Progress on the Chemistry of Dibenzocyclooctadiene Lignans

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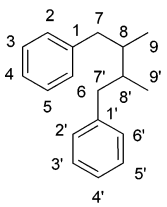
1. Introduction

Lignans are an important series of natural products.[1,2] A variety of lignan classes have been isolated from different plants, and the syntheses of these different lignan structural types have been published.[3−10] Lignans are usually classified into three classes based on the character of the C−C bond and oxygen bridge joining the two typical phenylpropane units that make up their general structure. The acyclic lignan derivatives constitute the first of these classes as illustrated by structure **1** (Figure 1). This class includes dibenzylbutanes, dibenzyl substituted tetrahydrofurans, dibenzylbutyrolactones, diphenyltetrahydrofuran[3,4-C]furofurans, and others.[11−23] A second class of lignans contains arylnaphthalene derivatives (see structure **2**), such as podophyllotoxin, which feature a C-6 and C-7′ connection between the two phenylpropane units.[24−44] Dibenzocyclooctadiene derivatives with a C-6, C-6′ biaryl bond as illustrated by structure **3** constitute a third lignan class.[45−83] The structural diversity of dibenzocyclooctadienes is derived from combinations of the following structural elements: (1) the substitution pattern of the biaryl unit with a possible replacement of hydrogen(s) with hydroxyl (or acyloxy), methoxyl, or methylenedioxy groups; (2) the substitution pattern and the configuration of stereocenters along the aliphatic bridge; (3) the absolute configuration of the biaryl axis. These variations result in a variety of dibenzocyclooctadiene derivatives including non-oxygen substituted (Figure



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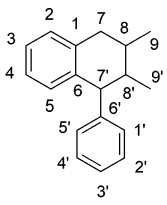

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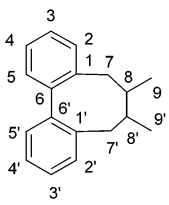

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Figure 1. Classes of lignan structures.

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Junbiao Chang was born in 1965 in Henan Province, P.R. China, and he received his B.S. in Chemistry at Henan University in 1986. He studied with professor Rongfeng Chen and Tianli Wang at Henan Institute of Chemistry, Henan Academy of Sciences, where he received his M.S. in 1989. He studied with Professor Jingxi Xie at Institute of Meteria Medica, Chinese Academy of Medical Sciences, where he received his Ph.D. in 1995. After postdoctoral fellowships with Professor C. K. Chu at the University of Georgia, Professor Kang Zhao at Genomics Institute of Novartis Research Foundation (USA), and Professor Yangjie Wu at Zhengzhou University of China, he joined the faculty at Henan Institute of Chemistry in China. From 1999 to 2002 he was professor and director of the Henan Institute of Chemistry, and since 2003 he has been Vice President of Xinxiang Medical College and director of Henan Key Laboratory of Fine Chemicals and has been the visiting professor at Tianjin University and University of Science and Technology of China. He has received several state awards. His research interests include the development of selective and efficient synthetic methodologies and the design of practical syntheses of natural products such as lignans and alkaloids and their application to biologically active systems.

John Reiner is Professor of Medicinal Chemistry in the College of Pharmaceuticals, Tianjin University, China, where he has been since 2004. His current research interests include flavanoid and podophyllotoxin derivatives as antiproliferative agents and methodology for the preparation of highly functionalized alkoxyamines and N–O-heterocycles. In the 10 years prior to his joining Tianjin University, he was a senior scientist with Corval International, a San Diego based biopharmaceutical company. His research at Corvas involved the design and synthesis of serine protease inhibitors of members in the coagulation cascade as well as cancer associated proteases.

2), C7-oxygen substituted (Figure 3), C8-hydroxy substituted (Figure 4), C7,C8-dioxygen substituted (Figure 5), C7,C7′-dioxygen substituted (Figure 6), and C7,C7′,C8-trioxygen substituted dibenzocyclooctadiene lignans (Figure 7), the *stegane* series of dibenzocyclooctadiene analogues containing a butyrolactone unit (Figure 8), and others. Other lignans such as neolignans are not covered in this review.

Jingxi Xie was born on September 8, 1928, in Wuxi City (China). He received his B.S. in 1950 at Pharmaceutical University of China. From 1950 to 1954 he was research assistant in the Central Research Institute of Health, China. Since 1985 he has been a professor in the Institute of Materia Medica, Chinese Academy of Science. He was visiting professor at the University of North Carolina for 3 years. After 1996, he was visiting professor at Henan Key Laboratory of Fine Chemicals. He received several state awards and discovered three drugs—dimethyl dicarboxy biphenyl (DDB), anisodamine, and anisodine, which are currently in clinical use. His research interests include the development of new synthetic methodologies and the total synthesis of natural products. He is a member of the Appraisal Commission for New Drug Research Foundation of China.

The dibenzocyclooctadiene lignans (structure **3**), because of their unique structural features and important biological properties, have long been recognized by organic chemists as interesting and challenging synthetic targets. Synthetic research on dibenzocyclooctadiene lignans has focused on new methodologies for forming the biaryl linkage of the lignan core structure. Due to the sensitive nature of the substituents commonly found on the lignan aromatic rings, research in this area has focused on milder oxidants with improved functional group tolerance. Additionally, control of the axial chirality of the biaryl moiety has inspired a variety of creative chemical solutions. Cationic oxidation is a commonly used strategy for biaryl construction.[85] Reagents such as $Fe(ClO_4)_3$, RuO_2, and $V(O)X_3$ (X = halide) have been reported to form this aryl−aryl linkage in high yields.[84,86,87] This methodology has been used as a key step in the asymmetric syntheses of (+)-schizandrin **(42)**, (+)-isoschizandrin **(43)**, (+)-deoxyschizandrin **(4)**, and (+)-gomisin A **(44)** (Figures 2 and 4).[88,89]

The non-phenolic oxidative coupling of 1,4-diarylbutanes to form dibenzocyclooctadiene derivatives has been accomplished using DDQ as an oxidizing reagent in TFA.[90−92] Other oxidants, including $Mn(OAc)_3$, $Tl(TFA)_3$, $Ru(TFA)_4$, and $V(O)X_3$, provide a wide range of alternative reagents for this transformation. Since a number of biologically active lignans contain the labile methylenedioxy group, mild reagents are required for the oxidative coupling. The RuO_2 oxidative system gives high yields when phenolic hydroxyl groups are present.[93] Therefore, this reagent can be modified for a lot of substrates to shorten the reaction time by using trifluoromethanesulfonic acid and its anhydride in place of TFA/TFAA or by using ultrasound. Oxidative coupling of a *cis*-lactone gave stegane analogue **166** (see Scheme 20).

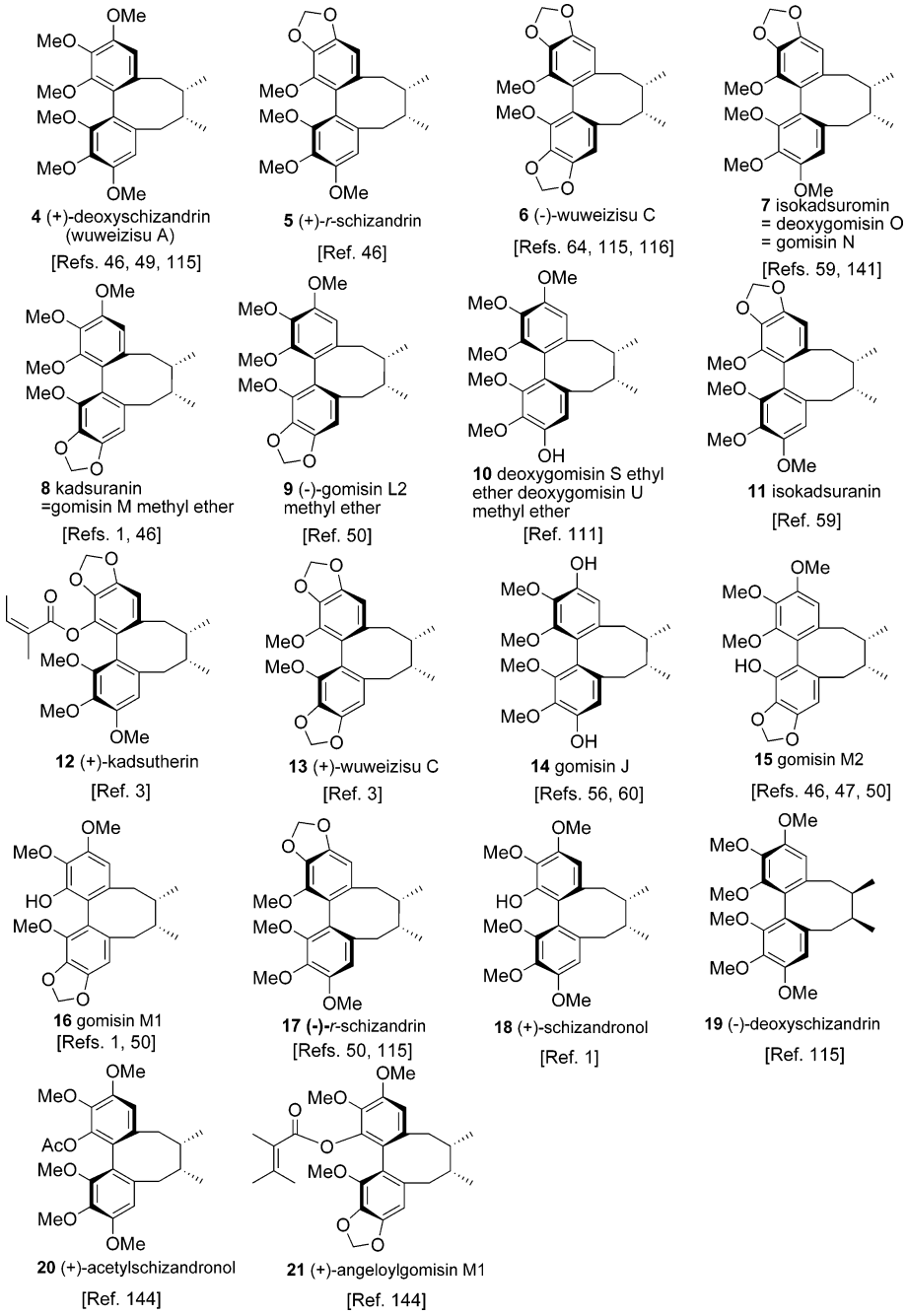


Figure 2. Non-oxygen substituted dibenzocyclootadiene lignans.

The first sections of this review cover the biological, structural, and spectral properties of the dibenzocyclooctadiene lignans and their derivatives (Figures 2−8). In the later sections, synthetic methodologies for the preparation of the dibenzocyclooctadiene ring system, including asymmetric synthesis strategies, are summarized. A final perspective on the future of dibenzocyclooctadiene lignan chemistry concludes this article. While some aspects of this subject have been contained in previous reviews of lignan chemistry, this article represents the first comprehensive review focusing solely on the dibenzocyclooctadiene lignan class with an emphasis on synthesis. The references to the literature included in this review article are primarily from the last 25 years to the middle of 2004.

2. Biological Activity of Dibenzocyclooctadiene Lignans

Approximately 100 lignan derivatives possessing the dibenzocyclooctadiene skeleton have been isolated from plants of the *schizandraceae* family,[1,2] and a wide variety of biological activities exhibited by these lignans have been uncovered. Extracts from lignan rich plants have been used as traditional Chinese medicines as anti-tussives and as tonics with antiviral activity.[94] In addition to insecticidal[95−98] and antifeedant activity,[99] dibenzocyclooctadiene lignans from *schizandraceae* have been reported to inhibit cyclic-AMP phosphodiesterases, enzymes which are integral to the regulation of many cellular processes.[100−102] Several lignan derivatives inhibit the binding of platelet activating factor to receptors on

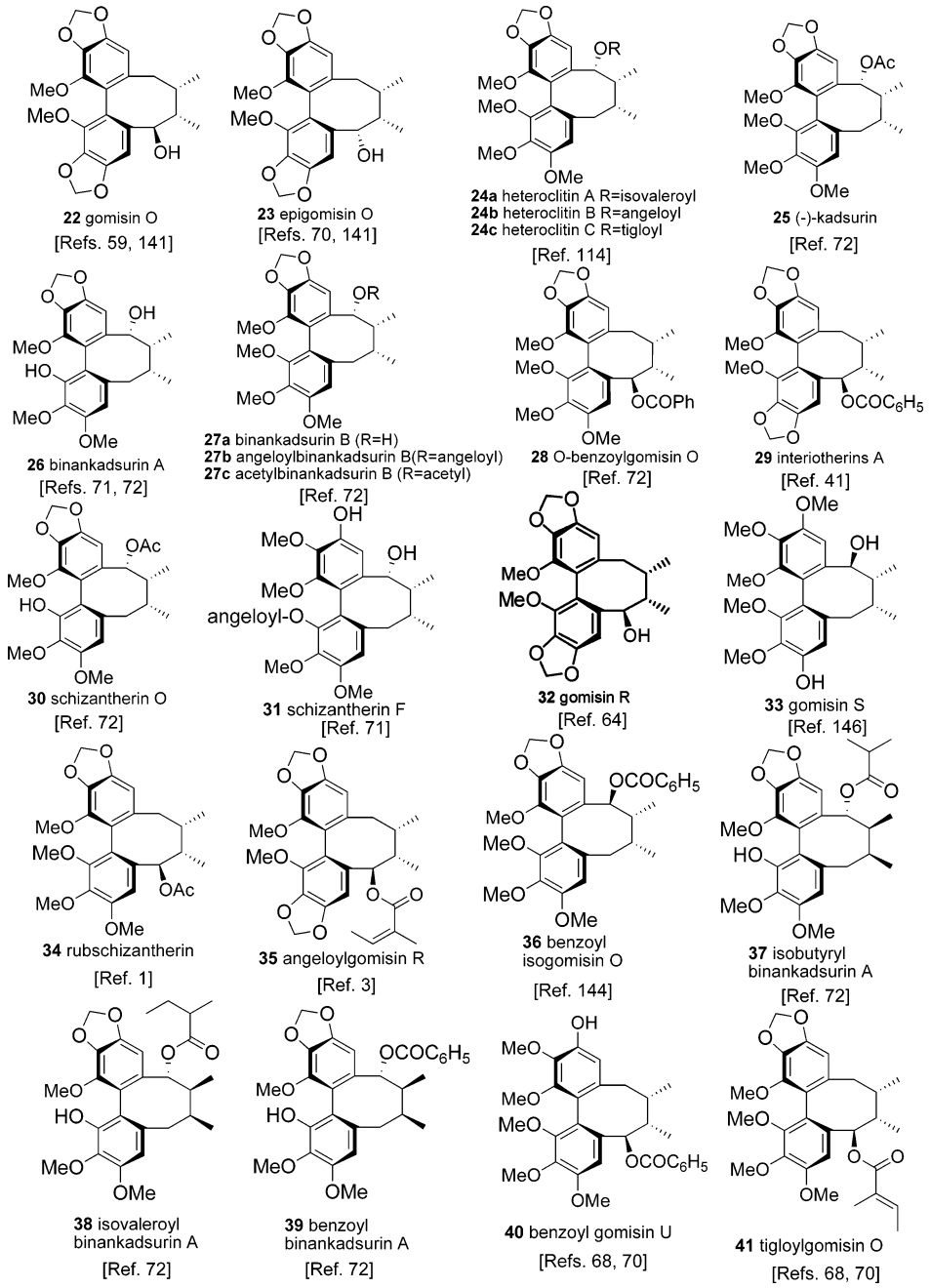


Figure 3. C7-oxygen substituted dibenzocyclootadiene lignans.

platelets.[103−105] A number of other derivatives suppress the proliferation of human peripheral blood lymphocytes and, thus, may be useful as immunosuppressive agents.[106] Several lignans exhibit significant biological activity, both *in vitro* and *in vivo* against carbon tetrachloride and galactosamine induced liver damage in different animal models.[107−123] (−)-Wuweizisu C **(6)** is considered a crucial component for the antihepatotoxic activity found in traditional Chinese medicine formulations of wuweizi lignan containing plants.[108,111,112] Lignans also exhibit inhibitory activity against viral reverse transcriptase. For example, the ethanol extracted lignans from the stems of *K. interior* were studied for inhibition of HIV replication,[80,124−126] and seven compounds from this extract displayed potent anti-HIV activity. Gomisin-G **(56)** (Figure 5) exhibited the most potent anti-HIV activity with an EC_{50} of 0.006 μg/mL and a therapeutic index (TI) of 300 while schizantherin-D *(***53***)* (Figure 5), kadsuranin **(8)**, and (−)-wuweizisu C **(6)** showed good activity with EC_{50} values of 0.5, 0.8, and 1.2 μg/mL and TI values of 110, 56, and 33.3, respectively. The results with these natural lignans suggested that 9-benzoyl and 8-hydroxy substituents might enhance the biological activity.[127]

3. Structural and Spectral Characteristics of Dibenzocyclooctadiene Lignans

3.1. Structural Characteristics of Dibenzocyclooctadiene Lignans

Naturally occurring dibenzocyclooctadiene classes of lignans can be further categorized into two series. The schizandrin type lignans, such as (+)-schizandrin **(42)**, (−)-wuweizisu C **(6)**, (−)-kadsurin **(25)**, and

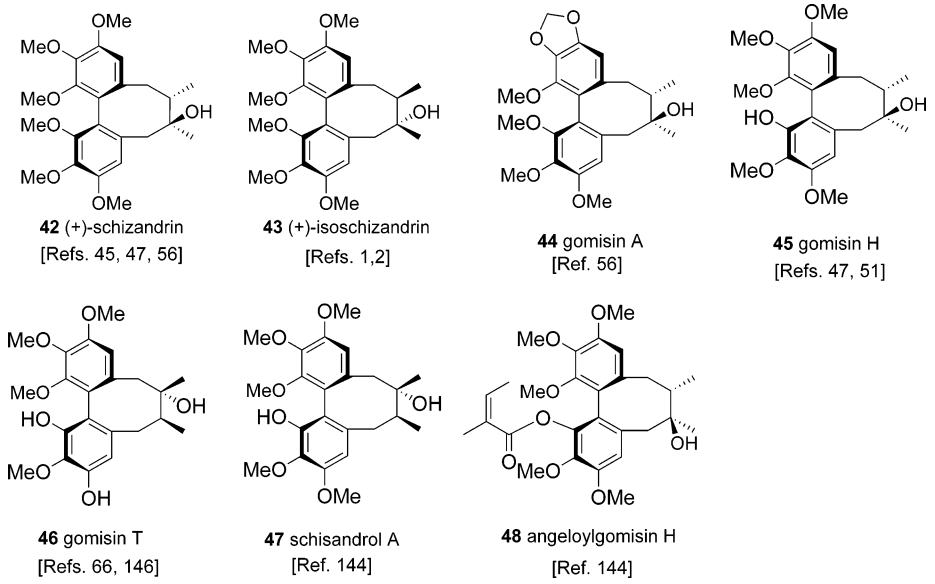


Figure 4. C8-hydroxy substituted dibenzocyclooctadiene lignans.

