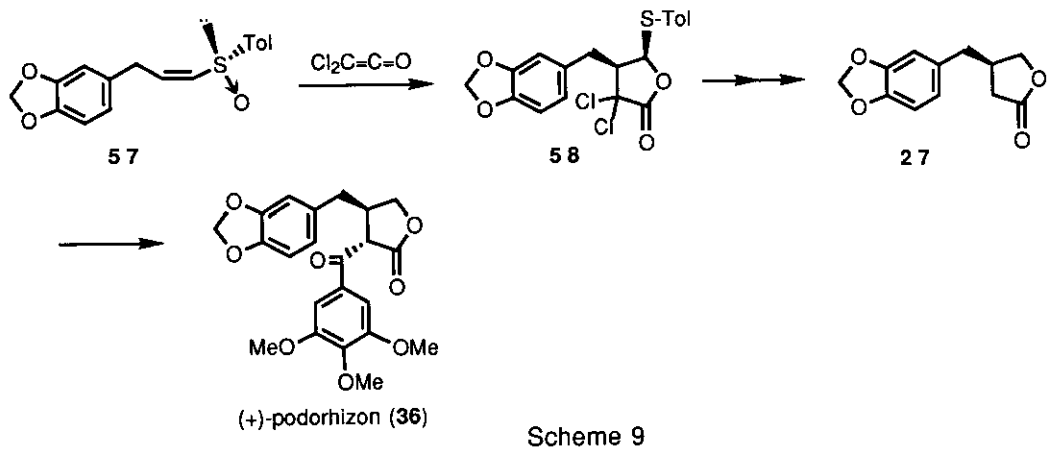
3. Synthesis of Optically Active Lignans Involving Diastereoselective Cycloaddition to Optically Active Vinyl Sulfoxides

Diastereoselective cycloaddition of dichloroketene to optically active vinyl sulfoxides (**56, 57, 59**) was used by Posner and co-workers, Kosugi and co-workers, and Marino and a co-worker for the synthesis of (-)- and (+)-podorhizons (**55, 36**)[28,29] and (+)-quercus (oak) lactone (**60**)[30] (Schemes 8-10).



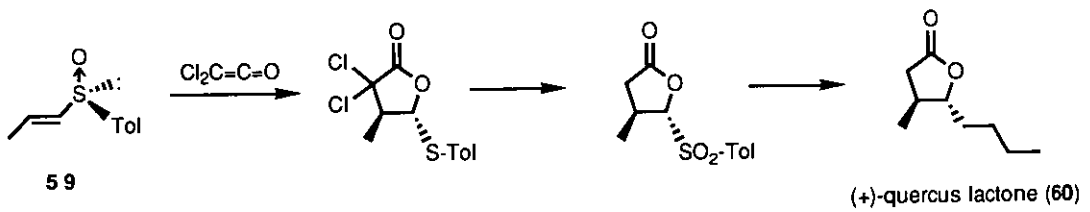
56 **54** (-)-podorhizon (**55**)

Scheme 8



57 **58** **27** (+)-podorhizon (**36**)

Scheme 9

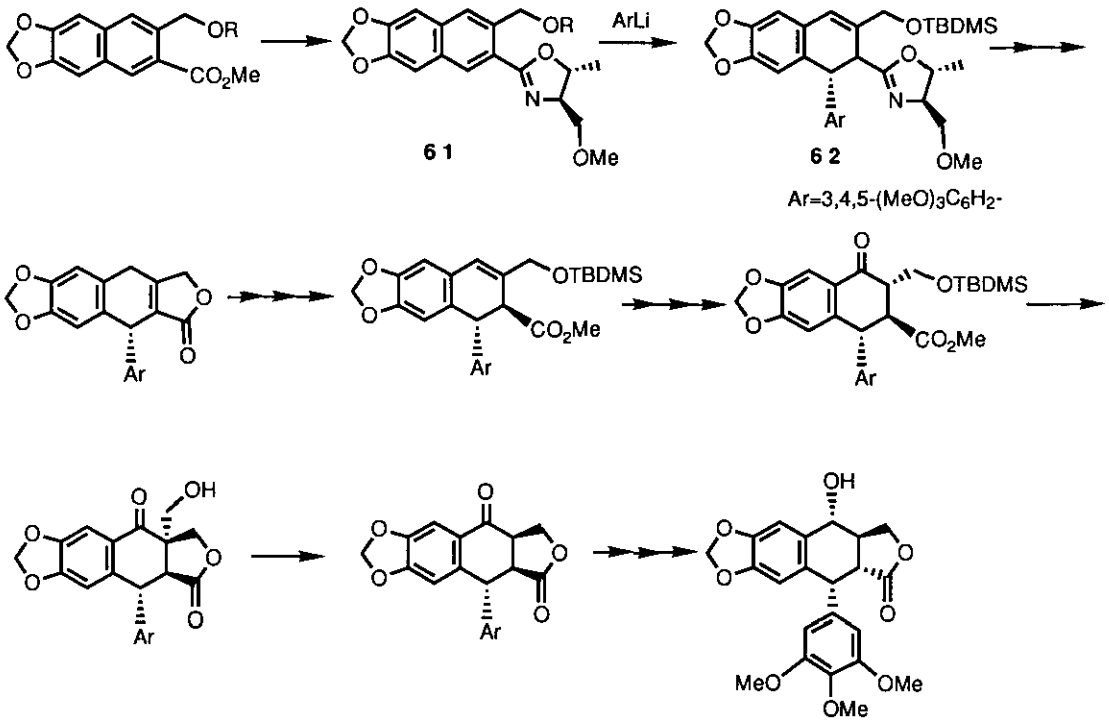


59 (+)-quercus lactone (**60**)

Scheme 10

4. Synthesis of Optically Active Lignans Involving Diastereoselective Addition to Arene-containing Optically Active Oxazolines

Meyers and co-workers reported the synthesis of (-)-podophyllotoxin (**63**),[31] (+)-phyltetralin (**66**),[32] and (-)-steganone (**40**)[33] using their original method *via* a diastereoselective addition of the appropriate aryllithiums to arene-containing chiral oxazolines (**61, 64, 67**) although it needed many reaction steps (Schemes 11-13).

