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Towards the Total Synthesis of Schisandrene: Stereoselective Synthesis of the Dibenzocyclooctadiene Lignan Core

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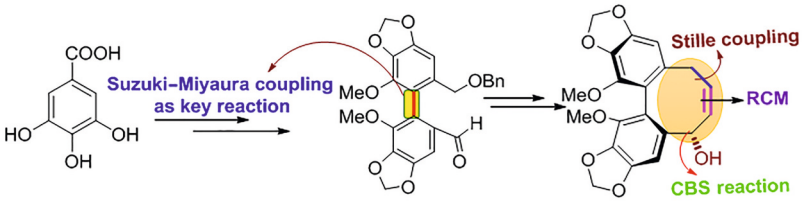

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Abstract A stereoselective synthesis of the dibenzocyclooctadiene lignan core of the natural product schisandrene is described. Starting from readily available gallic acid, the synthetic strategy involves Suzuki–Miyaura cross-coupling, Stille reaction, and ring-closing metathesis (RCM) in the reaction sequence. The required asymmetric center at C-7′ was established by an asymmetric reduction of a keto compound using the Corey–Bakshi–Shibata (CBS) catalyst. In our approach, the eight-membered ring was achieved by RCM for the first time.

Key words Suzuki–Miyaura cross-coupling, Stille reaction, ring-closing metathesis (RCM), schisandrene, dibenzocyclooctadiene lignan

Lignans are an important class of plant-derived phenols which were formed biosynthetically from two cinnamic acid (phenylpropanoid) skeletons through dimerization.[1] Among the different families of lignans, the dibenzocyclooctadiene lignans exhibit a wide range of biological activities such as sedation, hypnotic activity, anticonvulsant and neuroprotective effects, liver protection, calcium antagonism, anti-oxidative effects, a senility-delaying effect, promotion of osteoblastic formation and differentiation.[2] A significant number of these lignans exist in species of the *Schisandraceae* family[3] which were well represented in the traditional medicines of China, Korea, and Japan.[4] Structurally, dibenzocyclooctadiene lignans contain functionalized biaryl rings that are connected through C-2 and C-2′. Due to their fascinating structural features derived from the substitution pattern of the biaryl unit and configuration of stereogenic centers, along with the octadiene ring system, these targets have attracted considerable interest among organic chemists. As a consequence, the majority of synthetic research on these lignans has focused in developing new methods for forming the biaryl linkage of the lignan core structure.

As part of our ongoing research program focused on the chemistry and biology of dibenzocyclooctadiene lignans, we have recently isolated a wide variety of dibenzocyclooctadiene lignans with different substitutions on the aromatic rings from the fruits of *Schisandra chinensis* and *Schisandra grandiflora* and studied their biological profiles including their antioxidant and AGE inhibitory activities.[5] The potent biological activity of schisandrene (**1**, Figure 1),[6] coupled with its meagre availability from the natural source, prompted us to develop a general approach for the stereocontrolled synthesis of the core for extended biological studies. Therefore, we report herein our approach towards the first stereoselective synthesis of the schisandrene core utilizing the Suzuki–Miyaura cross-coupling, Stille reaction, and ring-closing metathesis (RCM) as key reactions in the synthetic sequence.

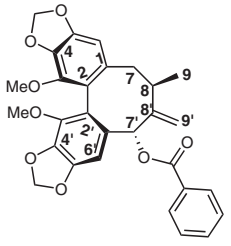
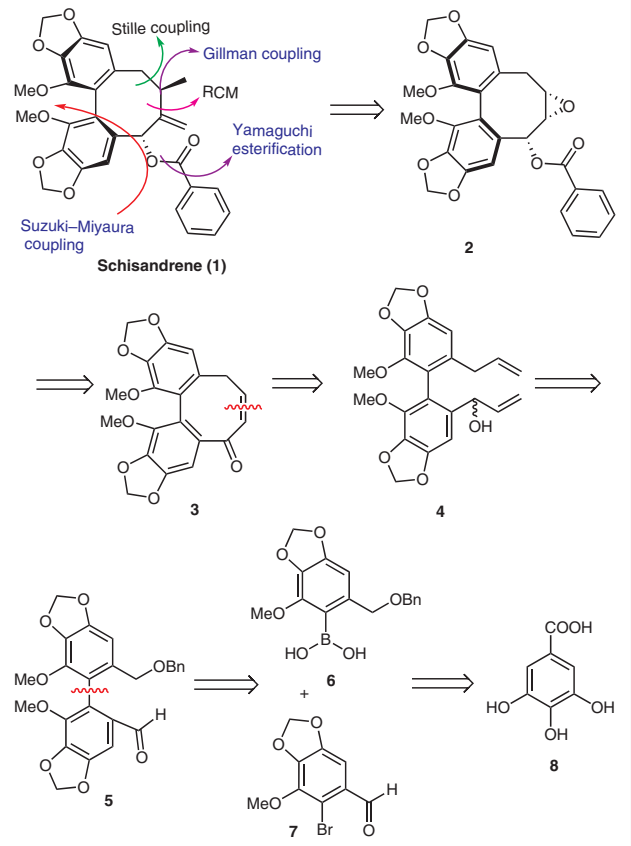


