Silver-Catalyzed One-Pot Synthesis of Arylnaphthalene Lactone Natural Products

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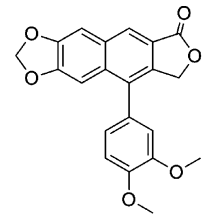
Naturally occurring arylnaphthalene lactone lignans have demonstrated a variety of valuable medicinal chemistry properties and have therefore been of continued interest to drug discovery research. Our group has demonstrated a silver-catalyzed one-pot synthesis of the arylnaphthalene lactone core using carbon dioxide, phenylpropargyl chloride, and phenylacetylene. This new approach has been employed in the synthesis of six arylnaphthalene lactone natural products: retrochinensin (**1**), justicidin B (**2**), retrojusticidin B (**3**), chinensin (**4**), justicidin E (**5**), and taiwanin C (**6**). Additionally, an arylnaphthalene lactone regioisomer was isolated (**9**), which we refer to as isoretrojusticidin B.

Arylnaphthalene lactones are a subgroup of the lignan class of molecules that are characterized by a phenylpropanoid dimer motif. Many of these arylnaphthalene lignans are components of traditional herbal remedies and have received increasing attention over the past several decades owing to their cytotoxic,[1] antiviral,[2] fungicidal, antiprotozoal,[3] and antiplatelet[4,5] activities in cell-based assays. New natural products within this class of compounds continue to be reported,[6,7] and ongoing studies have led to a better understanding of their biosynthetic origins with the hopes of finding a viable biotechnological production methodology.[8−11] Additionally, the desire to access these molecules for further investigation has led to the development of many successful synthetic approaches for arylnaphthalene lignans, some dating back to as early as 1895.[12−18] In an effort to explore new synthetic options for accessing this class of molecules, our group has recently demonstrated a silver-catalyzed, multicomponent approach to access the arylnaphthalene lactone core.[19,20] Here this multicomponent methodology was applied to the synthesis of the naturally occurring arylnaphthalene lignans retrochinensin (**1**), justicidin B (**2**), retrojusticidin B (**3**), chinensin (**4**), justicidin E (**5**), and taiwanin C (**6**).

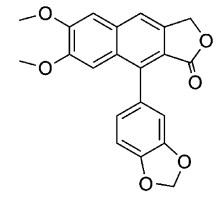
Results and Discussion

Similar to the approach first explored by Klemm et al.,[21,22] our approach utilizes an intramolecular cycloaddition reaction of a 1,6-diyne ester to generate the arylnaphthalene core. The advantage of the present work, however, is that it further incorporates a methodology developed by Inoue et al.[23] that allows for the diyne ester to be generated in situ from readily prepared acetylene precursors using catalytic silver iodide, potassium carbonate, and carbon dioxide at 1 atm. These conditions allow for the formation of a phenylpropargylic acid intermediate from phenylacetylene that can then participate in a nucleophilic attack on a phenylpropargyl halide, thus generating the diyne ester. Performing this reaction in a suitable solvent, such as *N*,*N*-dimethylacetamide (DMA), at elevated temperature (100 °C) further allows for intramolecular cyclization to take place, thus generating the desired aryl naphthalene lactone.

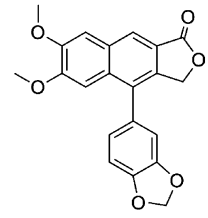
In efforts to optimize this methodology using model systems it was observed that the selection of chloride as the leaving group (LG) of the phenylpropargyl halide component offered higher conversion than when performed with phenylpropargyl bromide, likely due to the greater stability of the chloride under the reaction conditions. A variety of other LGs were investigated as well, including tosylate, triflate, and acetate; however, all of these gave low yields or no product all. These results suggested that the driving force of the silver halide interaction is critical to the success of the reaction.