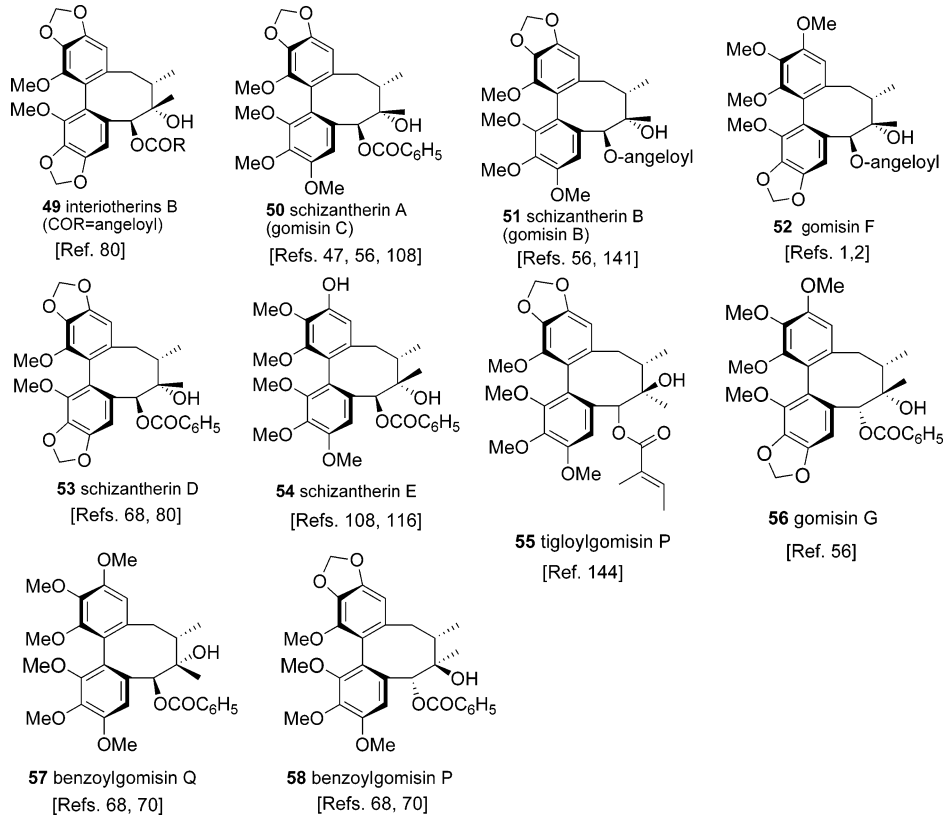


Figure 5. C7,C8-dioxygen substituted dibenzocyclooctadiene lignans.

schizantherin A **(50)**, isolated from *schizandraceae*, are members of the first series, in which the C-8 and C-8′ positions of the cyclooctadiene ring are substituted with methyl groups. A second series of dibenzocyclooctadiene lignans are the stegane type, in which the C-8 and C-8′ positions are fused to a lactone (Figure 8).

A number of new dibenzocyclooctadiene lignan derivatives have been synthesized by introducing different substituents onto the lignan core structure. The C-7 position on the cyclooctadiene ring is the most common position for further substitution. The 9,9′-lactone has been transformed into the corresponding 9,9′-lactam for different types of derivatization. The replacement of carbon atoms of the basic structure by heteroatoms has generated heterolignan derivatives.[128]

3.2. Conformational Analysis of the Dibenzocyclooctadiene Ring System

Anet and Yavari[129] studied the atropisomerism of unsubstituted dibenzocyclooctadiene by dynamic NMR spectroscopy. They discovered that the cyclooctadiene ring exists in approximately equal proportions of twist-boat-chair (TBC) and twist-boat (TB) conforma-

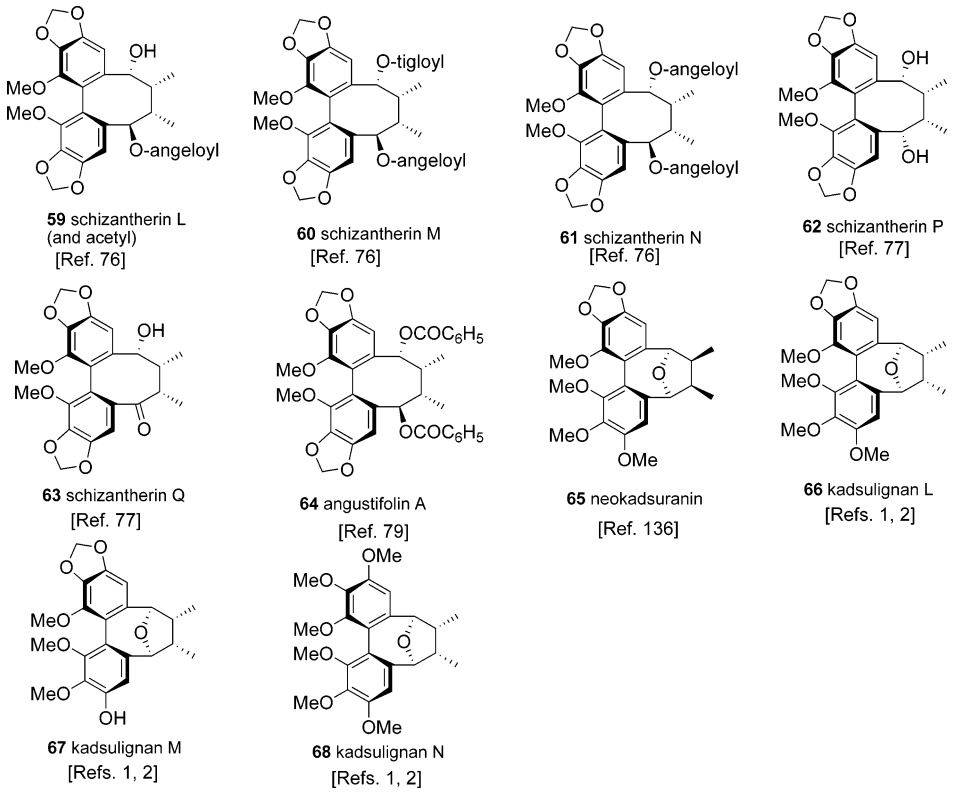


Figure 6. C7,C7′-dioxygen substituted dibenzocyclooctadiene lignans.

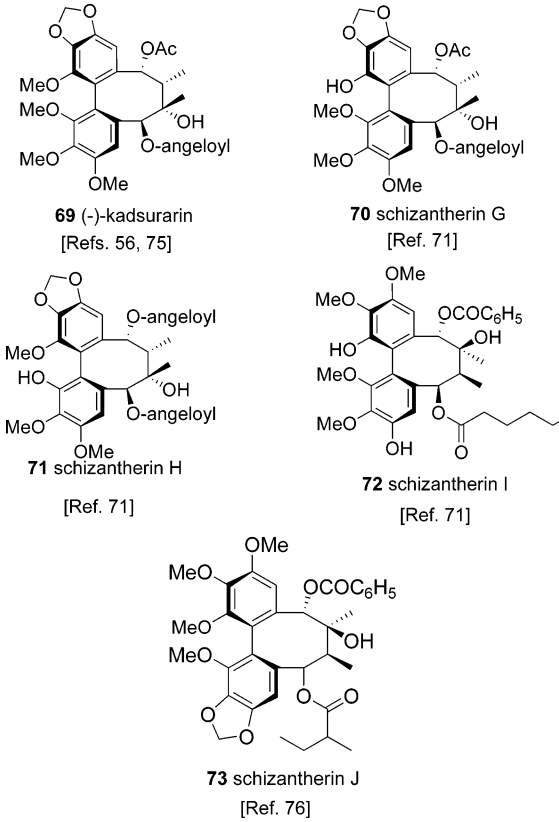


Figure 7. C7,C7′,C8-trioxygen substituted dibenzocyclooctadiene lignans.

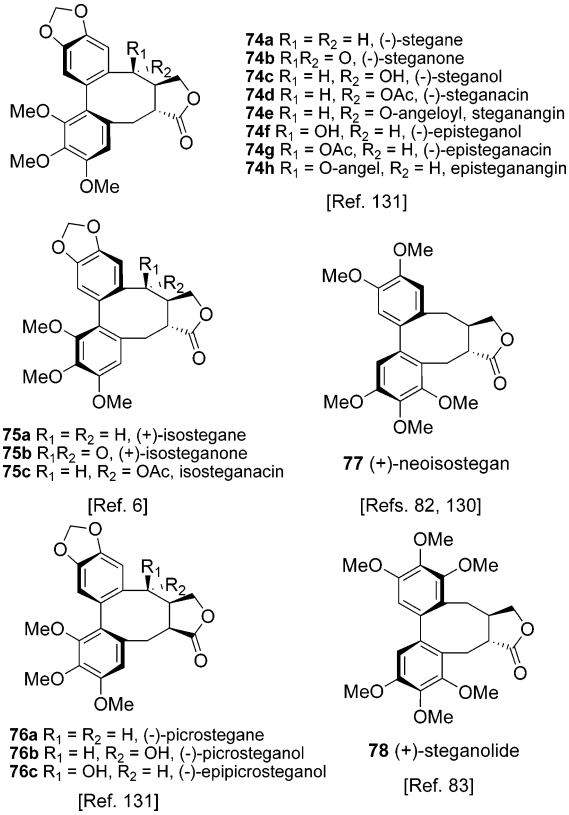


Figure 8. Stegane series of dibenzocyclooctadiene analogues.

tions in solution. As illustrated in Figure 9, the interconversions of the (*S*)-TB/(*S*)-TBC and (*R*)-TB/(*R*)-TBC conformers (step A) have potential energy barriers of 38 and 30 kJ·mol^{-1}, respectively. The interconversion between the (*S*)-TB/(*R*)-TB conformations (step B) requires a biphenyl bond rotation that has a high potential energy barrier.

If a substituent, such as a methoxy group, is located at the position *ortho* to the biphenyl bond, the potential barrier for this rotation is greater than

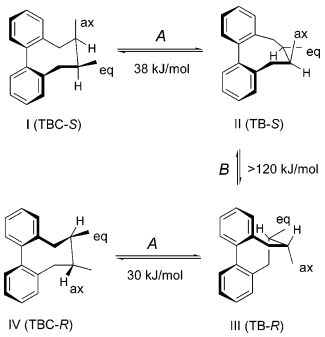


Figure 9. Interconversion of TB and TBC conformations.

145 kJ·mol^{-1}. As a result of these energy barriers, at 25 °C, the biphenyl unit has a stable *S* or *R* configuration, while the TBC and TB conformations of the medium ring are both populated and rapidly interconvert.

The wuweizi series of lignans illustrates the complexity involved in conformational analysis of differentially substituted aromatic rings by virtue of a stable biphenyl configuration, energetically accessible TB and TBC conformations of the cyclooctadiene ring, and asymmetric centers at the C-8 and C-8′ positions. When the phenyl rings of a lignan are differentially substituted, in theory it can have eight different stereoisomers, including four *cis* conformers [(8a, 8′e) TB, (8e, 8′a) TB, (8a, 8′e) TBC, and (8e, 8′a) TBC] and four *trans* conformers [(8a, 8′a) TB, (8e, 8′e) TB, (8a, 8′a) TBC, and (8e, 8′e) TBC]. When the substituents on the aromatic rings are identical, then there are four possible *trans* isomers (same as above), two *cis* isomers [(8e, 8′a) TB and (8a, 8′e) TBC], and a *meso* isomer (Figure 9). For the stegane series of lignans, the TB or TBC conformation depends on the arrangement of the stereogenic axis relative to the stereocenters of the molecule: (−)-stegane prefers a TB conformation[130] because a *trans* fused lactone ring in the TBC conformation is not energetically feasible, while (+)-isostegane type lactones exist in the TBC conformation without incurring any major ring strain.[131,132]

3.3. Spectral Characteristics of Dibenzocyclooctadiene Lignans

As discussed above, dibenzocyclooctadiene lignan derivatives have a number of chiral features and stereoisomers. Therefore, these compounds can be categorized into two series according to the absolute configuration of the biphenyl unit. The biphenyl derivatives (+)-schizandrin **(42)** and (−)-wuweizisu C **(6)** are representative examples of naturally occurring lignans with *R* and *S* biphenyl configurations, respectively; their structures and absolute configurations have been confirmed by crystallographic studies.[88,133,134] The most favorable conformation for the eight-membered ring is the twist-boat-chair (TBC), although the twist-boat (TB) conformation also exists. The stereostructure of dibenzocyclooctadiene has been characterized and verified unequivocally by NMR, IR, UV, MS, and CD spectroscopy. The more complex structural characteristics of wuweizi lignans have shown a good correlation with their spectral properties and have diagnostic value, as is discussed in the next subsections for various types of spectroscopy.

3.3.1. UV, CD, and IR Spectra

There are a number of important qualitative features useful in the structural analysis of lignan derivatives. Since the biphenyl chromophore of a dibenzocyclooctadiene does not have rotational freedom, it displays three absorption maxima at 220, 254, and 278 nm in its UV spectrum.[135] The absolute configuration of the biphenyl chromophore can be discerned by circular dichroism (CD) spectroscopy.[126,136,137] If the CD spectrum of a lignan derivative shows both a (+)-Cotton effect at 220 nm and a (−)-Cotton effect at 254 nm, the biphenyl unit has the *S* configuration. Conversely, a lignan with an *R* configuration yields a CD spectrum with a (−)-Cotton effect at 220 nm and a (+)-Cotton effect at 254 nm. For the stegane series of dibenzocyclooctadienes, however, these descriptors of the biphenyl axial configuration do not always hold true. It should be emphasized that the absolute configuration of the biphenyl axis is not automatically given by the stereochemical position of the "bridgeheads" of the eight-membered ring (as is sometimes intuitively assumed). Therefore, one has to follow the CIP nomenclature, in which the substituents with the highest priorities are decisive.[2]

Infrared (IR) spectra can be used to identify the cyclooctadiene ring oxidation and substitution pattern. In addition, it can also be used to identify TB or TBC conformations when the C-7 or C-7′ position of the compound has a carbonyl group. In a TB conformation, the benzylic carbonyl group is conjugated, resulting in a stretching vibration absorption peak below 1700 cm^{-1}. However, in a TBC conformation, the plane of the carbonyl group is perpendicular to the phenyl ring and the observed stretching frequency is near 1750 cm^{-1}.[138]

3.3.2. Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR spectroscopy has been the most effective approach in the investigation of dibenzocyclooctadiene lignan stereostructures. Ikeya reported a series of NMR correlative experiments and thoroughly analyzed the resulting data for diagnostic resonances.[139] Gottlieb further refined the ^{1}H NMR and ^{13}C NMR features pertinent to study in these structures.[140]

^{1}H NMR. The two phenyl protons (2-H and 2′-H) (see **3** in Figure 1), with chemical shifts between 6.4 and 7.0 ppm, can be quite useful for both stereochemical and conformational information. If the biphenyl unit has a symmetry plane (see, for example, deoxyschizandrin **(4)**, Figure 2), the two aromatic protons are equivalent, and the two methyl

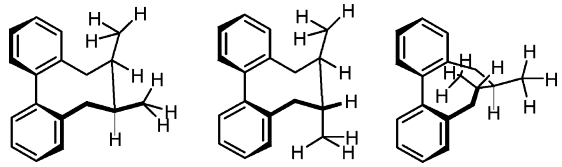
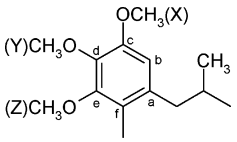


Figure 10. Stereostructures of dibenzocyclooctadienes.

Table 1. Effect[a] on ^{13}C NMR Chemical Shifts of Aromatic Carbons by Replacing a OMe Group with OH, OAc, or OCH_2O (ppm)



aromatic carbon	$OCH_3(X) \rightarrow OH$	$OCH_3(X) \rightarrow OAc$	$OCH_3(Z) \rightarrow OH$	$OCH_3(X,Y) \rightarrow OCH_2O$	$OH(X) \rightarrow OAc$
C-a	$+1.2 \pm 0.4$	$+0.7$	$+0.5$	-0.9 to 2.0	-0.5
C-b (protonated aromatic carbon)	$+2.8 \pm 0.3$	$+10.5$	-2.8	-4.1 ± 0.5	$+7.5$
C-c	-3.9 ± 0.2	-9.0	-1.3	-3.5 ± 0.5	-5.1
C-d	-2.4 ± 0.3	$+2.8$	-6.7	-4.5 ± 0.5	$+4.9$
C-e	-1.2 ± 0.2	$+0.1$	-4.7	-10.4 ± 0.4	$+1.3$
C-f	-0.8 ± 0.2	$+5.8$	-6.3	-0.8 to -2.7	$+6.4$

[a] + indicates a downfield chemical shift; − indicates an upfield chemical shift.

