Tetrahedron Vol. 49, No. 9, pp. 1793-1806, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Efficient Asymmetric Syntheses of Naturally Occurring Lignan Lactones Using Catalytic Asymmetric Hydrogenation as a Key Reaction[1†]

Toshiaki Morimoto, Mitsuo Chiba, and Kazuo Achiwa*

School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka 422, Japan

(*Received in Japan* 4 *November* 1992)

Abstract: Optically pure (*R*)-arylmethylsuccinic acid mono-methyl esters were obtained efficiently by using the catalytic asymmetric hydrogenation of arylidenesuccinic acid mono-esters with a rhodium(I) complex of a chiral bisphosphine, (4*S*,5*S*)-MOD-DIOP. Asymmetric total syntheses of some naturally occurring lignans, (+)-collinusin, (-)-deoxypodophyllotoxin, and (+)-neoisostegane, were achieved *via* several steps from (*R*)-γ-butyrolactones as key intermediates obtained by the reduction of (*R*)-arylmethylsuccinic acid mono-methyl esters.

INTRODUCTION

Naturally occurring lignans possessing various types of structures have attracted much interests on account of their broad range of biological activities.[2] Lignan lactones such as podophyllotoxin (**1**), epipodophyllotoxin (**2**), deoxypodophyllotoxin (**3**), collinusin (**6**), steganacin (**7**), and neoisostegane (**8**) are known to show cytotoxic activities (Fig. 1).[2] In these days, etoposide (**4**) and teniposide (**5**), which are derived from natural podophyllotoxin (**1**), are utilized as anti-cancer drugs.[3] Although there have been numerous types of syntheses of racemic lignans,[4] only a few asymmetric total syntheses of these compounds have appeared in the literatures,[5] and moreover, traditional methods do not seem to be convenient for the simple and large scale preparation of optically pure lignans due to the necessity of a stoichiometric amount of chiral sources and/or multi-step sequences.

One of the most efficient methods for the synthesis of optically active compounds is a catalytic asymmetric synthesis from prochiral starting materials.[6] In our recent studies on the development of efficient chiral bisphosphine ligands for asymmetric hydrogenations, we prepared several efficient ligands on the basis of our design concept.[7] Among them, a modified DIOP, (4*R*,5*R*)-4,5-bis[bis(4'-methoxy-3',5'-dimethylphenyl)phosphinomethyl]-2,2-dimethyl-1,3-dioxolane, abbreviated as (4*R*,5*R*)-MOD-DIOP (**9**), was revealed to show high enantioselectivity in the rhodium(I)-catalyzed asymmetric hydrogenation of itaconic acid and its derivatives (Scheme 1),[8] and the hydrogenation products could be easily purified as optically pure forms.

† Dedicated to Professor Shun-ichi Yamada on the occasion of his 77th birthday.

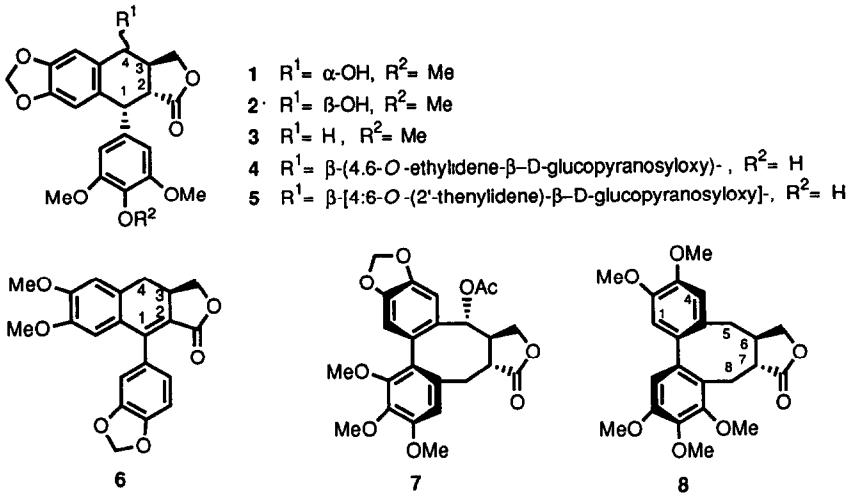
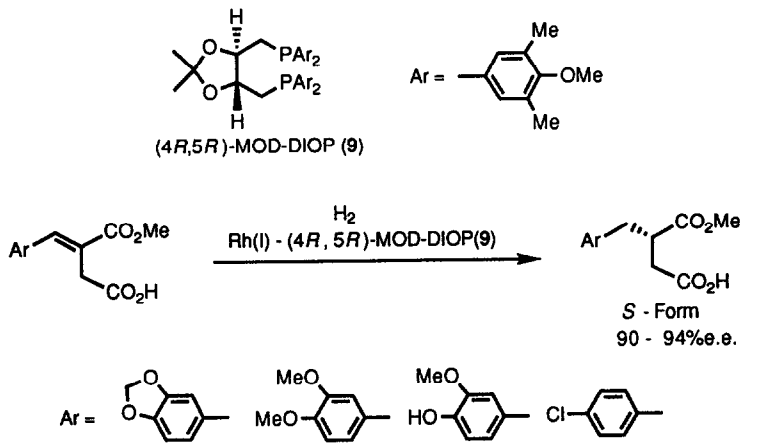


Fig. 1



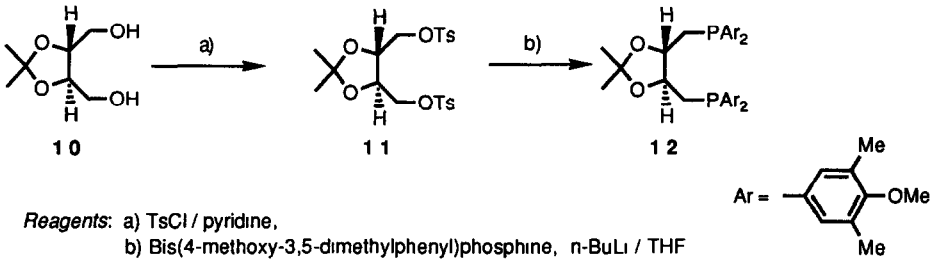
Scheme 1

Our strategy for the asymmetric total synthesis of naturally occurring lignans was based on the asymmetric hydrogenation of arylmethylenesuccinic acid mono-esters, followed by chemoselective reduction of the ester group yielding optically active β-arylmethyl-γ-butyrolactones, which were known to be useful key-intermediates for the synthesis of optically pure lignans *via* α–acylation or α–alkylation. In our previous communications, we have already reported the syntheses of several optically pure lignans.[9-11] In this paper, we wish to describe in detail the catalytic asymmetric synthesis of optically pure (*R*)-arylmethylsuccinic acid mono-methyl esters, their conversion to (*R*)-β-arylmethyl-γ-butyrolactones, and the asymmetric total syntheses of several naturally occurring lignan lactones such as (+)-collinusin (**6**), (-)-deoxypodophyllotoxin (**3**), and (+)-neoisostegane (**8**) using the γ-butyrolactones as the key intermediates.

