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Intramolecular Dehydro-Diels–Alder Reaction Affords Selective Entry to Arylnaphthalene or Aryldihydronaphthalene Lignans

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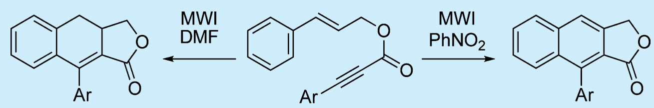
Supporting Information

ABSTRACT: Intramolecular dehydro-Diels–Alder (DDA) reactions are performed affording arylnaphthalene or aryldihydronaphthalene lactones selectively as determined by choice of reaction solvent. This constitutes the first report of an entirely selective formation of arylnaphthalene lactones utilizing DDA reactions of styrene-ynes. The synthetic utility of the DDA reaction is demonstrated by the synthesis of taiwanin C, retrohelioxanthin, justicidin B, isojusticidin B, and their dihydronaphthalene derivatives. Computational methods for chemical shift assignment are presented that allow for regioisomeric lignans to be distinguished.



Arylnaphthalene lignans and their dihydro- and tetrahydronaphthalene derivatives are medicinally relevant compounds with a wide range of pharmacalogical activity. Diphyllin and justicidin B are both cytotoxic compounds and demonstrate anticancer,[1] antiparasitic,[2] and antiviral[3] activities (Figure 1). *β*-Apopicropodophyllin displays pronounced activity against the fifth-instar larvae of *Brontispa longissima*, revealing the potential of podophyllotoxins as insecticides,[4] in addition to their possible application as immunosuppressive agents.[5] The most studied compound of this class is etoposide, an approved anticancer drug that functions as a topoisomerase inhibitor;[6] however, several toxic side effects of etoposide have resulted in a continued search for a better drug.[7] A glycosylated derivative diphyllin D11 has recently been shown to selectively inhibit topoisomerase II*α* despite its structural simplicity compared to etoposide,[8] highlighting the need for diphyllin analogs. Herein we report the synthesis of eight arylnaphthalene and aryldihydronaphthalene lignan natural products via a dehydro-Diels–Alder reaction of styrene-ynes.

Synthetic strategies used to prepare arylnaphthalene lignans include intermolecular Diels–Alder reactions, such as reactions of isobenzofurans **9** with dialkylacetylene dicarboxylates to generate naphthyl diesters **10** (Scheme 1).[9] Selective hydrolysis of the C-3 ester of **10**, followed by reduction of the resulting carboxylic acid and subsequent acid-assisted lactonization yields the lignan derivatives **11**.[9a,10] Alternatively, **10** can be accessed by acid-catalyzed cyclizations[11] or condensation reactions.[10] Another common strategy for arylnaphthalene lignan synthesis is by transition-metal-catalyzed multicomponent cycloaddition reactions. Both dienes **13** and diynes **14** can be reacted with $Pd_2(dba)_3$ and benzyne intermediates **12**, leading to formation of arylnaphthalenes **11**.[12,13]

Based on previously reported results from our laboratory, we envisioned that a thermal intramolecular dehydro-Diels–Alder (DDA) reaction could be utilized to obtain both arylnaphthalene and aryldihydronaphthalene lignans from a single precursor in only one synthetic step.[14] To test the feasibility of this strategy, the styrenyl precursor **15** was subjected to microwave irradiation (MWI) at 180 °C for 20 min in 1,2-dichlorobenzene-d_4 (*o*-DCB-d_4). This reaction afforded a 2:1