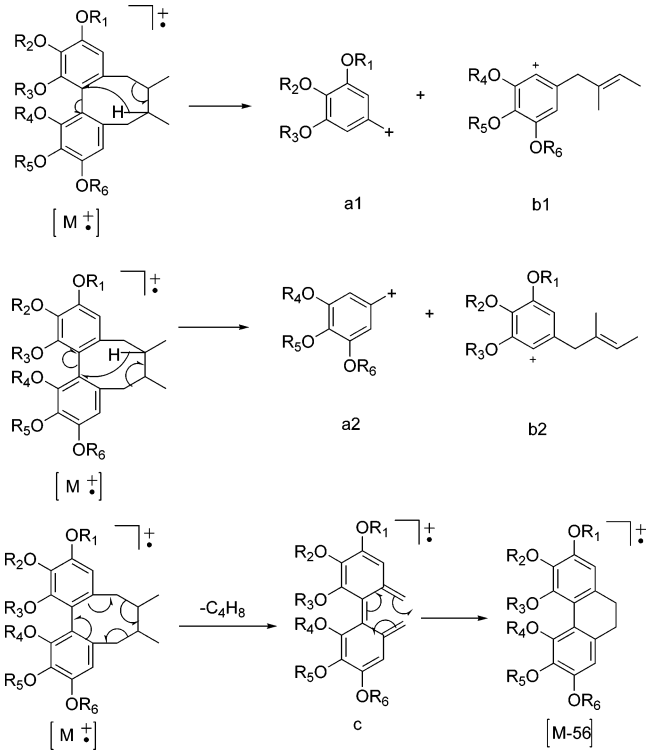


Figure 11. MS fragmentations for non-oxygen substituted dibenzocyclooctadiene lignans.

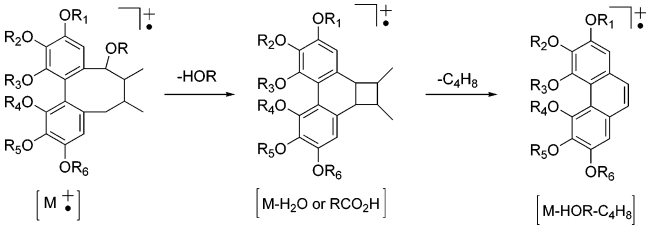


Figure 12. MS fragmentations for C7-oxygen substituted dibenzocyclooctadiene lignans.

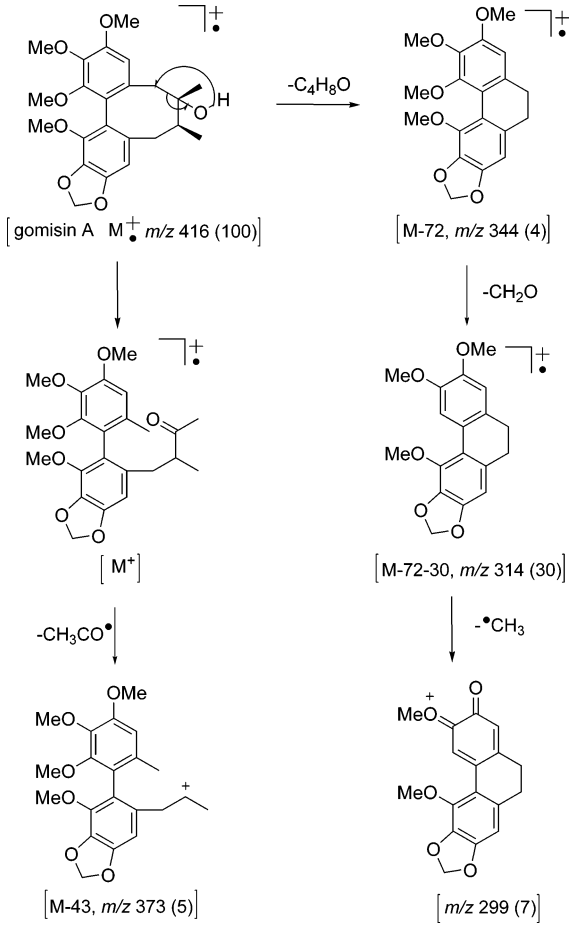


Figure 13. MS fragmentations for the C8-hydroxyl substituted dibenzocyclooctadiene lignan, gomisin A.

groups (8-CH_3, 8′-CH_3) are also equivalent if they have a *trans* relationship. If C-8 and C-8′ of the natural product lignan do not have oxygen substitution and the two methyl groups have a *cis* relationship, then these aromatic protons are doublets with different chemical shifts (δ 0.70−1.00, $J = 7.00$ Hz). In the TBC conformation, the chemical shifts of 7-H, 8-H, 7′-H, and 8′-H are influenced not only by polar substituents on the eight-membered ring but also by the configuration and the conformation of the eight-membered ring. When the configuration and conformation project these protons into the shielding area of the biphenyl rings, the protons will be shifted upfield. These features can be used to confirm the configuration and conformation of these cyclooctadiene lignans. Likewise, the chemical shifts of 5-OCH_3 and 5′-OCH_3 appear at higher field because of a shielding effect from the adjacent aromatic rings. At the C-8 and C-8′ positions, an axial (ax) methyl group or hydrogen is in the shielding region of the biphenyl rings and will display an upfield chemical shift. On the other hand, the aromatic rings have very little

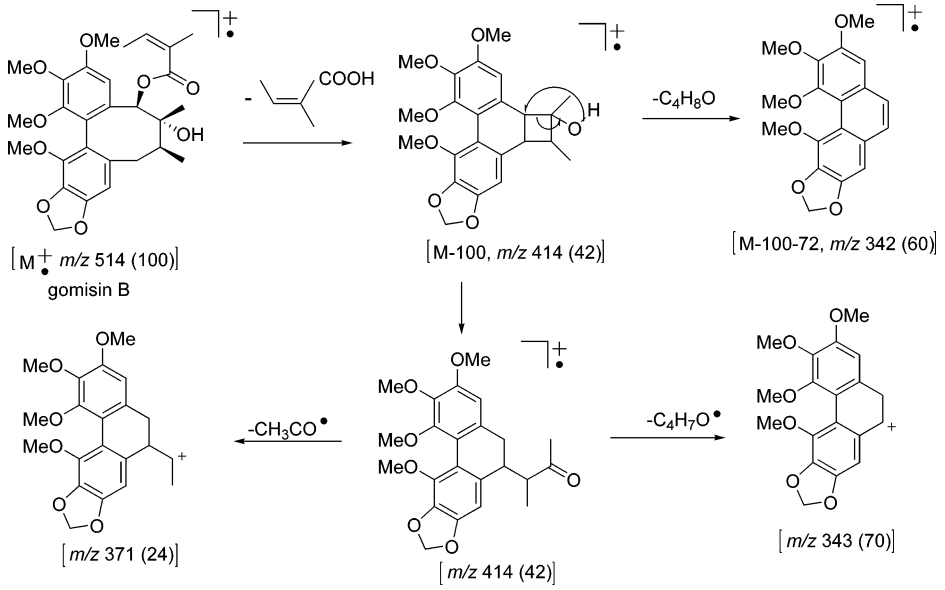


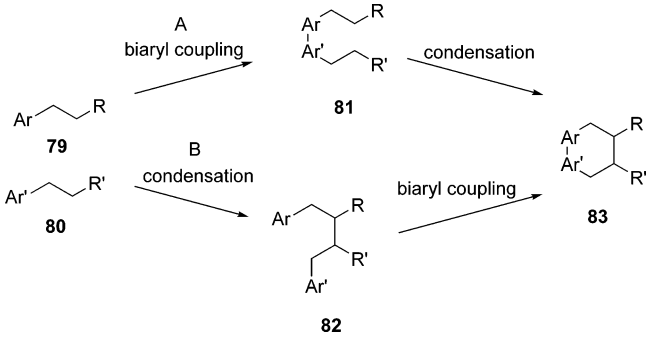
Figure 14. MS fragmentations for a C7,C8-dioxygen substituted dibenzocyclooctadiene lignan, gomisin B.

effect on equatorial (eq) groups. In addition, the *eq*- and *ax*-bonds at these two chiral centers are approximately perpendicular. Thus, the coupling constant of a *cis*-isomer is $J_{8,8'} \approx 0$ Hz, while the coupling constant of a *trans*-isomer is $J_{8,8'} > 0$ Hz (see structures in Figure 10). The coupling constants between the C-8 CHMe and the C-7 benzylic protons follow a similar pattern.[140]

^{13}C NMR. The chemical shift of a methoxy carbon adjacent to the biphenyl bond is approximately 5 ppm upfield compared to the cases of other methoxy carbons. For example, the chemical shift of 3-OCH_3 and 3′-OCH_3 is at 55.0 ppm, while other methoxy carbons appear at approximately 60.0 ppm. At the same time, the chemical shift of aromatic carbons is affected by a change in the substituents.[141] Table 1 illustrates the chemical shift changes induced by different substituents. If the eight-membered ring has a TBC conformation, the following effects are observed: (1) For an adjacent methyl group in an axial position, the chemical shift of an unsubstituted aromatic carbon (C-2) is at approximately 110.6 ppm; however, for an equatorially disposed adjacent methyl group, the chemical shift of the corresponding carbon is at approximately 107.3 ppm. (2) When an adjacent methoxy group (CH_3O-X) is replaced by an alcohol or acetate, the chemical shift of an unsubstituted aromatic carbon shifts downfield 3 to 10 ppm. (3) When a *para*-methoxy group (CH_3O-Z) is substituted by a hydroxyl group, the chemical shift of an unsubstituted aromatic carbon shifts upfield 3 ppm. (4) When *ortho*,*meta*-dimethoxy groups (CH_3O-X and $-Y$) are substituted by a methylenedioxy group, the chemical shift of an unsubstituted aromatic carbon shifts approximately 4 ppm upfield. The influence of these substituents on other aromatic carbons is shown in detail in Table 1.

The chemical shifts of C-7 and C-7′ are effected by hydroxyl or ester group substitution depending on the substituent's configuration. For 7-β, this substitution shifts C-7 (or C-7′) downfield ($\delta \geq 80$ ppm); for 7-α, the substitution shifts C-7 upfield ($\delta \sim 73$ ppm).

Scheme 1. Coupling Strategies for Dibenzocyclooctadiene Synthesis

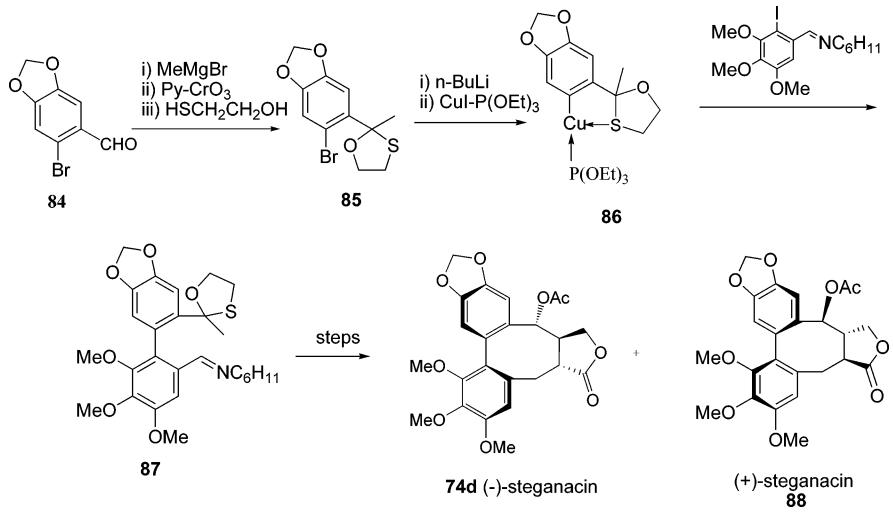


These ^{13}C NMR spectral features are helpful in identifying the aromatic substitution positions as well as the configuration and conformation of the eight-membered ring.

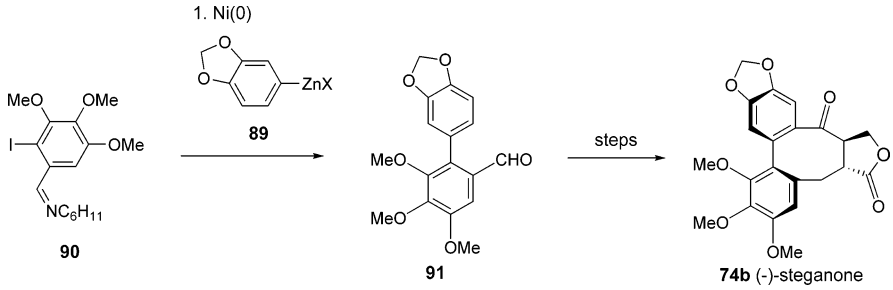
Solvent shift and NOE determination: With benzene (or deuterated benzene) as a ^{1}H NMR solvent (compared to chlorinated solvents), large chemical shift differences for methoxy groups adjacent to an aromatic proton are observed. This simple method can be used to identify the position of methoxy groups on the aromatic rings.[75−142] Operationally, the ^{1}H NMR spectrum is first recorded in $CDCl_3$ or CCl_4, and then the spectrum is rerecorded in benzene or deuterated benzene. An upfield induced shift of a methoxy group more than 0.45 ppm indicates that the methoxy group is *ortho* to the biaryl bond.

Intramolecular NOE is a powerful approach for identifying the aromatic substitution pattern and stereostructure of a lignan. The methylenedioxy groups of (−)-γ-schizandrin **(17)** and (−)-wuweizisu C **(6)** were originally incorrectly assigned as being at the 4/5 positions. From a combination of NOE studies and solvent shift determinations, these mistakes were discovered. Only one methoxy group of γ-schizandrin **(17)** gave an NOE effect with an aromatic proton, and the benzene induced upfield shift of this methoxy group was larger than 0.45 ppm; none of the methoxy groups of (−)-wuweizisu C **(6)**

Scheme 2. Synthesis of Steganacin by Nonsymmetrical Ullman Aryl Coupling



Scheme 3. Synthesis of (−)-Steganone (74b) Using the Negishi Coupling Reaction



gave an NOE with aromatic protons or a large benzene induced upfield shift. Therefore, (−)-γ-schizandrin **(17)** has one methoxy group adjacent to an aromatic proton, while (−)-wuweizisu C **(6)** does not have any methoxy groups adjacent to aromatic protons. Their structures were amended to the correct structures **17** and **6** (Figure 2).[143] For phenolic hydroxyl groups, derivatization to ethyl or benzyl ether derivatives can aid structure determination. From NOE effects between the methylene (CH_2) group of the ethoxy or benzyloxy substituent and adjacent aromatic protons, the position of a phenol has been accurately determined. The configuration and conformation of the eight-membered ring can also be defined based on NOE effects among the ring protons.[143] Presently, no other analytical methods are as effective as NOE for the characterization of lignan derivatives.

3.3.3. Mass Spectra

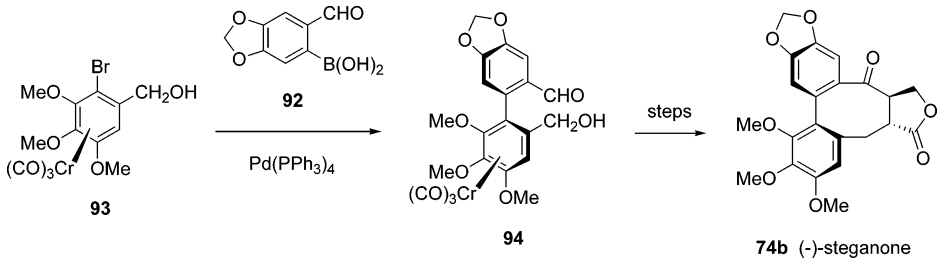
The bonds of the eight-membered rings in cyclooctadiene derivatives are weaker than the aromatic ring bonds. Therefore, the mass spectral bond cleavages of dibenzocyclooctadiene lignans preferentially occur at the aliphatic carbons of the eight-membered ring. The MS fragmentation products can be used to indicate the oxidation pattern of the aliphatic ring carbons (C7, C8, C7′, C8′), as will be discussed in the following subsections.

Non-Oxygen Substituted Cyclooctadienes. Except at the high mass range, ions a^1, b^1, a^2, b^2, and c are very useful for the identification of structures (Figure 11). Ions a^1 and b^1 are complementary, as are a^2 and b^2. If the substituents on the two phenyl rings are identical, then the molecular ions a^1 and a^2 and the ions b^1 and b^2, derived from the same type of cleavage pathway, will give the same molecular masses. Ion c is generated by loss of C_4H_8 (M − 56) from the eight-membered ring. The M − 56 ion is diagnostic for non-oxygen substituted dibenzocyclooctadiene lignans; that is, the C8 and C8′ positions of the lignan are not substituted by an oxygen atom. Note that all of the peaks corresponding to these ions are weak because of the difficulty of these cleavages (Figure 11). The two pairs of complementary ions resulting from the cleavage of the C7, C8 or C7′, C8′ bonds can also be useful for characterization of aromatic ring substitution.