RESULTS AND DISCUSSION

Synthesis of (*R*)-β-arylmethyl-γ-butyrolactones

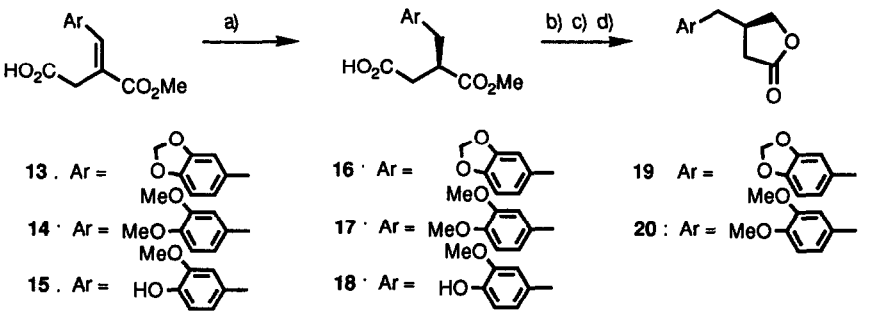
In our previous paper, it was revealed that the catalytic asymmetric hydrogenation of arylidenesuccinic acid mono-methyl esters using (4*R*,5*R*)-MOD-DIOP (**9**)-rhodium(I) complex gave (*S*)-arylmethylsuccinic acid mono-methyl esters,[8] which are the synthetic intermediates for "non-natural" antipode of lignans. In order to synthesize naturally occurring lignan lactones bearing *R*-configuration, the antipode, (4*S*,5*S*)-MOD-DIOP (**12**), was prepared from (-)-2,3-*O*-isopropylidene-D-threitol (**10**) by the route shown in Scheme 2.



Reagents: a) TsCl / pyridine,
b) Bis(4-methoxy-3,5-dimethylphenyl)phosphine, n-BuLi / THF

Scheme 2

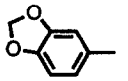
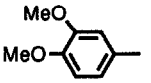
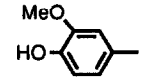
Synthetic route of (*R*)-β-arylmethyl-γ-butyrolactones is shown in Scheme 3. The starting materials, arylidenesuccinic acid mono-methyl esters (**13, 14, 15**) were easily obtained by Stobbe condensation of dimethyl succinate and the corresponding substituted benzaldehydes.[12] The asymmetric hydrogenation of **13, 14,** and **15** was carried out in methanol at 30 °C for 40 h under 1 atm of hydrogen pressure in the presence of triethylamine using the neutral rhodium(I) complex of (4*S*,5*S*)-MOD-DIOP(**12**) (molar ratio; substrate to the rhodium(I) complex = 500) prepared just prior to use by mixing [Rh(1,5-cyclooctadiene)Cl]$_2$ and MOD-DIOP (**12**) in methanol. As the results are summarized in Table 1, all the reactions gave *R*-products (**16, 17, 18**) in

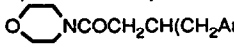


Reagents · a) H_2 (1 atm), (4*S*,5*S*)- MOD-DIOP(**12**) + [Rh(COD)Cl]$_2$ ([Subst] / [Rh]=500), NEt_3 ([Subst.] / [NEt_3]=1) / MeOH; b) KOH/MeOH; c) $Ca(BH_4)_2$/EtOH; d) dil. HCl

Scheme 3

Table 1. **Asymmetric hydrogenation of arylidenesuccinic acid mono-methyl esters (13,14,15) with Rh(I)-(4*S*,5*S*)-MOD-DIOP (12)**

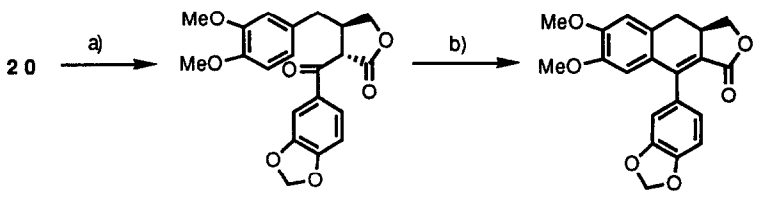
Substrate	Ar	Convn /%[a]	Product	[α]D	e.e./%[b]	Config
13		100	16	+27.2° (22°C) (*c* 2.10, methanol)	93	*R*
14		100	17	+23.8° (23°C) (*c* 1.47, ethanol)	94	*R*
15		100	18	+26.2° (23°C) (*c* 1.27, methanol)	95	*R*

a) Determined by ^{1}H NMR analysis. b) Determined by HPLC analysis of its morpholine amide derivative,  , on Chiralcel OC (Daicel) (isopropyl alcohol / hexane = 1/1).

high optical purity (>93% e.e.) and quantitative chemical yields. The hydrogenation could be also carried out even in larger molar ratios of substrate to the catalyst (2000-5000) under a hydrogen pressure of 5 atm at 30-50 °C, resulting in similar or slightly lower optical yields. Optically pure (*R*)-arylmethylsuccinic acid mono-methyl esters (**16, 17, 18**) were easily obtained by a single recrystallization of the products from isopropyl ether. The optically pure half-esters (**16, 17**) were converted to (*R*)-arylmethyl-γ-butyrolactones (**19, 20**) in high yields by the chemoselective reduction of the ester group with calcium borohydride according to the procedure reported by Brown.[13]

Synthesis of (+)-collinusin

(+)-Collinusin is one of the chemical constituents of *Cleistanthus collinus* (Roxb.), a highly poisonous plant.[14] The structure was determined to be **6** by its chemical transformations and spectral data[15] or by a racemic synthesis from a cinnamyl phenylpropiolate,[16] but the absolute configuration of C-3 was not clarified. Since most of natural lignan lactones have *R*-configuration at the β-position, we planed to synthesize the



Reagents. a) LDA, HMPA, 3,4-$CH_2(O)_2C_6H_3COOCOOEt$ /THF, b) HCl / MeOH

Scheme 4

optically pure collinusin bearing *R*-configuration at C-3 starting from optically pure (*R*)-γ-butyrolactone (**20**) *via* α-acylation followed by dehydrative ring-closure.

