An Efficient Synthesis of Heterocyclic Analogs of 1-Arylnaphthalene Lignans[1]

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The heterocyclic analogs **5a–f**, **16**, and **20** of 1-arylnaphthalene lignans were synthesized by Diels–Alder reactions of acetoxy aldehydes **11a–f**, **14**, and **18** with dimethyl acetylenedicarboxylate. A pathway for formation of **5a–f**, **16**, and **20** through the intermediacy of heteroaromatic isobenzofurans derived from acetoxy aldehydes is discussed.

Introduction

In recent years, much attention has been focused on polycyclic heteroaromatics which exhibit interesting biological activity.[2] One of the successful methods for synthesis of these compounds involves the application of the Diels–Alder reaction to construct the basic skeletons.[3] The method depends critically on the availability of the appropriate dienes. Heterocyclic quinodimethanes[4] and their stable analogs[5] have been utilized in this regard. On the other hand, the use of heteroaromatic isobenzofurans as dienes is emerging as a powerful alternative to the above method.[6–9] The methods so far reported for generation of heteroaromatic isobenzofurans include those based on the Grignard reagent promoted cyclization of thienyl-2-oxazolinium derivatives leading to thieno[2,3-*c*]furans,[6] the thermal retro Diels–Alder reactions of 1,4-epoxides leading to furo[3,4-*c*]pyridines,[7] and thermolysis of (alkynylfuryl)oxiranes leading to furo-[2,3-*c*]furans.[8] However, these methods suffer some disadvantages, the most notable one being the requirement of drastic conditions and/or multistep processes.

In conjunction with our search for lignan derivatives having potent antihyperlipidemic activity,[10] we wish to describe a new method for the generation of heteroaromatic isobenzofurans **1** and its application in the synthesis of heterocyclic analogs of 1-arylnaphthalene lignans **2** (Figure 1).

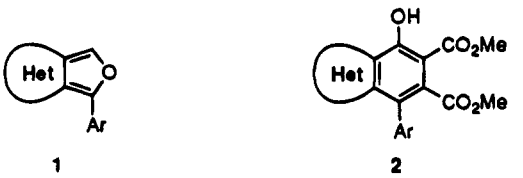

Figure 1.

Results and Discussion

The most direct and concise method for the generation of isobenzofurans involves the acid-catalyzed intramolecular transetherification-1,4-conjugate elimination of hydroxy acetals.[11] This method has been widely used in the one-pot synthesis of 1-aryl-4-hydroxynaphthalene lignans from the corresponding hydroxy acetals.[12] On the basis of this precedent, we initially anticipated that the reaction of an isobenzofuran, generated from a heteroaromatic hydroxy acetal, with a dienophile under the acidic conditions would lead to the desired bicyclic heteroaromatic analogs of lignans. However, treatment of the thienyl alcohol **3** with dimethyl acetylenedicarboxylate (DMAD) in the presence of trifluoroacetic acid in benzene resulted in the formation of the methoxy aldehyde **4** in 74% yield along with the desired benzo[*b*]thiophene **5a** in 10% yield. Furthermore, the pyridyl alcohol **6** did not undergo Diels–Alder reaction under similar reaction conditions (Scheme 1). These discouraging results led us to devise a new general route to these ring systems via heteroaromatic isobenzofurans. We envisaged that the acetoxy aldehyde **7** would be converted to the carbonium ion **8** which, upon intramolecular cyclization and subsequent deprotonation, would generate the isobenzofuran **1**. Interception of **1** with DMAD would lead to the formation of the desired lignan derivatives **2** (Scheme 2).

The requisite acetoxy aldehyde **7** can be readily synthesized from the corresponding heteroaromatic aldehyde. Thus, treatment of 3-thiophenecarbaldehyde **9** with a mixture of lithiated *N,N,N'*-trimethylethylenediamine (LTMDA), butyllithium, and LDA followed by