Figure 1 Structure of schisandrene (**1**)

As shown in Scheme 1, we envisaged that schisandrene (**1**) could be obtained from **2** through Sharpless epoxidation, Gilman coupling, C-1 Wittig olefination, and Yamaguchi esterification. The intermediate **2** can be the advanced intermediate for **1**, which can be readily accessed from **3**, which is further disconnected between C_8 and $C_{8'}$, identifying **4** as the RCM precursor. Further disconnections at the biaryl linkage in key fragment **5** gives Suzuki–Miyaura

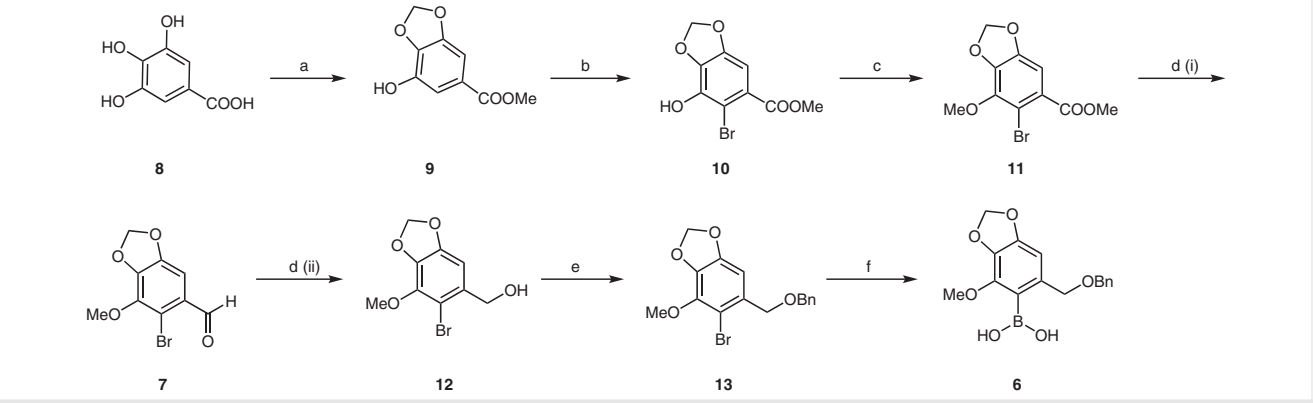


Scheme 1 Retrosynthetic analysis of schisandrene (**1**)

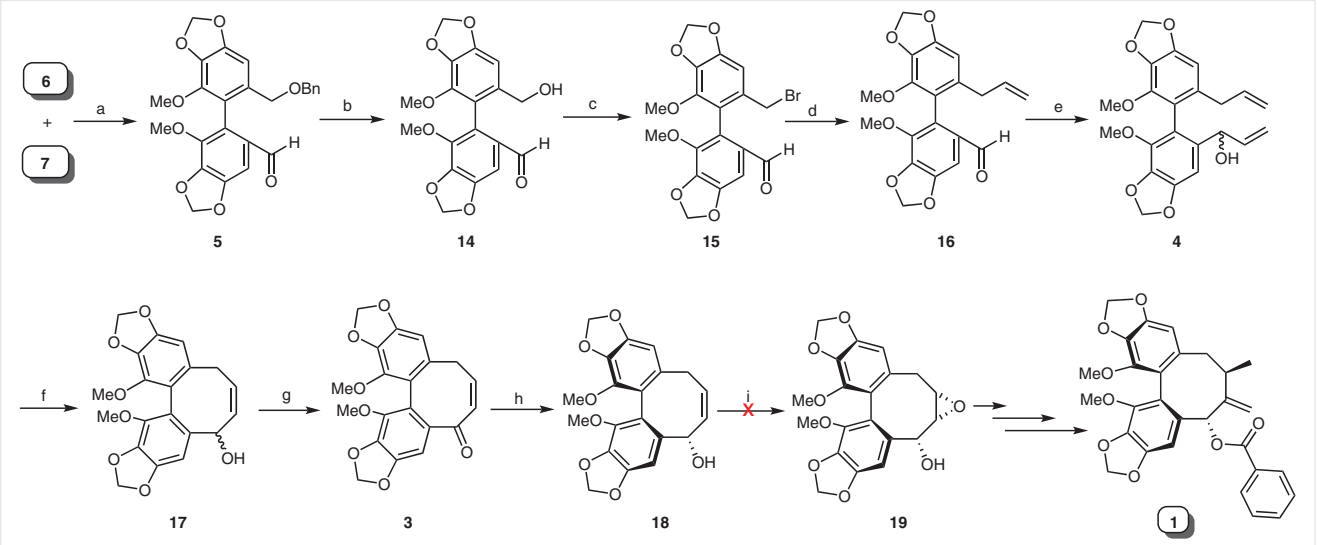
precursors **6** and **7**, which in turn can be accessed from gallic acid (**8**). Thus, our synthetic strategy relies on the construction of the biaryl fragment utilizing the Suzuki–Miyaura coupling reaction and the asymmetric center at C-7′ in **2** is to be introduced by an asymmetric reduction of a keto compound **3** using the CBS reaction.