Our synthetic route of natural collinusin is shown in Scheme 4. The lactone (**20**) was treated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) in the presence of hexamethylphosphoramide (HMPA), yielding the lithium enolate, which was allowed to react with a mixed anhydride prepared from piperonylic acid and ethyl chloroformate. After the reaction mixture was quenched with aqueous ammonium chloride, α-piperonylated lactone (**21**) was isolated in 70% yield by column chromatography. Dehydrative ring-closure of **21** was achieved by heating with methanolic hydrogen chloride, affording (+)-collinusin (**6**) in 63% yield after purification by recrystallization from acetone. Its melting point (192.5-193.5 °C) and optical rotation value ($[\alpha]_D^{25}$ +134.2° (c 1.01, chloroform)) were in good agreement with the reported values for the natural (+)-collinusin (mp 196 °C, $[\alpha]_D$ +132.48° (c 2.04, chloroform)).[14] In its ^{1}H NMR spectra, signals of the methoxy groups and the methylenedioxy group were observed as two singlets at δ 3.68 and 3.93 and as two doublets at δ 6.02 and 6.04, respectively, and the other signals were also attributed to the structure. Its IR spectra showed an absorption at 1750 cm^{-1} characteristic to the carbonyl group of α,β-unsaturated lactone. Thus the asymmetric total synthesis of natural (+)-collinusin was achieved, and the absolute configuration of C-3 was determined to be *R* .

Synthesis of (-)-deoxypodophyllotoxin

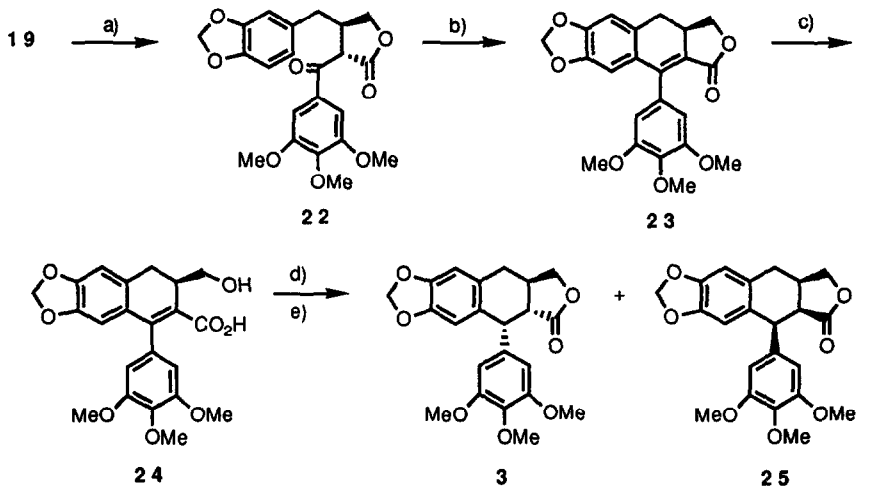
(-)-Deoxypodophyllotoxin (**3**) was isolated from some different sources, *Anthriscus sylvestris*,[17] *Hernandia ovigera* Linn (or *Hernandia peltata* Meissn.),[18] and *Juniperus silicicola*,[19] and named anthricin, hernandion, and silicicolin, respectively. The structure of silicicolin was confirmed by Hartwell and co-workers.[20] These three compounds were found to be the same[21] and designated as (-)-deoxypodophyllotoxin (**3**) in relation to podophyllotoxin. (-)-Deoxypodophyllotoxin and podophyllotoxin are well known to have strong cytotoxic activity.[2] Among numerous semi-synthetic derivatives of natural podophyllotoxin, glycoside derivatives of epipodophyllotoxin were found to have lower toxicity against to normal cells, and now etoposide (**4**) and teniposide (**5**) are widely utilized as unique anti-cancer drugs.[3]

Although numerous elegant syntheses of podophyllotoxin and its derivatives have been reported,[4, 22] most of them are racemic ones, and very few asymmetric total syntheses of these compounds are known; for example, the synthesis involving diastereoselective addition of aryllithium to arene-containing chiral oxazoline[23] and the enantioselective synthesis involving conjugated addition on chiral butenolide.[24]

Our synthetic strategy of (-)-deoxypodophyllotoxin (**3**) was based on the asymmetric hydrogenation, followed by reductive lactonization, acylation, and dehydrative ring-closure to afford γ-apopicropodophyllin (**23**) in a similar way as used for the synthesis of (+)-collinusin (**6**). In podophyllotoxin and its derivatives, 1,2-*cis* and 2,3-*trans* stereorelationship is crucially important for exhibiting cytotoxic activity, and how to construct the stereorelationship is a major problem in their total synthesis. The catalytic hydrogenation of racemic **23** was well-known to yield the racemic isodeoxypicropodophyllin (**25**) of all-*cis* configurations,[25] and a modified method involving electroreduction of racemic **23** was reported to afford *rac*-deoxypicropodophyllin,[26] which was convertible to **3** by metal enolation and succeeding kinetic controlled protonation.[27] More recently, Yamaguchi and co-workers developed another convenient method for construction of 1,2-*cis* and 2,3-*trans* configurations involving saponification of similar racemic 3,4-dihydronaphthalene lactones, followed by catalytic hydrogenation.[28] Since (-)-deoxypodophyllotoxin (**3**) is

microbially convertible to (-)-epipodophyllotoxin (**2**),[29] the development of the method for the asymmetric synthesis of **3** implies the formal total synthesis of etoposide (**4**) and teniposide (**5**).

Our synthetic route of **3** is outlined in Scheme 5. In a similar manner as described for the synthesis of (+)-collinusin (**6**), the lactone (**19**) was acylated with 3,4,5-trimethoxybenzoyl chloride to give (+)-podorhizon (**22**) in 70% yield, followed by dehydrative ring-closure to afford (+)-γ-apopicropodophyllin (**23**) in 80% yield. Saponification of **23** with sodium hydroxide followed by acidification gave (-)-γ-



Reagents. a) 3,4,5-$(MeO)_3C_6H_2COCl$, LDA, HMPA/THF; b) HCl/MeOH; c) NaOH/H_2O-MeOH; d) H_2, 5%Pd-C/EtOH; d) DCC/$CHCl_3$

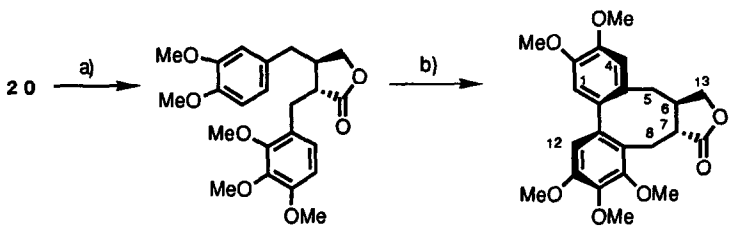
Scheme 5

apopodophyllic acid (**24**) in 64% yield. Catalytic hydrogenation of **24** using 5% palladium on carbon under 20 atm of hydrogen pressure gave an oily product, which was directly lactonized with *N,N'*-dicyclohexylcarbodiimide (DCC) in chloroform, affording a mixture of two lactones. The mixture was separated by preparative thin layer chromatography (PTLC), followed by recrystallization from ethanol, giving **3** and (+)-deoxyisopicropodophyllin (**25**) in 37% and 25% yields, respectively. (-)-Deoxypodophyllotoxin (**3**) thus obtained showed a melting point 168-170 °C and an optical rotation value $[\alpha]_D^{28}$ -113.4° (c 0.50, chloroform), both of which were in good agreement with those of natural deoxypodophyllotoxin [mp 168-169 °C,[21] mp 167-168°C,[30] $[\alpha]_D^{20}$ -115° (c 0.5, chloroform),[21] $[\alpha]_D^{23}$ -116° (c 2, chloroform)[30]]. The ^1H NMR data including two singlets at δ 3.75 and 3.81 (methoxy groups) and two doublets at δ 5.93 and 5.95 (a methylenedioxy group) perfectly match with those of authentic naturally occurring (-)-deoxypodophyllotoxin. This was the first successful asymmetric total synthesis of (-)-deoxypodophyllotoxin using catalytic asymmetric hydrogenation as a key reaction.