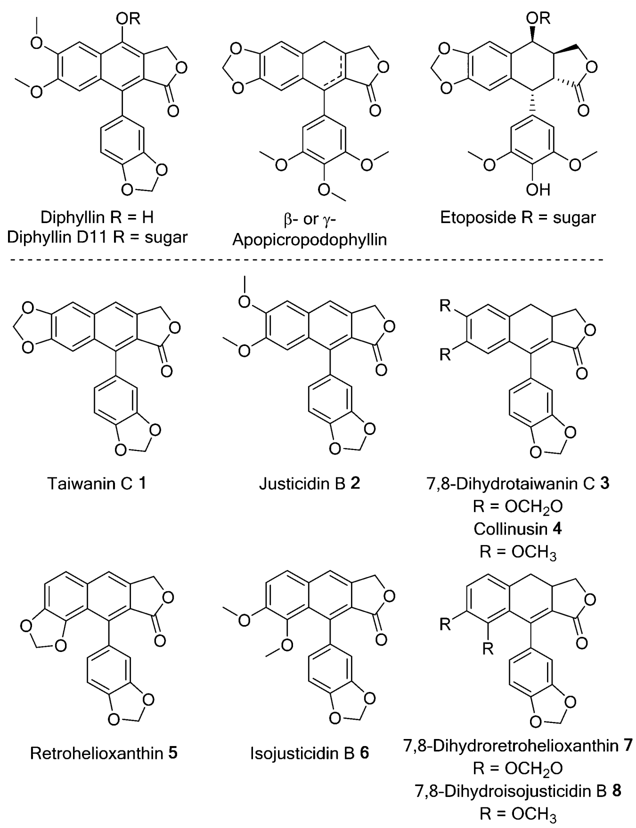


Figure 1. Representative structures of important arylnaphthalene lignans and their derivatives (top) along with those synthesized using the DDA reaction (bottom).

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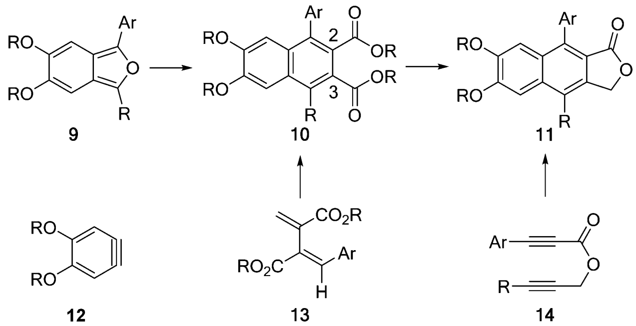
Scheme 1. Previous Synthetic Strategies To Access Arylnaphthalene Lignans

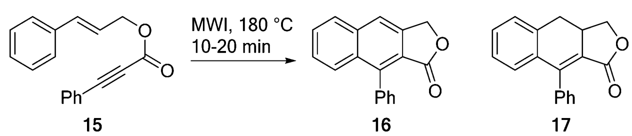


mixture of lactones **16** and **17**, consistent with previous DDA reactions of precursors containing heteroatoms, esters, or amides in the styrene-yne tether (Table 1, entry 1).[15] The potential of this DDA strategy was first recognized by Klemm[16] and others who have validated this approach;[17,18] however, low yields, mixtures of naphthalene and dihydronaphthalene products, and mixtures of regioisomers were often obtained.[16,19]

With an eye toward increasing the synthetic utility of the DDA reaction of styrene-ynes, we set out to control the product selectivity by making variations to the reaction conditions. While increasing the concentration of the reaction mixture and altering the reaction temperature had minor to moderate effects on product selectivity, modifying the solvent from *o*-DCB to the more polar DMF resulted in exclusive formation of **17** in 90% isolated yield after irradiation for 15 min at 180 °C (Table 1, entry 2). Changing the reaction temperature and concentration in DMF did not affect the product selectivity. DMF has previously been shown to act as a hydrogen atom donor,[21] and we speculated that this may be a factor accounting for the selectivity observed when the DDA reaction was performed in DMF. However, a similar substrate was subjected to the DDA reaction conditions in DMF-d_7 and no deuterium incorporation was detected in the resulting dihydronaphthalene product. Efforts to understand the selectivity obtained for the DDA reaction in DMF are currently underway.