As outlined in Scheme 2, the synthesis started with readily available gallic acid (**8**), which was converted into its corresponding methyl ester,[7] followed by protection of two phenolic hydroxy groups by using CH_2I_2 and K_2CO_3 in DMF at 110 °C to give methylenedioxy ester (**9**) in 58% yield.[8] The regioselective bromination of **9** with freshly recrystallized *N*-bromosuccinamide (NBS) gave brominated compound **10** exclusively[9] in 85% yield, in which the hydroxyl group was subsequently methylated using MeI and K_2CO_3 in DMF under reflux to afford **11**.[10] The ester functionality in **11** was converted into an aldehyde using DIBAL-H in dry DCM at –78 °C[11] to give **7** which is one of the precursors for the Suzuki–Miyaura coupling. We then addressed the preparation of its counterpart for the Suzuki–Miyaura coupling. Thus, reduction of aldehyde **7** using $NaBH_4$ gave its corresponding alcohol **12**[12] in 98% yield, in which the primary alcohol was protected with BnBr to give its benzyl ether **13**[13] in 95% yield. Finally, benzyl-protected compound **13** was treated with *n*-BuLi, and triisopropyl borate at –78 °C in dry THF to give its corresponding boronic acid derivative **6**[14] in 75% yield as a white solid.

With both compounds **6** and **7** in hand, we next planned to synthesize the key coupling fragment **5** through Suzuki–Miyaura coupling. Therefore, as shown in Scheme 3, boronic acid **6** and bromoaldehyde **7** were subjected to Pd-mediated Suzuki–Miyaura cross-coupling with $Pd_2(dba)_3$ (1 mol%) and K_3PO_4 in the presence of S-Phos ligand in a sealed tube to give the sterically hindered biaryl **5**[15] in 82% yield. Removal of the benzyl group in **5**[16] using Pd/C (5% mol on activated carbon) gave primary alcohol **14**, which was then subjected to bromination with CBr_4 and Ph_3P in dry DCM at –15 °C to give bromo compound **15**,[17] which was immediately subjected to Stille reaction[18] with CH_2=CHSn[CH_3 ($CH2)_3$]$_3$, $Pd_2(dba)_3$, and TFP as ligand to give **16** in 78% yield. Compound **16** was subjected to Grignard reaction[19] with vinyl magnesium bromide to give in 85% yield the corresponding secondary alcohol **4**, which was subjected to



Scheme 2 *Reagents and conditions*: (a) i. MeOH, H_2SO_4, reflux, 12 h, 70%; ii. CH_2I_2, K_2CO_3, DMF, 110 °C, 8 h, 58%; (b) NBS, THF, 25 °C, 1 h, 85%; (c) MeI, K_2CO_3, acetone, rt, 5 h, 90%; (d) i. DIBAL-H, DCM, –78 °C, 30 min, 95%; ii. $NaBH_4$, MeOH, 0 °C to rt, 1 h, 98%; (e) NaH, BnBr, DMF, 12 h, 95%; (f) *n*-BuLi, dry THF, triisopropyl borate, –78 °C, 12 h, 75%.



