Concise Synthesis of Arylnaphthalene Lignans by Regioselective Intramolecular Anionic Diels–Alder Reactions of 1,7-Diaryl-1,6-diynes

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Abstract: Total synthesis of phyllamycin A and C, justicidin B, and retrojusticidin B from simple arylalkynyl alcohols and (3,4-methylenedioxyphenyl)propynal was accomplished in 4–5 steps by employing an intramolecular anionic Diels–Alder reaction as the key step.

Key words: lignan, natural products, total synthesis, Diels–Alder reaction, carbanions

Arylnaphthalene lignans are widely occurring natural products isolated from plant species. They consist of various alkoxy-substituted arylnaphthalenes with regioisomerically fused lactones (**A** and **B** in Figure 1) and exhibit a broad range of biological activities (Figure 1).[1] As a result, they have attracted attention as lead compounds for novel drugs. Interestingly, arylnaphthalene lignans with regioisomerically fused lactones exhibit completely different biological activity. For example, justicidin B (**3**) inhibit calcium release from fetal long-bone cultures[2] and exhibits antiviral activity.[3] Meanwhile, the corresponding retrofused lactone isomer, retrojusticidin B (**4**) exhibits inhibitory activity against HIV-1 reverse transcriptase.[4] Therefore, it is important to develop a highly regioselective method for the construction of the arylnaphthalene and fused lactone moieties in arylnaphthalene lignans.

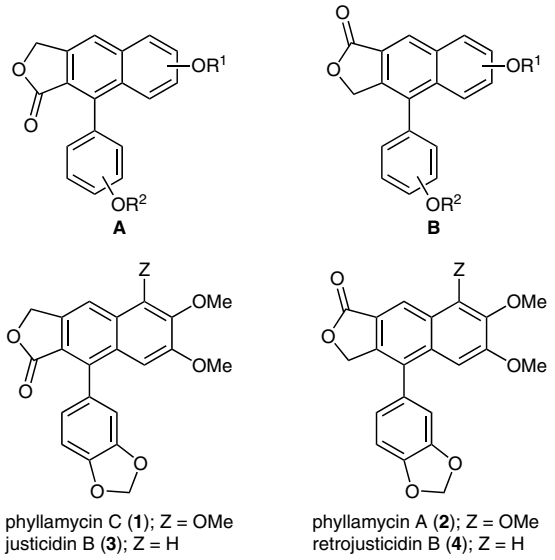
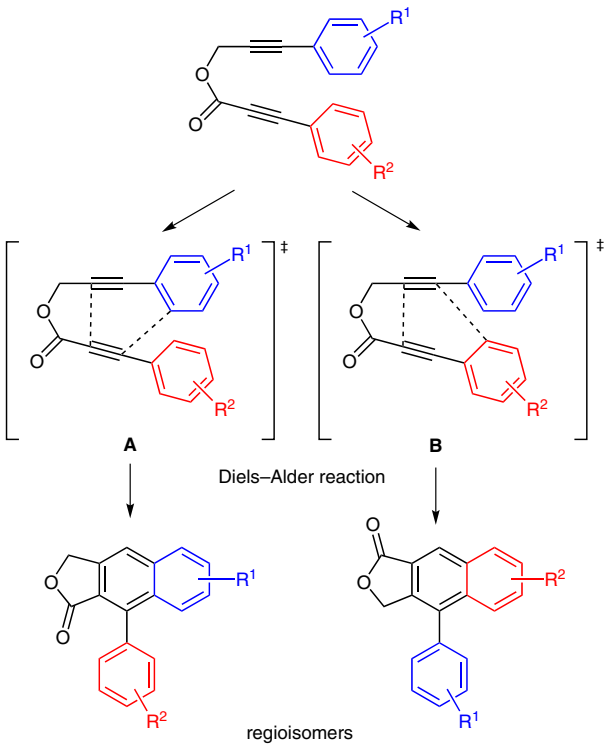