Synthesis of (+)-neoisostegane

(+)-Neoisostegane (**8**) was isolated by Robin[31] and Sneden[32] from *Steganotaenia araliaceae* (Apiaceae) as one of the chemical constituents having some cytotoxity. The structure was elucidated to be a new type of a

bisbenzocyclooctadiene lignan lactone from its ^1H and ^{13}C NMR spectra and by chemical correlation with known steganes. Furthermore, Robin and co-workers reported the total synthesis of racemic **8** and its analogs *via* intramolecular non-oxidative biaryl coupling with ruthenium(IV) tetrakis(trifluoroacetate),[33] and the structure of neoisostegane was definitely determined to have *M**,6*R**,7*R**-configuration. However, the absolute configuration was not clarified. In connection with natural bisbenzocyclooctadiene lignan synthesis, optically active stegane, steganacin and steganone were synthesized by Koga et al.[34, 35] or Meyers[36] *via* multi-steps from L-glutamic acid or *via* a biaryl coupling of a chiral aromatic oxazoline.



Reagents: a) 2,3,4-$(MeO)_3C_6H_2CH_2Br$, LDA, HMPA/THF;
b) TTFA, BF_3OEt_2, CF_3CO_2H/CH_2Cl_2

Scheme 6

Our synthetic route of **8** essentially similar to the Robin's is shown in Scheme 6. The lactone (**20**) was lithiated with LDA, and allowed to react with 2,3,4-trimethoxybenzyl bromide, affording α,β-dibenzyl lactone (**26**) as a syrup in 96% yield after purification by column chromatography. Non-oxidative coupling of **26** was carried out with thallium(III) trifluoroacetate (TTFA) in the presence of boron trifluoride etherate. Purification by column chromatography and recrystallization from isopropyl ether gave (+)-neoisostegane (**8**) as prisms, mp 156-157 °C, $[\alpha]_D^{19}$ +107.7° (c 0.51, chloroform) in 48% yield.

The product (**8**) showed a melting point and an optical rotation value different from the reported values (mp 71-74 °C, $[\alpha]_D^{20}$ +65±5° (c 0.35, chloroform)).[31] However, the NMR data were in good agreement with those of natural neoisostegane reported by Robin;[31] the coupling constant between the proton on C-6 (δ 2.22) and the proton on C-7 (δ 2.02) was 12.8 Hz, both the coupling constant between the proton on C-6 and the proton on C-5 (δ 2.57) and the coupling constant between the proton on C-7 and the proton on C-8 (δ 3.68) were 0 Hz, and the other ^1H NMR signals and ^{13}C NMR data were also consistent with the structure. The elemental analysis of our product also established the molecular formula ($C_{23}H_{26}O_7$) consistent with **8**. By inquiry to Prof. Robin, we were informed that the sample obtained from the natural source in a very small quantity was regarded to contain fatty materials as impurities. Thus, the physical data of our product was considered as the true ones of natural (+)-neoisostegane (**8**), and the absolute configuration was determined to be (*M*,6*R*,7*R*).

CONCLUSION

Efficient asymmetric total syntheses of naturally occurring lignan lactones such as (+)-collinusin, (-)-deoxypodophyllotoxin, and (+)-neoisostegane were achieved using the catalytic asymmetric hydrogenation of

arylidenesuccinic acid derivatives with the rhodium(I) complex of a chiral bisphosphine, (4*S*,5*S*)-MOD-DIOP, in the key step, and the absolute configurations of naturally occurring (+)-collinusin and (+)-neoisostegane were determined to be *R*-forms. Our method has provided a new efficient procedure for synthesizing several types of optically pure lignans. A remarkable feature of this method is that a large amount of optically pure key intermediates are easily obtainable with a very small amount of chiral source, (4*S*,5*S*)-MOD-DIOP (molar ratios of substrate to catalyst = 500~5000) under mild reaction conditions (under 1~5 atm of hydrogen pressure at rt~50 °C).

ACKNOWLEDGEMENT

The authors are grateful to Professor H. Yamaguchi, Osaka University of Pharmaceutical Sciences, for providing an authentic specimen of natural deoxypodophyllotoxin and its spectral data, and to Professor J.-P. Robin, University of Maine, for sending a sample of racemic neoisostegane and a copy of ^{1}H NMR spectra of natural one. This work was partially supported by a Grant in Aid (No. 03557096) for Scientific Research from the Ministry of Education, Science, and Culture of Japan.

EXPERIMENTAL SECTION

General Method. All melting points and boiling points are uncorrected. IR spectra were recorded on a JASCO A-202 spectrometer. The NMR spectrometers used in this study were as follows; the ^{1}H and ^{13}C NMR spectra were measured with a Hitachi R-24 (60 MHz), a JEOL FX-90Q (90 MHz), or a JEOL GX-270 (270 MHz) spectrometer using tetramethylsilane as an internal standard. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Chiral HPLC analysis for the determination of enantiometric excess was carried out with a JASCO HPLC assembly consisting of a JASCO 880-PU solvent delivery system, a JASCO 880-50 degasser, and a JASCO 875-UV/VIS detector (at 254 nm), equipped with a Labchart 180 integrator using a chiral stationary phase column, Chiralcel OC (Daicel) employing hexane/isopropyl alcohol as the solvent system. Column chromatography was carried out on silica gel (Wakogel C-200, 100-200 mesh or Silica gel 60, 70-230 mesh, Merck). Precoated silica gel in PTLC was Kieselgel 60 F_{254}, Merck.