C7-Oxygen Substituted Cyclooctadienes. The main cleavages of C7-hydroxy substituted dibenzocyclooctadiene lignans are loss of water and C_4H_8. C7-Acryloyl O-substituted dibenzocyclooctadiene lignans mainly lose a carboxylic acid group followed by loss of C_4H_8, although some lignan derivatives simply lose a methyl or methoxy group rather than C_4H_8 (Figure 12). The cleavage at C7 of the oxygen substituted dibenzocyclooctadiene lignans gives M − HOR, which further fragments with loss of C_4H_8 or methyl and a methoxy group.

C8-Hydroxy Substituted Cyclooctadienes. The characteristic ions of C8-hydroxy substituted dibenzocyclooctadiene lignans are as follows (see Figure 13): M − 43 is formed by the loss of the acetyl group, from a 1,3-hydrogen shift; M − 102, formed in relatively high abundance, is generated by the cleav-

Scheme 4. Suzuki Biaryl Coupling Approach to (−)-Steganone (74b)



ages of both C8, C8′ together with substituents (being equivalent to M − 56) and one molecule of formaldehyde; and the M − 72 ion is usually produced in low abundance.[144]

C7,C8-Dioxygen Substituted Cyclooctadienes. The main cleavages for this class of compound are loss of water and carboxylic acid groups. The most important ions are M − 72 or M − HOR (R = H or acyloxy) = −71 or −72. They all have common *m/z* values of 343, 342, 328, 313, 312, 301, and 300. The *m/z* 343 and 342 peaks correspond to M − HOR = −71 or −72. Other ions are generated by further functional cleavages of these two ions. In addition to the molecular ion loss of C_4H_8O (M − 72), the C7, C8 diol derivatives also generate the C7, C8 double bond, α-cleavage, and biphenyl cleavage products. All ester derivatives generate acyl ions (see Figure 14). Therefore, the main cleavages of C7, C8 dioxygen substituted dibenzocyclooctadiene lignans are loss of water and carboxylic acid groups, and further loss of C_4H_7O and C_4H_8O. The free C7, C8 diol derivatives also give biphenyl bond cleavage, which is very important for structural characterization.[144−147]

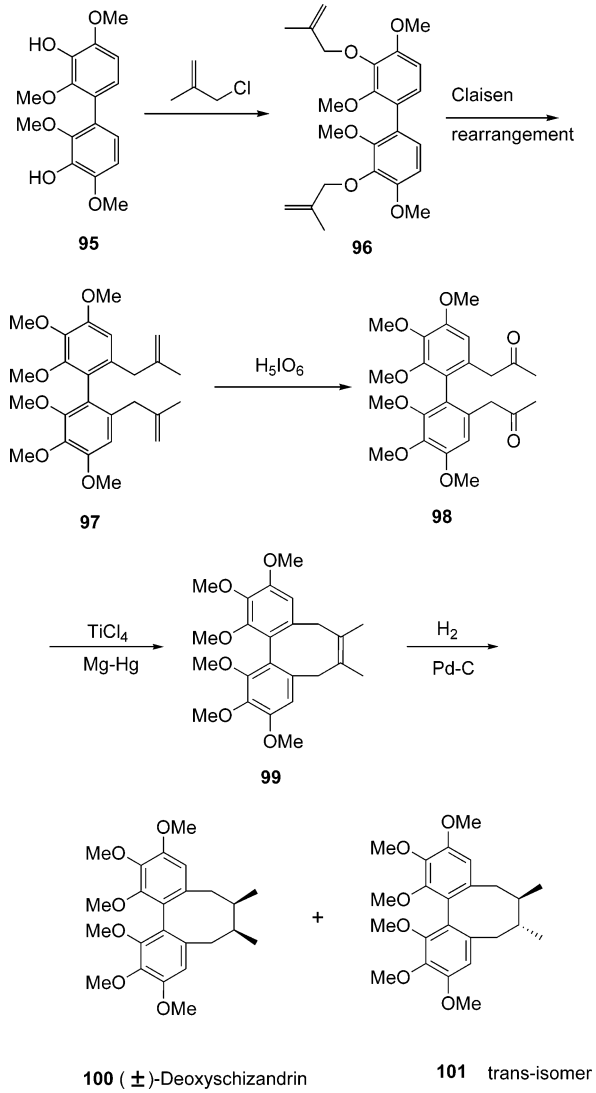
4. Progress on Dibenzocyclooctadiene Synthetic Chemistry

Retrosynthetic analysis indicates that the core structure **(83)** of dibenzocyclooctadiene lignan derivatives can be obtained by two major pathways, the cyclization of biphenyl compound **81** or 1,4-diaryl compound **82** (Scheme 1). A key to the total synthesis of dibenzocyclooctadiene lignans is the synthesis of key intermediates **81** and **82** and the challenging biaryl unit.[148] These strategies differ in the ordering of the biaryl coupling and eight-membered ring closure steps. Pathway A for the synthesis of compound **83** via intermediate **81** uses an intermolecular biaryl coupling prior to eight-membered ring closure, whereas in pathway B via intermediate **82** the two aryl groups are coupled in an intramolecular reaction to produce the eight-membered ring. Both the intermolecular and intramolecular aryl coupling reactions as applied to dibenzocyclooctadiene synthesis are highlighted in the following sections.

4.1. Intermolecular Biphenyl Coupling Reactions

The first syntheses of dibenzocyclooctadiene derivatives (Scheme 1) typically proceeded by aryl coupling to form the biphenyl compound **81**, followed by an intramolecular condensation reaction between the two aliphatic side chains to give the corresponding dibenzocyclooctadiene **83**.

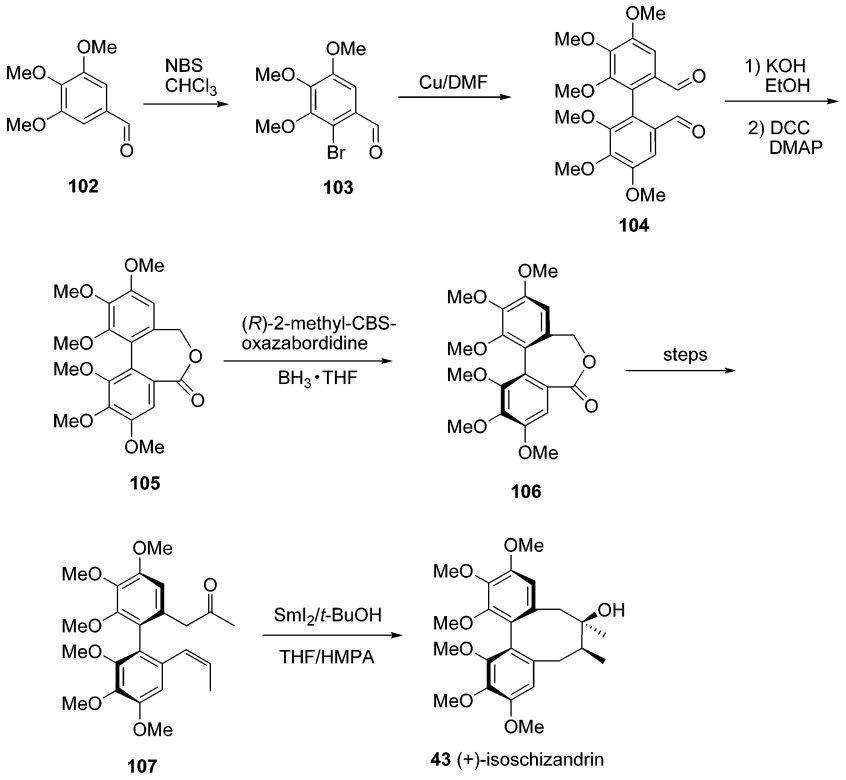
Scheme 5. Synthesis of (±)-Deoxyschizandrin by Intermolecular Coupling



4.1.1. Synthesis of Biphenyl Compounds

The Ullmann reaction is a classical method to synthesize biphenyl derivatives. The coupling reaction of aryl halides in the presence of active copper powder occurs at high temperature. The coupling reaction of a single halide provides the symmetrical biphenyl derivative, while the coupling reaction of two different aryl halides, such as Ar_1X and Ar_2X, gives a mixture of the three possible biphenyl derivatives Ar_1-Ar_1, Ar_1-Ar_2, and Ar_2-Ar_2. Alternatively, two separate steps are required for the synthesis of nonsymmetrical biphenyl derivatives. First, one aryl halide Ar_1X is converted to an aryl metal derivative

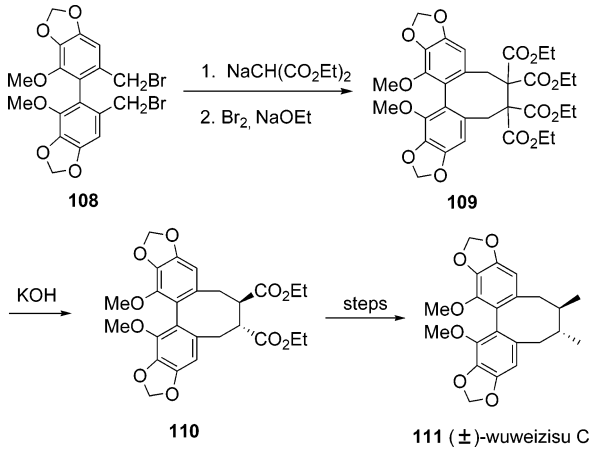
Scheme 6. Synthesis of (+)-Isoschizandrin (43)



(e.g. Ar_1-Cu) by its reaction with metallic copper (Cu). The coupling of the aryl copper intermediate with a second aryl halide Ar_2X occurs at low temperature to give the corresponding nonsymmetrical biphenyl derivative Ar_1-Ar_2.[149] The reaction conditions for this biaryl coupling protocol are mild and work well even for sterically hindered aromatic halides with two *ortho*-substituents, a reaction that is problematic under classical Ullmann conditions. The biaryl units of (−)-steganacin **(74d)** and (+)-steganacin **(88)** were synthesized using this method of coupling two different aromatic intermediates[150] (Scheme 2).

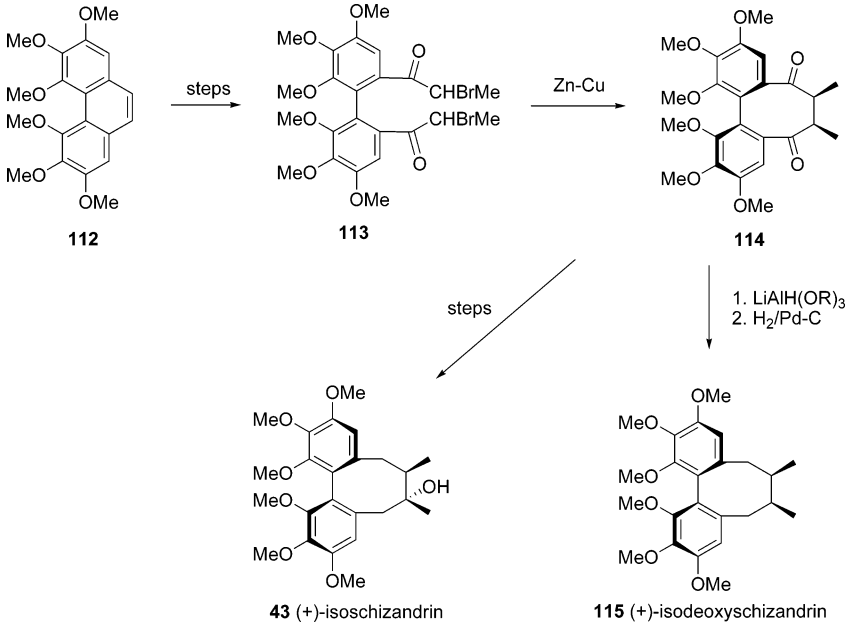
During the 1970s and 1980s, some new methods for aryl−aryl bond formation including the Kharasch,[151] Negishi,[152] Stille,[153] and Suzuki[154] reactions were discovered. These coupling reactions are used to synthesize various nonsymmetrical biphenyl derivatives in the presence of nickel or palladium complexes as catalysts. In the Kharasch coupling reaction, a Grignard reagent Ar_1MgX is reacted with an aryl halide Ar_2X catalyzed by a Ni- or Pd-complex to yield a biphenyl compound. Aryl halides Ar_2X substituted with electron withdrawing groups, such as RC=O, COOR, and NO_2, fail to react with the Grignard reagent. In addition, the coupling of *ortho* substituted aryl halides gives low yields because of steric hindrance. In the related Negishi reaction, aryl zinc reagents Ar_1ZnX are coupled with an aryl halide or aryl triflate Ar_2X (X = Hal, Tf) also catalyzed by Ni(0) or Pd(0). Because the aryl zinc complex is a milder reagent, many functional groups, such as RC=O, COOR, NO_2, and CN on the substrates are not deleterious to the coupling reaction. Biphenyl compound **91,** synthesized from compounds **89** and **90** by Larson[155] through a Negishi reaction in 80% yield, was a key intermediate in the total synthesis of (−)-steganone **(74b)** (Scheme 3).

Scheme 7. Synthesis of (±)-Wuweizisu C

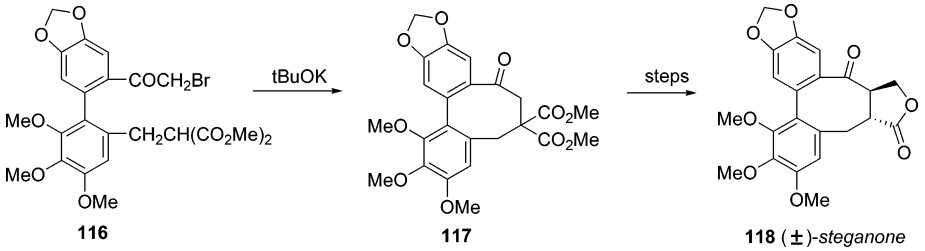


In the Stille reaction, an aryl tin reagent Ar_1SnR_3 (R = Me, Bu) is used as the aryl metal for the coupling reaction. The neutral reaction conditions in the Stille reaction can be applied to a wide range of substrates having a variety of functional groups; however, the organotin reagents and tin byproducts are quite toxic. Similar to the Stille reaction, the Suzuki reaction has been widely utilized for the synthesis of natural products. In this coupling reaction, the aryl boronic acid $Ar_1B(OH)_2$ is reacted with an aryl halide or aryl triflate Ar_2X (X = Hal, Tf) in the presence of a Pd complex (e. g. $Pd(PPh_3)_4$). Typically, an aqueous solution of a weak base, such as Na_2CO_3, K_3PO_3 or $Ba(OH)_2$, is used as the reaction solvent. The Suzuki reaction gives high yields of biphenyl derivatives, even with highly substituted substrates such that tri-*ortho* substituted

Scheme 8. Synthesis of (+)-Isodeoxyschizandrin and (+)-Isoschizandrin



Scheme 9. Synthesis of (±)-Steganone



biphenyl compounds may be prepared.[156] Biphenyl intermediate **94** (Scheme 4) was synthesized through a Suzuki reaction between **92** and **93**[157,158] which upon further manipulation provided the natural product (−)-steganone **(74b)**.

4.1.2. Cyclization of Biphenyl Side Chains

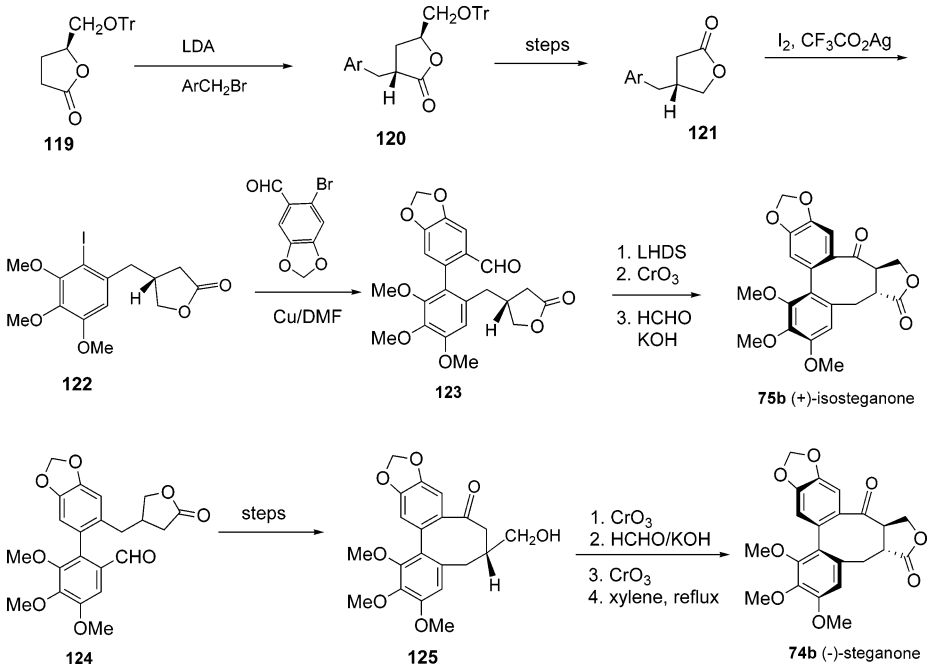
The side chains of biphenyl derivatives can be cyclized by various intramolecular coupling strategies to close the eight-membered ring of lignan structures. Carroll and co-workers[159] have utilized $TiCl_4$ and Mg−Hg as reagents for the intramolecular coupling of biphenyl diketone **98**, prepared in an efficient manner from compound **95**, as a viable approach to the synthesis of the dibenzocyclooctadiene ring system of lignans such as (±)-deoxyschizandrin **(100)**. Compared to other routes, this method provides an efficient means of accessing 8,8′-dimethyldibenzocyclooctadiene lignans (Scheme 5).[159]

Recently, reductive cyclization reactions catalyzed by samarium(II) diiodide have been applied to the formation of a wide variety of carbocyclic skeletons.[160] Research on both the reaction mechanism and factors influencing stereochemical control in the reaction have been reported.[161] In the context of lignan synthesis, the intramolecular bond formations of halo−carbonyl or olefin−carbonyl groups appended to the biphenyl moiety have been used to afford the cyclooctadiene ring system in high yields.[162,163] Molander has utilized the SmI_2 promoted ketyl−olefin cyclization as a key step in the total synthesis of (+)-isoschizandrin **(43)**[164] (Scheme 6). In addition to the good chemical yield of the ring closure reaction, the ketyl−olefin coupling proceeded with excellent stereoselectivity as well as 8-endo regioselectivity.