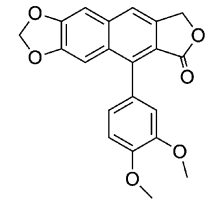
retrochinensin (**1**)



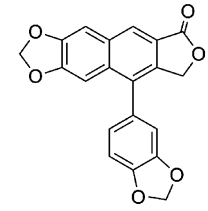
justicidin B (**2**)



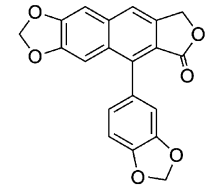
retrojusticidin B (**3**)



chinensin (**4**)



justicidin E (**5**)



taiwanin C (**6**)

In addition to substrate selection, the use of a phase transfer catalyst (PTC) was required to promote desirable conversion rates. Potassium carbonate and silver halides are largely insoluble in DMA and thus require the presence of a PTC to participate effectively under these conditions. Although several ammonium- and phosphonium-based PTC reagents were found to be reasonably effective, 18-crown-6 ether appeared to give the best results in this capacity.

Using the most favorable conditions observed in our model systems, it was envisioned that we could access a variety of naturally occurring arylnaphthalene lactones beginning with known starting materials. Treating 3,4-methylenedioxyphenylpropargyl alcohol and 3,4-dimethoxyphenylpropargyl alcohol with thionyl chloride in DMA generated the desired phenylpropargyl chlorides **7a** and **7b** in 96% and 84% yields, respectively. These substituted phenylpropargyl chlorides, together with phenylacetylenes **8a** and **8b**, could then be taken on to the multicomponent tandem coupling reaction in the permutations described in entries 1−3 in Scheme 1.

The overall yield from entry 2 in Scheme 1 was comparable to what was observed in the model systems, whereas the yields from

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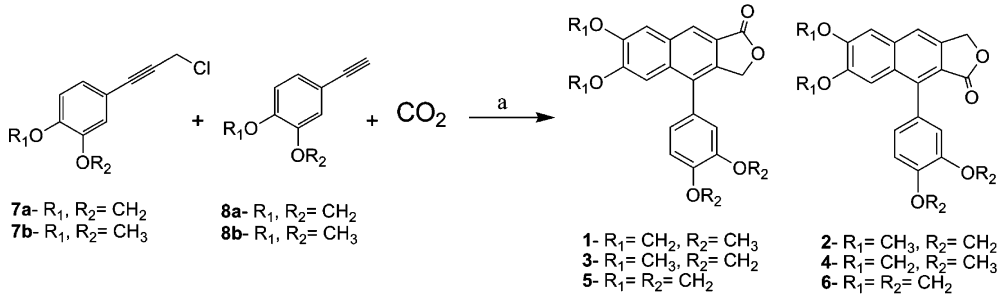
Scheme 1. Preparation of Arylnaphthalene Lactones **1**−**6** and Respective Isolated Yields[a]

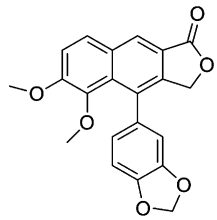


Entry	Starting Materials	Isolated Products	Yield
1	**7b, 8a**	retrochinensin (**1**)	16%
		justicidin B (**2**)	16%
2	**7a, 8b**	retrojusticidin B (**3**)	31%
		chinensin (**4**)	26%
		isoretrojusticidin B (**9**)	0.6%
3	**7a, 8a**	justicidin E (**5**)	18%
		taiwanin C (**6**)	14%

[a] Reagents and conditions: (a) $SOCl_2$, DMA; (b) K_2CO_3, 18-crown-6, 4 Å molecular sieves, DMA, 100 °C.

entries 1 and 3 were slightly lower than expected. These results can likely be attributed to instability of phenylacetylene **8a** under the reaction conditions. Indeed we found that this compound required storage at 0 °C away from light to prevent degradation. Regardless, we were able to obtain significant quantities of all of the desired natural products with this fairly abbreviated synthetic route.