Figure 1 Representative examples of arylnaphthalene lignan natural products

Many synthetic routes to arylnaphthalene lignans have been developed, such as Stobbe/Claisen condensations,[5] rearrangement of aryl(*gem*-dihalocyclopropyl)methanols,[6] nucleophilic addition of aryl lithiums to naphthyloxazolines,[7] conjugate addition–aldol reactions,[8] Pd-catalyzed [2+2+2] cocyclization of arynes and diynes,[9] gold-catalyzed intramolecular sequential electrophilic addition and benzannulation,[10] and Diels–Alder reactions.[11,12] Among them, the intramolecular Diels–Alder reaction of the 1,7-diaryl-1,6-diyne system by Klemm's group[11a] and Stevenson's group[11b–d] is one of the most straightforward and efficient approaches to arylnaphthalene lignans (Scheme 1). However, in this system, the substituted phenylethynyl units can serve as both the diene and dienophile in the Diels–Alder reaction; thus two regioisomers may arise through transition state **A** and **B**



Scheme 1 Diels–Alder approach for the synthesis of arylnaphthalene lignans using 1,7-diaryl-1,6-diyne

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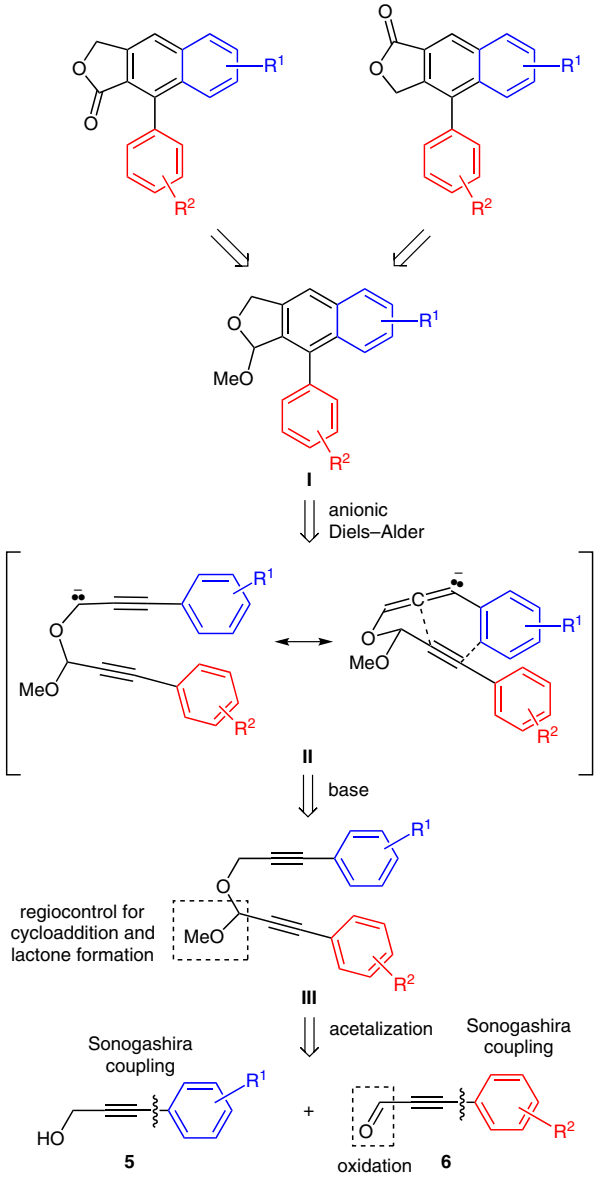
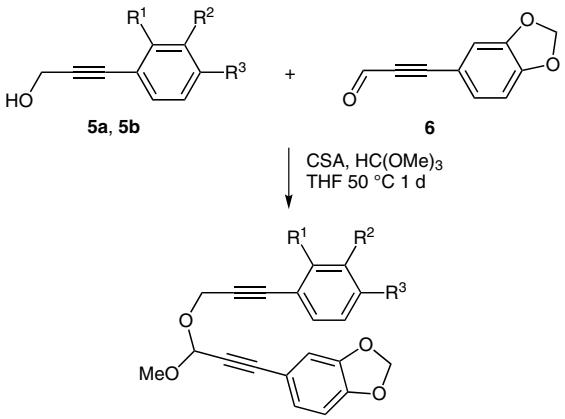
in Scheme 1. Moreover, if a diyne with an unsymmetric phenyl substituent is used, two additional regioisomers may form. This lack of selectivity makes the intramolecular Diels–Alder approach difficult to apply to the synthesis of differentially substituted arylnaphthalene lignans. In this study, we present a novel process for the selective synthesis of differentially substituted arylnaphthalene lignans by the intramolecular anionic Diels–Alder reaction (IMADA)[13] of 1,7-diaryl-1,6-diynes containing an acetal linker.