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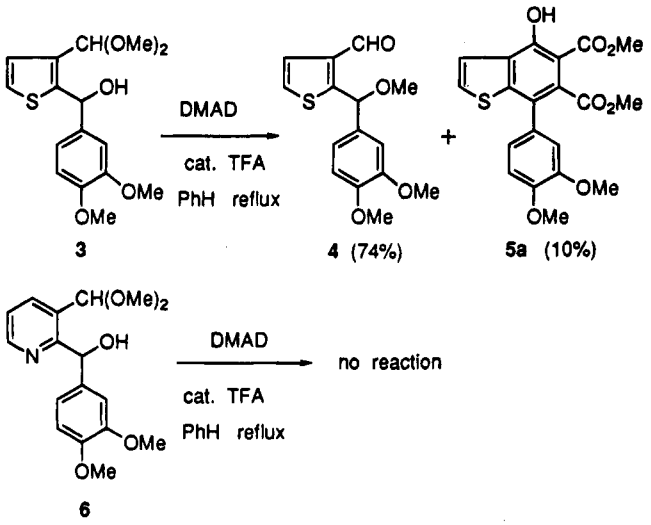
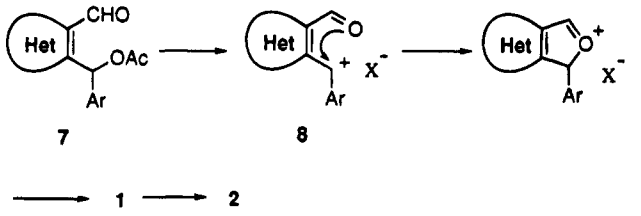
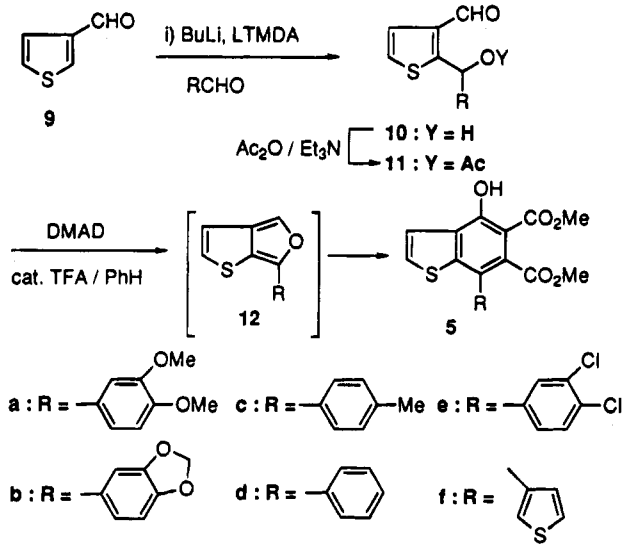
Scheme 1



Scheme 2



Scheme 3



addition of 3,4-dimethoxybenzaldehyde afforded the hydroxy aldehyde **10a**.[13] Subsequent acetylation of **10a** with acetic anhydride gave the acetoxy aldehyde **11a** (83% from **9**) (Scheme 3). The reaction of **11a** with DMAD was examined in the presence of a variety of acid catalysts. The results are shown in Table 1. The best conditions utilized refluxing benzene in the presence of 3 mol % of trifluoroacetic acid, whereupon the benzo[*b*]thiophene **5a** was isolated in 88% yield. When the reaction was carried out in the presence of catalysts other than trifluoroacetic acid, **5a** was obtained in poor yield or not obtained at all (Table 1). The procedure described above worked well when applied to the synthesis of a series of benzo[*b*]thiophenes **5b–f** in which the 3,4-dimethoxyphenyl group is replaced by the other aryl groups (Table 2). It is noteworthy that in the case of **11e**, which has electron-withdrawing substituents on the benzene ring, the reaction proceeded more slowly than with the other substituents on the benzene ring. This rate retardation is probably due to the decreased leaving ability of the acetoxyl group of **11e**.

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Table 1. Acid-Mediated Diels–Alder Reaction of 11a with DMAD[a]

run	catalyst	reaction time (h)	yield of **5a**[c] (%)
1	AcOH	6	0
2	TFA	1	88
3	TsOH	1	42
4	H_2SO_4	1	56
5	$BF_3{\cdot}Et_2O$[b]	3	0

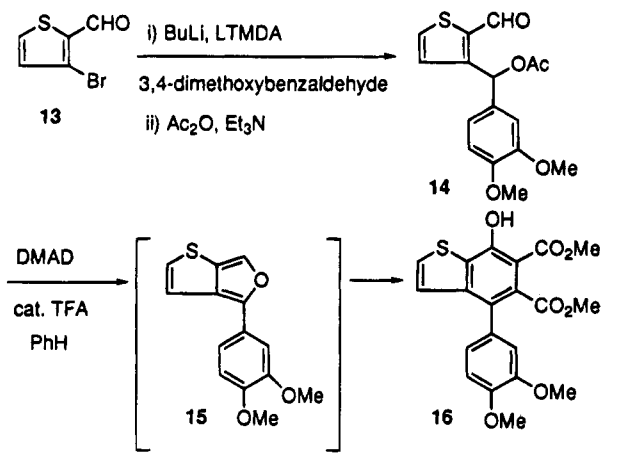
[a] A mixture of **11a** (10 mmol) and DMAD (11 mmol) was heated under reflux in benzene in the presence of catalyst (0.3 mmol). [b] The reaction was carried out at room temperature. [c] Isolated yield.

Table 2. Reactions of Acetoxy Aldehydes 11a–f with DMAD[a]

entry	acetoxy aldehyde	reaction time (h)	product[b]	yield[c] (%)
1	**11a**	1	**5a**	88
2	**11b**	1	**5b**	73
3	**11c**	3	**5c**	80
4	**11d**	3	**5d**	83
5	**11e**	10	**5e**	66
6	**11f**	3	**5f**	70

[a] The reaction was carried out on a 10 mmol scale under the same reaction conditions as those described in the typical procedure. [b] All products were characterized based on ^1H NMR, IR, and mass spectra and elemental analyses. [c] Isolated yield.