Materials. All solvents and reagents were obtained commercially in high purity, and were used without further purification unless indicated. Arylidenesuccinic acid mono-methyl esters were prepared by the condensations of dimethyl succinate with the corresponding substituted benzaldehydes catalyzed by sodium methoxide or lithium methoxide, and were purified by recrystallization. **13**: mp 137-139 °C (water-ethanol). **14**: mp 141-142 °C (water-ethanol). **15**: mp 141-142 °C (water). Bis(4-methoxy-3,5-dimethylphenyl)-phosphine (bp 210-215 °C / 2 mmHg / bulb-to-bulb) was prepared according to the method reported in our previous paper.[8]

(4*S*,5*S*)-4,5-Bis(*p*-toluenesulfonyloxymethyl)-2,2-dimethyl-1,3-dioxolane (11). This compound was prepared by the literature procedure.[37] (-)-2,3-*O*-Isopropylidene-D-threitol (2.05 g, 12.6 mmol) was dissolved in dry pyridine (30 ml), and cooled to -15 °C. To the solution with stirring was added in

three portions *p*-toluenesulfonyl chloride (9.50 g, 49.8 mmol). After stirring overnight at -15 °C, water (50 ml) was added, and the mixture was warmed up to room temperature. White solid precipitates were collected by filtration, washed with water, and dried *in vacuo*. Recrystallization from ethanol gave **11** as needles (5.43 g, 91%), mp 91-92 °C, $[\alpha]_D^{27}$ +12.2° (c 4.00, chloroform) [Lit.,[37] the antipode, mp 91.5-92.5 °C, $[\alpha]_D^{20}$ -12.4° (c 3.2, chloroform)].

(4*S*,5*S*)-4,5-Bis[bis(4'-methoxy-3',5'-dimethylphenyl)phosphinomethyl]-2,2-dimethyl-1,3-dioxolane [(4*S*,5*S*)-MOD-DIOP, (12)]. To a solution of bis(4-methoxy-3,5-dimethylphenyl)-phosphine[8] (1.02 g, 3.4 mmol) in dry THF (15 ml) was added *n*-butyllithium (1.6 M in *n*-hexane solution, 2.1 ml, 3.4 mmol) at -30 °C under an argon atmosphere, and the resulting yellow solution was stirred for 30 min. To the solution was added slowly a solution of **11** (423 mg, 0.90 mmol) in dry THF (15 ml). After stirring for 1 h, the solution was allowed to warm to room temperature, and evaporated *in vacuo*. The residue was extracted twice with benzene. The combined extracts were washed with water and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The resulting viscous oil was purified by column chromatography (benzene/ethyl acetate, 9:1) to give **12** (371 mg, 56%) as a white solid. Recrystallization from ethanol gave needles, mp 128.5-129.5 °C, $[\alpha]_D^{27}$ -14.4° (c 1.02, benzene). *Anal.* Calcd for $C_{43}H_{56}O_6P_2$: C, 70.67; H, 7.72. Found: C, 70.35; H, 7.63. ^1H NMR ($CDCl_3$) δ: 1.36 (6H, s), 2.24 (24H, s), 2.00-2.45 (4H, m), 3.68 (12H, s), 3.50-3.95 (2H, m), 7.08 (8H, dd, J=3.4, 7.6 Hz).

Asymmetric hydrogenation of arylidenesuccinic acid mono-methyl esters (13, 14, 15). General procedure. A solution of a neutral rhodium(I) complex catalyst was prepared by mixing [Rh(1,5-cyclooctadiene)Cl]$_2$ (obtained from Kanto Chemical Co., Inc.) (1.0 mg, $2x10^{-3}$ mmol) and (4*S*,5*S*)-MOD-DIOP (**12**) (3.5 mg, $4.8x10^{-3}$ mmol) in degassed methanol (1 ml) under an argon atmosphere. To a solution of arylidenesuccinic acid mono-methyl ester (**13**,**14**, or **15**) (2.0 mmol) and triethylamine (202 mg, 2.0 mmol) in degassed methanol (3 ml) was added the above solution of the rhodium(I) complex catalyst. The hydrogenation was carried out under 1 atm of hydrogen pressure at 30 °C for 40 h. After the reaction was completed, the reaction mixture was evaporated *in vacuo*. The conversion rate was determined by ^1H NMR analysis. The evaporation residue was dissolved in aqueous NaOH (0.5 M, 4 ml), and extracted with dichloromethane to remove the catalyst. The aqueous layer was acidified with dil. HCl, and extracted twice with ether and the combined extracts were dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the hydrogenation products in quantitative yields. The absolute configurations of the products were determined by comparing their optical rotation values with the reported ones. The optical purities of the hydrogenation products were measured by HPLC analysis of their mono-morpholine amide derivatives on a chiral column, Chiralcel OC (Daicel), using isopropyl alcohol-hexane (1:1) as the eluent with a flow rate of 1 ml/min. The mono-morpholine amide derivatives were prepared as follows. To a solution of the hydrogenation product (0.5 mmol) in dichloromethane (1.5 ml) were added at 0 °C *N*,*N*'-dicyclohexylcarbodiimide (103 mg, 0.5 mmol) and, 15 min later, morpholine (44 mg, 0.5 mmol). After the reaction mixture was stirred for 1 h, the solvent was removed by evaporation. To the resulting residue was added ethyl acetate (10 ml), and insoluble materials were filtered off. Evaporation of the solvent gave the mono-morpholine amide derivatives for the HPLC analysis.

Optically pure (*R*)-arylmethylsuccinic acid mono-methyl esters (16, 17, 18). Recrystallization of the hydrogenation products from isopropyl ether gave pure esters (**16**,**17**,**18**) as white solid in about 80% yields. Their optical purities were determined to be >99% ee by HPLC analysis of their corresponding mono-morpholine amide derivatives. **16**: mp 101-102 °C, $[\alpha]_D^{23}$ +28.4° (c 2.01, methanol) [Lit.,[13] mp 102-104 °C, $[\alpha]_D^{20}$ +30.4° (c 2, methanol)]. **17**: mp 99-100 °C, $[\alpha]_D^{23}$ +26.1° (c 1 23, ethanol) [Lit.,[38] mp 99-101.5 °C, $[\alpha]_D$ +27° (c 1.2, ethanol) **18**: mp 99-99.5 °C, $[\alpha]_D^{20}$ +28.1° (c 1.28, methanol) [Lit.,[39] mp 97.5-100.5 °C, $[\alpha]_D$ +29° (c 1.2, methanol)].