Although two predominant regioisomers were formed in each of these reactions, it is mechanistically feasible to expect a small percentage of regioisomers with substitution on the 7 and 8 positions of the naphthalene core. There was, in fact, evidence in entries 1 and 3 of the presence of these regioisomers by ^{1}H NMR, but they were present in only trace quantities and isolation was not deemed practical based on the scale at which we were working. However, with regard to entry 2, it was possible to isolate regioisomer **9** (as shown), which we provisionally refer to as isoretrojusticidin B. To our knowledge this compound has been reported only once previously as a semisynthetic derivative of a natural extract.[24] This would then constitute the first fully synthetic preparation of this compound.



isoretrojusticidin B (**9**)

Chromatographic separation was problematic using an isocratic solvent system and thus required a continuous gradient from 10% to 40% ethyl acetate in heptanes to achieve separation. Where mixed fractions were encountered, the desired product could often be obtained through simple trituration using heptane with a minimal amount of ethyl acetate, followed by filtration.

Despite the slightly attenuated yields of the multicomponent step, this reaction can generate fully elaborated arylnaphthalene lactones from readily accessible, if not commercially available, phenylacetylene precursors in a single, catalytic step. This suggests that this methodology could be used to generate a broad range of arylnaphthalene lactones and closely related analogues, both naturally occurring and otherwise, in a parallel or high-throughput fashion, thereby allowing for rapid exploration of the properties of this class of compounds.

Experimental Section

General Experimental Procedures. NMR spectra were recorded on Bruker Avance 400 and 500 MHz spectrometers as specified. ^{1}H and ^{13}C NMR spectra were measured and reported in ppm (δ) by using the $CDCl_3$ residual solvent peaks (δ H 7.27 and δ C 77.2, respectively) as internal standards. ESMS and FT-ICR were performed on a Q-TOF Micro (Waters Corporation, Milford, MA) instrument and a 9.4T Fourier transform ion cyclotron resonance MS instrument (Bruker Daltonics, Billerica, MA), respectively. Chromatographic separations were carried out by conventional column chromatography on Siliflash F60 silica gel (230−450 mesh).

3,4-Methylenedioxyphenylpropargyl Chloride (7a). DMA (40 mL) and 3,4-methylenedioxyphenylpropargyl alcohol (1.7 g, 9.6 mmol) were combined in a round-bottom flask under N_2 and cooled in an ice bath while stirring. Thionyl chloride (1.1 mL, 14.5 mmol) was then added dropwise. The solution was allowed to stir for 3 h while warming to rt. Once the reaction was complete as indicated by TLC, the mixture was quenched with H_2O, neutralized with $NaHCO_3$, extracted three times with EtOAc, dried with Na_2SO_4, filtered, and concentrated. The crude mixture was purified by column chromatography using 1:12 EtOAc/hexane to afford 1.8 g (96%) of **7a** as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (dd, J = 1.4, 8.0, 1H), 6.91 (d, J = 1.2, 1H), 6.78 (d, J = 8.0, 1H), 6.00 (s, 2H), 4.38 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 147.8, 127.1, 115.6, 112.2, 108.9, 101.8, 86.7, 82.62, 31.7.

3,4-Dimethoxyphenylpropargyl Chloride (7b). In a round-bottom flask under N_2, DMA (8.0 mL) and 3,4-dimethoxyphenylpropargyl alcohol (490 mg, 2.55 mmol) were cooled in an ice bath while stirring. Thionyl chloride (0.2 mL, 2.8 mmol) was then added dropwise, and the solution was allowed to slowly warm to rt over several hours. Once the reaction was complete as indicated by TLC, the mixture was quenched with H_2O, neutralized with $NaHCO_3$, extracted three times with EtOAc, dried with Na_2SO_4, filtered, and concentrated. The crude mixture was purified by column chromatography using 1:12 EtOAc/hexane to afford 450 mg (84%) of **7b** as a yellow oil that crystallized upon cooling: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, J = 1.8, 8.3, 1H), 6.98 (d, J = 1.8, 1H), 6.83 (d, J = 8.3, 1H), 4.41 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 149.0, 125.7, 114.9, 114.5, 111.3, 86.9, 82.8, 56.3, 56.3, 31.8; HRMS *m*/*z* 211.05187 $[M + H]^+$ (calcd for $C_{11}H_{12}ClO_2$, 211.05203).