Scheme 4

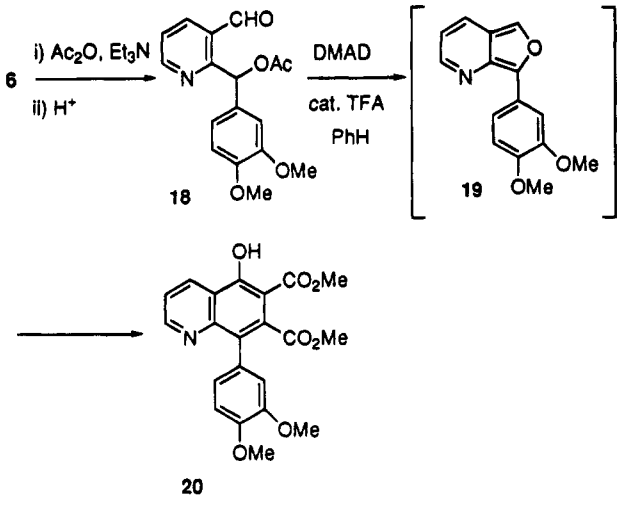


The scope of this reaction was subsequently studied using various heteroaromatic acetoxy aldehydes. We chose 7-hydroxybenzo[*b*]thiophene **16**, a structural isomer of **5a**, as the next target compound. The key intermediate **14** was prepared from 3-bromo-2-thiophenecarbaldehyde **13** (Scheme 4). Reaction of **14** with DMAD under standard conditions proceeded smoothly, and the desired product **16** was obtained in 83% yield.

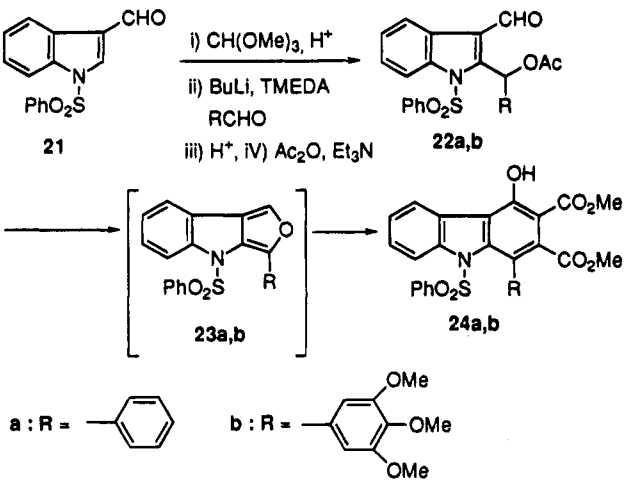
The utility of the method was also demonstrated by the synthesis of the benzo[*b*]pyridine **20** via the furo[3,4-*b*]pyridine **19**, a hitherto unknown ring system (Scheme 5). Treatment of the acetoxy aldehyde **18**, prepared from 2-bromopyridine-3-carbaldehyde, with DMAD afforded **20** in 66% yield.

Finally, we extended this method to the synthesis of the carbazoles **24a,b**. The starting aldehyde **21** was

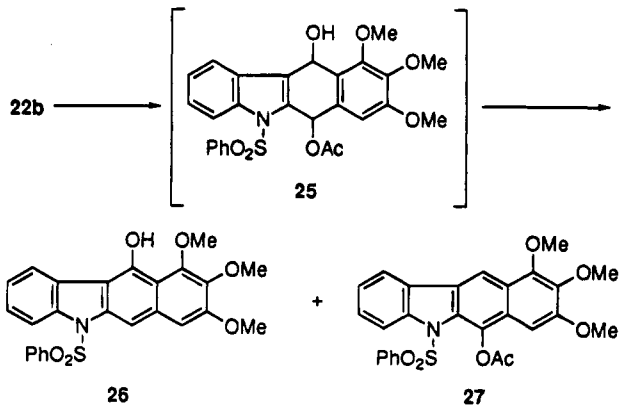
Scheme 5



Scheme 6



Scheme 7



converted into the acetoxy aldehydes **22a,b** by the usual method (Scheme 6). Reaction of the acetoxy aldehyde **22a** with DMAD gave the desired **24a** in 87% yield. The reaction of **22b**, however, led to the unexpected result that the desired **24b** was obtained only in 46% yield. Two byproducts were isolated in this reaction; these were identified as the phenol **26** (23%) and the acetate **27** (15%) (Scheme 7). It seems likely that **26** and **27** are produced via the intramolecular hydroxyalkylation of **22b** to generate the tetracyclic intermediate **25**, which undergoes 1,4-elimination reactions to form **26** and **27**. The increased nucleophilicity of the benzene ring of **22b** appears to arise from the electron-donating nature of the substituents.

