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 styreneynes. 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 pharmacological activity. Diphyllin and justicidin B are both cytotoxic compounds and demonstrate anticancer, antiparasitic, and antiviral activities (Figure 1). β-Apopicropodophyllin displays pronounced activity against the fifth-instar larvae of Brontispa longissima, revealing the potential of podophyllotoxins as insecticides, in addition to their possible application as immunosuppressive agents. The most studied compound of this class is etoposide, an approved anticancer drug that functions as a topoisomerase inhibitor; however, several toxic side effects of etoposide have resulted in a continued search for a better drug. A glycosylated derivative diphyllyn D11 has recently been shown to selectively inhibit topoisomerase IIα despite its structural simplicity compared to etoposide, highlighting the need for diphyllyn analogs. Herein we report the synthesis of eight arylnaphthalene and aryldihydronaphthalene lignan natural products via a dehydro-Diels–Alder reaction of styreneynes.

Synthetic strategies used to prepare arylnaphthalene lignans include intramolecular Diels–Alder reactions, such as reactions of isobenzofurans 9 with dialkylacetylene dicarboxylates to generate naphthyl diesters 10 (Scheme 1). 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. Alternatively, 10 can be accessed by acid-catalyzed cyclizations or condensation reactions. 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 Pd2(dba)3 and benzene intermediates 12, leading to formation of arylnaphthalenes 11.

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. 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-d4 (o-DCB-d4). This reaction afforded a 2:1 mixture of the desired arylnaphthalene and aryldihydronaphthalene lignan products.
Scheme 1. Previous Synthetic Strategies To Access Arylnaphthalene Lignans

Table 1. Controlling Selectivity of the DDA Reaction

| entry | solvent (ε) | concn (M) | yield (%) | 16:17<sup>a</sup> |
|-------|-------------|-----------|-----------|----------------|
| 1     | o-DCB<sub>4</sub> (9.93) | 0.06      | 75        | 2:1           |
| 2     | DMF (36.7)  | 0.06      | 90        | 0:1           |
| 3     | PhNO<sub>2</sub> (34.8) | 0.06      | 93        | 1:0           |
| 4     | PhNO<sub>2</sub> (34.8) | 0.24      | –         | 2.5:1         |
| 5     | NMP (32.2)  | 0.06      | –         | 1:12          |

<sup>a</sup>Ratios of 16:17 determined by <sup>1</sup>H NMR spectroscopy.

potential of this DDA strategy was first recognized by Klemm<sup>16</sup> and others who have validated this approach.<sup>17,18</sup> However, low yields, mixtures of naphthalene and dihydronaphthalene products, and mixtures of regioisomers were often obtained.<sup>16,19</sup>

With an eye toward increasing the synthetic utility of the DDA reaction of styrene-yne, 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,<sup>21</sup> 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<sub>4</sub> 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<sub>2</sub>) 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<sub>2</sub> 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<sub>2</sub>, 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<sub>2</sub> 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).<sup>20</sup>

The complete selectivity for arylnaphthalene products in the presence of PhNO<sub>2</sub> as the reaction solvent can be explained by the oxidative ability of PhNO<sub>2</sub>. It has previously been shown that PhNO<sub>2</sub> can act as an oxidant to form heteroaromatic systems when utilized as the reaction solvent.<sup>22</sup> We reasoned that if PhNO<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> to o-DCB is the minimal amount of PhNO<sub>2</sub> 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 cinnamyl alcohols were then coupled with arylpropionic 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.<sup>23</sup>

Styrenyl precursors 21a–c were then subjected to the optimized DDA reaction conditions. Irradiation of 21a in PhNO<sub>2</sub> 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 arylpropionate, 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 aryl-dihydronaphthalene 24 as a 2:1 mixture with its regioisomer 25 in 90% combined yield, while irradiation of 21b produced 7,8-dihydrataiwanin C (3) in 90% yield as a 1:8:1 mixture with 7,8-dihydroidrohelioxanthin (7). Irradiation of 21c gave colinussin (4) and 7,8-dihydroisojusticidin B (8) in 81% yield as a 1:5:1 ratio of products.<sup>24</sup>
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, 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. Lowest energy conformers were first determined, and ¹H and ¹³C 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 (Δδ)² of 6 times lower than that of the B3LYP functional for ¹³C 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 depicts the error associated for each carbon in taiwanin C (1), where carbon 1 denotes the most downfield resonance. Also, the maximum Δδ of calculated and experimental values were significantly lower and the coefficient of determination (R²) values higher for the EDF2 method. Reports by Bifulco²⁷ and Rychnovsky²⁵a,c indicated that R² values greater than 0.995 and an average Δδ 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 ¹³C NMR spectrum was also predicted for a Boltzmann distribution of the conformers. In most cases, the lowest energy conformer had average Δδ and R² values fitting the above criteria; however, Boltzmann distribution predicted spectra typically showed lower average Δδ and greater R² values indicative of a better match with experimental spectra (Table S27). Computational predictions for ¹H NMR spectra were also conducted for taiwanin C derivatives, and while the average Δδ were similar for both the EDF2 and B3LYP functionals, they were not as precise as those for the predicted ¹³C 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 PhNO₂ afforded arylnapthalene lactones selectively. This constitutes the first report of an entirely selective formation of arylnapthalene 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 arylnapthalene 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 ¹³C 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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