Representative Procedure for the Arylnaphthalene Lactone Multicomponent Tandem Coupling Reaction to give Retrochinensin (1) and Justicidin B (2). In a round-bottom tube equipped with an airtight septum, phenylpropargyl chloride **7b** (105 mg, 0.5 mmol), phenylacetylene **8a** (73 mg, 0.5 mmol), silver iodide (12 mg, 0.05 mmol), 18-crown-6 (27 mg, 0.1 mmol), DMA (2.0 mL), and 4 Å molecular sieves (100 mg) were combined. The flask was then purged of atmosphere under vacuum and subsequently placed under 1 atm of CO_2 using a balloon-needle apparatus. The reaction mixture was then stirred at 100 °C for 15 h under CO_2 atmosphere. The reaction was cooled to rt, diluted with EtOAc, neutralized with 1 N HCl, extracted three times with EtOAc, washed once with brine, dried with Na_2SO_4, filtered, and concentrated. The crude residue was then purified with flash column chromatography using a 10% → 20% → 30% → 40% EtOAc/heptane gradient. Trace contaminants coeluted with compound **1** and thus required trituration with heptane and a drop of EtOAc. A white solid (**1**, 28 mg, 16%) was isolated after filtration. Compound **2** (28 mg, 16%, of white solid) was collected from concentrated desired fractions without further purification.

Retrochinensin (1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.35 (s, 1H), 7.13 (s, 1H), 7.07 (d, $J = 8.2$, 1H), 6.94 (dd, $J = 1.9$, 8.1, 1H), 6.87 (d, $J = 1.9$, 1H), 6.13 (s, 2H), 5.28−5.18 (m, 2H), 4.01 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 150.9, 149.8, 149.5, 148.8, 138.8, 133.8, 133.3, 131.7, 128.9, 125.0, 122.1, 122.0, 112.6, 112.1, 105.7, 102.5, 102.2, 69.9, 56.5, 56.4; HRMS *m/z* 365.10185 $[M + H]^+$ (calcd for $C_{21}H_{17}O_6$, 365.101965). NMR spectra were in excellent agreement with those reported previously.[15]

Justicidin B (2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.20 (s, 1H), 7.12 (s, 1H), 6.99 (d, $J = 7.6$, 1H), 6.88 (s, 1H), 6.85 (d, $J = 9.5$, 1H), 6.12 (d, $J = 1.5$, 1H), 6.07 (d, $J = 1.5$, 1H), 5.40 (s, 2H), 4.07 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 152.2, 150.5, 148.0, 147.9, 140.1, 139.9, 133.6, 129.3, 128.8, 123.9, 118.9, 118.7, 111.0, 108.6, 106.4, 106.2, 101.7, 68.5, 56.5, 56.2; HRMS *m/z* 365.10200 $[M + H]^+$ (calcd for $C_{21}H_{17}O_6$, 365.101965). NMR spectra were in excellent agreement with those reported previously.[15]

Retrojusticidin B (3), Chinensin (4), and Isoretrojusticidin B (9). Phenylpropargyl chloride **7a** (97 mg, 0.5 mmol) and phenylacetylene **8b** (81 mg, 0.5 mmol) were reacted according to the general procedure. Combination and concentration of desired fractions after chromatography gave compounds **3** (56 mg, 31%), **4** (46 mg, 26%), and **9** (8.0 mg, 0.6%) without further purification.