Various attempts to isolate the heteroaromatic isobenzofurans **12**, **15**, and **19** were unsuccessful owing to their extreme instability. In order to confirm our working hypothesis, we tried to isolate the furo[3,4-*b*]indole **23a** which is a known and stable compound.[9c] Treatment of the acetoxy aldehyde **22a** with a catalytic amount of TFA in refluxing benzene for 30 min gave **23a** in 36% yield. The reaction of **23a** with DMAD in the presence of TsOH gave the carbazole **24a** in 72% yield. The production of **5**, **16**, and **20** as well as the isolation of **23a** is consistent with the generation of the corresponding isobenzofurans **12**, **15**, and **19**, respectively.

In conclusion, we have developed a practical and efficient synthesis of heterocyclic analogs **5a–f**, **16**, and **20** of 1-arylnaphthalene lignans. The key reaction involves Diels–Alder cycloaddition of reactive intermediates **12a–f**, **15**, and **19** generated from the acetoxy aldehydes **11a–f**, **14**, and **18** with a dienophile. This method should find application in the synthesis of various heteroaromatics.

Experimental Section

General. 3-Thiophenecarbaldehyde and indole-3-carbaldehyde were purchased from Aldrich. 2-Bromopyridine, 2,3-dibromothiophene, and *N,N,N'*-trimethylethylenediamine were purchased from Tokyo Kasei Co. Butyllithium was the 1.6 M solution in hexane supplied by Asia Lithium Co.

Preparation of the Hydroxy Acetals 3 and 6. 2-(α-Hydroxy-3,4-dimethoxybenzyl)thiophene-3-carbaldehyde Dimethyl Acetal (3). 3-Thiophenecarbaldehyde dimethyl acetal was prepared from 3-thiophenecarbaldehyde in 93% yield according to the reported method:[14] bp 60 °C (2 Torr). To a solution of the acetal (15.8 g, 0.1 mol) in 100 mL of THF was dropwise added BuLi (62.5 mL, 0.1 mol) at −78 °C under nitrogen atmosphere, and the mixture was stirred for 0.5 h. 3,4-Dimethoxybenzaldehyde (16.6 g, 0.1 mol) in 50 mL of THF was added dropwise, and the resulting mixture was stirred at −78 °C for 1 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic extract was washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 26.9 g (83%) of the hydroxy acetal **3**: oil; IR (film) 3450, 1135, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.34 (s, 6H), 3.77–4.03 (m, 1H), 3.90 (s, 6H), 5.54 (s, 1H), 6.22 (d, J = 4.0Hz, 1H), 6.85–7.45 (m, 5H); MS *m/z* 324 (M^+).

2-(α-Hydroxy-3,4-dimethoxybenzyl)pyridine-3-carbaldehyde Dimethyl Acetal (6). 2-Bromopyridine-3-carbaldehyde was prepared according to the reported method.[15] The aldehyde was transformed into the dimethyl acetal in 90% yield by refluxing in 21% HCl–MeOH: bp 85 °C (0.146 Torr). The dimethyl acetal was transformed into the requisite hydroxy acetal **6** in 83% yield by the same method for the preparation of the hydroxy acetal **3**: mp 91–92 °C; IR (Nujol) 3330 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.15–3.30 (m, 6H), 3.80–3.93 (m, 7H), 5.24 (s, 1H), 5.98 (s, 1H), 6.76–6.90 (m, 3H), 7.29 (dd, J = 8.5 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 8.60 (d, J = 5.0 Hz, 1H); MS *m/z* 319 (M^+). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.77; H, 6.81; N, 4.42.

Reaction of the Hydroxy Acetal 3 with DMAD. A mixture of the hydroxy acetal **3** (3.24 g, 10 mmol) and DMAD (1.56 g, 11 mmol) was heated under reflux in 15 mL of benzene in the presence of 0.02 mL of trifluoroacetic acid. After 1 h, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography to give 2.07 g (74%) of the methoxy aldehyde **4** and 0.40 g (10%) of the desired benzo[*b*]thiophene **5a**.

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2-(α-Methoxy-3,4-dimethoxybenzyl)thiophene-3-carbaldehyde (4): oil; IR (film) 1670, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.37 (s, 3H), 3.82 (s, 6H), 6.01 (s, 1H), 6.70–7.05 (m, 3H), 7.15 (d, J = 5.0 Hz, 1H), 7.32 (d, J = 5.0 Hz, 1 H), 9.96 (s, 1H); MS m/z 292 (M^+).

4-Hydroxy-5,6-bis(methoxycarbonyl)-7-(3,4-dimethoxyphenyl)benzo[*b*]thiophene (5a): mp 147–148 °C; IR (KBr) 1730, 1660, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (s, 3H), 3.86 (s, 3H), 3.93 (s, 6H), 6.94 (s, 3H), 7.38 (d, J = 6.0 Hz, 1H), 7.65 (d, J = 6.0 Hz, 1H), 11.73 (s, 1H); MS m/z 402 (M^+). Anal. Calcd for $C_{20}H_{18}O_7S$: C, 59.69; H, 4.51; S, 7.97. Found: C, 59.77; H, 4.52; S, 8.27.