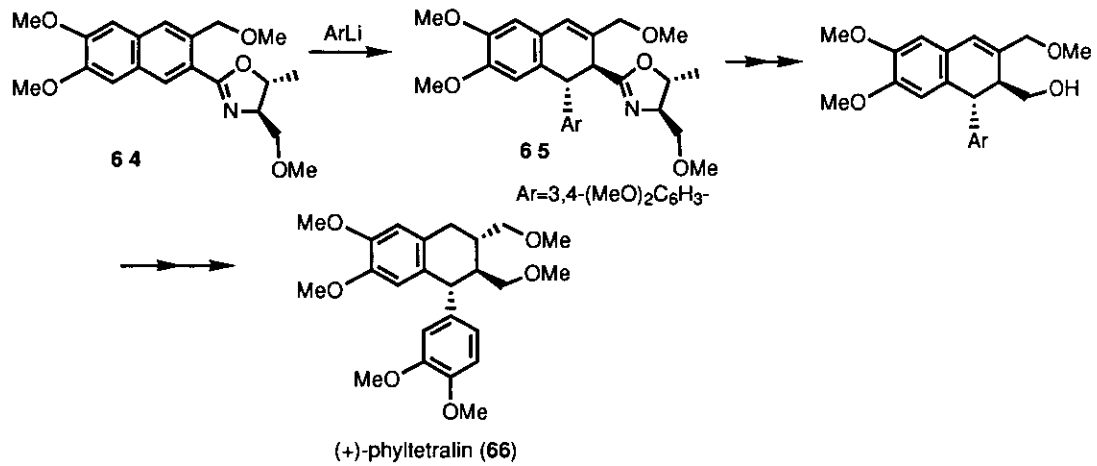


Scheme 11 (-)-podophyllotoxin (**63**)

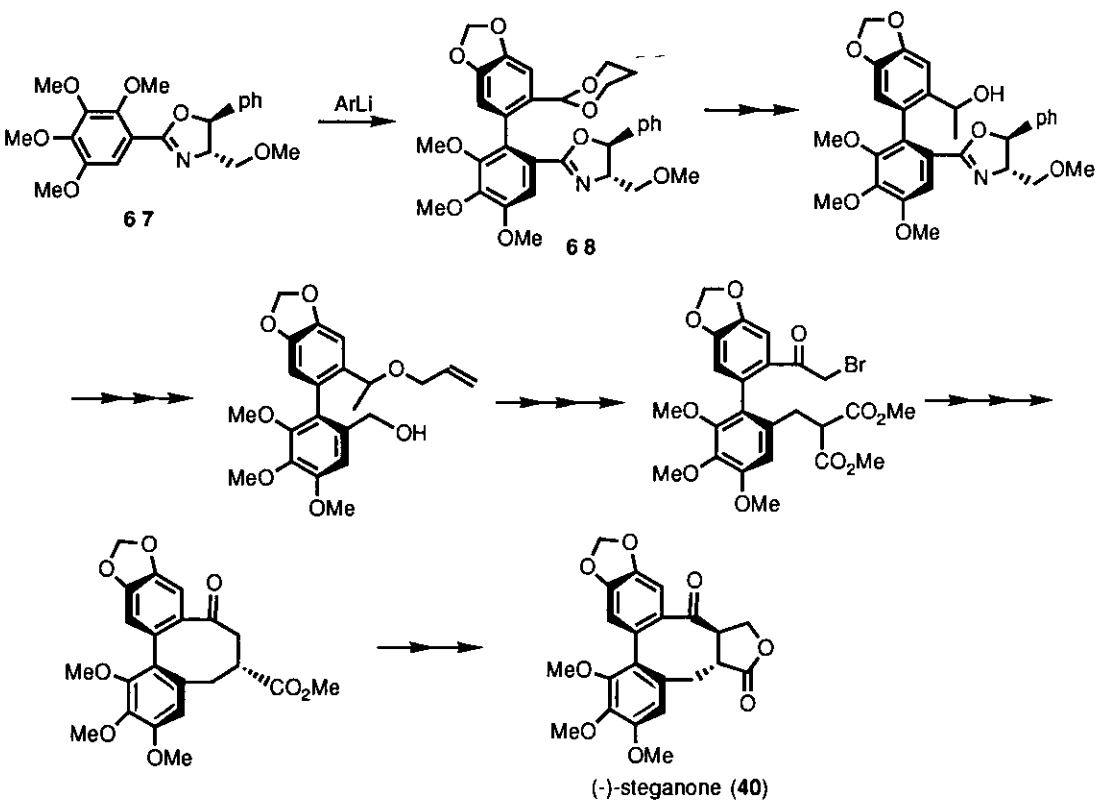
5. Synthesis of Optically Active Lignans Involving Optical Resolution of Racemic Carboxylic Acids

Optical resolutions of racemic carboxylic acids (**69, 73**) with optically active amines were used as the traditional methods for the synthesis of natural lignans such as (-)-hinokinin (**28**),[34] (-)-cubebin(**72**),[34] and *trans*-(-)-3,4-bis[(3-hydroxyphenyl)methyl]-γ-butyrolactone (**76**)[35] (Schemes 14, 15).