(*R*)-β-Arylmethyl-γ-butyrolactones (19, 20). The optically pure succinic acid mono-methyl ester (**16** or **17**) (5.0 mmol) was dissolved in methanol (2.5 ml), and cooled in an ice bath with stirring. To the solution was added dropwise aqueous KOH (2 M, 2.5 ml), and the mixture was stirred for 15 min. After evaporation of the solvent, the resulting solid was dissolved in ethanol (30 ml) and cooled in an ice bath. To the stirred solution was added powdered calcium chloride (1.39 g, 12.6 mmol). After stirring for 15 min, a suspension of sodium borohydride (0.76 g, 20.0 mmol) and KOH (0.12 g) in ethanol (10 ml) was added, and the suspended mixture was stirred for 3 h at room temperature. Then the reaction mixture was cooled in an ice bath, and acidified (to pH 1) with dil. HCl. After stirring for 30 min, the mixture was evaporated *in vacuo*, and the residue was extracted several times with dichloromethane. The combined extracts were washed with a small amount of saturated brine, and dried over $MgSO_4$. After evaporation of the solvent, an oily residue was purified by column chromatography (toluene-ethyl acetate, 4:1) to give the corresponding lactone as an oil. **19**: 97% yield, $[\alpha]_D^{25}$ +4.8° (c 1.19, chloroform) [Lit.,[13] $[\alpha]_D^{20}$ +4.87° (c 0.87, chloroform)]. IR (KBr): 1778 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ: 2.13-2.93 (5H, m), 3.75-4.42 (2H, m), 5.73 (2H, s), 6.30-6.73 (3H, m). **20**: 95% yield, $[\alpha]_D^{21}$ +6.2° (c 1.23, chloroform) [Lit.,[38] $[\alpha]_D$ +8° (c 2.69, chloroform)]. IR (KBr): 1780 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ: 2.21-3.01 (5H, m), 3.80 (6H, s), 3.90-4.47 (2H, m), 6.47-6.80 (3H, m).

(2*R*,3*R*)-3-(3',4'-Dimethoxybenzyl)-2-(3',4'-methylenedioxybenzoyl)-4-butanolide (21). A solution of diisopropylamine (688 mg, 6.6 mmol) in dry THF (21 ml) was chilled to -60 °C under an argon atmosphere. To the solution were added dropwise *n*-butyllithium (1.6 M in hexane, 4.2 ml, 6.6 mmol), successively HMPA (1.18 g, 6.6 mmol), and, 10 min later, a solution of **20** (709 mg, 3.0 mmol) in THF (3 ml). The mixture was stirred at -60 °C for 30 min. To the reaction mixture was added a mixed anhydride (857 mg, 3.6 mmol), prepared from piperonylic acid and ethyl chloroformate, and the whole was stirred at -60 °C for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 ml), and extracted twice with ethyl acetate. The combined extracts were washed with dil. HCl, water, and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (toluene-ethyl acetate, 4:1) to give **21** (810 mg, 70%) as a white solid, mp 122-123 °C (ethanol), $[\alpha]_D^{24}$ +73.4° (c 1.08, chloroform). *Anal.* Calcd for $C_{21}H_{20}O_7$: C, 65.61; H, 5 24. Found: C, 65.88; H, 5.24. IR (KBr): 1760 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ: 2.75 and 2.85 (1H, 1H, dd, J=8, 14 Hz), 3.03-3.40 (1H, m), 3.80 (3H, s), 3.85 (3H, s), 4.13 (1H, dd, J=5.5, 9 Hz), 4.20 (1H, d, J=6 Hz), 4.52 (1H, dd, J=7, 9 Hz), 6.27-7.39 (6H, m).

(+)-Collinusin (6). The butanolide (**21**) (250 mg, 0.65 mmol) was heated under reflux for 30 min in methanol (30 ml) saturated with dry HCl. After evaporation of the solvent, the residue was treated with

saturated aqueous $NaHCO_3$ (30 ml) and extracted twice with chloroform. The combined extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was recrystallized from ethanol to give **6** (130 mg) as needles. The mother liquor was condensed and purified by column chromatography (toluene-ethyl acetate, 4:1) gave additional **6** (20 mg). The total yield was 63%, mp 192.5-193.5 °C, $[\alpha]_D^{25}$ +134.2° (c 1.01, chloroform). *Anal.* Calcd for $C_{21}H_{18}O_6$: C, 68.84; H, 4.97. Found: C, 68.57; H, 5.00. ^1H NMR ($CDCl_3$) δ. 2.80 (1H, t, J=15 Hz), 2.94 (1H, dd, J=15, 7 Hz), 3.41 (1H, m), 3.68 (3H, s), 3.93 (3H, s), 4.01 (1H, t, J=8.8 Hz), 4.70 (1H, t, J=8.8 Hz), 6.02 (1H, d, J=1.5 Hz), 6.04 (1H, d, J=1.5 Hz), 6.56 (1H, s), 6.78 (1H, s), 6.75-6.95 (3H, m).

(+)-Podorhizon (22). In a similar procedure for the synthesis of **21** except for the use of 3,4,5-trimethoxybenzoyl chloride (1.34 g, 5.81 mmol) as an acylating reagent, **19** (1.07 g, 4.8 mmol) was converted to **22** in 70% yield. Colorless needles, mp 129-130 °C (ethanol), $[\alpha]_D^{26}$ +79.6° (c 0.68, chloroform) [Lit.,[40] mp 129-130 °C, $[\alpha]_D^{21}$ +79.5° (c 0.588, chloroform); Lit.,[41] mp 131-132 °C, $[\alpha]_D$ +78.8° (c 0.57, chloroform)]. The spectral data were in good agreement with the reported data.[40-42]

(+)-γ-Apopicropodophyllin (23). In the same procedure for the synthesis of **6**, the compound **23** was synthesized in 80% yield by the reaction of **22** with methanolic HCl. Colorless needles, mp 285-286 °C (ethanol) (Lit.,[43] racemate, mp 250.1-251.0 °C), $[\alpha]_D^{27}$ +112.8° (c 0.63, chloroform). IR (KBr): 1750 cm^{-1} (C=O), 1650 cm^{-1} (C=C). ^1H NMR ($CDCl_3$) δ: 2.80 (1H, t, J=15 Hz), 2.85-3.13 (1H, m), 3.15-3.60 (1H, m), 3.83 (6H, s), 3.92 (3H, s), 3.85-4.12 (1H, m), 4.67 (1H, t, J=15 Hz), 5.93 (2H, s), 6.50 (3H, s), 6.75 (1H, s).

(-)-(γ)-Apopodophyllic acid (24). To a solution of NaOH (464 mg, 11.6 mmol) in 50% aqueous ethanol (3.8 ml) was added **23** (450 mg, 1.14 mmol) and the mixture was heated under reflux for 15 min. After addition of hot water (20 ml), the mixture was cooled in an ice bath, and acidified with 2M HCl. The mixture was extracted with chloroform, washed with saturated aqueous NaCl, and dried over anhydrous $MgSO_4$. After removal of the solvent, the resulting solid was recrystallized from water-ethanol to give **24** (303 mg, 64%) as felt-like colorless needles, mp 284-285 °C (Lit.,[43] racemate, mp 251 °C), $[\alpha]_D^{24}$ -24.7° (c 0.65, chloroform). IR (KBr): 3300 cm^{-1} (OH), 1690 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ: 2.63-3.18 (3H, m), 3.5-3.9 (2H, m), 3.75 (6H, s), 3.82 (3H, s), 5.2 (2H, br s), 5.82 (2H, s), 6.22 (1H, s), 6.28 (2H, s), 6.60 (1H, s).