Scheme 2 Synthetic plan for the preparation of arylnaphthalene lignans by the anionic Diels–Alder reaction of 1,6-diaryldiynes

Our synthetic plan is illustrated in Scheme 2. Both isomeric arylnaphthalene lignans with regioisomeric fused lactones would be synthesized by the oxidation of **I**. The substituted arylnaphthalene ring of **I** would be constructed via the IMADA of an anion containing the activated diene **II**, which would be formed by the deprotonation of the propargylic position in **III**. The cycloaddition precursor **III** would be obtained from the mixed acetal condensation of aldehyde **6** with alcohol **5**. This acetal moiety would be expected to work as the key for controlling the regioselectivity of the IMADA and the regioselective construction of the lactone. The requisite alcohols **5** are easily synthesized by the Sonogashira coupling of the corresponding aryl halides with 2-propyn-1-ol, and aldehyde **6** is available by the oxidation of arylalkynyl alcohols prepared by Sonogashira coupling reactions.[14]

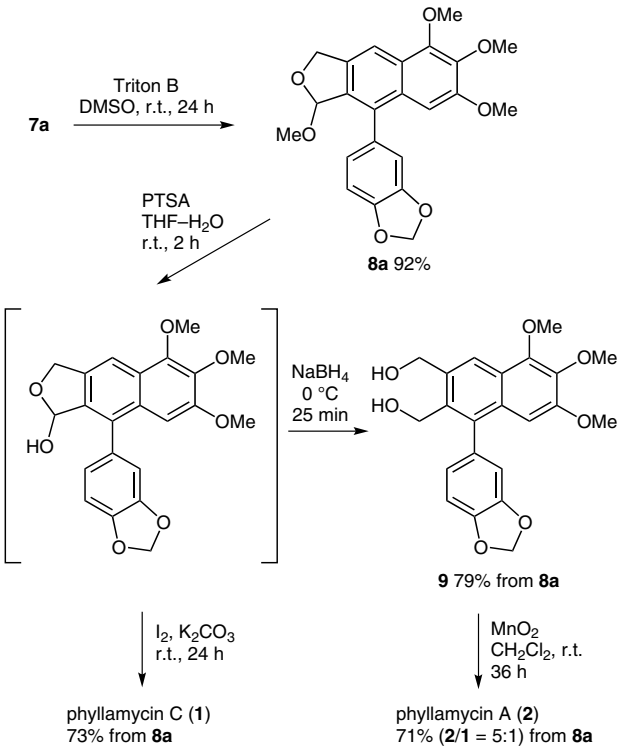
The synthesis of the IMADA precursors is depicted in Scheme 3. In preliminary experiments, the acid-catalyzed acetalization of (3,4-methylenedioxyphenyl)propynal (**6**) with an excess of the corresponding alcohols **5a** and **5b** in the presence of trimethyl orthoformate gave **7a** and **7b**, respectively, in good yields (**7a**: 79%, **7b**: 63%) based on the recovered dimethyl acetal of **6** (72% for **7a**, 37% for **7b**). The recovered alcohols **5a** and **5b** and the dimethyl acetal of **6** can be reused for the synthesis of **7a** and **7b**.