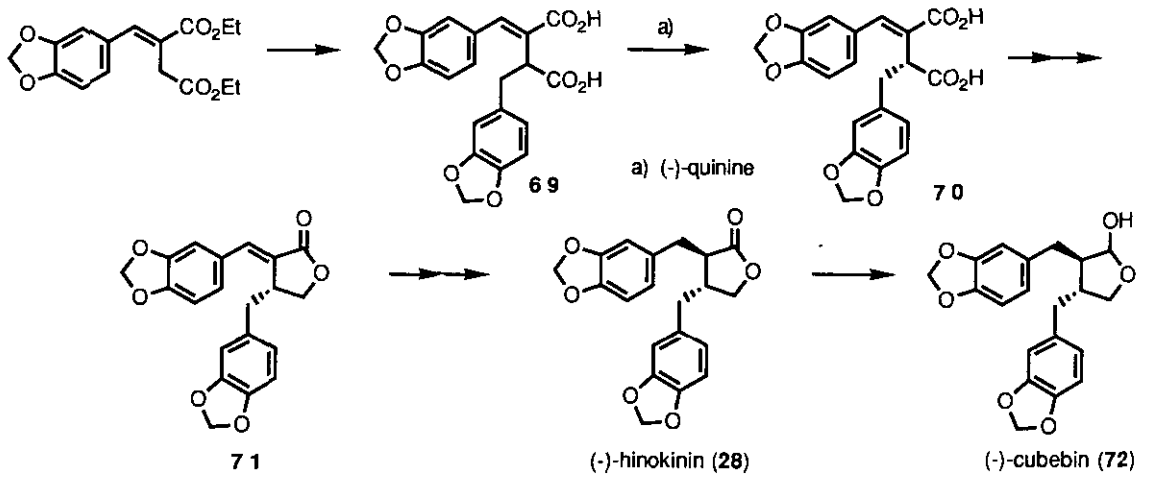
Larson and co-workers[36] synthesized (-)-steganone (**40**) *via* optical resolution of an intermediary carboxylic acid (**77**) by converting it to a mixture of diastereomeric amides (**78**) (Scheme 16).



