Pergamon

Tetrahedron Letters 39 (1998) 1377–1380

TETRAHEDRON LETTERS

# A Synthesis of 1-Pyridylnaphthalene Lignan Analogs

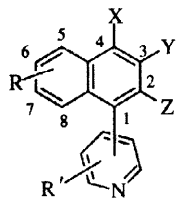
Masakatsu Sugahara, Yasunori Moritani, Yoshihiro Terakawa, Tsuyoshi Ogiku, Tatsuzo Ukita,* and Tameo Iwasaki

Lead Optimization Research Laboratory, Tanabe Seiyaku Co., Ltd., 3-16-89, Kashima, Yodogawa, Osaka 532, Japan

Received 20 November 1997; revised 8 December 1997; accepted 12 December 1997

***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.

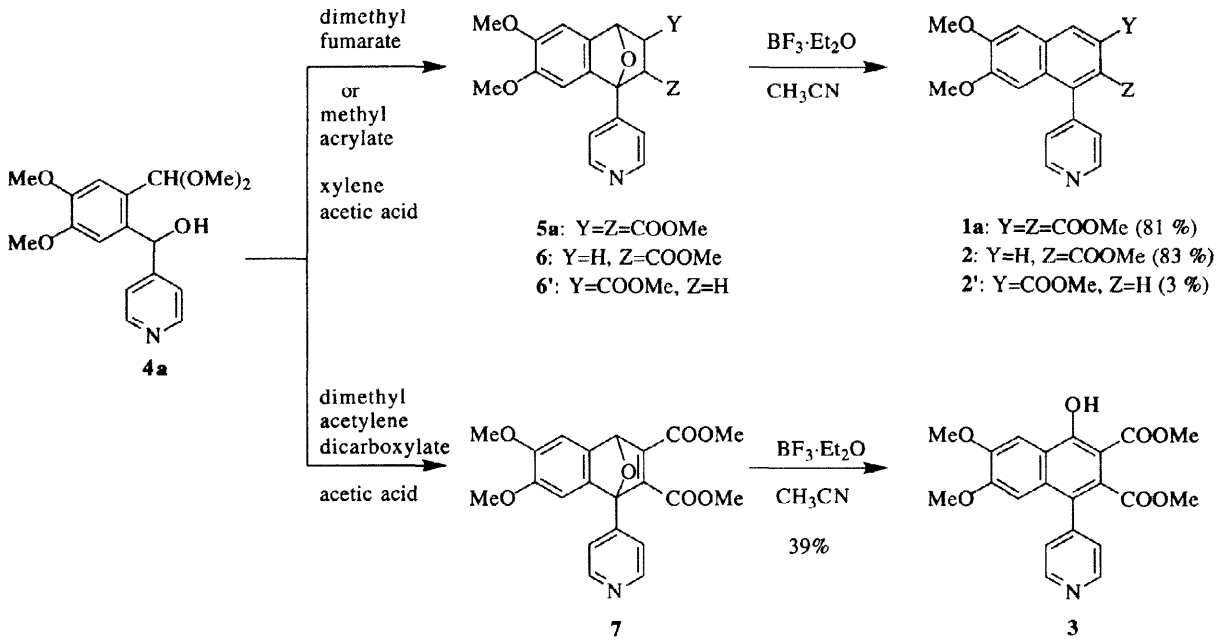



**1**: X=H, Y=Z=COOMe
**2**: X=H, Y=H, Z=COOMe
**3**: X=OH, Y=Z=COOMe

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

0040-4039/98/$19.00 
*PII:* S0040-4039(97)10849-8

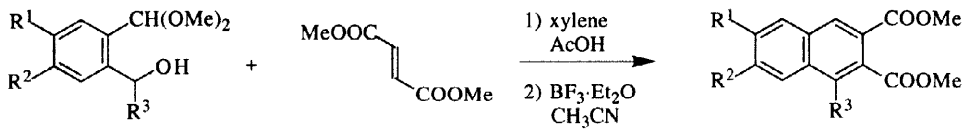
refluxed in $CH_3CN$ (180 mL) for two hours in the presence of $BF_3 \cdot Et_2O$ (68.6 mL, 0.558 mol) to afford the aromatized product, 1-(4-pyridyl)naphthalene (**1a**) in 81 % yield from **4a**. The use of a Brønstead acid such as *p*-TsOH or $MeSO_3H$ did not afford **1a** in a satisfactory yield; 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

1. The synthesis of heteroaromatic analogs of the 1-arylnaphthalene lignan series has already been reported by Kuroda, T. *et al.* of our company.; (a) Kuroda, T.; Takahashi, M.; Ogiku, T.; Ohmizu, H.; Kondo, K.; Iwasaki, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1635–1636. (b) Kuroda, T.; Takahashi, M.; Ogiku, T.; Ohmizu, H.; Nishitani, T.; Kondo, K.; Iwasaki, T. *J. Org. Chem.* **1994**, *59*, 7353–7357.

