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A Synthesis of 1-Pyridylnaphthalene Lignan Analogs

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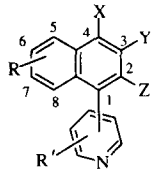
Abstract: A new series of 1-arylnaphthalene lignan analogs having a variety of pyridyl substituents at the C-1 position were synthesized in moderate to good yields by means of the Diels-Alder reaction by utilizing 1-pyridylisobenzofuran precursors with dimethyl fumarate, methyl acrylate, or dimethyl acetylene dicarboxylate, followed by $BF_3{\cdot}Et_2O$-mediated aromatization.

Heterocyclic analogs of 1-arylnaphthalene lignans have recently attracted considerable interest with the discovery of their interesting biological activities, such as antihyperlipidemic and 5-lipoxygenase inhibitory activities.[1, 2] Current synthetic methods of 1-arylnaphthalene lignans[3, 4] include those based on the Diels-Alder reaction utilizing phenylpropionic acid derivatives[5] or 1-arylisobenzofurans,[6] cyclization of the Stobbe condensation products,[7] nucleophilic addition of aryllithium to naphthyloxazolines,[8] and the conjugate addition-aldol reaction utilizing thioacetals[9] or *O*-(*t*-butyldimethylsilyl) cyanohydrins.[10] These methods, however, cannot be applied to the synthesis of arylnaphthalene lignan analogs having an electron-deficient aryl group, such as pyridyl group at the C–1 position. In connection with our efforts in search of new compounds having interesting biological activities, we now disclose a synthesis of 1-pyridylnaphthalene lignan analogs **1**—**3** by means of the Diels-Alder reaction of pyridylisobenzofuran with dimethyl fumarate, methyl acrylate, or dimethyl acetylene dicarboxylate, followed by $BF_3{\cdot}Et_2O$-mediated aromatization.



1: X=H, Y=Z=COOMe
2: X=H, Y=H, Z=COOMe
3: X=OH, Y=Z=COOMe

We first examined the Diels-Alder reaction by utilizing isobenzofuran precursor **4a** and dimethyl fumarate; **4a** was prepared by the usual method[6] from 3,4-dimethoxy-6-bromobenzaldehyde dimethyl acetal and commercially available isonicotinaldehyde. Treatment of **4a** (59.5 g, 0.186 mol) with dimethyl fumarate (28.2 g, 0.195 mol) in the presence of acetic acid (25 mL) for 3 hr in refluxing xylene (100 mL) gave a mixture of 2-*exo*- and 2-*endo*-cycloadducts **5a** (*ca.* 1.4:1); **4a** was not observed by TLC analysis. The reaction proceeded very sluggishly in the absence of acetic acid. Without purification of **5a**, the mixture was

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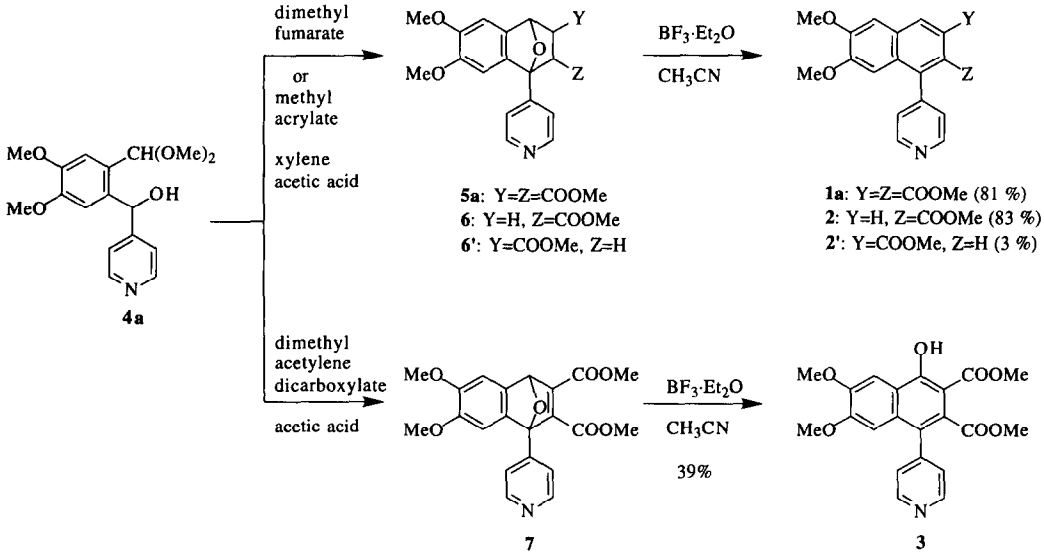
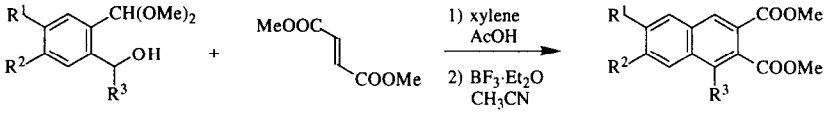
refluxed in CH_3CN (180 mL) for two hours in the presence of $BF_3 \cdot Et_2O$ (68.6 mL, 0.558 mol) to afford the aromatized product, 1-(4-pyridyl)naphthalene (**1a**) in 81 % yield from **4a**. The use of a Brønstead acid such as *p*-TsOH or $MeSO_3H$ did not afford **1a** in a satisfactory yield; significant amounts of hydrolyzed compounds were obtained along with **1a**. The good result obtained by the use of $BF_3 \cdot Et_2O$ is probably due to its ability to trap water produced during the course of the reaction. We next examined the Diels-Alder reaction by using **4a** with methyl acrylate in the same reaction conditions to furnish cycloadducts **6** and **6'**. Without their being purified, the mixture was treated with $BF_3 \cdot Et_2O$ to afford aromatized products **2** and its regio isomer **2'** in 86 % yield from **4a**; the ratio of **2** to **2'** was determined to be 96:4 based on isolated yield. We further examined the Diels-Alder reaction by using **4a** with dimethyl acetylene dicarboxylate. In this reaction, however, the cycloadduct **7** was obtained in a very low yield. After examination of the reaction conditions, the use of acetic acid as a solvent and dropwise addition of dienophile gave a fairly satisfactory result to furnish 4-hydroxy-1-(4-pyridyl)naphthalene (**3**) in 39% yield after treatment of **7** with $BF_3 \cdot Et_2O$.