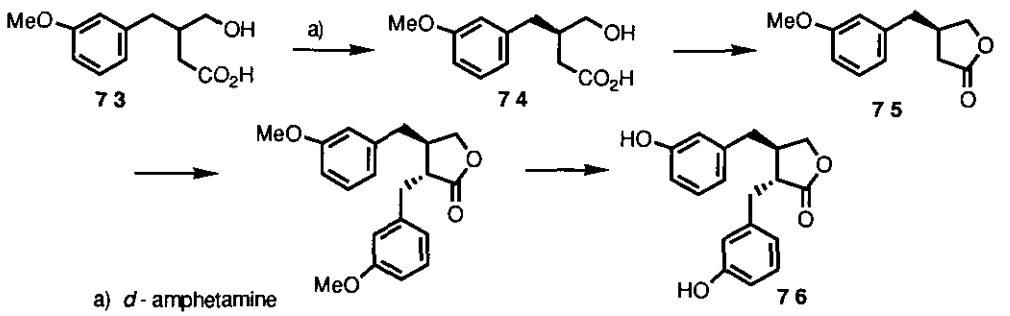
Scheme 12



Scheme 13

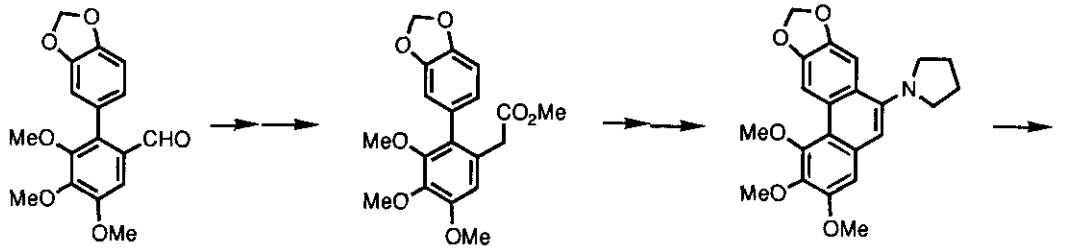


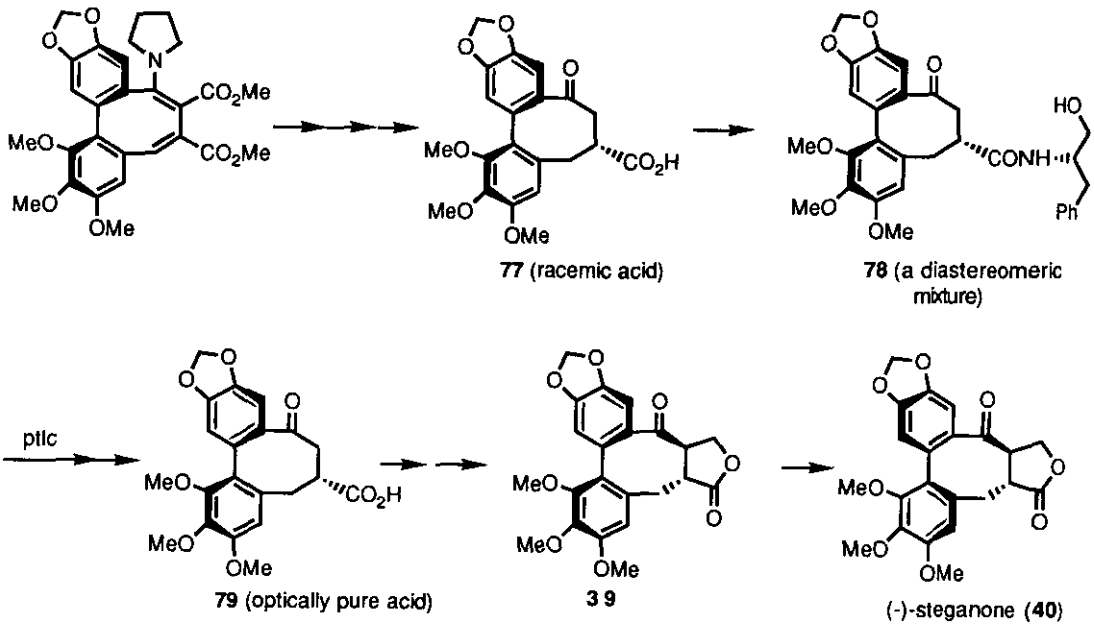
Scheme 14



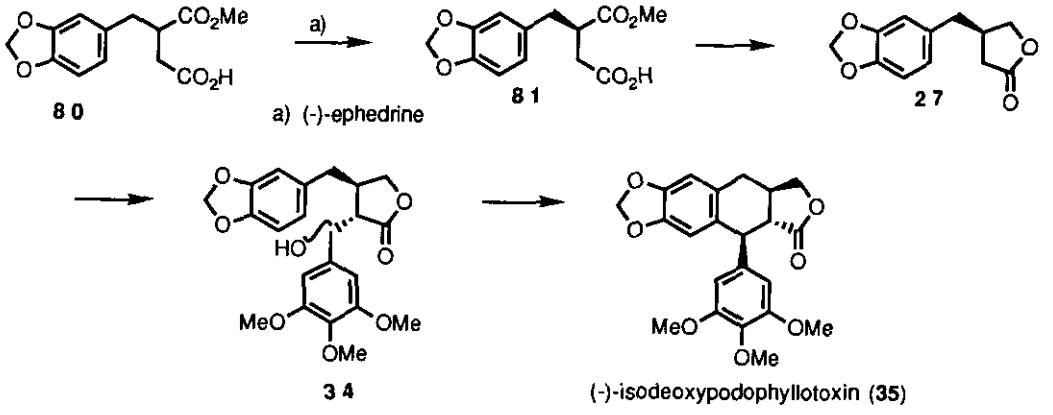
Scheme 15

Brown and co-workers reported the general method for the synthesis of several optically active lignan lactones using optical resolution of arylmethylsuccinic acid half-esters (**80, 82, 92**) and subsequent reduction leading to key intermediates, β-arylmethyl-γ-butyrolactones (**27, 84, 94**). They prepared many lignans such as (-)-isodeoxypodophyllotoxin (**35**),[37] (+)-dimethylisolariciresinol (**86**),[38] (-)-kusunokinin (**87**),[38] (-)-3,4-dimethoxy-3,4-desmethylenedioxycubebin (**88**),[38] (-)-dimethylmatairesinol (**89**),[38] (-)-kusunokinol (**90**),[38] (-)-