General Procedure for the Preparation of Acetoxy Aldehydes 11a–f. To a solution of *N,N,N'*-trimethylethylenediamine (4.6 mL, 36 mmol) in 100 mL of THF was added BuLi (20.6 mL, 33 mmol) at −78 °C. After 5 min, 3-thiophenecarbaldehyde **9** (3.33 g, 30 mmol) was added, and the mixture was allowed to stir for an additional 15 min. Diisopropylamine (4.7 mL, 33 mmol) and BuLi (37.5 mL, 60 mmol) were added, and the flask was sealed and put in a freezer (−20 °C) for 6 h. The appropriate aryl aldehyde (30 mmol) in 50 mL of THF was added at −78 °C, and the mixture was allowed to warm to room temperature (30 min). The mixture was poured into vigorously stirring cold water (200 mL) and extracted with EtOAc. The organic extract was washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give the hydroxy aldehyde **10**. The hydroxy aldehyde **10** was transformed into the acetoxy aldehyde **11** by the usual method (Ac_2O, Et_3N/CH_2Cl_2) and purified by silica gel chromatography.

2-(α-Acetoxy-3,4-dimethoxybenzyl)thiophene-3-carbaldehyde (11a) was prepared in 83% yield from **9** and 3,4-dimethoxybenzaldehyde. **11a**: mp 91–92 °C; IR (KBr) 1730, 1675, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14 (s, 3H), 3.85 (s, 6H), 6.73–7.07 (m, 3H), 7.20 (d, J = 5.0 Hz, 1H), 7.37 (d, J = 5.0Hz, 1H), 7.56 (s, 1H), 9.99 (s, 1H); MS m/z 320 (M^+). Anal. Calcd for $C_{16}H_{16}O_5S$: C, 59.99; H, 5.03; S, 10.01. Found: C, 59.99, H, 5.05; S, 9.90.

2-(α-Acetoxy-3,4-(methylenedioxy)benzyl)thiophene-3-carbaldehyde (11b) was prepared in 84% yield from **9** and 3,4-(methylenedioxy)benzaldehyde. **11b**: mp 103–105 °C; IR (KBr) 1735, 1690, 1520, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 5.93 (s, 2H), 6.72–7.03 (m, 3H), 7.22 (d, J = 5.1 Hz, 1H), 7.38 (d, J = 5.1 Hz, 1H), 7.61 (s, 1H), 10.01 (s, 1H); MS m/z 304 (M^+). Anal. Calcd for $C_{15}H_{12}O_5S$: C, 59.20; H, 3.97; S, 10.54. Found: C, 59.11; H, 4.03; S, 10.37.

2-(α-Acetoxy-4-methylbenzyl)thiophene-3-carbaldehyde (11c) was prepared in 81% yield from **9** and *p*-tolaldehyde. **11c**: oil; IR (film) 1735, 1680, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.80 (s, 3H), 6.81–7.05 (m, 4H), 7.20 (d, J = 5.1 Hz, 1H), 7.39 (d, J = 5.1 Hz, 1H), 7.50 (s, 1H), 9.98 (s, 1H); MS m/z 274 (M^+).

2-(α-Acetoxybenzyl)thiophene-3-carbaldehyde (11d) was prepared in 84% yield from **9** and benzaldehyde. **11d**: oil; IR (film) 1730, 1680, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 7.25–7.48 (m, 7H), 7.65 (s, 1H), 10.05 (s, 1H); MS m/z 260 (M^+).

2-(α-Acetoxy-3,4-dichlorobenzyl)thiophene-3-carbaldehyde (11e) was prepared in 81% yield from **9** and 3,4-dichlorobenzaldehyde. **11e**: mp 97–99 °C; IR (KBr) 1735, 1686, 1524, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 7.26–7.61 (m, 6H), 10.01 (s, 1H); MS m/z 328 (M^+). Anal. Calcd for $C_{14}H_{10}Cl_2O_3S$: C, 51.08; H, 3.06; Cl, 21.54; S, 9.74. Found: C, 51.02; H, 3.32; Cl; 21.29; S, 9.66.

2-(α-Acetoxy-3-thienylmethyl)thiophene-3-carbaldehyde (11f) was prepared in 80% yield from **9**. **11f**: oil; IR (film) 1740, 1680, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 7.02–7.43 (m, 5H), 7.70 (s, 1H), 10.00 (s, 1H); MS m/z 266 (M^+).

General Procedure for the Reaction of Acetoxy Aldehydes with DMAD. A mixture of the appropriate acetoxy aldehyde (10 mmol) and DMAD (1.56 g, 11 mmol) was heated under reflux in 15 mL of benzene in the presence of 0.02 mL of trifluoroacetic acid. After the time indicated in Table 2, the solvent was removed under reduced pressure. To the mixture was added 50 mL of methanol. The resulting crystals were collected by filtration to afford the desired benzo[*b*]thiophene **5**.