Scheme 3 Synthesis of cycloaddition precursors **7a** and **7b**

With the cycloaddition precursors in hand, we attempted the synthesis of phyllamycin C (**1**) and phyllamycin A (**2**, Scheme 4). These compounds were isolated from *Phyllanthus myrtifolius* in 1995 and are relatively new arylnaphthalene lignans.[15] The IMADA of **7a** smoothly proceeded following treatment with 120 mol% $(C_6H_5CH_2)(CH_3)_3N^+OH^-$ (Triton B) in DMSO at room temperature and gave the desired product **8a** in excellent yield.[16] To synthesize **1** from **8a**, we examined the transformation of the acetal moiety of **8a** to the lactone. The acidic hydrolysis of **8a** to the hemiacetal followed by oxidation using iodine under basic conditions gave **1** in 73% yield. Next, we attempted to synthesize **2**, which is the lactone regioisomer of **1**. After the acidic hydrolysis of **8a**, the resultant hemiacetal was immediately reduced to the corresponding diol with $NaBH_4$. The obtained crude diol was then oxidized to the lactone with manganese dioxide (MnO_2). Oxidation preferentially occurred at the less sterically hindered alcohol to provide a 5:1 mixture of **2** and

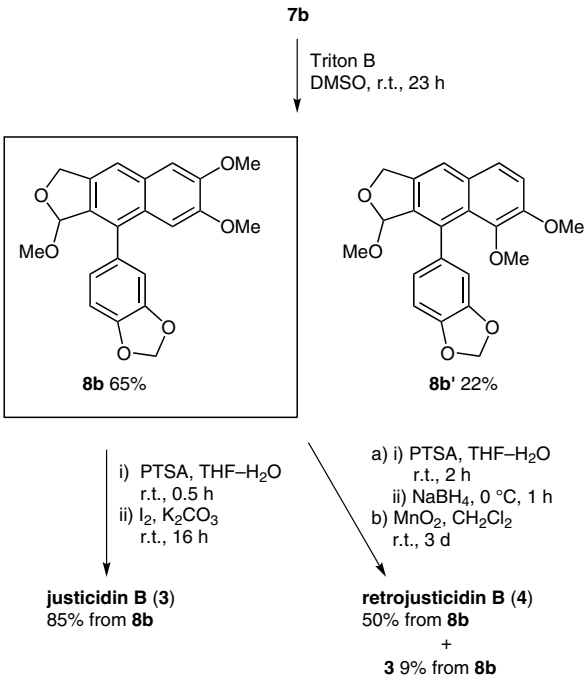
1 in 71% combined yield. The mixture was carefully purified by column chromatography to give pure **2**. All ^{1}H NMR and ^{13}C NMR data for synthesized **1** and **2** were identical to the data reported in the literature for the natural compounds.[15a,17,18] Thus, we achieved the first total synthesis of **1** and **2**.



Scheme 4 Synthesis of phyllamycin C (**1**) and phyllamycin A (**2**)

Encouraged by these results, we next attempted to synthesize **3** and **4** (Scheme 5). The IMADA of **7b** provided a mixture of the two differently substituted arylnaphthalenes **8b** and **8b′** in high yield (**8b**: 65% yield, **8b′**: 22% yield). These two products must have arisen from the reaction of two different dienes containing an allene moiety generated as the result of the isomerization of the alkyne and the contiguous π bond of the 3,4-dimethoxyphenyl substituent in **7b**. After the chromatographic separation of these two products, the transformation of **8b** into **3** and **4** was examined. Following the same transformation procedure as used for the synthesis of **1** and **2**, we succeeded in synthesizing **3** in 85% from **8b** in one step and **4** in 50% isolated yield from **8b** in two steps. All ^{1}H NMR and ^{13}C NMR data for synthesized **3** and **4** were identical to the data reported in the literature.[5c,19,20]

In conclusion, we demonstrated the concise total synthesis of 4-arylnaphthalene lignans using IMADA as the key transformation. Our synthetic process requires only 4–5 steps from easily synthesizable arylalkynyl alcohols and arylalkynyl aldehydes. It is applicable to the synthesis of a wide variety of arylnaphthalene lignan natural products simply by changing the combination of starting alcohols and aldehydes.