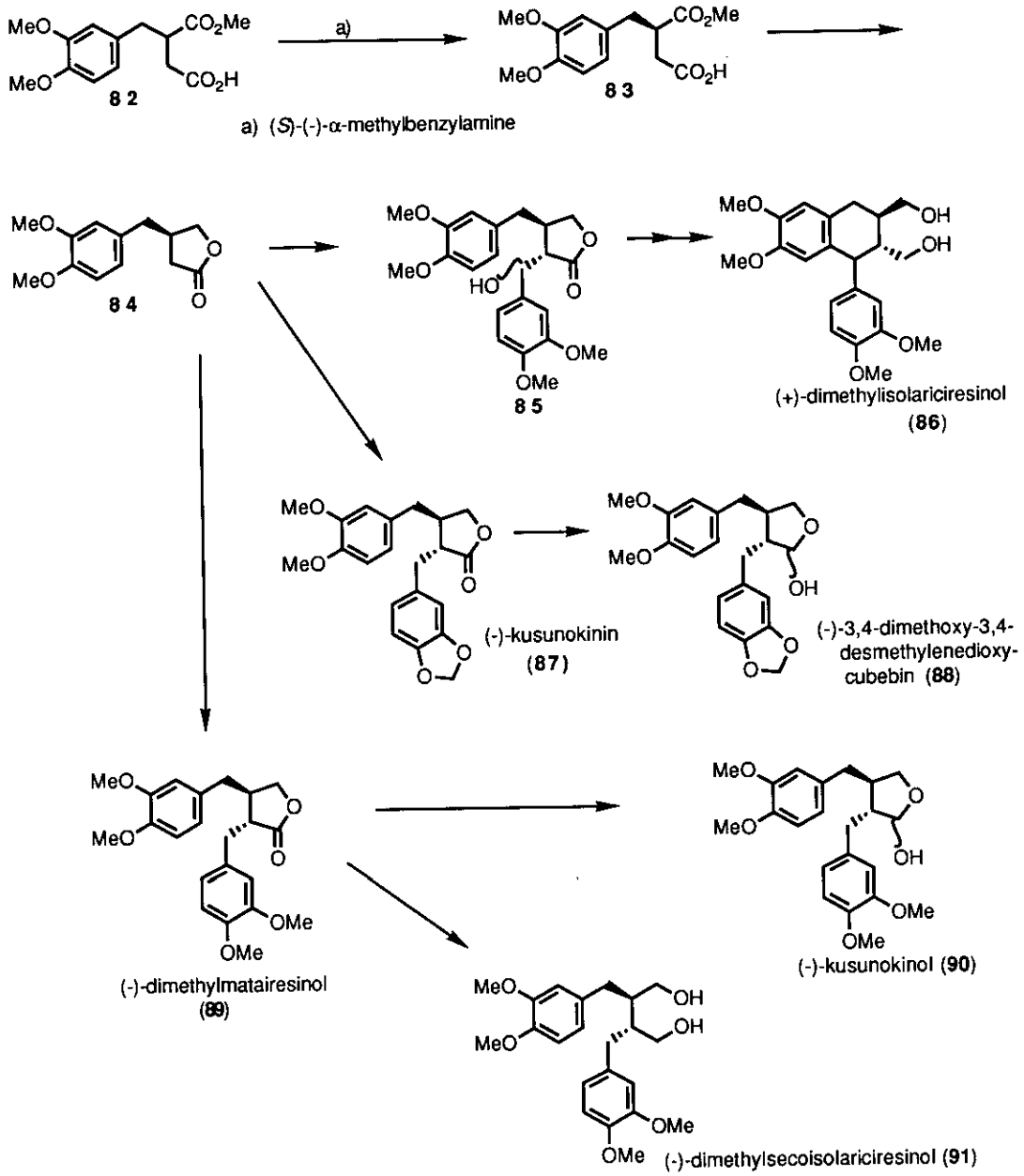


Scheme 16

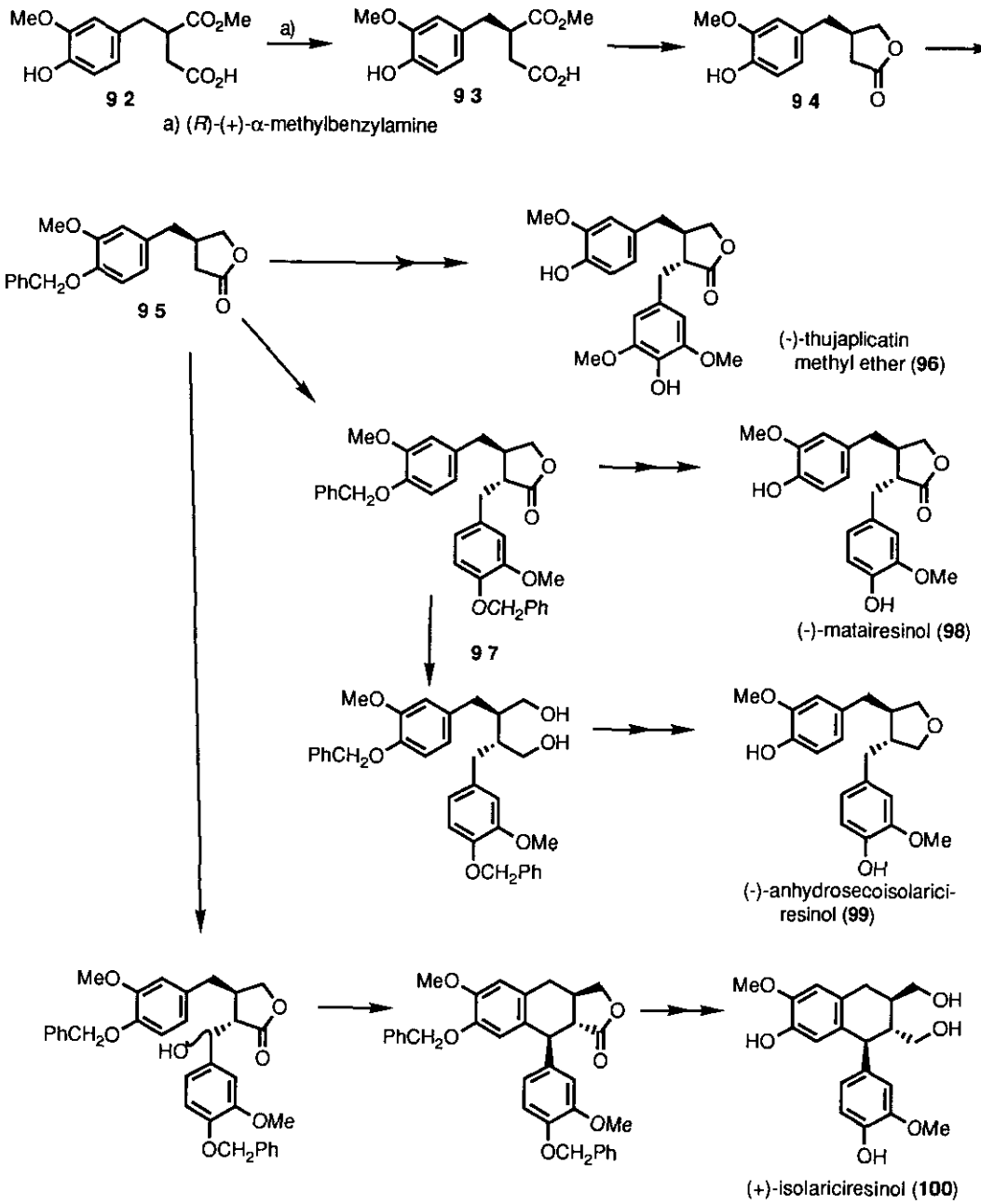


Scheme 17

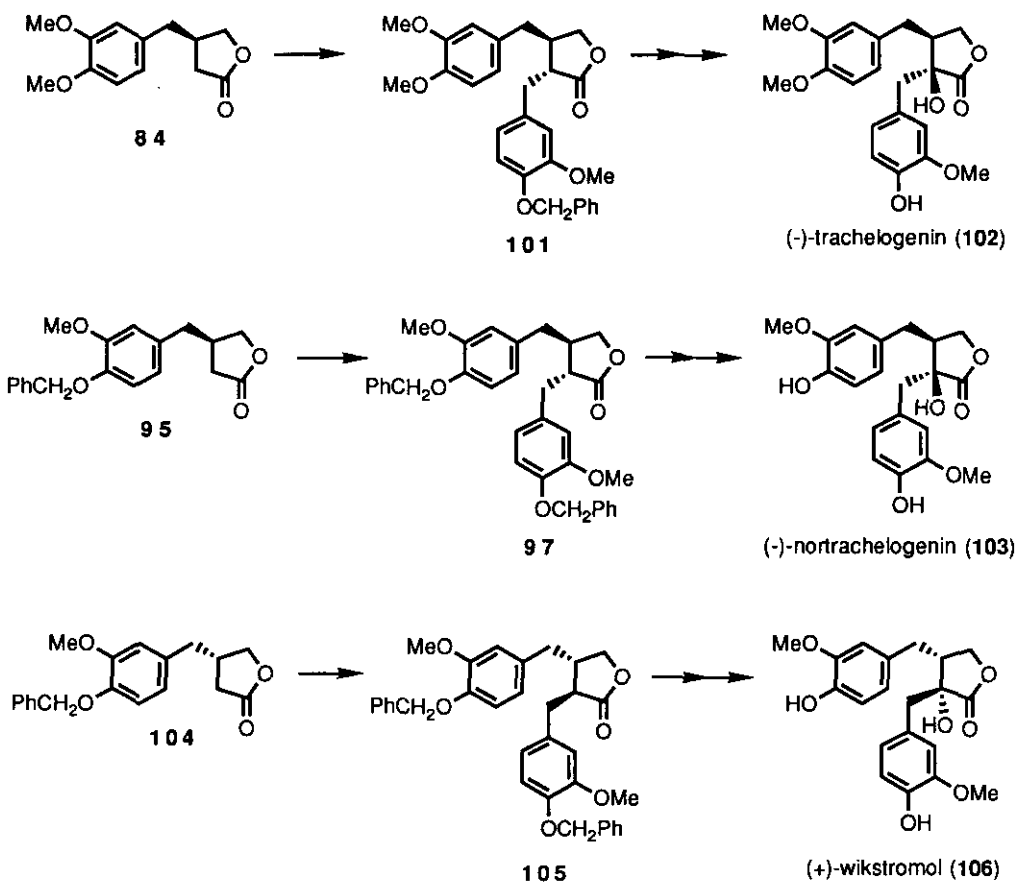
dimethylsecoisolariciresinol (**91**),[38] (-)-thujaplicatin methyl ether (**96**),[39] (-)-mataireSinol (**98**),[39] (-)-anhydrosecoisolariciresinol (**99**),[39] (+)-isolariciresinol (**100**),[39] (-)-trachelogenin (**102**),[40] (-)-nortrachelogenin (**103**),[40] and (+)-wikstromol ((+)-nortrachelogenin) (**106**)[40] (Schemes 17-20).


MeO
MeO
CO2Me
CO2H
82
a)
MeO
MeO
CO2Me
CO2H
83
a) (S)-(-)-α-methylbenzylamine
MeO
MeO
O
O
84
MeO
MeO
HO
O
O
OMe
OMe
85
MeO
MeO
OH
OH
OMe
OMe
(+)-dimethylisolariciresinol
(86)
MeO
MeO
O
O
O
(-)-kusunokinin
(87)
MeO
MeO
O
OH
O
(-)-3,4-dimethoxy-3,4-
desmethylenedioxy-
cubebin (88)
MeO
MeO
O
O
OMe
OMe
(-)-dimethylmatairesinol
(89)
MeO
MeO
O
OH
OMe
OMe
(-)-kusunokinol (90)
MeO
MeO
OH
OH
OMe
OMe
(-)-dimethylsecoisolariciresinol (91)

Scheme 18


MeO
CO2Me
HO
CO2H
a)
92
93
94
a) (R)-(+)-α-methylbenzylamine
PhCH2O
95
(-)-thujaplicatin
methyl ether (96)
OMe
OH
OCH2Ph
97
(-)-matairesinol (98)