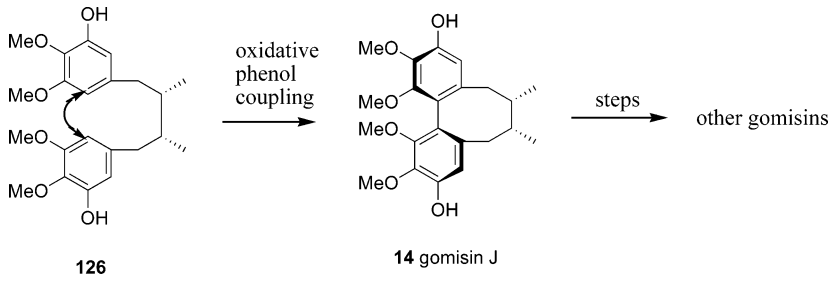
In addition to the oxidative coupling reaction, the intramolecular nucleophilic substitution of the side chains of biphenyl derivatives can provide the corresponding eight-membered ring biphenyl compounds. Xie and co-workers synthesized the key intermediate, diester **110** available from gallic acid via an Ullmann coupling reaction, using this approach (Scheme 7).[165,166] Interestingly, decarboxylation of the tetraester **109** gave the *trans*-6,7-diester **110**, which was converted to a *cis*-anhydride at low pressure and high temperature (structure not shown) by taking advantage of the epimerizable center adjacent to the carbonyl group. Further reactions provided (±)-wuweizisu C **(111)** (Scheme 7). Other examples of this approach to the synthesis of the cyclooctadiene ring system are illustrated in Scheme 8 using a reductive alkylation and in Scheme 9 using malonic esters. The biphenyl derivatives were obtained either from the oxidative cleavage of phenanthrene derivatives[167−169] or by standard Ullman coupling methods.[150,170]

Syntheses of the steganone type of lignans, with a fused lactone−cyclooctadiene ring system, have employed similar intramolecular alkylation or carbonyl addition strategies. In the synthesis of (±)-steganone

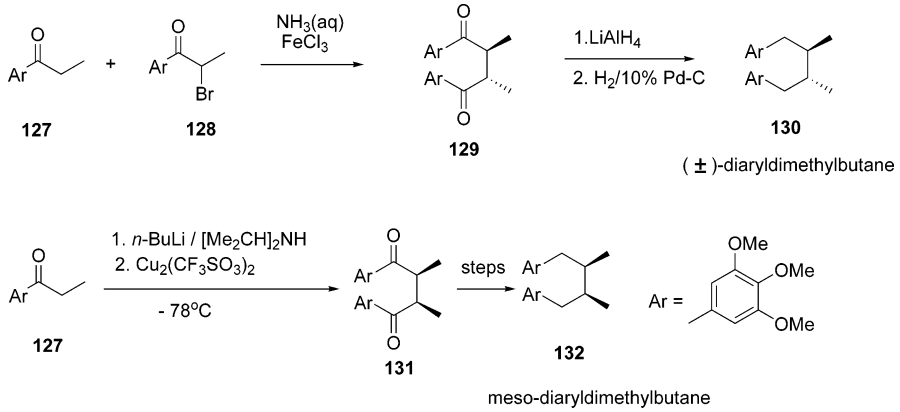
Scheme 10. Synthesis of (−)-Steganone and (+)-Isosteganone



Scheme 11. Proposed Biogenetic Origin of Dibenzocyclooctadiene Lignans from Acyclic Precursors



Scheme 12. Synthesis of Dibenzylbutane Lignans



(118), an intramolecular malonic ester alkylation to close the cyclooctadiene ring was a key C−C bond connection (Scheme 9).[150,170]

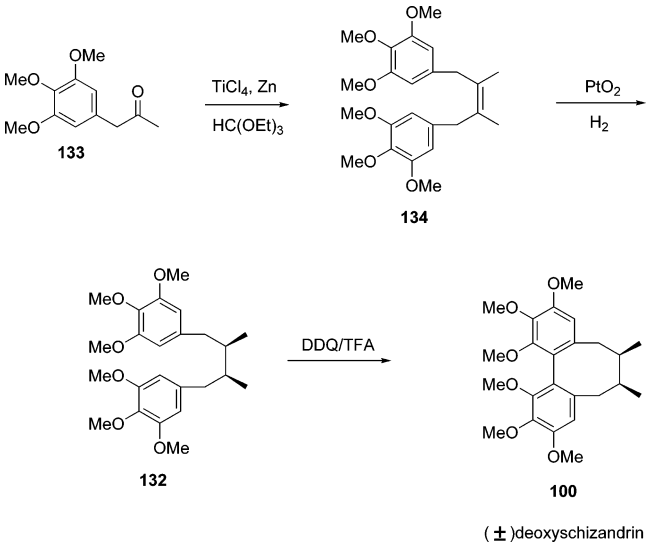
The cyclooctadiene unit of (+)-isosteganone **(75b)** and (−)-steganone **(74b)** was synthesized through an intramolecular aldol condensation between biphenyl aldehyde and lactone substituents promoted by silyl amide[168,171] base (Scheme 10).

Monovich and co-workers successfully utilized SmI_2 methodology for the simultaneous construction of the eight-membered and γ-lactone rings of steganone (see Scheme 4).[157]

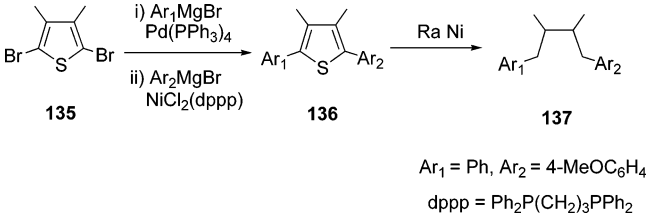
4.2. Intramolecular Biphenyl Coupling Reactions

According to biogenesis theory, biosynthesis is the most efficient process with respect to energy consumption and material throughput. In nature, the mechanism of the enzyme catalyzed formation of the dibenzocyclooctadiene series of lignans is believed to proceed through an oxidative coupling process via radical cation intermediates generated from the phenyl groups of acyclic lignans.[2,52,172−175] This pathway has stimulated researchers to consider utilizing a biomimetic strategy for the synthesis of dibenzocyclooctadiene lignans as illustrated in Scheme 11.

Scheme 13. Synthesis of Deoxyschizandrin Using McMurry Coupling



Scheme 14. Synthesis of Nonsymmetrical Diaryl Lignans



4.2.1. Formation of the C8–C8′ Bond for Synthesis of Acyclic Lignans

The dibenzyl substituted butane (and butyrolactone) types of acyclic lignans (see structure **1** in Figure 1) are not only abundant and diverse natural products with various biological activities, but they are also key precursors for the synthesis of the arylnaphthalene series of lignans **2** and the dibenzocyclooctadiene series of lignans **3**.

4.2.2. Synthesis of the Dibenzylbutane Series of Lignans

The dibenzyl butane series of lignans can be synthesized by an oxidative coupling reaction[177] or a Grignard coupling[84b,176] of two arylpropane units. The relative stereochemistry at C-8, C-8′ of the butane unit can be controlled depending on the reduction conditions (see Scheme 12).[177] The coupling reaction of 3,4,5-trimethoxypropiophenone (**127**) with α-bromoketone **128** gave the product (±)-diketone **129** in excellent yield. A two step deoxygenation of compound **129** produced *meso*-1,4-bis(3,4,5-trimethoxyphenyl)-2,3-dimethylbutane **(130)**, an intermediate in the synthesis of (±)-deoxyschizandrin **(100)**. [177]

The McMurry reaction, a reductive coupling of carbonyl groups mediated by low valent Ti, has been used for the synthesis of the wuweizi lignans.[178] Chang and Xie studied the Ti induced reductive dimerization of aryl acetone **133**[179,180] to give the alkene intermediates **134**. Hydrogenation provided **132** (Scheme 13), which after intramolecular biaryl coupling produced (±)-deoxyschizandrin **(100)**.

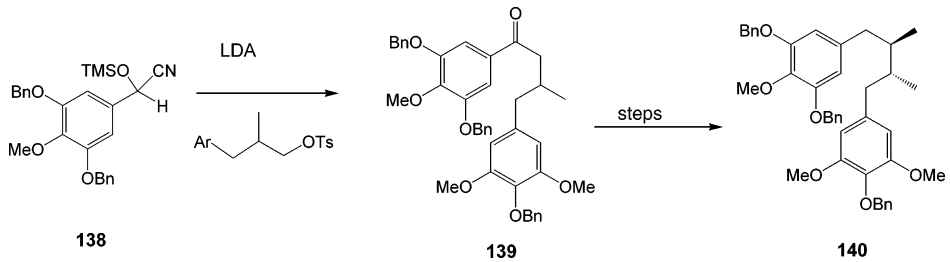
The synthetic strategy discussed above, intermolecular dimerization by C-8, C-8′ bond formation, to prepare dibenzyl butane derivatives is practical only for the synthesis of symmetrical lignan derivatives. A more general synthetic strategy, which can also be used for the synthesis of nonsymmetrical lignan derivatives with different substituents on the two aromatic moieties, is depicted in Scheme 14.[181] Preliminary results indicate that aryl Grignard reagents may be sequentially cross-coupled with dihalothiophenes, which, following desulfurization, provides a simple and efficient route for the synthesis of unsymmetrically substituted dibenzocyclooctadiene lignans.

Nonsymmetrical, acyclic lignans have been constructed through alternative C−C bond connections. The acyl anion equivalent **138** could be alkylated with a tosylate to form the C-7, C-8 bond of lignan **140** (Scheme 15).[103−105]

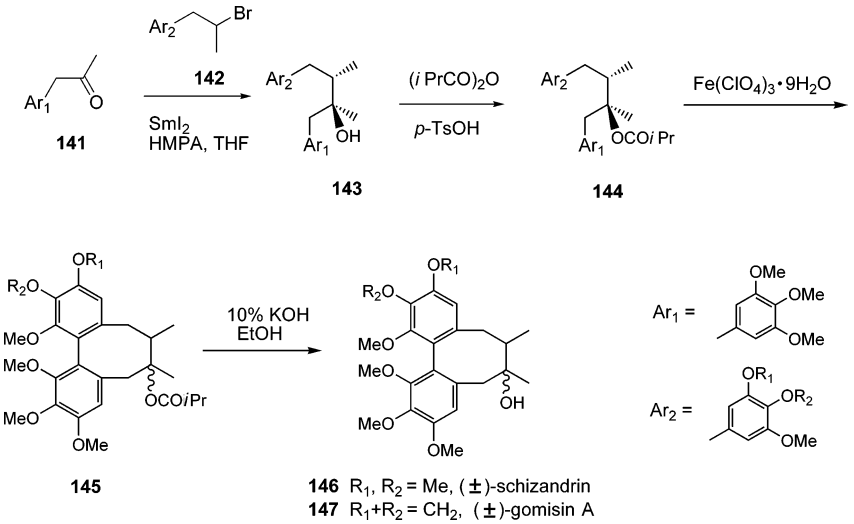
Another example of an anion/carbonyl union as an approach to nonsymmetrical lignans uses the well developed samarium−Grignard reaction. In this reductive coupling of a phenylpropyl bromide **142** and a phenylacetone derivative **141**, the *erythro*-butanol **143** results. Although the oxidative aryl−aryl coupling reaction produced the target lignans **146** and **147**, this approach suffers from a low yield and poor stereocontrol[182] (Scheme 16).

The dibenzyl butyrolactone series of lignans, such as **151** or **152** (Scheme 17), are precursors for the synthesis of the steganacin series of lignans. Due to their structural similarities, numerous synthetic pathways to these lignans have been investigated. Since the early 1980s, stereoselective methods for lignan synthesis have become increasingly important;[9,10] the most commonly used synthetic routes to the benzylbutyrolactones **150** are by benzylation of the lactone **148**, readily accessible from L-glutamic acid,[10,131,168] or by enantiospecific hydrogenation of itaconic acid derivative **149** and subsequent lactonization.[176,183−185] A second benzylation gives **151**, or a condensation gives the benzylidene **152** (Scheme

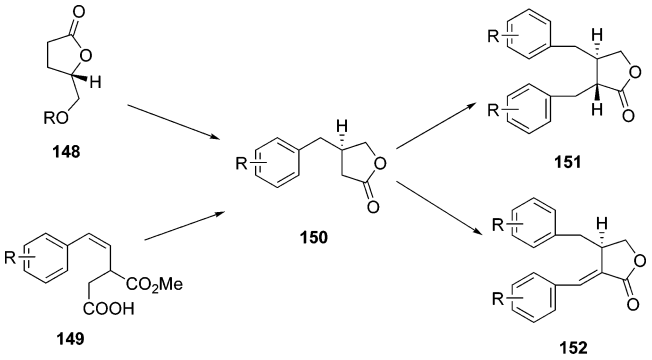
Scheme 15. Synthesis of Nonsymmetrical Diaryl Lignans Using an Acyl Anion Equivalent



Scheme 16. Approach to Wuweizi Lignans Using SmI_2 to Prepare Acyclic Lignan Precursors



Scheme 17. Synthesis of Nonsymmetrical Dibenzylbutyrolactone Lignans



17). This is the key methodology for synthesis of unsymmetrical dibenzyl-γ-lactone lignans.

The coupling of a dianion with two aryl substituted electrophiles is another successful strategy for the preparation of dibenzylbutyrolactone lignans, as illustrated in Scheme 18. Belletire and co-workers[186] discovered that the succinamide dianion **153** could be coupled with 2 equiv of benzyl halide simultaneously to give **154**, a precursor to the disubstituted butyrolactone **155** (see reaction I in Scheme 18). The dianion **156** was used for the synthesis of nonsymmetrically substituted lactone **158** through intermediate **157** (see reaction II in Scheme 18).[187]

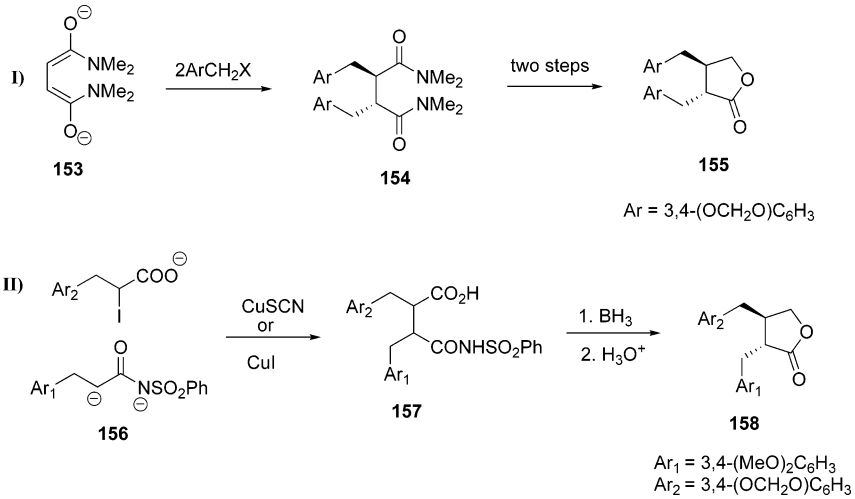
4.2.3. Intramolecular Biaryl Oxidative Coupling

The intramolecular aryl oxidative coupling reaction is the pivotal step in the synthesis of the wuweizi series of lignans following a biomimetic strategy. The reagents used in this oxidative aryl coupling are critical for the success of the reaction. Most of the older oxidative aryl coupling reagents are complicated by side reactions, such as peroxidation, and are not generally applicable to substrates containing a phenol group; hence, they are known as non-phenol oxidative coupling reagents. Recently, a new group of oxidizing agents that perform well in biaryl coupling reactions such as hypervalent iodine reagents, ruthenium oxide, and others have been discovered; the mildness of these reagents allows them to be used even with phenol containing substrates.