Scheme 3 *Reagents and conditions*: (a) $Pd_2(dba)_3$, S-Phos, K_3PO_4, toluene, 110 °C, 12 h, 82%; (b) Pd/C (5 mol% on activated carbon), EtOAc, rt, 4 h 80%; (c) CBr_4, Ph_3P, CH_2Cl_2, –15 °C to rt, 1 h, 80%; (d) CH_2=$CHSn[CH_3(CH_2)_3]_3$, $Pd_2(dba)_3$, TFP, NMP, toluene, 80 °C, 8 h, 78%; (e) vinylmagnesium bromide, dry THF, –15 °C, 2 h, 85%; (f) Grubbs II (25 mol%), CH_2Cl_2, reflux, 20 h, 89%; (g) MnO_2, DCM, 4 h, 90%; (h) (*s*)-CBS, BH_3·DMS, dry THF, –78 °C to rt, 2 h, 85%; (i) $Ti(OiPr)_4$, (–)-DET, MS 4 Å and *t*-BuOOH, dry DCM, –20 °C, 12 h.

RCM[20] using the Grubbs second-generation catalyst (10 mol%) in dry deoxygenated DCM at reflux to yield the eight-membered RCM product **17** in 89% yield. Subsequent oxidation of **17** with MnO_2 gave keto compound **3**[21] in 90% yield. Finally, **3** was subjected to Corey–Bakshi–Shibata (CBS) reduction[22] to give **18**[23] in 85% yield with good enantiomeric excess (*ee* 98%, determined by chiral HPLC).

Once compound **18** was prepared, we planned to carry out a Sharpless asymmetric epoxidation followed by ring opening with a methyl Grignard and subsequent Wittig olefination to complete the total synthesis of schisandrene (**1**). Thus, initially, compound **18** was subjected to a Sharpless asymmetric epoxidation[24] with $Ti(OiPr)_4$, (–)-DET and *t*-BuOOH in dry DCM in an attempt to obtain the corresponding epoxide **19**, but no reaction occurred. Therefore we considered changing the (–)-DIPT ratio (Table 1). However, in all cases the starting material was completely recovered. Alternatively, we also tried a Jacobsen–Katsuki asymmetric epoxidation with (*S*,*S*)-(salen)MnCl used as catalyst and various oxidants such as 10% aq NaOCl, *m*-CPBA, and PhIO[25] (Table 1), but all reaction conditions failed to give the desired product. The reason may be due to the perpendicular orientation of the two biphenyl rings, which makes the system too sterically hindered for the reaction to proceed.

In summary, utilizing high-yielding chemical transformations, we have delineated a stereoselective and convergent approach toward the synthesis of the backbone segment of schisandrene. The establishment of the dibenzocyclooctadiene core serves the dual purpose of providing an advanced intermediate toward the synthesis of schisandrene and an entry into an array of analogues through the attachment of various side chains at C-7′.

Table 1 Various Reaction Conditions for Epoxidation of **18**

Entry	Conditions	Result
1	$Ti(OiPr)_4$/(–)-DET/*t*-BuOOH	no reaction, starting material recovered
2	$Ti(OiPr)_4$/(–)-DIPT/*t*-BuOOH	no reaction, starting material recovered
3	(*S*,*S*)-(salen)MnCl, 10% aq NaOCl	sluggish
4	(*S*,*S*)-(salen)MnCl, *m*-CPBA	sluggish
5	(*S*,*S*)-(salen)MnCl, PhIO	sluggish

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Supporting Information

Supporting information (experimental procedures and spectroscopic data for all the intermediate compounds) for this article is available online at https://doi.org/10.1055/s-0036-1591539.

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(23) **Synthetic Procedure for 18**
A solution of *S*-(−)-2-methyl-CBS-oxazaborolidine (1 M solution in toluene, 4.9 mmol) in THF (5 mL) was treated with BH_3·DMS (2.0 M solution in THF, 0.2 mL, 04.1 mmol) at 0 °C for 15 min. A solution of enone **3** (0.150 g, 4.1 mmol) in THF (8 mL) was added slowly at −78 °C, and the reaction mixture was stirred for 1 h maintaining the temperature. After the reaction was complete, saturated NH_4Cl solution was added. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 10% EtOAc/hexane to give compound **18** (0.128 g, 85%, *ee* 98%) as a colorless liquid: $[\alpha]_D^{25}$ −2.53 (*c* 4.8, $CHCl_3$). IR (KBr): ν_{max} = 3562, 2972, 2920, 2847, 1586, 1448, 1227, 1107, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.73 (s, 1 H), 6.33 (s, 1 H), 5.93–5.84 (m, 5 H), 5.77–5.70 (m, 1 H), 4.88–4.82 (m, 1 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 2.93–2.86 (m, 1 H), 2.76–2.70 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.7, 149.4, 140.0, 139.6, 135.5, 135.4, 134.8, 134.7, 130.0, 129.2, 121.1, 119.9, 103.5, 101.1, 100.9, 98.8, 68.9, 59.4 (2 C), 31.9 ppm. HRMS: *m/z* calcd for $C_{20}H_{20}O_7$: 371.1052; 371.1048 $[M + H]^+$.

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