(-)-anhydrosecoisolarici-
resinol (99)
(+)-isolariciresinol (100)

Scheme 19



Scheme 20

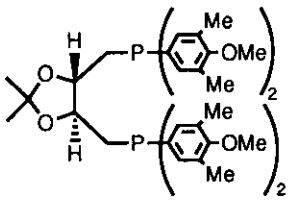
IV. Efficient Asymmetric Synthesis of Naturally Occurring Ligands Using Catalytic Asymmetric Hydrogenation as a Key Step

Although the traditional methods described above are useful for the synthesis of naturally occurring lignans, they do not seem to be convenient for a simple and large scale preparation of their optically active key intermediates due to the necessity of a large amount of optically active sources, many reaction steps, and/or tedious optical resolution. Such problems have been recently dissolved by introduction of the efficient method using the catalytic asymmetric hydrogenation of arylidenesuccinic acid half-esters.[41-43] One of the most convenient route to optically active lignan lactones using the catalytic asymmetric hydrogenation will be described in this section.

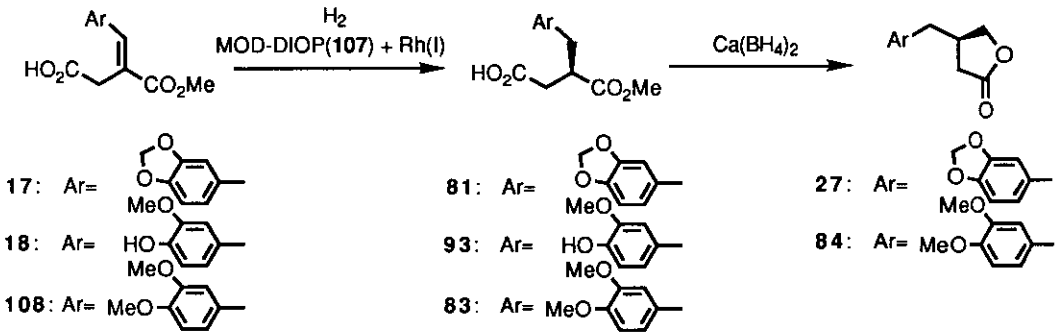
1. Synthesis of Optically Active γ-Butyrolactones Using Asymmetric Hydrogenation with a Rhodium(I)-