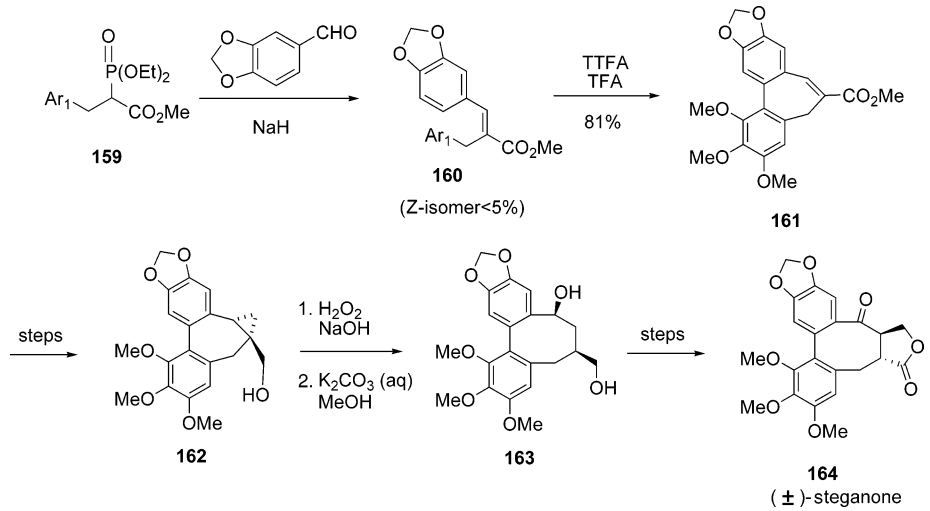
4.2.4. Non-Phenol Aryl Oxidative Coupling

Since the original report in 1976, VOF_3 has been successfully utilized as an oxidizing agent for non-

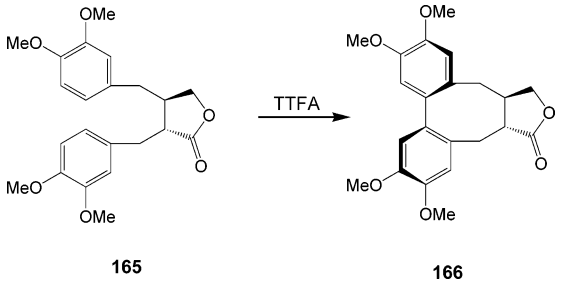
Scheme 18. Dianion Alkylation Strategies for the Synthesis of Lactone Lignans



Scheme 19. Synthesis of (±)-Steganone



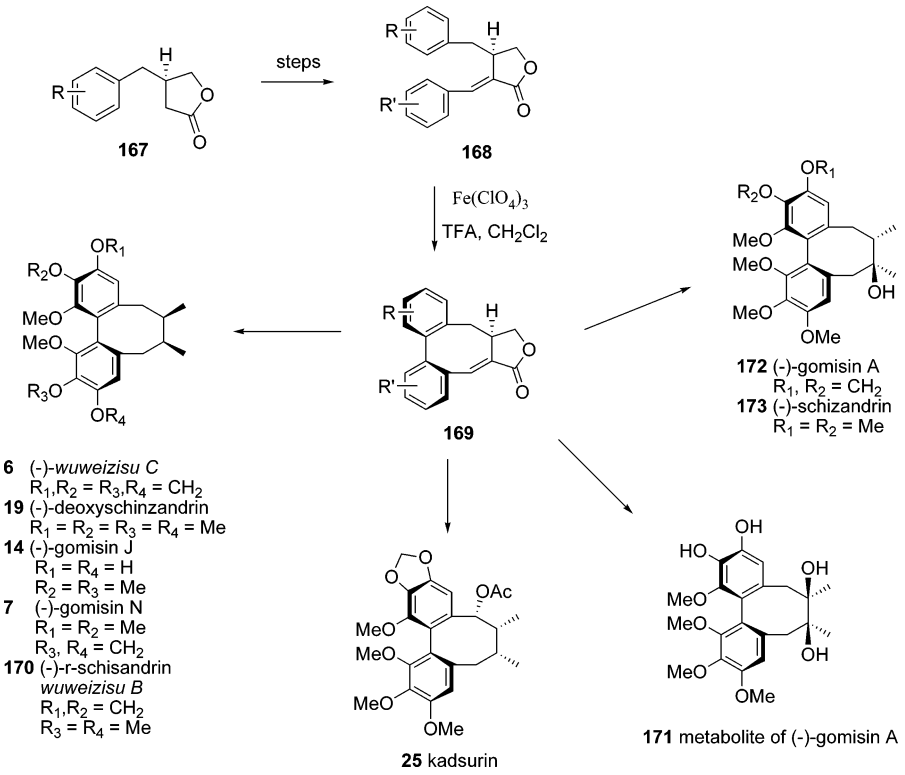
Scheme 20. Synthesis of an Unnatural Stegane Analogue



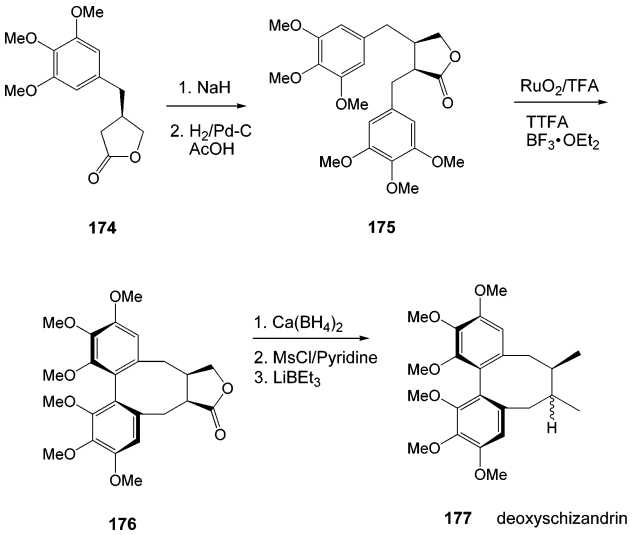
phenol oxidative aryl coupling reactions.[84b] Although this reagent is prone to side reactions such as peroxidation, rearrangement, and demethylation, it has still received a great deal of attention because it greatly simplified the total syntheses of dibenzocyclooctadiene derivatives.[84b] In the search for better non-phenol oxidative coupling reagents, researchers have discovered a variety of transition metal oxides or their salts, such as Tl(III), Mn(II), Fe(III), Co(III), and Ru(IV), that promote aryl−aryl couplings including intramolecular cases.[188]

In one application, TTFA was found to be a more efficient non-phenol oxidative coupling reagent than VOF_3.[189] Magnus *et al.*[190] employed TTFA as an oxidative coupling reagent and used a Simmons−Smith ring expansion reaction for the total synthesis of (±)-steganone **(164)** in nine steps and 24% overall yield (Scheme 19). With TTFA, the oxidative coupling yield approximately doubled the best previous results reported in steganone syntheses. In a parallel series of experiments, *E*-**160** was converted to **161** using $Tl(OCOCF_3)_3$, and surprisingly, the pure *Z*-**160** iso-

Scheme 21. Asymmetric Synthesis of a Key Intermediate Used To Make Various Wuweizi Lignans



Scheme 22. Synthesis of Deoxyschizandrin Using RuTFA



mer was also converted to **161**. In addition, the dibenzyl substituted, acyclic butyrolactone lignan **165** could be cyclized by utilizing a combination of TTFA and $BF_3{\cdot}Et_2O$ to give the 8,5-ring system of **166** in high yield[190,191] (Scheme 20).

The coupling efficiency of non-phenol oxidation reagents was found to closely correlate with substrate structure. For example, while TTFA was useful for the intramolecular oxidative coupling of substrates **165** to form 8,5-bicyclic systems, $Fe(ClO_4)_3$ was superior to TTFA for the intramolecular oxidative coupling of **160** and the dibenzylbutane lignans **130**.[176] Subsequently, Tanaka and co-workers[176] applied this biaryl coupling strategy to the asymmetric syntheses of several members of the wuweizi lignan family from the intermediates **168**. The lignans gomisin A **(172)**, schizandrin **(173)**, kadsurin **(25),** and the gomisin A metabolite **171** were all synthesized in optically pure form (Scheme 21).

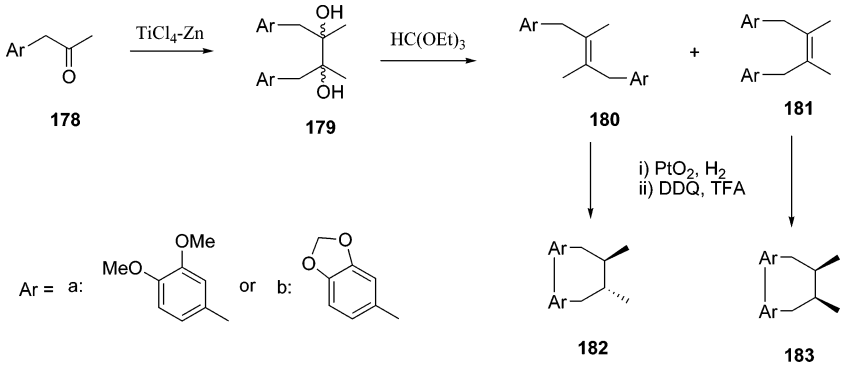
Robin and co-workers[192] found RuTFA gave excellent results in an intramolecular oxidative coupling of dibenzylbutyrolactone **175** (Scheme 22), as the key step in a synthesis of deoxyschizandrin **(177)**. Intermediate **176** was obtained as the stereospecific product in 90−95% yield. Utilizing TTFA as an alternative oxidative coupling agent produced the same intermediate, but in a moderate 65% yield (Scheme 22). An interesting observation was that phenolic hydroxyl groups in substrates were tolerated by the RuTFA oxidant. The aryl coupling occurred at the positions *para* and *ortho* to the phenol hydroxyl group and generally in high 80−85% yield.[192−194] However, this reagent was unsuccessful for substrates containing either methylenedioxy or benzyloxy groups. Under RuTFA conditions, the oxidative coupling of substrate **130** (Scheme 12) produced a mixture of dibenzocyclooctadiene and aryl naphthalene compounds **2** (Figure 1) in nearly equal amounts. These results indicated that RuTFA, while a suitable oxidative coupling reagent for the synthesis of deoxyschizandrin lignans without a methylenedioxy group, is not suitable for the synthesis of the wuweizisu type of lignans.

Robin and co-workers[195] systematically studied the aryl coupling reaction of substrate **165** (see structure in Scheme 20) with various transition metal oxides in a CH_2Cl_2−TFA−TFAA medium. They found that Tl_2O_3 resulted in the best yields (60−65%) for substrates with a methylenedioxy group. Other coupling reagents generally produced large amounts of oily impurities. For substrates only substituted by methoxy groups, the oxidizing agent of choice was Re_2O_7, while $RuO_2{\cdot}2H_2O$, V_2O_5, and $Cu(OAc)_2{\cdot}H_2O$ also provided the product in moderate yields. Since in general these oxidation reagents do not epimerize preexisting chiral centers in the acyclic lignan starting material, the intramolecular oxidative coupling of chiral acyclic lignan substrates has become an important method for the asymmetric synthesis of dibenzocyclooctadiene lignans.

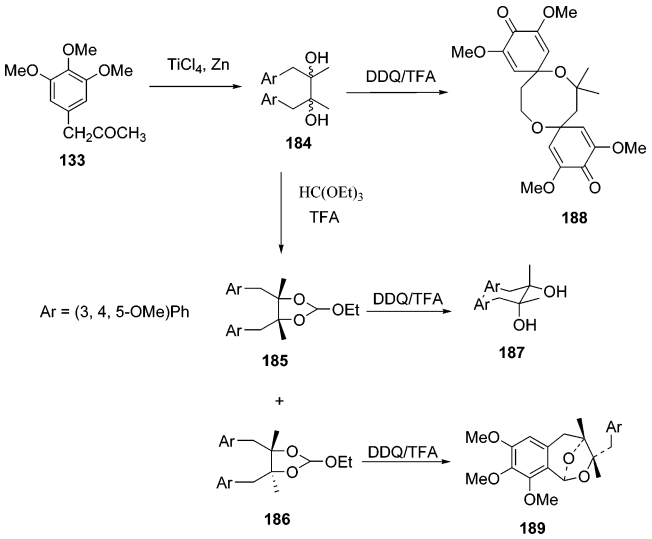
In 1987, Rao,[196] while studying functional group conversion of benzylic carbons with DDQ in TFA, unexpectedly isolated a dibenzocyclooctadiene. DDQ was the first non-phenol oxidative coupling reagent that was not a transition metal. Due to its reasonable cost and accessibility, Chang and Xie used DDQ in detailed studies on the non-phenol oxidative coupling reaction directed toward the synthesis of the wuweizi series of lignans. As illustrated by the general structures in Scheme 23, a variety of lignans including schizandrin[197−203] were synthesized during this investigation. Subsequent research verified that DDQ could be used in asymmetric versions of dibenzocyclooctadiene lignan derivative synthesis.[204]

Studies of DDQ as an oxidant for the synthesis of the hydroxyl substituted lignan schizandrol **(187)** are summarized in Scheme 24. Xie and co-workers used as starting material aryl ketone **133**, available from gallic acid in five steps, which was subjected to a

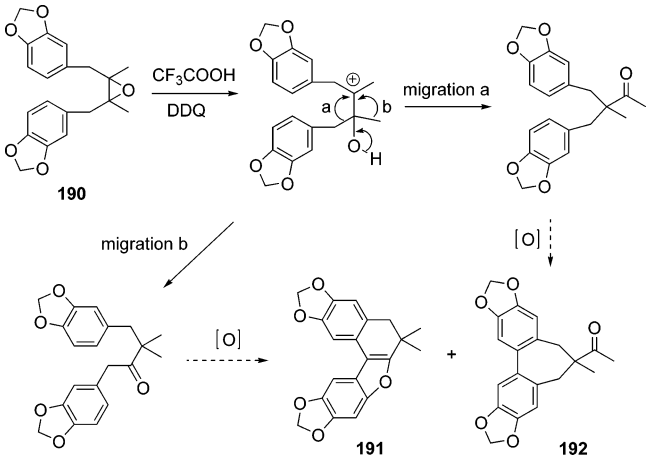
Scheme 23. Synthesis of Wuweizi Series of Lignans via DDQ Coupling



Scheme 24. Synthesis of Schizandrol 187 from an Orthoformate Intermediate



Scheme 25. Competitive 1,2-Alkyl Shifts To Account for the Formation of 191 and 192



pinacol coupling with activated Ti to give the intermediate **184**. Treatment of **184** with DDQ in TFA unexpectedly resulted in the formation of compound **188** (Scheme 24).[203] To avoid unproductive reactions with the hydroxyl groups, triethyl orthoformate was employed for the protection of the pinacol intermediate **184** to form a mixture of *erythro* **185** and *threo* **186** cyclic ortho esters.[197] The oxidative coupling of **185** by DDQ in TFA gave schizandrol **(187)**, while compound **186** only generated the rearrangement product **189** (Scheme 24).

Treament of compound **179** (Scheme 23) with triethyl orthoformate under refluxing conditions gave *cis*- and *trans*-olefins, which were further oxidized to the epoxide derivative **190**. Oxidative coupling of **190**, prepared by epoxidation of olefin **181**, in the presence of acid was expected to produce a schizandrin structure via biaryl coupling and epoxide ring opening (Scheme 25). However, two rearrangement products, **191** and **192**, were obtained by competing migrations from a presumed cation species generated in the acid-catalyzed ring opening of epoxide **190**.[198−200]

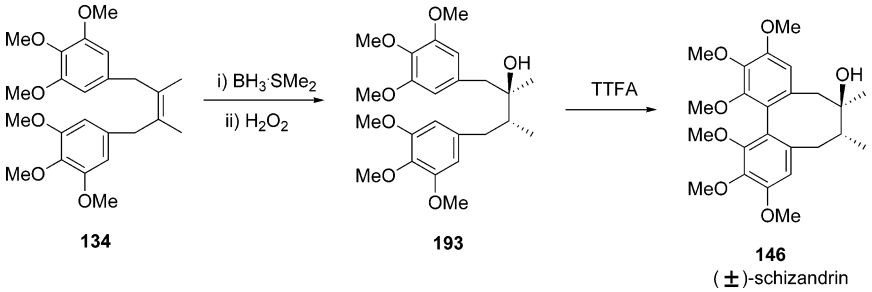
As the non-phenol oxidative coupling of epoxide **190** did not give eight-membered ring lignan derivatives, introduction of an alcohol at C-8 prior to aryl coupling was investigated (Scheme 26). Hydroboration of **134** with a diborane−dimethyl sulfide complex, followed by peroxidation, produced the tertiary alcohol derivative **193**. After the hydroxyl group was protected by trifluoroacetylation, the TTFA−BF_3·Et_2O oxidative coupling gave the expected product (±)-schizandrin **(146)**, and this approach suffers from a low yield.[201]

4.2.5. Oxidative Coupling in the Phenol Series

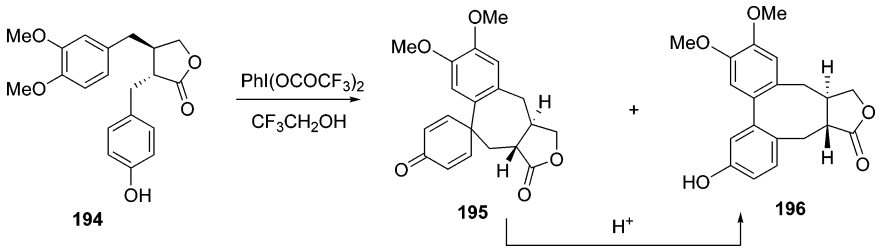
In 1992, Ward and co-workers used the hypervalent iodine reagent $PhI(OCOCF_3)_2$ for the oxidative coupling of acyclic lignans containing a phenol hydroxyl group to synthesize the dibenzocyclooctadiene structure **196** (Scheme 27).[205,206] This method also produced a new spirodienone compound **195** which under acidic conditions was easily converted into the dibenzocyclooctadiene product through an intramolecular rearrangement. Compound **195** was hypothesized to be an intermediate in the biosynthesis of this type of lignan. The ratio of the two products, cyclooctadiene **196** and spirodienone **195**, was dependent on reaction time. The spirodienone **195** was the major product after 1 h (47%), while cyclooctadiene **196** became the major product (48%) after 24 h (Scheme 27).