Scheme 5 Synthesis of justicidin B (**3**) and retrojusticidin B (**4**)

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(16) **General Procedure for the Intramolecular Anionic Diels–Alder Reaction of 7a**
To a solution of **7a** (444 mg, 1.08 mmol) in DMSO (6 mL) was added Triton B (40 wt% in MeOH) (0.6 mL, 120 mol%) at r.t. The mixture was stirred at r.t. for 24 h. After completed the reaction, sat. NH_4Cl aq solution was added to this and extracted with hexane–EtOAc (3:1). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by a rotary evaporator. The residue was purified by column chromatography to afford cycloadduct **8a** (408 mg, 92%).
(17) **Analytical Data for Phyllamycin C (1)**
Mp 193.8–194.3 °C; R_f = 0.57 (1:1 hexane–EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 4.02 (s, 3 H), 4.08 (s, 3 H), 5.412 (s, 1 H), 5.416 (s, 1 H), 6.05 (d, 1 H, *J* = 1.7 Hz), 6.11 (d, 1 H, *J* = 1.7 Hz), 6.82 (dd, 1 H, *J* = 1.6, 7.7 Hz), 6.85 (d, 1 H, *J* = 1.6 Hz), 6.93 (s, 1 H), 6.97 (d, 1 H, *J* = 7.7 Hz), 8.13 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.8, 61.1, 61.5, 68.2, 101.2, 102.3, 108.1, 110.5, 114.0, 120.0, 123.4, 128.25, 128.33, 130.4, 138.6, 139.7, 143.1, 147.3, 147.5, 147.6, 153.4, 169.7. IR (KBr): 2940, 1768, 1476, 1227, 1058 cm^{-1}.
Analytical Data for Phyllamycin A (2)
Mp 231.4–231.3 °C. R_f = 0.63 (3:1 hexane–EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 3.99 (s, 3 H), 4.10 (s, 3 H), 5.21 (s, 2 H), 6.07 (d, 1 H, *J* = 1.4 Hz), 6.10 (d, 1 H, *J* = 1.4 Hz), 6.80–6.83 (m, 2 H), 6.88 (s, 1 H), 6.98 (d, 1 H, *J* = 8.2 Hz), 8.74 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.8, 61.1, 61.6, 69.3, 100.2, 101.4, 108.9, 109.5, 120.5, 120.8, 122.7, 125.5, 129.6, 131.9, 132.9, 139.2, 141.1, 147.7, 148.3, 149.1, 155.6, 171.4. IR (KBr): 2941, 1767, 1482, 1234, 1027 cm^{-1}.
Analytical Data for Justicidin B (3)
R_f = 0.23 (1:1 hexane–EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 4.05 (s, 3 H), 5.380 (s, 1 H), 5.384 (s, 1 H), 6.05 (d, 1 H, *J* = 1.6 Hz), 6.10 (d, 1 H, *J* = 1.6 Hz), 6.83 (dd, 1 H, *J* = 8.0, 1.7 Hz), 6.86 (d, 1 H, *J* = 1.7 Hz), 6.97 (d, 1 H, *J* = 8.0 Hz), 7.11 (s, 1 H), 7.19 (s, 1 H), 7.70 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.8, 56.0, 68.0, 101.2, 106.0, 106.1, 108.2, 110.6, 118.2, 118.6, 123.5, 128.5, 128.9, 133.2, 139.5, 139.7, 147.6 × 2, 150.2, 151.9, 169.8. IR (KBr): 2938, 1754, 1506, 1238, 1158, 1036 cm^{-1}.
Analytical Data for Retrojusticidin B (4)
Mp 224.0–223.5 °C; R_f = 0.40 (1:1 hexane–EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 4.05 (s, 3 H), 5.21 (s, 2 H), 6.07 (d, 1 H, *J* = 1.4 Hz), 6.11 (d, 1 H, *J* = 1.4 Hz), 6.82–6.85 (m, 2 H), 6.99 (d, 1 H, *J* = 8.5 Hz), 7.09 (s, 1 H), 7.29 (s, 1 H), 8.30 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.8, 55.9, 69.3, 101.4, 104.1, 107.7, 108.9, 109.5, 121.4, 122.7, 124.0, 129.7, 129.9, 131.6, 131.9, 137.9, 147.6, 148.3, 150.2, 152.2, 171.3. IR (KBr) 2923, 1751, 1505, 1231 cm^{-1}.