(4*S*,5*S*)-MOD-DIOP Complex Catalyst

Since the hydrogenation products (**21-24**) of arylidenesuccinic acid derivatives (**17-20**) using (4*R*,5*R*)-MOD-DIOP (**15**)-rhodium(I) complex were found to have *S*-configuration as described above, the antipode, (4*S*,5*S*)-MOD-DIOP (**107**)[41] was synthesized from D-(-)-diethyl tartarate in order to synthesize naturally occurring



(4*S*,5*S*)-MOD-DIOP (**107**)



Scheme 21

Table 5. **Asymmetric Hydrogenation of ß-Aryl-Substituted Itaconic Acid Half-Esters with (4*S*,5*S*)-MOD-DIOP(107)**

Substrate	Convn/%	$[\alpha]_D$	e.e./%[a]	Confign
17	100	+27.2°(22°C) (*c* 2.10, methanol)	93	*R*
18	100	+26.2°(23°C) (*c* 1.27, methanol)	95	*R*
108	100	+23.8°(23°C) (*c* 1.47, ethanol)	94	*R*

a) Determined by hplc analysis of its morpholino derivative, O⌒NCOCH$_2$CH(CH$_2$Ar)CO$_2$Me on Chiralcel OC (Daicel).

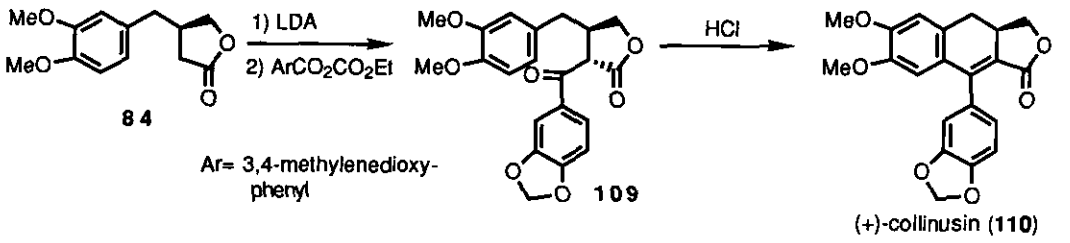
lignan lactones bearing *R*-configuration. Asymmetric hydrogenation of arylidenesuccinic acids (**17, 18, 108**) was carried out with a neutral rhodium(I) complex of (4*S*,5*S*)-MOD-DIOP (**107**) (Scheme 21) under the similar conditions (substrate/catalyst=500, 1 atm of H_2, 30 °C) described above.[11] As the results are summarized in Table 5, all the reactions gave the *R*-products (**81, 93, 83**) in high optical yields (≥ 93% ee) and quantitative chemical yields.[41-43] The hydrogenations could be also carried out even with larger molar ratios of substrate to catalyst (2000~5000) under a hydrogen pressure of 5 atm at 30~50 °C, producing the *R*-products in similar or slightly lower optical yields. The optically pure (*R*)-arylmethylsuccinic acid half-esters (**81, 93, 83**) were obtained by a single recrystallization of the hydrogenation products.

The optically pure products (**81, 83**) were converted to (*R*)-β-arylmethyl-γ-butyrolactones (**27, 84**) in high yields by the selective reduction of the ester group with calcium borohydride according to the procedure reported by Brown.[43] Thus far, only a few methods for the synthesis of (*R*)-β-arylmethyl-γ-butyrolactones have been reported. As described above, the lactones (**27, 84, 94**), the key intermediates for natural lignans, were previously synthesized by derivation *via* many steps from L-glutamic acid,[19-21] by using Michael addition of optically active vinyl sulfoxides (**56, 57**),[28-30] or by using the optical resolution of arylmethylsuccinic acid half-esters (**80, 82, 92**) with chiral amines.[37-39] Our method for the preparation using catalytic asymmetric hydrogenation is most efficient and practical, since the previous methods needed a lot of optical active compounds such as L-glutamic acid and chiral amines, many reaction steps from chiral sources, and/or tedious optical resolution of racemic carboxylic acids. Optically pure (*R*)-β-arylmethyl-γ-butyrolactones (**27, 84, 94**) are useful key intermediates for various lignans and biologically active lignan analogues.

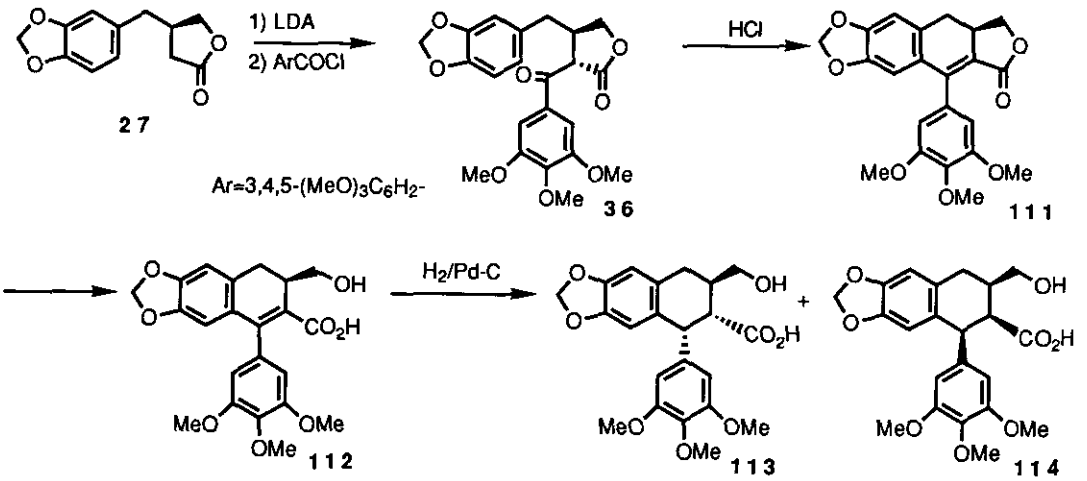
2. Synthesis of (+)-Collinusin Using (*R*)-(+)-β-Veratryl-γ-butyrolactone as a Key Intermediate