4-Hydroxy-5,6-bis(methoxycarbonyl)-7-((3,4-methylenedioxy)phenyl)benzo[*b*]thiophene (5b): mp 156–157 °C; IR (Nujol) 1740, 1665, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.64 (s, 3H), 3.91 (s, 3H) 5.98 (s, 2H), 6.86–6.98 (m, 3H), 7.37 (d, J = 5.0 Hz, 1H), 7.64 (d, J = 5.0 Hz, 1H), 11.70 (s, 1H); MS m/z 386 (M^+). Anal. Calcd for $C_{19}H_{14}O_7S$: C, 59.06; H, 3.65; S, 8.30. Found: C, 59.21; H, 3.61; S, 8.17.

4-Hydroxy-5,6-bis(methoxycarbonyl)-7-(*p*-tolyl)benzo[*b*]thiophene (5c): mp 100–101 °C; IR (KBr) 3100, 1740, 1660, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.82 (s, 3H), 3.90 (s, 3H), 6.95 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 9.0 Hz, 2H), 7.38 (d, J = 6.0 Hz, 1H), 7.65 (d, J = 6.0 Hz, 1H), 11.70 (s, 1H); MS m/z 356 (M^+). Anal. Calcd for $C_{19}H_{16}O_5S$: C, 64.03; H, 4.53; S, 9.00. Found: C, 64.10; H, 4.46; S, 8.76.

4-Hydroxy-5,6-bis(methoxycarbonyl)-7-phenylbenzo[*b*]thiophene (5d): mp 113–115 °C; IR (KBr) 3100, 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.58 (s, 3H), 3.95 (s, 3H), 7.37–7.50 (m, 6H), 7.70 (d, J = 6.0 Hz, 1H), 11.86 (s, 1H); MS m/z 342 (M^+). Anal. Calcd for $C_{18}H_{14}O_5S$: C, 63.15; H, 4.12; S, 9.37. Found: C, 64.33; H, 4.17; S, 9.12.

4-Hydroxy-5,6-bis(methoxycarbonyl)-7-(3,4-dichlorophenyl)benzo[*b*]thiophene (5e): mp 130–131 °C; IR (KBr) 3100, 1720, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.64 (s, 3H), 3.92 (s, 3H), 7.20–7.57 (m, 4H), 7.66 (d, J = 6.0 Hz, 1H), 11.80 (s, 1H); MS m/z 410 (M^+). Anal. Calcd for $C_{18}H_{12}Cl_2O_5S$: C, 52.57; H, 2.94; S, 7.80; Cl, 17.24. Found: C, 52.41; H, 2.89; S, 7.13; Cl, 17.21.

4-Hydroxy-5,6-bis(methoxycarbonyl)-7-(3-thienyl)benzo[*b*]thiophene (5f): mp 107–109 °C; IR (KBr) 3100, 1735, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.63 (s, 3H), 3.91 (s 3H), 7.02–7.47 (m, 4H), 7.66 (d, J = 7.0 Hz, 1H), 11.76 (s, 1H); MS m/z 348 (M^+). Anal. Calcd for $C_{16}H_{12}O_5S_2$: C, 55.16; H, 3.47; S, 18.41. Found: C, 55.09; H, 3.55; S, 18.33.

Preparation of 3-(α-Acetoxy-3,4-dimethoxybenzyl)-thiophene-2-carbaldehyde (14). To a solution of *N,N,N'*-trimethylethylenediamine (4.6 mL, 36 mmol) in 100 mL of THF was added BuLi (20.6 mL, 33 mmol) at −78 °C. After 5 min, 3-bromo-2-thiophenecarbaldehyde[16] (5.73 g, 30 mmol) was added, and the mixture was allowed to stir for an additional 15 min. BuLi (37.5 mL, 60 mmol) was added, and the reaction mixture was stirred at the same temperature for 0.5 h. 3,4-Dimethoxybenzaldehyde (5.0 g, 30 mmol) in 50 mL of THF was added at −78 °C, and the reaction mixture was gradually warmed to 0 °C (1 h), diluted with water, and extracted with EtOAc. The organic extract was washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated under reduced pressure. The crude hydroxy aldehyde was transformed into the acetoxy aldehyde under the same conditions as the preparation of **11a–f**. The crude product was purified by silica gel chromatography to give 24.0 g (75%) of the acetoxy aldehyde **14**: mp 113–115 °C; IR (KBr) 1720, 1680, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 3.83 (s, 6H), 6.71–7.09 (m, 3H), 7.17 (d, J = 5.0 Hz, 1H), 7.32 (d, J = 5.0 Hz, 1H), 7.51 (s, 1H), 10.01 (s, 1H); MS m/z 320 (M^+). Anal. Calcd for $C_{16}H_{16}O_5S$: C, 59.99; H, 5.03; S, 10.01. Found: C, 59.83, H, 5.12; S, 9.97.

Reaction of 14 with DMAD was carried out in the same manner as the reaction of **11a–f** with DMAD to give the desired benzo[*b*]thiophene **16** in 83% yield.