(-)-Deoxypodophyllotoxin (3). The catalytic hydrogenation of **24** (178 mg, 0.43 mmol) was carried out with 5% palladium on carbon (35 mg) in ethanol (15 ml) under 20 atm of hydrogen pressure for 20 h at room temperature. After filtration of the catalyst, the filtrate was evaporated *in vacuo* and the residue was dissolved in chloroform (50 ml). To the solution was added DCC (168 mg, 0.81 mmol) and the mixture was stirred at room temperature for 2.5 h. After removal of the solvent, the residue was elaborately purified by PTLC (three times) (toluene-ethyl acetate, 4:1) to give **3** (63 mg, 37%) and (-)-deoxyisopicropodophyllin (**25**) (43 mg, 25%). **3**: mp 168-170 °C, $[\alpha]_D^{28}$ -113.4° (c 0.50, chloroform). [Lit.,[21] mp 168-169°C, $[\alpha]_D^{20}$ -115° (c 0.50, chloroform), Lit.,[30] mp 167-168 °C, $[\alpha]_D^{23}$ -116° (c 2, chloroform)]. *Anal.* Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.29; H, 5.55. IR (KBr): 1768 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ: 2.63-2.84 (3H, m), 3.00-3.14 (1H, m), 3.75 (6H, s), 3.81 (3H, s), 3.92 (1H, pseudo t, J=9.3 Hz), 4.46

(1H, dd, J=8.4, 6.2 Hz), 5.93 (1H, d, J=1.5 Hz), 5.95 (1H, d, J=1.5 Hz), 6.35 (2H, s), 6.52 (1H, s), 6.67 (1H, s). **25**: mp 203.5-205.5 °C, $[\alpha]_D^{26}$ +117° (c 0.53, chloroform) [Lit.,[44] the antipode, mp 202.3-203.2 °C, $[\alpha]_D^{20}$ -114° (c 0.51, chloroform); Lit.,[45] the racemate, mp 198-199 °C]. The spectral data of **25** were in good agreement with the reported data.[45]

(+)-(2*R*,3*R*)-3-(3',4'-Dimethoxybenzyl)-2-(2',3',4'-trimethoxybenzyl)-4-butanolide (26). The lactone (**20**) (473 mg, 2.0 mmol) was treated with 2,3,4-trimethoxybenzyl bromide (627 mg, 2.4 mmol) in a similar manner for the synthesis of **21**. The crude product was purified by column chromatography (toluene-ethyl acetate, 4:1-3:1) to afford **26** (803 mg, 96%) as a syrup. Although the racemic **26** was reported to be a solid of mp 113.5-114.5 °C, a syrup **26** thus obtained was regarded to be pure by ^{1}H NMR and used without further purification in the next step. $[\alpha]_D^{22}$ -48.6° (c 1.23, chloroform). ^{1}H NMR δ: 2.35 and 2.67 (1H, 1H, dd, dd, J=13, 9 Hz), 2.46-2.70 (2H, m), 2.84 and 3.16 (1H, 1H, dd, dd, J=13, 5 Hz), 3.83 (3H, s), 3.84 (6H, s), 3.86 (3H, s), 3.91 (3H, s), 3.87-3.98 (1H, m), 4.11 (1H, dd, J=9, 7 Hz), 6.54-6.62 (3H, m), 6.73 (1H, d, J=8.8 Hz), 6.89 (1H, d, J=8.4 Hz).

(+)-Neoisostegane (8). The butanolide **26** (208 mg, 0.50 mmol) was dissolved in dichloromethane (2 ml), and chilled to -20 °C. To the solution were added a solution of TTFA in trifluoroacetic acid (0.8 M, 0.75 ml, 0.60 mmol) and boron trifluoride etherate (85 mg, 0.6 mmol). The mixture was stirred for 3 h, and poured into water (5 ml), and extracted twice with dichloromethane. The combined extracts were washed with water, saturated aqueous $NaHCO_3$, and saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (toluene-ethyl acetate, 4:1). Recrystallized from isopropyl ether gave **8** (100 mg, 48%) as prisms, mp 156-157 °C, $[\alpha]_D^{19}$ +107.7° (c 0.51, chloroform). *Anal.* Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.50; H. 6.43. IR (KBr): 1776 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$) δ: 1.91 (1H, dd, J=13.2, 9.2 Hz, $H_{8\alpha}$), 2.02 (1H, dd, J=12.8, 9.2 Hz, H_7), 2.22 (1H, dddd, J=12.8, 11.4, 9.9, 6.6 Hz, H_6), 2.41 (1H, dd, J=13.2, 9.9 Hz, $H_{5\beta}$), 2.67 (1H, d, J=13.2 Hz, $H_{5\alpha}$), 3.68 (1H, d, J=13.2 Hz, $H_{8\beta}$), 3.78 (1H, dd, J=11.4, 8.4 Hz, $H_{13\beta}$), 3.85 (3H, s, CH_3O), 3.88 (3H, s, CH_3O), 3.93 (6H, s, 2xCH_3O), 3.96 (3H, s, CH_3O), 4.38 (1H, dd, J=8.4, 6.6 Hz, $H_{13\alpha}$), 6.51 (1H, s, H_{12}), 6.69 (1H, s, H_4), 6.72 (1H, s, H_1). ^{13}C NMR ($CDCl_3$) δ: 24.1 (t), 34.2 (t), 46.8 (d), 49.7 (d), 56.1 (q), 60.8 (q), 61.1 (q), 69.9 (t), 109.7 (d), 112.1 (d), 114.0 (d), 126.6 (s), 130.9 (s), 132.4 (s), 136.1 (s), 141.9 (s), 147.3 (s), 148.9 (s), 150.6 (s), 151.5 (s), 176.2 (s).

REFERENCES AND NOTES

1. Asymmetric Reactions Catalyzed by Chiral Metal Complexes. LV.
2. For a review, see: MacRae, W. D.; Towers, G. H. *Phytochemistry*, **1984**, *23*, 1207.
3. For reviews, see: a) Jardin, I. *Anticancer Agents Based on Natural Product Models*, ed. by Cassady, J. M. b) Pouros, J. D., Academic Press, Inc., New York, 1980, p.319; Issell, B. F. *Cancer Chemother. Pharmacol.*, **1982**, *7*, 73.
4. For a review, see: Ward, R. S. *Chem Soc. Rev* , **1982**, *11*, 75.
5. For reviews, see: a) Morimoto, T ; Chiba, M.; Achiwa, K. *Heterocycles*, **1992**, *33*, 435; b)Ward, R. S. *Tetrahedron*, **1990**, *46*, 5029.
6. For reviews, see: a) Noyori, R.; Kitamura, M. *Modern Synthetic Methods*, Vol. 5, ed. by Scheffold,

R., Springer-Verlag, Berlin Heiderberg, 1989, pp. 115-198. b) *Asymmetric Synthesis*, Vol. 5, ed. by Morrison, J. M., Academic Press, Orland, 1985. c) Nogradi, M. *Stereoselective Synthesis*, VHC, Weinheim, 1987; Brunner, H. *Synthesis*, **1988**, 645.