(*R*)-(+)-β-Veratryl-γ-butyrolactone (**84**) was used as a key intermediate by Brown for the total syntheses of many natural lignans in optically pure forms as described above.[38]

We reported the first efficient synthesis of natural (+)-collinusin (**110**), one of the chemical constituents of a poisonous plant, using the catalytic asymmetric hydrogenation as a key reaction,[41] although the racemic one had been prepared by using another route involving cyclization of a cinnamyl phenylpropiolate.[45] The synthetic route is outlined in Scheme 22. Benzoylation of **27** followed by dehydrative ring-closure gave (+)-collinusin (**110**). Thus, the absolute configuration of natural (+)-collinusin (**110**) was determined to be 3*R*.



Scheme 22



Scheme 23

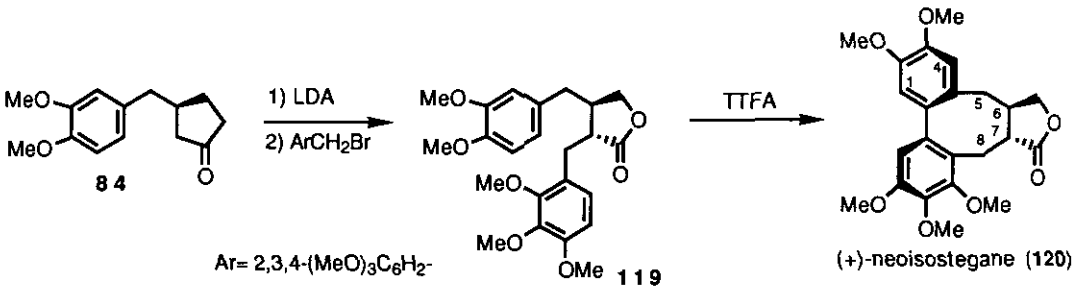
3. Synthesis of (-)-Deoxypodophyllotoxin Using (*R*)-(+)-β-Piperonyl-γ-butyrolactone as a Key Intermediate

Podophyllotoxin (**63**) and its analogues such as epipodophyllotoxin (**51**) and deoxypodophyllotoxin (**115**) are naturally occurring or modified, cytotoxic lignans, and can serve as precursors to clinical antitumor agents, etoposide (**117**) and teniposide (**118**). Only a few asymmetric total syntheses of podophyllotoxins have been reported,[26,31] although there have been many elegant syntheses of racemic podophyllotoxin and its analogues.[6,46]

Our synthetic route of (-)-deoxypodophyllotoxin (**115**) is outlined in Scheme 23.[43] α-Acylation of (*R*)-β-piperonyl-γ-butyrolactone (**27**) with 3,4,5-trimethoxybenzoyl chloride gave *trans*-lactone (**36**), which was treated with methanolic hydrogen chloride to afford (+)-γ-apopicropodophyllin (**111**). Since the catalytic hydrogenation of racemic **111** was known to yield racemic isodeoxypicropodophyllin (**116**) having all-*cis* configurations,[47] we used another method[48] for construction of 1,2-*cis* and 2,3-*trans* stereorelatioship, which is of crucial importance for exhibiting cytotoxic activity. The method involved saponification of the lactone ring, followed by catalytic hydrogenation with Pd on carbon. Finally, dehydration with DCC gave natural (-)-deoxypodophyllotoxin (**115**) as a major product together with (+)-isodeoxypicropodophyllin (**116**). Since **115** is microbially convertible to (-)-epipodophyllotoxin (**51**),[49] our synthetic method involving a highly enantioselective hydrogenation and a stereoselective hydrogenation provided a new convenient route to (-)-podophyllotoxin (**63**), etoposide (**117**), and teniposide (**118**).

4. Synthesis of (+)-Neoisostegane Using (*R*)-(+)-β-Veratryl-γ-butyrolactone as a Key Intermediate

(+)-Neoisostegane (**120**), which was isolated by Robin[50] and Sneden[51] as one of the compounds having some cytotoxity, has a new type of structure of a bisbenzocyclooctadiene. The total synthesis of racemic one and its analogues was reported by Robin,[52] but the absolute configuration was not clarified. Our synthesis of (+)-neoisostegane (**120**) essentially according to the route reported by Robin is shown in Scheme 24.[42] Non-oxidative coupling of *trans*-α,β-bis(arylmethyl)-γ-butyrolactone (**119**) with thallic trifluoroacetate (TTFA) gave (+)-neoisostegane (**120**), whose absolute configuration was determined to be *M*,6*R*,7*R*.



Scheme 24

V. Conclusion

The methodology involving the catalytic asymmetric hydrogenation of itaconic acid derivatives with modified DIOPs-rhodium(I) complexes has provided a new efficient method for synthesizing several types of optically pure lignans. A remarkable feature of of this method is that a large amount of optically pure key intermediates are easily obtainable with a small amount of chiral source, (4*S*,5*S*)-MOD-DIOP [*molar ratio of substrate to catalyst = 500~5000*] under mild reaction conditions [*under 1~5 atm of hydrogen pressure at rt~50 °C*]. Since (4*S*,5*S*)- and (4*R*,5*R*)-MOD-DIOPs are now commercially available from Kanto Chemical Co., Inc. (Japan), further application of this methodology is expected to be explored to the synthesis of many other optically pure natural and unnatural compounds having biological and physiological activities .

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