In addition to the biaryl coupling methodologies mentioned previously, the intramolecular Ullmann coupling, a so-called template reaction, has also been widely used for the synthesis of nonsymmetrical biphenyl lignan derivatives.[207] In this process, two different aryl halides were sequentially linked to salicyl alcohol (**197**) (the template) to generate a bridged dihalide **200** (Scheme 28). An intramolecular Ullmann coupling gave a high yield of the cyclic product **201**. The temporary salicyl bridge was then removed and the asymmetric synthesis of the lignan analogue **203** was completed by functional group interconversion and cyclization of the biphenyl side chains.[165,207,208]

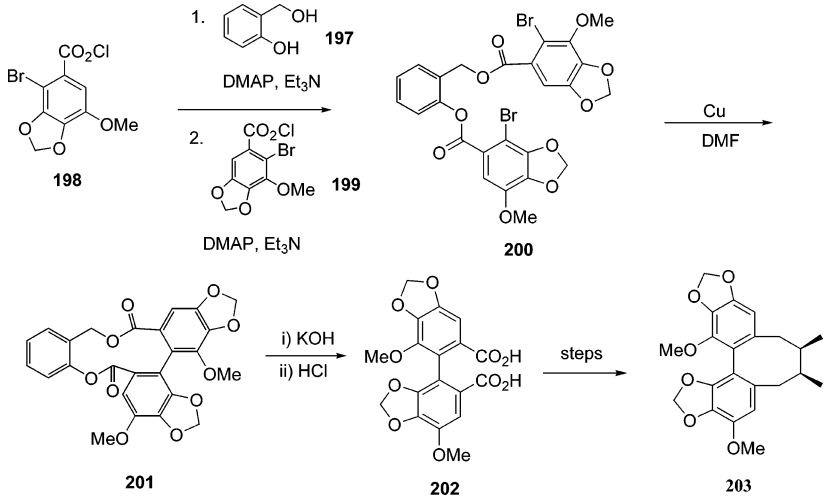
Scheme 26. Synthesis of (±)-Schizandrin



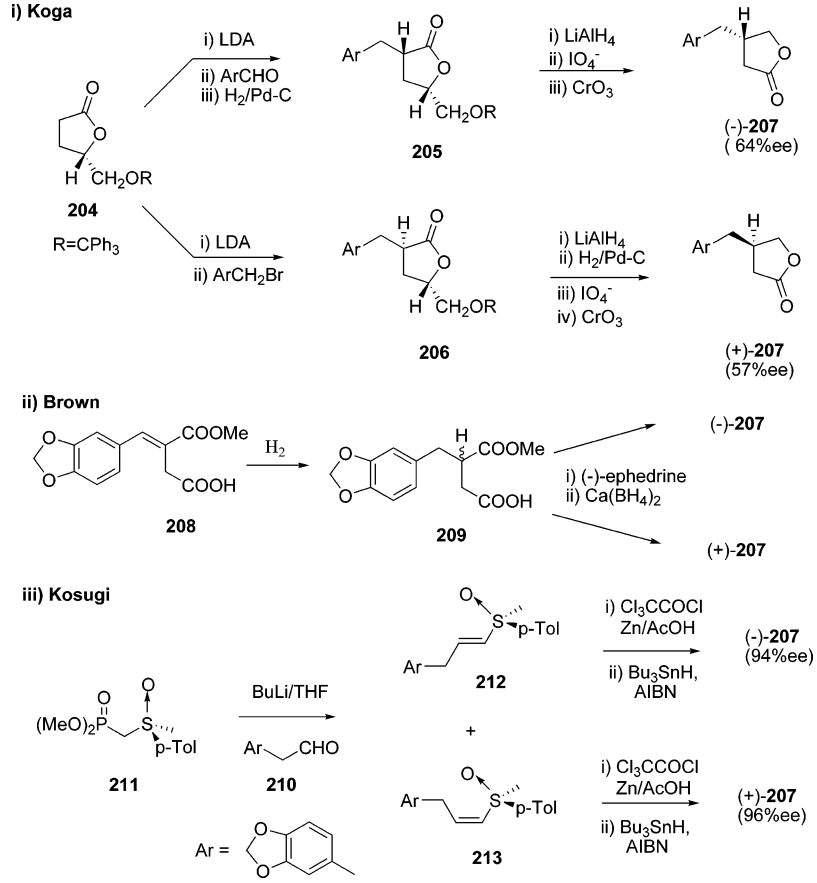
Scheme 27. Biomimetic Approach to Dibenzocyclooctadiene Lignans Using a Hypervalent Iodine Oxidative Coupling Reagent



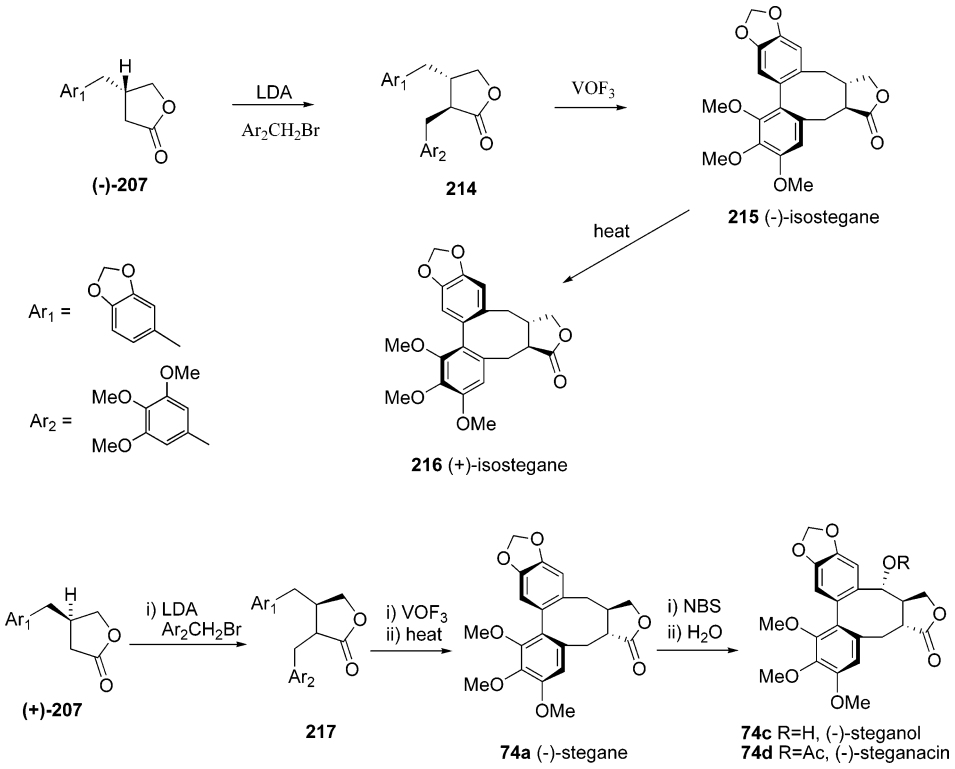
Scheme 28. Template Assisted Ullman Biaryl Coupling in Synthesis of Nonsymmetrical Lignan 203



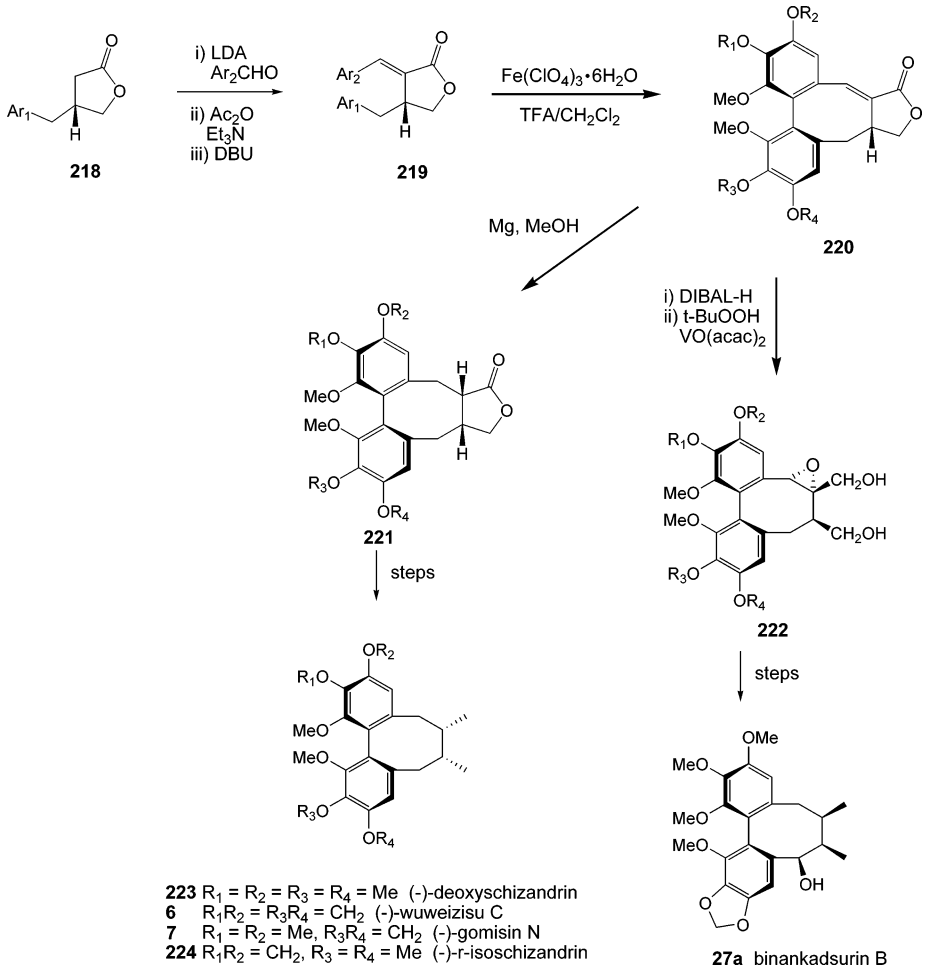
Scheme 29. Preparations of Optically Active Benzyl Substituted Butyrolactones



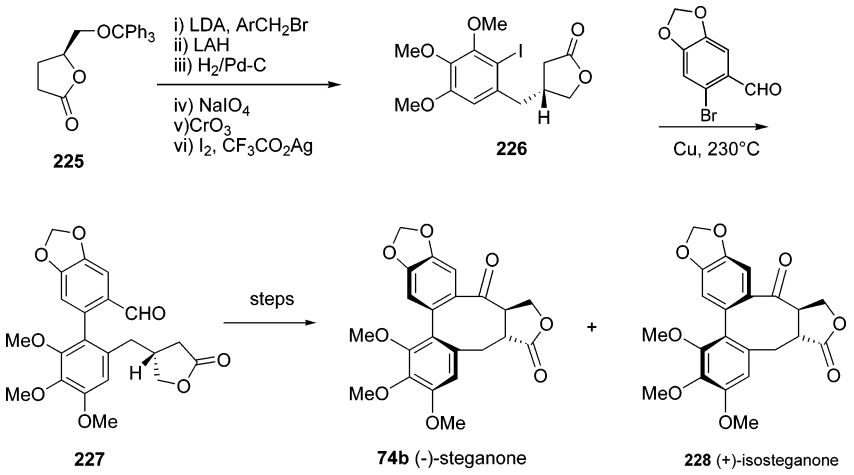
Scheme 30. Synthesis of Steganacin Analogues



Scheme 31. Synthesis of Schizandrin Analogues



Scheme 32. Synthesis of (+)-Isosteganone and (−)-Steganone



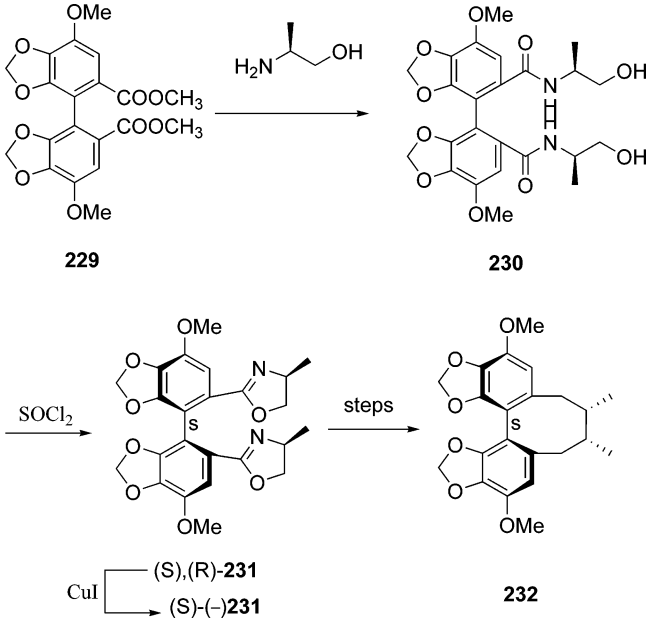
5. Asymmetric Synthesis of Chiral Dibenzocyclooctadiene Lignans

Naturally occurring dibenzocyclooctadienes generally contain several asymmetric centers as well as a configurationally stable axial chiral biaryl moiety. It is not surprising that these challenging targets have been the focus of asymmetric syntheses as one of the most active fields in natural products synthesis since the 1980s. In addition to their intriguing structures, Tomioka[209] and others[210−212] discovered that the absolute configuration of the biphenyl unit and the conformation of the lactone carbonyl were the keys to the observed antitumor activity for steganacin and its analogues. These results prompted further asymmetric syntheses of other chiral lignans and analogues. Presently, at least 10 different methods for the asymmetric synthesis of dibenzocyclooctadiene lignans have been reported. These methods can be classified into four general types that are discussed in the following sections.

5.1. Diastereoselective Alkylation of Chiral Butyrolactones

Preparation of monosubstituted butyrolactone **207** by the formal asymmetric β-alkylation of a lactone starting material has been one solution to the required lignan precursors since a second benzyl group could be stereoselectively introduced at the α-position of the lactone using standard enolate alkylation conditions (Scheme 29). Koga and co-workers[213] used the protected 4-(hydroxymethyl)butyrolactone from L-glutamic acid to access (+)- or (−)-**207** via diastereoselective alkylation followed by carbonyl transposition. A second approach to **207** reported by Brown and co-workers[214−216] proceeded by Stobbe condensation, hydrogenation, chiral resolution, and lactonization. In a third approach, lignan precursors (−)-**207** and (+)-**207** could be obtained through the stereospecific cyclization of alkenyl sulfoxides **212** or **213** with dichloroketene (Pummerer rearrangement) in 94% ee or 96% ee, respectively[217] (Scheme 29). Because the chiral alkenyl sulfoxides **212** and **213** are readily available, this synthetic route for the synthesis of a variety of β-substituted butyrolactones

Scheme 33. Efficient Chiral Resolution of Intermediate in (−)-Wuweizisu C Analogue Synthesis



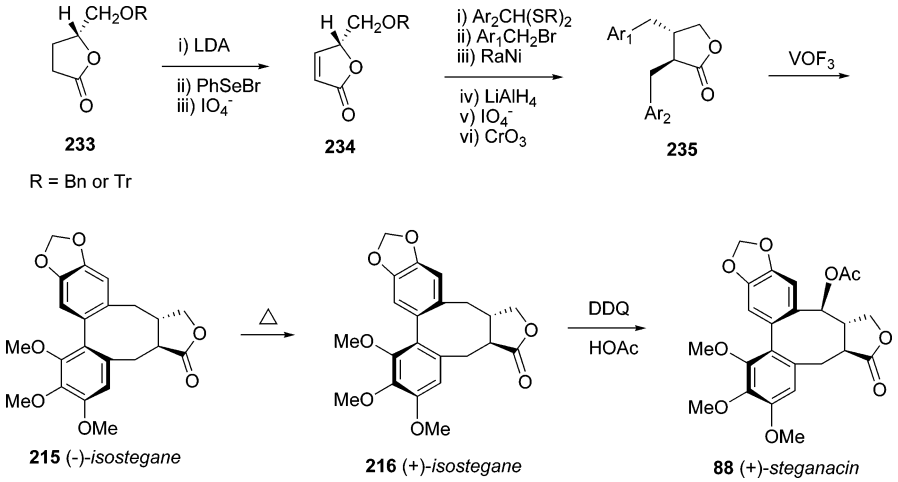
of high optical purity is more convenient than the other routes described.

Tomioka and co-workers[218,219] utilized an optically active dibenzyl lactone for the asymmetric synthesis of a series of steganacin analogues **215**, **216**, **74c**, and **74d** (Scheme 30).

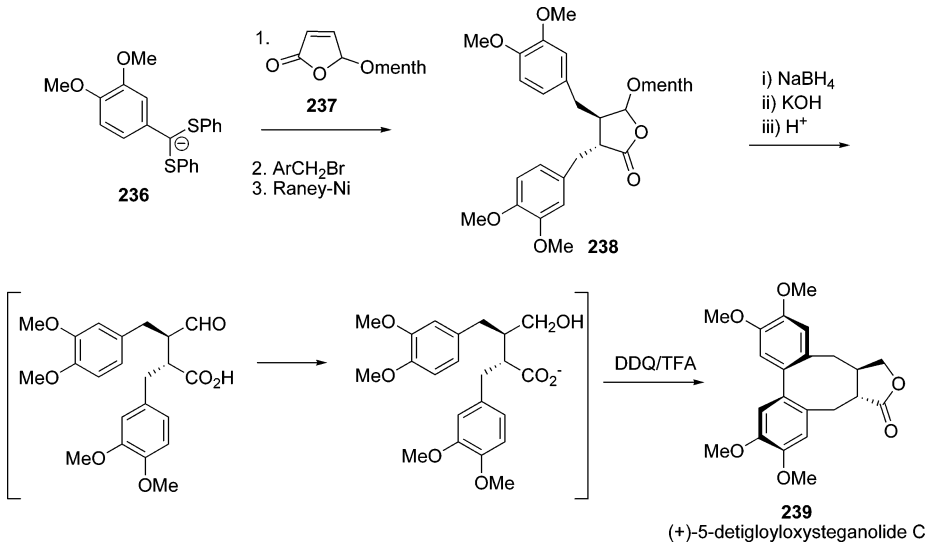
Tanaka and co-workers[176,184,185,220−222] synthesized a variety of schizandrin analogues by a similar approach (Scheme 31). In these syntheses, recently developed oxidative coupling conditions were effectively utilized for the stereoselective total syntheses of dibenzocyclooctadiene lignans.