The above results prompted us to synthesize a variety of 1-pyridylnaphthalene lignan analogs by using this novel method. In order to examine the effect of substituents R^1, R^2, and R^3 on this reaction, the isobenzofuran precursors **4b—i** were prepared by the procedure described above.[11] The precursors **4b, c** were firstly treated with dimethyl fumarate and acetic acid in xylene, followed by $BF_3 \cdot Et_2O$. As shown in Table 1 (entries 1 and 2), 1-(4-pyridyl)naphthalenes (**1b, c**) were obtained in moderate to good yields. We next examined the reaction of **4d—h** with dimethyl fumarate under the same reaction conditions to afford the desired 1-pyridylnaphthalene lignan analogs **1d—h** having the regioisomeric and/or halogenated pyridyl group on C-1 position of the naphthalene ring (entries 3—7). We were extremely interested in the bromo- or chloropyridyl derivatives which would be powerful synthetic intermediates for complex derivatives in this series of compounds. 1-(4-Quinolyl)naphthalene lignan analog **4i** was also obtained in a good yield by the

same procedure. In the case of compounds **1c** and **h**, significant amounts of debenzylated products were obtained during the $BF_3 \cdot Et_2O$-mediated aromatization step. To avoid this side reaction, the aromatization was conducted by using 10 equivalents of $BF_3 \cdot Et_2O$ at room temperature for three days. The yields of **1b—i** are summarized in Table 1.

Table 1. Diels-Alder reaction by using **4b—i** with dimethyl fumarate and aromatization



4b-i **1b-i**

entry	R^1	R^2	R^3	substrate	product	yield (%)[a]
1	EtO	EtO	4-pyridyl	**4b**	**1b**[12]	70
2[b]	$PhCH_2O$	EtO	4-pyridyl	**4c**	**1c**	41
3	MeO	MeO	2-pyridyl	**4d**	**1d**[12]	50
4	MeO	MeO	3-pyridyl	**4e**	**1e**	76
5	MeO	MeO	2-bromo-4-pyridyl	**4f**	**1f**	60
6	MeO	MeO	3-bromo-5-pyridyl	**4g**	**1g**	72
7[b]	MeO	$PhCH_2O$	2-chloro-4-pyridyl	**4h**	**1h**	48
8[c]	EtO	EtO	4-quinolyl	**4i**	**1i**	65

a) Isolated yield. b) Aromatization was conducted by using 10 equivalents of $BF_3 \cdot Et_2O$ at room temperature for 3 days. c) Toluene was used instead of xylene.

In summary, we accomplished the syntheses of 1-pyridylnaphthalene lignan series **1—3** by means of the Diels-Alder reaction by utilizing 1-pyridylisobenzofuran precursors with dimethyl fumarate, methyl acrylate, or dimethyl acetylene dicarboxylate, followed by $BF_3 \cdot Et_2O$-mediated aromatization. This efficient and practical method should find wide application in the synthesis of this series of lignan derivatives having intriguing biological activities.

References and Notes

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11. In the case of **4f**—**h**, the reversal addition method was employed in order to avoid lithium-halogen exchange between a lithium salt of benzaldehyde dimethyl acetal derivative and a halogenopyridinecarbaldehyde; a lithium salt of benzaldehyde dimethyl acetal derivative in THF was added dropwise to a THF solution of halogenopyridinecarbaldehyde at –78℃.
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