4-(3,4-Dimethoxyphenyl)-5,6-bis(methoxycarbonyl)-7-hydroxybenzo[*b*]thiophene (16): mp 188 °C; IR (KBr) 1730, 1660, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (s, 3H), 3.86 (s, 3H), 3.93 (s, 6H), 6.90 (s, 3H), 7.06 (d, J = 5.4 Hz, 1H), 7.61 (d, J = 5.4 Hz, 1H), 11.81 (s, 1H); MS m/z 402 (M^+). Anal. Calcd for $C_{20}H_{18}O_7S$: C, 59.69; H, 4.51; S, 7.97. Found: C, 59.75; H, 4.57; S, 8.11.

Preparation of the 2-(α-Acetoxy-3,4-dimethoxybenzyl)pyridine-3-carbaldehyde (18). The hydroxy acetal **6** was transformed into the corresponding acetoxy acetal by the usual method (Ac_2O, Et_3N/CH_2Cl_2). The acetoxy acetal was

(16) Gronowitz, S.; Moses, P.; Hornfeld, A.-B.; Hakkansson, R. *Ark. Kemi* **1961**, *17*, 165.

hydrolyzed by refluxing a solution of oxalic acid (7 g) in acetone–water (1:1, 100 mL) for 10 min. The mixture was cooled to room temperature and extracted with EtOAc. The organic extract was washed with saturated aqueous $NaHCO_3$ and brine. The organic mixture was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give the acetoxy aldehyde **18** in 76% yield: mp 193–195 °C; IR (KBr) 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3H) 3.85 (s, 3H), 3.86 (s, 3H), 6.81 (d, J = 8.2 Hz, 1H), 7.49 (s, 1H), 7.44 (dd, J = 7.8, 4.8 Hz, 1H), 8.14 (dd, J = 7.8, 1.8 Hz, 1H), 8.83 (dd, J = 4.8, 1.8 Hz, 1H), 10.34 (s, 1H); MS m/z 315 (M^+). Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.46; H, 5.62; N, 4.71.

Reaction of 18 with DMAD was carried out in the same manner as the reaction of **11a–f** with DMAD (0.5 h) to give the desired benzo[*b*]pyridine **20** in 66% yield.

5-Hydroxy-6,7-bis(methoxycarbonyl)-8-(3,4-dimethoxyphenyl)quinoline (20): mp 183–184 °C; IR (KBr) 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.60 (s, 3H), 3.86 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 6.87–6.98 (m, 3H), 7.48 (dd, J = 8.4, 4.3 Hz, 1H), 8.79 (dd, J = 8.4, 1.8 Hz, 1H), 9.02 (dd, J = 4.3, 1.8 Hz, 1H), 12.42 (s, 1H); MS m/z 397 (M^+). Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.25; H, 4.96; N, 3.68.

Preparation of the Acetoxy Aldehyde 22a,b. 1-(Phenylsulfonyl)indole-3-carbaldehyde (**21**)[9] (79 g, 0.28 mol) was transformed into the corresponding dimethyl acetal in 87% yield in the same manner as the preparation of the thiophene-3-carbaldehyde dimethyl acetal. A solution of the acetal (0.24 mol) and TMEDA (28 g, 0.24 mol) in dry THF (400 mL) was cooled to −78 °C under nitrogen atmosphere and BuLi (165 mL, 0.26 mol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 1 h. The resulting mixture was cooled to −78 °C and was added to a solution of the appropriate arylaldehyde (0.24 mol) in 100 mL of THF. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was diluted with 10% aqueous HCl (300 mL) and stirred for 1 h at room temperature. The resulting mixture was extracted with EtOAc, and the organic extract was washed with brine and dried over $MgSO_4$. The organic mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography to give the hydroxy aldehyde. The hydroxy aldehyde was transformed into the acetoxy aldehyde by the usual method (Ac_2O, Et_3N/CH_2Cl_2).

1-(Phenylsulfonyl)-2-(α-acetoxybenzyl)indole-3-carbaldehyde (22a) was prepared in 68% yield from **21** and benzaldehyde: mp 170–172 °C; IR (KBr) 1750, 1665, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 7.34–7.61 (m, 11H), 7.90–7.94 (m, 2H), 8.11–8.16 (m, 1H), 8.40–8.44 (m, 1H), 10.58 (s, 1H); MS m/z 433 (M^+). Anal. Calcd for $C_{24}H_{19}NO_5S$: C, 66.50; H, 4.42; N, 3.23; S, 7.40. Found: C, 66.56; H, 4.51; N, 3.21; S, 7.19.