Nitrobenzene ($PhNO_2$) was also tested as a reaction solvent because of its similar dielectric constant to DMF. Surprisingly, irradiation of **15** for 15 min at 180 °C in $PhNO_2$ produced **16** exclusively in 93% yield (Table 1, entry 3). While increasing the temperature of the reaction did not affect the selectivity or yield of the reaction in $PhNO_2$, increasing the reaction concentration from 0.06 to 0.24 M did result in decreased selectivity for **16** (entry 4). Despite the observed selectivity for **16** and **17** in $PhNO_2$ and DMF, respectively, conducting the reaction in NMP, a solvent of similar dielectric constant, resulted in a 1:12 mixture of **16**:**17** (entry 5).[20]

Table 1. Controlling Selectivity of the DDA Reaction[20]



entry	solvent (ε)	concn (M)	yield (%)	**16**:**17**[a]
1	*o*-DCB-d_4 (9.93)	0.06	75	2:1
2	DMF (36.7)	0.06	90	0:1
3	$PhNO_2$ (34.8)	0.06	93	1:0
4	$PhNO_2$ (34.8)	0.24	–	2.5:1
5	NMP (32.2)	0.06	–	1:12

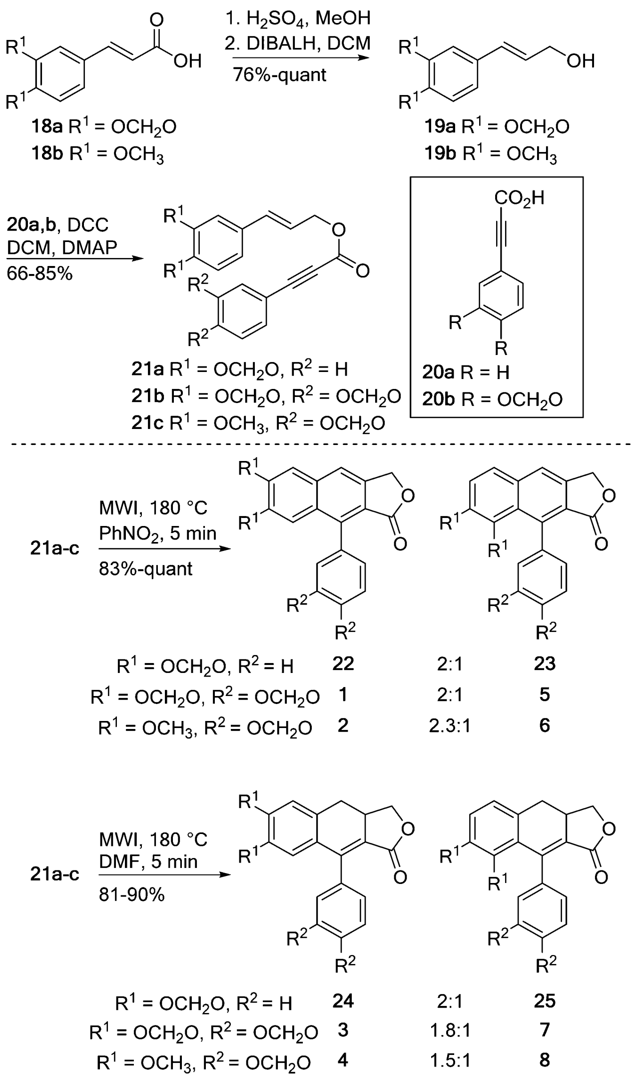
[a]Ratios of **16**:**17** determined by ^1H NMR spectroscopy.

The complete selectivity for arylnaphthalene products in the presence of $PhNO_2$ as the reaction solvent can be explained by the oxidative ability of $PhNO_2$. It has previously been shown that $PhNO_2$ can act as an oxidant to form heteroaromatic systems when utilized as the reaction solvent.[22] We reasoned that if $PhNO_2$ is acting as an oxidant, it need not be the primary solvent and that the quantity present in the reaction could be lessened. To test this hypothesis, incremental reductions were made to the amount of $PhNO_2$ added to a solution of **15** in *o*-DCB, and the effect on the product selectivity of the dehydrogenative DDA reaction was noted. Reducing the amount of $PhNO_2$ from 20% (v/v %) in *o*-DCB, which showed complete selectivity for the naphthalene product **16** in 75% yield, to 10% resulted in a 13:1 ratio of **16**:**17**. Decreasing the concentration of $PhNO_2$ further to 5% generated a 7:1 ratio of **16**:**17**, an almost proportional decrease in selectivity. These results indicate that a 1:5 ratio of $PhNO_2$ to *o*-DCB is the minimal amount of $PhNO_2$ required to achieve complete selectivity for the naphthalene product in the dehydrogenative DDA reaction.