7. For a review, see: Takahashi, H.; Morimoto, T.; Achiwa, K. *J. Synth. Org. Chem., Jpn*, **1990**, *48*, 29.
8. Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett.*, **1989**, *30*, 735.
9. Morimoto, T.; Chiba, M.; Achiwa, K. *Chem. Pharm. Bull.*, **1989**, *37*, 3161.
10. Morimoto, T.; Chiba, M.; Achiwa, K. *Heterocycles*, **1990**, *30*, 363.
11. Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett.*, **1990**, *31*, 261.
12. For a review, see: Johnson W. S.; Daub, G. H. *Organic Reactions*, Vol. 6, ed. by Adams, R., John Wiley & Sons, Inc., New York, 1951, pp. 1-73.
13. Brown, E.; Daugan, A. *Tetrahedron Lett.*, **1985**, *26*, 3997.
14. Govindachari, T. R.; Sathe, S. S.; Viswanathan, N. *Tetrahedron Lett.*, **1967**, 4183.
15. Govindachari, T. R.; Sathe, S. S.; Viswanathan, N. *Tetrahedron*, **1969**, *25*, 2815.
16. Block, W.; Stevenson, R. *J. Org. Chem.*, **1971**, *36*, 3453.
17. Noguchi, K.; Kawanami, M. *J. Pharm. Soc. Jpn*, **1940**, *60*, 629.
18. Hata, C. *J. Chem. Soc. Jpn*, **1942**, *63*, 1540.
19. Hartwell, J. L.; Johnson, J. M.; Fitzgerald, D. B.; Belkin, M. *J. Am. Chem. Soc.*, **1952**, *74*, 4470.
20. Schrecker, A. W.; Hartwell, J. L. *J. Am. Chem. Soc.*, **1953**, *75*, 5916.
21. Hartwell, J. L.; Schrecker, A. W. *J. Am. Chem. Soc.*, **1954**, *76*, 4034.
22. a) Macdonald, D. I.; Durst, T. *J. Org Chem* , **1988**, *53*, 3633. b) Macdonald, D. I.; Durst, T. *J. Org. Chem.*, **1986**, *51*, 4749. c) Jones, D. W.; Thompson, A. M. *J Chem. Soc., Chem. Commun.*, **1987**, 1797. d) Vyas, D. M.; Skonezny, P. M.; Jenks, T. A.; Doyel, T. W. *Tetrahedron Lett.*, **1986**, *27*, 3099. e) Kaneko, T.; Wong, H. *Tetrahedron Lett.*, **1987**, *28*, 517. f)Jung, M. E.; Lowen, G. T. *Tetrahedron Lett.*, **1986**, *27*, 5319. g) Murphy, W. S.; Wattanasın, S. *J. Chem. Soc., Perkin Trans. 1*, **1982**, 271. h) Rajapaka, D.; Rodorigo, R. *J Am. Chem. Soc.*, **1981**, *103*, 6208. i) Eycken, J. V.; DecClerqu, P.; Vanderwalle, M. *Tetrahedron Lett.*, **1985**, *26*, 3871.
23. Andrews, R. C.; Teague, S. T.; Meyers, A. I. *J. Am. Chem. Soc.*, **1988**, *110*, 7854.
24. Speybroeck, R. V.; Guo, H.; Eycken, J. V.; Vandewalle, M. *Tetrahedron*, **1991**, *47*, 4675.
25. Klemm, L. H.; Gopinath, K.; Lee, D. H.; Kelly, F. W.; Trod, E.; McGuire, T. M. *Tetrahedron*, **1966**, *22*, 1797.
26. Klemm, L. H.; Olson, D. R.; White, D. V. *J. Org. Chem.*, **1971**, *36*, 3740.
27. a) Gensler, W. J.; Gatsonis, C. D. *J. Org. Chem.*, **1966**, *31*, 4004. b) Kende, A. S.; King, M. L.; Curran, D. P. *J. Org. Chem.*, **1981**, *46*, 2826.
28. Tanoguchi, M.; Kashima, T.; Saika, H.; Inoue, T.; Arimoto, M.; Yamaguchi, H. *Chem. Pharm. Bull.*, **1989**, *37*, 68.
29. Kondo, K.; Ogura, M.; Midorıkawa, Y.; Kozawa, M.; Tsujibo, H.; Baba, K.; Inamori, Y. *Agric. Biol. Chem.*, **1989**, *53*, 777.
30. Yamaguchi, H.; Arimoto, M.; Yamamoto, K.; Numata, A. *Yakugaku Zasshi*, **1979**, *99*, 674.
31. Taafruot, M.; Rouessac, F.; Robin, J.-P. *Tetrahedron Lett.*, **1983**, *24*, 2983.
32. Hicks, R.P.; Sneden, A. T. *Tetrahedron Lett.*, **1983**, *24*, 2987.
33. a) Landais, Y.; Robin, J.-P. *Tetrahedron Lett.*, **1986**, *27*, 1785. b) Taafrout, M.; Landais, Y.; Robin,

J.-P. *Tetrahedron Lett.*, **1986**, *27*, 1781.

34. Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron*, **1984**, *40*, 1303.
35. Robin, J.-P.; Gringore, O; Robin, E. *Tetrahedron Lett.*, **1980**, *21*, 2709.
36. Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc* , **1987**, *109*, 5446.
37. Murrer, B. A.; Brown, J. M.; Chaloner, P. A.; Nicholson, P. N.; Parker, D. *Synthesis*, **1979**, 350.
38. Brown, E.; Daugan, A. *Tetrahedron Lett.*, **1986**, *27*, 3719.
39. Brown, E.; Daugan, A. *Heterocycles*, **1987**, *26*, 1169.
40. Kuhn, M.; Wartbrug, A. *Helv. Chim. Acta*, **1967**, *50*, 1546.
41. Kosugi, H.; Tagami, K.; Takahashi, A.; Kanna, H.; Uda, H. *J. Chem. Soc., Perkin Trans. I*, **1989**, 935.
42. The antipode, (-)-podorhizon· Tomioka, K.; Mizuguchi, H.; Koga, K. *Chem. Pharm. Bull.*, **1982**, *30*, 4304. (±)-Podorhizon: Robin, J.-P.; Dhal, R.; Brown, E. *Tetrahedron*, **1982**, *38*, 3667.
43. Schrecker, A. W.; Hartwell, J. L. *J. Am Chem. Soc.*, **1952**, *74*, 5672.
44. The antipode was derived from (-)-podophyllotoxin [Schrecker, A. W.; Hartwell, J. L. *J. Am Chem. Soc.*, **1953**, *75*, 5916].
45. Forsey, S. P.; Rajapaksa, D.; Taylor, N. J.; Rodrigo, R. *J. Org Chem.*, **1989**, *54*, 4280.