Retrojusticidin B (3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.33 (s, 1H), 7.12 (s, 1H), 7.02 (d, $J = 8.2$, 1H), 6.89 − 6.86 (m, 2H), 6.14 (d, $J = 1.3$, 1H), 6.11 (d, $J = 1.3$, 1H), 5.25 (s, 2H), 4.08 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 152.4, 150.6, 148.7, 148.1, 138.4, 132.3, 132.1, 130.3, 130.2, 124.6, 123.1, 121.8, 109.9, 109.4, 108.1, 104.4, 101.9, 69.9, 56.5, 56.3; HRMS *m/z* 365.10193 $[M + H]^+$ (calcd for $C_{21}H_{17}O_6$, 365.101965). NMR spectra were in excellent agreement with those reported previously.[15]

Chinensin (4): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.24 (s, 1H), 7.15 (s, 1H), 7.06 (d, $J = 8.2$, 1H), 6.94 (dd, $J = 2.0$, 8.1, 1H), 6.89 (d, $J = 1.9$, 1H), 6.11 (s, 2H), 5.41 (s, 2H), 4.01 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 149.9, 148.9, 148.6, 148.5, 140.4, 139.8, 134.6, 130.5, 127.2, 122.4, 118.9, 118.7, 113.3, 110.7, 103.7, 103.6, 101.8, 67.9, 55.9, 55.8; HRMS *m/z* 365.10217 $[M + H]^+$ (calcd for $C_{21}H_{17}O_6$, 365.101965). NMR spectra were in excellent agreement with those reported previously.[15]

Isoretrojusticidin B (9): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.90 (d, $J = 9.1$, 1H), 7.45 (d, $J = 9.1$, 1H), 6.91 (d, $J = 7.8$, 1H), 6.84 −6.77 (m, 2H), 6.06 (d, $J = 3.1$, 2H), 5.15 (AB, $J = 15.2$, 2H), 4.03 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 152.9, 147.6, 147.1, 144.5, 141.4, 133.5, 131.3, 130.8, 130.8, 127.8, 127.4, 121.4, 121.3, 115.6, 109.6, 108.1, 101.5, 70.3, 61.1, 56.9; HRMS *m/z* 365.10197 $[M + H]^+$ (calcd for $C_{21}H_{17}O_6$, 365.101965). NMR spectra were in excellent agreement with those reported previously.[24]

Justicidin E (5) and Taiwanin C (6). Phenylpropargyl chloride **7a** (97 mg, 0.5 mmol) and phenylacetylene **8a** (73 mg, 0.5 mmol) were reacted according to the general procedure. Once the desired fractions were combined and concentrated, both product **5** and **6** required trituration with heptane and a drop of EtOAc. After filtration compound **5** was isolated as a white solid (32 mg, 18%) and compound **6** was isolated as an off-white solid (25 mg, 14%).

Justicidin E (5): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.32 (s, 1H), 7.11 (s, 1H), 6.98 (d, $J = 8.3$, 1H), 6.83−6.78 (m, 2H), 6.10 (m, 4H), 5.26−5.16 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 150.5, 148.4, 148.2, 147.7, 138.4, 133.4, 132.6, 131.2, 129.6, 124.7, 122.7, 121.6, 109.6, 109.0, 105.2, 102.0, 101.8, 101.4, 69.4; HRMS *m/z* 349.07078 $[M + H]^+$ (calcd for $C_{20}H_{13}O_6$, 349.070665). NMR spectra were in excellent agreement with those reported previously.[14]

Taiwanin C (6): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.23 (s, 1H), 7.14 (s, 1H), 6.99 (d, $J = 7.8$, 1H), 6.84−6.80 (m, 2H), 6.13−6.08 (m, 4H), 5.40 (d, $J = 1.0$, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 150.3, 149.1, 148.0, 147.9, 140.5, 140.2, 135.0, 130.9, 128.8, 123.9, 119.5, 119.3, 110.9, 108.6, 104.1, 104.1, 102.2, 101.7, 68.4; HRMS *m/z* 349.07080 $[M + H]^+$ (calcd for $C_{20}H_{13}O_6$, 349.070665). NMR spectra were in excellent agreement with those reported previously.[14]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1**−**6**, **7a**,**b**, and **9** are available free of charge via the Internet at http://pubs.acs.org.

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