With conditions in hand to prepare either the naphthalene or dihydronaphthalene product selectively from a common precursor, we set out to explore this reaction in the synthesis of more functionalized substrates. The highly oxygenated structures of many arylnaphthalene lignans and their derivatives inspired us to prepare styrenyl precursors **21a**–**c** containing 3,4-methylenedioxy and 3,4-dimethoxy functionalities (Scheme 2). Esterification of commercially available cinnamic acids **18a**,**b** using sulfuric acid and methanol followed by reduction with DIBALH generated cinnamyl alcohols **19a**,**b** in 76% to quantitative yield over two steps. The cinammyl alcohols were then coupled with arylpropiolic acids **20a**,**b** via a DCC coupling reaction to produce styrenyl precursors **21a**–**c** in 66%–85% yield. Alternate coupling reagents to DCC were also successfully utilized.[23]

Styrenyl precursors **21a**–**c** were then subjected to the optimized DDA reaction conditions. Irradiation of **21a** in $PhNO_2$ for 5 min at 180 °C afforded a quantitative yield of arylnaphthalene lactone **22** as a 2:1 mixture with its regioisomer **23** (Scheme 2). Likewise, irradiation of **21b** under the same reaction conditions resulted in an 83% yield of the arylnaphthalene lignan taiwanin C (**1**) as a 2:1 mixture with retrohelioxanthin (**5**), which was then separated by HPLC for characterization. Irradiation of **21c** also provided a similar 2.3:1 ratio of arylnaphthalene lignans justicidin B (**2**) and isojusticidin B (**6**) in 83% yield, which were readily separable by column chromatography. Thus, four arylnaphthalene lignan natural products were formed after a short reaction time and in high combined yields. Attempts to increase the regioselectivity of the DDA reaction by adding bulkier functionality to the arylpropiolate, such as a 3,4-dimethoxy moiety, were not successful. Similarly, irradiation of **21a** for 5 min at 180 °C in DMF led to formation of aryldihydronaphthalene **24** as a 2:1 mixture with its regioisomer **25** in 90% combined yield, while irradiation of **21b** produced 7,8-dihydrotaiwanin C (**3**) in 90% yield as a 1.8:1 mixture with 7,8-dihydroretrohelioxanthin (**7**). Irradiation of **21c** gave collinusin (**4**) and 7,8-dihydroisojusticidin B (**8**) in 81% yield as a 1.5:1 ratio of products.[24]

Scheme 2. Synthesis of Styrenyl Precursors and Their DDA Reactions To Produce Lignan Natural Products



Confirming the identity of lignan regioisomers and assigning the individual resonances using NMR spectroscopy was challenging, as these spectra were closely related. Similar structural assignment challenges for natural and synthetic products have been addressed by utilizing modern computational methods,[25] where predicted NMR spectra are compared with experiment. In light of these studies, computational predictions of NMR spectra using Spartan 10 software were conducted for the eight lignans to confirm the identity of each regioisomer.[26] Lowest energy conformers were first determined, and ^{1}H and ^{13}C NMR spectra were predicted with either EDF2/6-31G* and/or B3LYP/6-31G* methods. Experimental and calculated ^{13}C NMR spectra were matched directly by descending order of chemical shift, similar to the protocol employed by Goodman for when structural assignments are lacking.[25b]