Brown and co-workers[223] described an asymmetric total synthesis of (+)-isosteganone **228** and (−)-steganone **74b** from precursor **225**. This synthesis differs from previous routes by the sequence in which the two aryl groups are introduced onto the lactone core structure. The absolute configuration of the biphenyl moiety could be manipulated either before or after the eight-membered ring formation (Scheme 32).

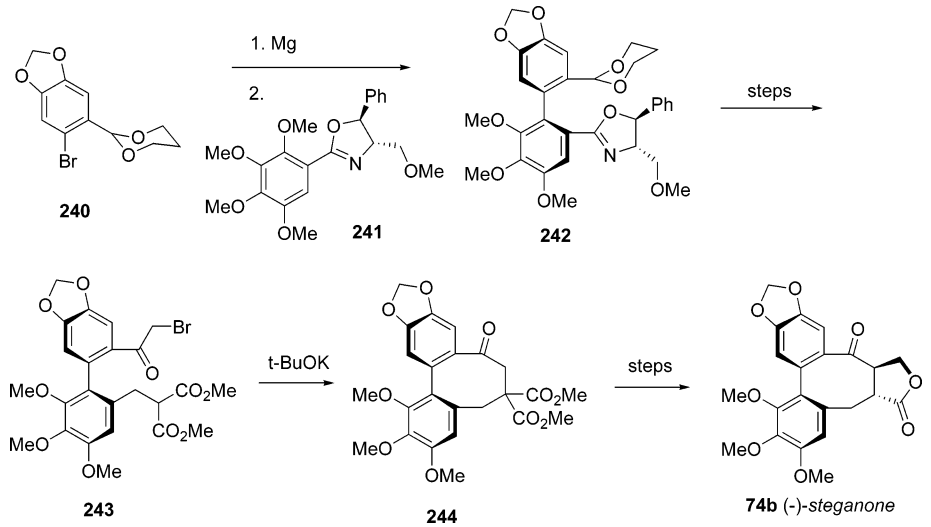
Scheme 34. Synthesis of (+)-Isostegane and (+)-Steganacin



Scheme 35. Efficient Synthesis of Dibenzocyclooctadiene Lignans



Scheme 36. Asymmetric Synthesis of (−)-Steganone

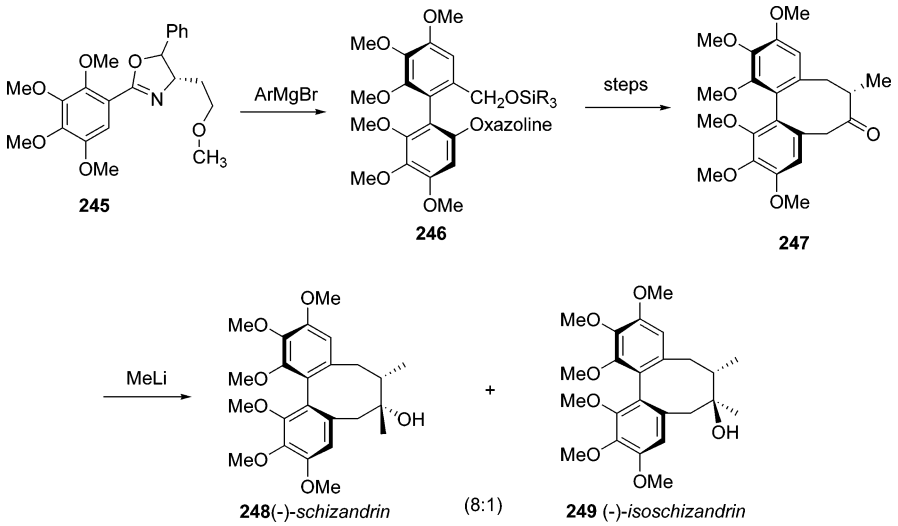


Cheng and co-workers[224] efficiently prepared chiral biphenyl derivatives *(S)*-(−)-**231** from **229**. Compound *(S)*-(−)-**231** was further utilized for the synthesis of wuweizisu C analogues **6** according to Xie's procedure (Scheme 33).[165,166]

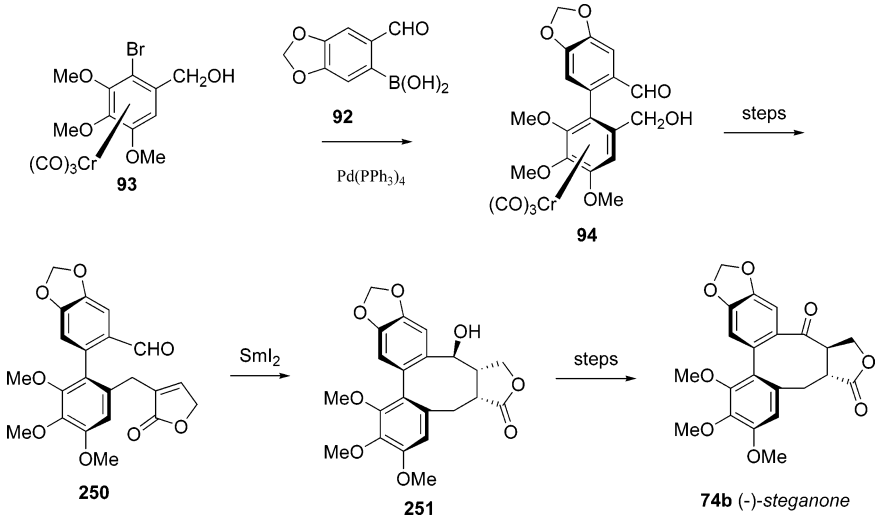
5.2. Diastereoselective Addition to Chiral Butenolactones

As a supplementary method to the lactone based methodologies described above, Koga and co-

Scheme 37. Chiral Oxazoline Route to (−)-Schizandrin and (−)-Isoschizandrin



Scheme 38. Chiral Cr−Aryl Complexes Applied to an Efficient Synthesis of Steganone



workers[225] converted the butyrolactone **233** to the butenolide **234** (Scheme 34). The conjugate addition of a bissulfide stabilized carbanion followed by alkylation afforded the dibenzyl substituted butyrolactone **235**. Biaryl ring closure of **235** provided (−)-isostegane **(215)**, which on heating could be isomerized to (+)-isostegane **(216)**. Further oxidation of (+)-isostegane **(216)** to (+)-steganacin **(88)** occurred by treatment with DDQ in acetic acid (Scheme 34).

A similar conjugate addition, alkylation sequence reported by Pelter and co-workers[226] utilized a different chiral butenolactone precursor **237** (Scheme 35). The tandem addition−alkylation to **237** afforded asymmetric lignan derivative **238** in high yield. Completion of this very simple and efficient route for the asymmetric synthesis of the dibenzocyclooctadiene lignan **239** entailed a stereoselective oxidative coupling using DDQ in TFA (Scheme 35).

5.3. Application of Chiral Oxazolines

The Kharasch coupling reaction for the asymmetric preparation of biaryl derivatives has been accomplished using an oxazoline chiral auxiliary. Meyers and co-workers[227] reported the synthesis of the chiral biphenyl derivatives **242** with a diastereomeric ratio of 7:1, via the intermolecular coupling reaction of **240** and chiral oxazoline **241**. The minor diastereomer could be removed prior to the cyclization of **242** to (−)-steganone **(74b)** (Scheme 36).

The strategy of using a chiral oxazoline to prepare optically active biaryls was also successfully applied to the synthesis of (−)-schizandrin **(248)** and (−)-isoschizandrin **(249)** (Scheme 37).

5.4. Application of Chromium Tricarbonyl Complexes

In 1994, Uemura *et al.*[228] found that aromatic compounds derivatized as $Cr(CO)_3$ complexes have planar chirality. The chiral chromium complexed benzene (**93**) could be coupled with substituted aryl boronic acids (**92**) to afford the chiral biaryl complexes **94**. The chromium tricarbonyl complex, which controlled the axial chirality during biaryl formation, could be decomplexed by photooxidation. The asymmetric synthesis of (−)-steganone **(74b)** was achieved

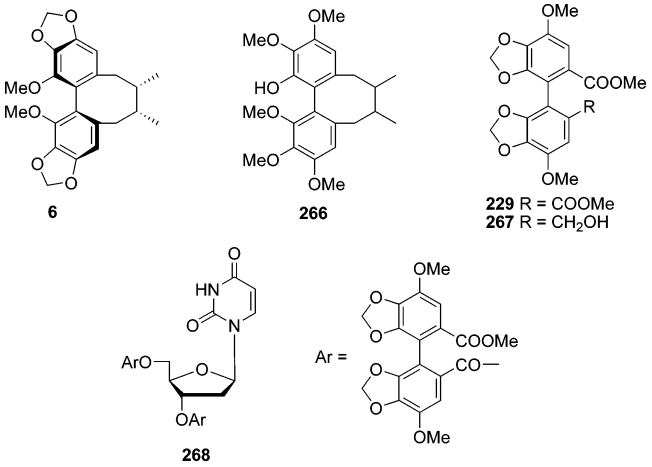


Figure 15. Lignan and related biaryl compounds with anti-HBV activity.

based on this $Cr(CO)_3$ complex chemistry as a practical method for preparing the optically active biaryl intermediate.[158] By taking advantage of the stability of the aryl chromium tricarbonyl complex in the presence of SmI_2,[229,230] Monovich *et al.*[157] completed an enantioselective synthesis of steganone **(74b)** (Scheme 38).

6. Perspectives of Dibenzocyclooctadiene Lignan Analogues

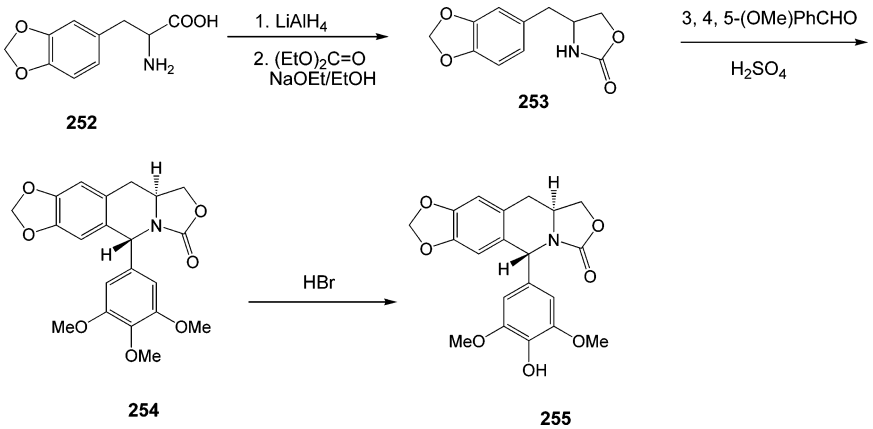
6.1. Research and Development of Schizandrin, DDB, and Derivatives

In the 1970s, the Chinese medicine wuweizi was found to exhibit activity that decreased SGPT and improved hepatopathic symptoms.[107−123] Further clinical and pharmacological studies indicated that gomisin A, gomisin J, and wuweizisu C showed a potent SGPT-lowering effect in animal models without prolonging barbital sleeping time. Studies to determine a mechanism of action for these compounds provided evidence that an inhibition of lipid peroxidation was mainly responsible for their antihepatotoxic and hepatoprotective activities as well as their stimulating effects on liver regeneration. (+)-Schizandrin (**42**) (Figure 4) and (+)-isoschizandrin **(43)** (Figure 4) act as antianxiety and neuroprotective agents. Furthermore, they also exhibit an inhibitory effect on stress-induced gastric ulceration.[66,231] Schizandra phenol **266** shows an antioxidant effect with an activity 10 times higher than that of vitamin E, which suggests that these lignans have the potential to be developed into new medicines. Xie and coworkers[165,166] have been studying the total synthesis of (±)-wuweizisu C (Scheme 7) and its isomers since 1974, and they have synthesized numerous biphenyl analogues.[232−237] Deuterium and tritium labeled DDB have been synthesized for PK studies in animals.[238] On the basis of chemical analysis and pharmacological studies,[239−244] DDB **(229)** is being developed as a new medicine[242] for hepatopathy. The biphenyl compound **267** derived from DDB by minor modification showed very potent SGPT lowering and anti-HBV activities. In consideration of the anti-HBV activity of some nucleosides and the high accumulated concentration of DDB in the liver, compound **268**,[245] having both nucleoside and biaryl characteristics, was designed and synthesized in the hope of finding a new dual-active medicine to treat hepatitis (Figure 15). To determine the optimal pattern of biphenyl substitution and the role of the cyclooctane ring, Chen and co-worker synthesized a series of hexahydroxybiphenyl derivatives and evaluated their biological activity. The results suggested that the relative position and type rather than the number of substituents on the biphenyl rings were of importance, while the cyclooctane ring might not be essential for anti-HIV activity.[127] Further structural modification of biphenyl compounds may produce more clinically relevant compounds.

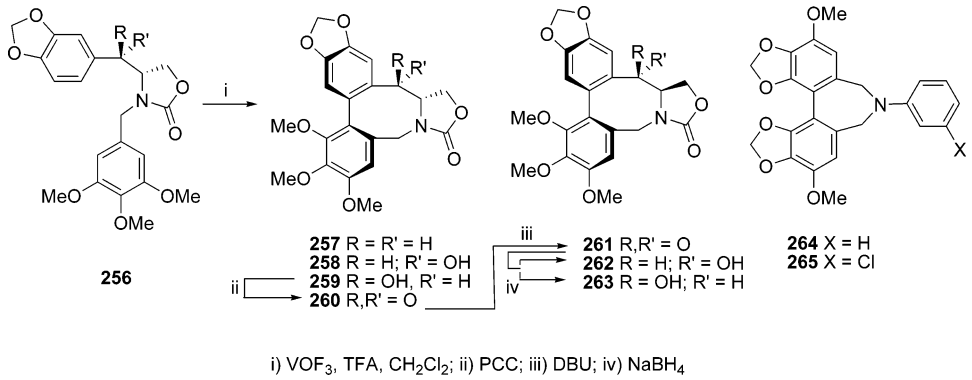
6.2. Research Perspectives of Heterocyclic Lignans

Heterocyclic lignans are lignan analogues in which a carbon atom of the lignan core structure is substituted by a non-carbon atom such as nitrogen or oxygen. Presently, most of the work in this area has focused on heteroatom substitution on the four-atom bridge linking the biaryl unit.[246,247] The rationale behind this interest is twofold. First, the presence of heteroatoms in lignan molecules may alter or improve pharmacological activity, leading to opportunities for new potential medicines. Second, from a

Scheme 39. Synthesis of Aza-podophyllotoxin Analogues



Scheme 40. Synthesis of Heterocyclic Lignans



synthetic point of view, hetero-lignans can be synthesized more efficiently than their carbon analogues due to the ease of forming carbon−heteroatom bonds as compared to carbon−carbon bonds. Most of the methodologies developed for the synthesis of the natural lignans can be applied to the synthesis of heterocyclic lignans. For instance, a hetero-lignan analogue 8′-azapodophyllotoxin, was efficiently synthesized[248] (Scheme 39).

Azasteganes **257**−**263** (Scheme 40), the aza-analogues of steganone, and dibenzoazepins **264** and **265**, stegane analogues, have also been prepared.[249−251] The hetero analogues of lignans will likely be an area of medicinal chemistry that continues to expand as the interest in the lignan natural products as therapeutic agents progresses.

7. Concluding Remarks

The synthetic methodologies for dibenzocyclooctadiene lignans can be divided into intermolecular and intramolecular biaryl couplings. The intermolecular strategies tend to require multiple linear steps, which, while classical, efficient, and reliable, generate the lignans in low overall yields. In contrast, the biomimetic inspired intramolecular biaryl coupling approach, in which two or more relatively advanced fragments are used to make a fully functionalized intermediate, often realizes a reduction in synthetic steps and an increase in overall yield. The intramolecular oxidative coupling reaction of non-phenolic compounds needs to be further improved. A series of oxidative coupling reagents can be employed for this purpose; however, unexpected results are often observed even with only minor structural modifications to the substrates. Therefore, further research in this regard is still required for the advancement of lignan chemistry.

Asymmetric syntheses of the dibenzocyclooctadiene lignans have received considerable attention in recent years, driven by reports of biological activity and the need for analogue synthesis in SAR studies.[206] An alternative strategy for obtaining optically active dibenzocyclooctadiene lignans is by chromatographic separation of diastereomeric acyclic biphenyl derivatives.[252−255] The pure diastereomers can be converted to the corresponding optically active dibenzocyclooctadiene lignans utilizing Xie's procedure.[165,166]

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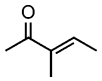
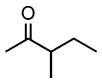
9. Abbreviations

CD	circular dichroism
CIP	Cahn−Ingold−Prelog
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDB	dimethyl-4,4′-dimethoxy-5,6,5′,6′-dimethylene dioxybiphenyl-2,2′-dicarboxylate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMA	*N*,*N*-dimethyl acetamide
DMAP	4-*N*,*N*-dimethylaminopyridine
DIBAL-H	diisobutylaluminum hydride
Hal	halogen
HBV	hepatitis B virus
LHDS	$(Me_3Si)_2NLi$
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorus triamide
IR	infrared
LDA	lithium diisopropylamide
Menth	1-menthyloxy
MS	mass spectrometry
NBS	*N*-bromosuccinimide
nm	nanometer
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PK	pharmacokinetics
RuTFA	ruthenium trifluoroacetate
SAR	structure−activity relationship
SGPT	serum glutamic pyruvic transaminase
TB	twist-boat
TBAF	tetrabutylammonium fluoride
TBC	twist-boat-chair
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TI	therapeutic index
Tr	triphenylmethyl or trityl
Ts	tosylate or tosyl
TTFA	thalium trifluoroacetate
UV	ultraviolet

angeloyl 

tigloyl 

isovaleroyl 

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