2. Delorma, D.; Ducharme, Y.; Brideau, C.; Chan, C.-C.; Chauret, N.; Desmarais, S.; Dubé, D.; Falgueyret, J.-P.; Fortin, R.; Guay, J.; Hamel, P.; Jones, T. R.; Lépine, C.; Li, C.; McAuliffe, M.; McFarlane, C. S.; Nicoll-Griffith, D. A.; Riendeau, D.; Yergey, J. A.; Girard, Y. *J. Med. Chem.* **1996**, *39*, 3951–3970.

3. (a) Ayres, D. C.; Loike, J. D. *Lignans*; Cambridge Univ. Press: Cambridge, 1990. (b) Yalowich, J. C.; Fry, D. W.; Goldman, I. D. *Cancer Res.* **1982**, *42*, 3648–3653 and references cited therein. (c) Kimura, M.; Suzuki, J.; Yamada, T.; Yoshizaki, M.; Kikuchi, T.; Kadota, S.; Matsuda, S. *Planta Med.* **1985**, 291–293. (d) Nishibe, S.; Tsukamoto, H.; Hisada, S.; Nikaido, T.; Ohmoto, T.; Sankawa, U. *Shoyakugaku Zasshi* **1986**, *40*, 89–94.

4. For reviews, see: (a) Rao, C. B. S. *Chemistry of lignans*; Andhra University Press: Andhra Pradesh, 1978.; (b) Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, 75–125; *Tetrahedron* **1990**, *46*, 5029–5041. (c) Yamamura, S. *J. Synth. Org. Chem. Jpn.* **1985**, *43*, 583–593. (d) Shizuri, Y. *J. Synth. Org. Chem. Jpn.* **1984**, *42*, 889–899. (e) Ohmizu, H.; Iwasaki, T. *J. Syn. Org. Chem. Jpn.* **1995**, *53*, 593–603, and references cited therein.

5. (a) Block, E.; Stevenson, R. *J. Org. Chem.* **1971**, *36*, 3453–3455. (b) Joshi, B. S.; Viswanathan, N.; Balakrishnan, V.; Gawad, D. H.; Ravindranath, K. R. *Tetrahedron* **1979**, *35*, 1665–1671.

6 (a) Rodrigo, R. *J. Org. Chem.* **1980**, *45*, 4538–4540. (b) Forsey, S. P.; Rajapaksa, D.; Taylor, N. J.; Rodrigo, R. *J. Org. Chem.* **1989**, *54*, 4280–4290.

7. (a) Heller, H. G.; Strydom, P. J. *J. Chem. Soc., Chem. Commun.* **1976**, 50–51. (b) Brown, E.; Daugan, A. *Tetrahedron* **1989**, *45*, 141–154.

8. (a) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611–4624. (b) Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7854–7858.

9. (a) Ziegler, F. E.; Schwartz, J. A. *J. Org. Chem.* **1978**, *43*, 985–991. (b) Pelter, A.; Ward, R. S.; Pritchard, M. C.; Kay, I. T. *J. Chem. Soc., Perkin Trans. I* **1988**, 1603–1613. (c) González, A. G.; Pérez, J. P.; Trujillo, M. *Tetrahedron* **1978**, *34*, 1011–1013.

10. (a) Ogiku, T.; Seki, M.; Takahashi, M.; Ohmizu, H.; Iwasaki, T. *Tetrahedron Lett.* **1990**, *31*, 5487–5490. (b) Ogiku, T.; Yoshida, S.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1995**, *60*, 4585–4590.

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℃.

12. Iwasaki, T.; Kondo, K.; Kuroda, T.; Moritani, Y.; Yamagata, S.; Sugiura, M.; Kikkawa, H.; Kaminuma, O.; Ikezawa, K. *J. Med. Chem.* **1996**, *36*, 2696–2704.