Comparison of the EDF2 and B3LYP functionals for the taiwanin C derivatives showed that the EDF2 functional had an average chemical shift deviation ($\Delta\delta$) 2−6 times lower than that of the B3LYP functional for ^{13}C NMR data, indicating that a more accurate prediction was obtained using the EDF2 method (Table S27). As a graphical representation of the disparity between the EDF2 and B3LYP methods, Figure 2

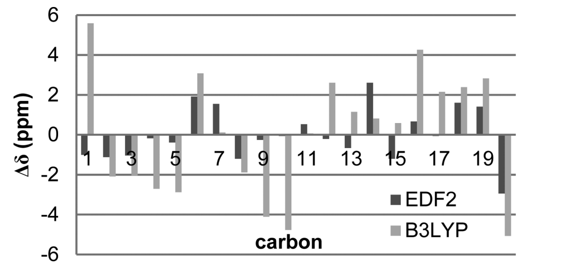


Figure 2. Average $\Delta\delta$ per carbon in taiwanin C (**1**) for EDF2 and B3LYP functionals.

depicts the error associated for each carbon in taiwanin C (**1**), where carbon 1 denotes the most downfield resonance. Also, the maximum $\Delta\delta$ of calculated and experimental values were significantly lower and the coefficient of determination (R^2) values higher for the EDF2 method. Reports by Bifulco[27] and Rychnovsky[25a,c] indicated that R^2 values greater than 0.995 and an average $\Delta\delta$ of less than 2 ppm, respectively, represent a good match between predicted and experimental spectra, which is consistent with our EDF2 results. In examples where multiple conformers exist, as for the justicidin B analogs, a ^{13}C NMR spectrum was also predicted for a Boltzmann distribution of the conformers. In most cases, the lowest energy conformer had average $\Delta\delta$ and R^2 values fitting the above criteria; however, Boltzmann distribution predicted spectra typically showed lower average $\Delta\delta$ and greater R^2 values indicative of a better match with experimental spectra (Table S27). Computational predictions for ^{1}H NMR spectra were also conducted for taiwanin C derivatives, and while the average $\Delta\delta$ were similar for both the EDF2 and B3LYP functionals, they were not as precise as those for the predicted ^{13}C NMR spectra (Table S28).[28]

In conclusion, solvent was shown to have a determinate effect on product selectivity in the intramolecular DDA reaction of styrene-ynes. Employing DMF as the reaction solvent allowed for exclusive formation of aryldihydronaphthalene lactones, while $PhNO_2$ afforded arylnaphthalene lactones selectively. This constitutes the first report of an entirely selective formation of arylnaphthalene lactones utilizing a DDA reaction of styrene-ynes. The synthetic potential of these selective DDA reactions was realized by the preparation of eight natural products from two precursors. The DDA approach to arylnaphthalene and aryldihydronaphthalene lignans is currently being investigated for the preparation of novel topoisomerase inhibitors, and the mechanism will be reported shortly. Computational EDF2 methods were also applied for the prediction of lignan ^{13}C NMR spectra and demonstrated good correlation with experimental spectra, often showing a less than 1 ppm deviation. While the lignans synthesized herein were previously characterized and are distinguishable, these results validate the original structural assignments and the use of computational calculations to aid in the differentiation of lignan derivatives that have not been fully characterized.

■ ASSOCIATED CONTENT

Supporting Information

Reaction optimization, experimental procedures, characterization of compounds, computational methods, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(23) EDC and BOP-Cl were tested and produced **21c** in equivalent yields and in higher purity.

(24) A recent report by Seo and Shin demonstrated that MWI of **21b** in Ac_2O at 140 °C led to the regioselective production of **3** (ref 17d). In our hands, irradiation of **21b** utilizing the conditions reported by Seo and Shin resulted in a 1.6:1 mixture of **3**:**7**, a similar ratio to what was obtained by irradiation in DMF.

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(28) Other data supporting the accuracy of this computational method for prediction of ^{13}C NMR spectra, such as the results of mismatching spectra and comparison with literature 2D NMR structural assignments, are described in detail within the Supporting Information.