1-(Phenylsulfonyl)-2-(α-acetoxy-3,4,5-trimethoxybenzyl)indole-3-carbaldehyde (22b) was prepared in 66% yield from **21** and 3,4,5-trimethoxybenzaldehyde: mp 185–187 °C; IR (KBr) 1755, 1660, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 3.77 (s, 6H), 3.86 (s, 3H), 6.62 (s, 2H), 7.34–7.61 (m, 5H), 7.84–7.89 (m, 2H), 8.11–8.20 (m, 2H), 8.40–8.44 (m, 1H), 10.68 (s, 1H); MS m/z 523 (M^+). Anal. Calcd for $C_{27}H_{25}NO_8S$: C, 61.94; H, 4.81; N, 2.68; S, 6.12. Found: C, 61.76; H, 4.96; N, 2.90; S, 6.03.

Reaction of acetoxy aldehyde 22a with DMAD was carried out under the same conditions as the reaction of acetoxy aldehydes **11a–f** with DMAD.

4-Hydroxy-2,3-bis(methoxycarbonyl)-1-phenyl-9-(phenylsulfonyl)carbazole (24a): mp 202–203 °C; IR (KBr) 1735, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 3.93 (s, 3H), 7.12–7.53 (m, 12H), 8.17 (d, J = 7.2 Hz, 1H), 8.39 (s, J = 7.2 Hz, 1H), 11.25 (s, 1H); MS m/z 515 (M^+). Anal. Calcd for $C_{28}H_{21}NO_7S$: C, 65.23; H, 4.11; N, 2.72; S, 6.22. Found: C, 65.42; H, 4.18; N, 2.61; S, 6.05.

Reaction of acetoxy aldehyde 22b with DMAD was carried out under the same conditions as the reaction of acetoxy aldehyde **11a–f** with DMAD. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography to give the desired benzo[*b*]indole **24b** (46%) along with the benzo[*b*]carbazoles **26** (23%) and **27** (15%).

4-Hydroxy-2,3-bis(methoxycarbonyl)-1-(3,4,5-trimethoxyphenyl)-9-(phenylsulfonyl)carbazole (24b): mp 192–193 °C; IR (Nujol) 1750, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.54 (s, 3H), 3.71 (s, 6H), 3.89 (s, 3H), 3.94 (s, 3H), 6.44 (s, 2H), 7.24–7.55 (m, 7H), 8.14 (d, J = 7.2 Hz, 1H), 8.37 (d, J = 7.2 Hz, 1H), 11.97 (s, 1H); MS m/z 605 (M^+). Anal. Calcd for $C_{31}H_{27}NO_{10}S$: C, 61.48; H, 4.49; N, 2.31; S, 5.29. Found: C, 61.32; H, 4.58; N, 2.45; S, 5.13.

11-Hydroxy-8,9,10-trimethoxy-5-(phenylsulfonyl)-5*H*-benzo[*b*]carbazole (26): mp 187–189 °C; IR (KBr) 3600, 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.96 (s, 3H), 4.03 (s, 3H), 4.20 (s, 3H), 7.11 (s, 1H), 7.24–7.46 (m, 5H), 7.80–7.84 (m, 2H), 8.10 (s, 1H), 8.24–8.30 (m, 2H), 10.23 (s, 1H); MS m/z 463 (M^+). Anal. Calcd for $C_{25}H_{21}NO_6S$: C, 64.78; H, 4.57; N, 3.02; S, 6.92. Found: C, 64.65; H, 4.75; N, 3.16; S, 7.02.

6-Acetoxy-8,9,10-trimethoxy-5-(phenylsulfonyl)-5*H*-benzo[*b*]carbazole (27): mp 191–193 °C; IR (KBr) 1735, 1330 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.63 (s, 3H), 3.98 (s, 3H), 4.02 (s, 3H), 4.09 (s, 3H), 6.98 (s, 1H), 7.10–7.50 (m, 7H), 7.86 (d, J = 7.2 Hz, 1H), 8.30 (d, J = 7.2 Hz, 1H), 8.13 (s, 1H); MS m/z 505 (M^+). Anal. Calcd for $C_{27}H_{23}NO_7S$, C, 64.15; H, 4.59; N, 2.77; S, 6.34. Found: C, 63.98; H, 4.63; N, 2.85; S, 6.23.

3-Phenyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (23a). A stirred solution of **22a** (1.0 g, 2.31 mmol) in dry benzene (20 mL) was treated with TFA (0.01 mL) and heated under reflux for 0.5 h. The reaction mixture was cooled to room temperature and washed with saturated aqueous $NaHCO_3$ and brine. The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography to give 310 mg (36%) of **23a** as colorless crystals: mp 147–149 °C (lit.[9c] mp 148.5–149.5 °C). Other analytical data were in accord with those reported by Gribble.[9c]

Reaction of Furo[3,4-*b*]indole (23a) with DMAD. A mixture of **23a** (290mg, 0.67mmol) and DMAD (142mg, 1.0 mmol) was heated under reflux in benzene (5 mL) in the presence of $TsOH·H_2O$ (6 mg, 0.03 mmol). After 1 h, the solvent was removed under reduced pressure. To the mixture was added Et_2O (1 mL). The resulting crystals was collected by filtration to afford the carbazole **24a** in 72% yield.