Total syntheses of three natural products, vignafuran, 2-(4-hydroxy-2-methoxyphenyl)-6-methoxybenzofuran-3-carboxylic acid methyl ester, and coumestrol from a common starting material

Kou Hiroya, Naoyuki Suzuki, Akito Yasuhara, Yuya Egawa, Atsushi Kasano and Takao Sakamoto*

Graduate School of Pharmaceutical Sciences, Tohoku University, Aoba-ku, Sendai 980-8578, Japan. E-mail: sakamoto@mail.pharm.tohoku.ac.jp; Fax: +81-22-217-6864

Vignafuran **2**, 2-(4-hydroxy-2-methoxyphenyl)-6-methoxybenzofuran-3-carboxylic acid methyl ester **3**, and coumestrol **4** were efficiently synthesized from the same starting material, 4-bromoresorcinol **14a**, through the common intermediate, diarylacetylene **7**. The key steps of these syntheses were the tetrabutylammonium fluoride (TBAF)-catalyzed benzo[*b*]furan ring formation for **2** and the carbonylative ring closure methodology catalyzed by a Pd complex for **3** and **4**.

Introduction

Heterocyclic compounds, particularly indole[1] and benzo[*b*]furan[2] derivatives, are of interest because they occur widely in Nature and have unique biological activities.[3] Many synthetic methods for indole and benzo[*b*]furan structures have already been reported.[4,5] Among them, the cyclization reaction of 2-ethynylphenol or 2-ethynylaniline derivatives is a powerful method for constructing such ring systems because of the availability of the starting materials and its efficiency.[4,5] For the last few decades, many efforts toward developing new methods using this strategy have been published, and most studies have been carried out using metal species, *e.g.,* copper(I) species,[6] NaAuCl$_4$·H$_2$O,[7] palladium(II) species,[8–10] and metal alkoxides.[11]

Between 1966 and 1969, Castro *et al.*[6a,b] reported pioneering work involving the copper(I) halide-catalyzed sequential coupling and cyclization reactions of 2-iodophenol and 2-iodoaniline with Cu-acetylide derivatives to give benzo[*b*]furans and indoles, respectively (Scheme 1). In spite of its usefulness,
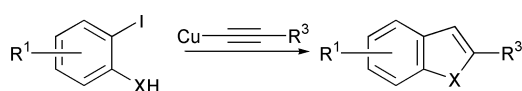

X = O or NR^2; R^1 = Me, OH, halogen; R^2 = H, Et, Me; R^3 = Ph, Pr, pyridinyl

Scheme 1

Castro's method has not seen wide use, because explosive Cu-acetylides have to be prepared and isolated. Subsequently, Owen[6c] and Nilsson[6d] independently improved this problem by using Cu$_2$O in pyridine or ^{t}BuOCu in pyridine, respectively, although heating was necessary for the cyclization reaction.

The palladium(II) species-promoted cyclization reaction of 2-ethynylaniline and/or 2-ethynylphenol derivatives, which was first reported in the middle 1980s,[8a,b] was found to have wide applicability because of the milder reaction conditions than the previously reported methods.[8–10] Later on, this methodology was extended for constructing 2,3-disubstituted benzo[*b*]furans and indoles using disubstituted acetylenic compounds as the starting materials.[9] More recently, the trapping methodologies of the resulting 3-substituted Pd species have been well investigated.[10] (Scheme 2).

During the course of our continuous interests in the syn-

X = O or NR; E = electrophile
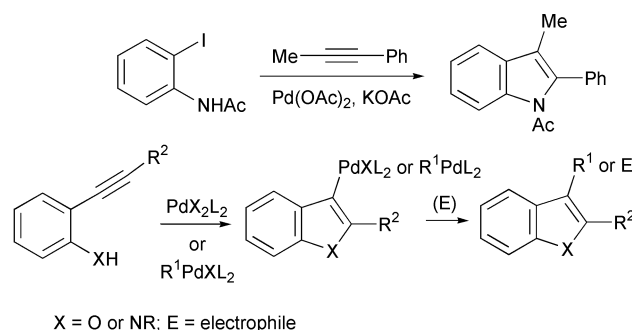
Scheme 2

theses of substituted heterocyclic compounds, we have already published efficient synthetic procedures for 2-mono- and 2,3-disubstituted indoles and/or benzo[*b*]furans, which involve (1) the cyclization reaction of 2-ethynylphenylcarbamates to indoles under basic conditions (sodium ethoxide in ethanol or potassium *tert*-butoxide in *tert*-butyl alcohol),[11] (2) the Pd-catalyzed cyclization followed by alkenylation,[10k] (3) the Pd-catalyzed carbonylative cyclization reaction,[10a] and (4) the tetrabutylammonium fluoride (TBAF)-promoted cyclization reaction (Scheme 3).[12]

However, other synthetic procedures for the methyl 2-substituted indole-3-carboxylate derivatives have recently been independently reported by Yang[10j] and Scammells.[10h,i] Yang argued about the difficulty in reproducing the reaction conditions reported by Scammells,[10h,i] which are almost the same as those we have already reported.[10a] Consequently, Yang reported an improved procedure for trapping the C-Pd species by carbon monoxide, although their catalytic system seems to be slightly complicated.[10j]

Based on the above background about the heterocyclic ring system syntheses, we report here the synthesis of three different natural products from the same starting materials utilizing our own method.

Results and discussion

(a) Target molecules and synthetic strategy

Vignafuran **2**, isolated from the leaves of cowpea seedlings (*Vigna unguiculata* (L.) Walp.) grown in daylight and infected
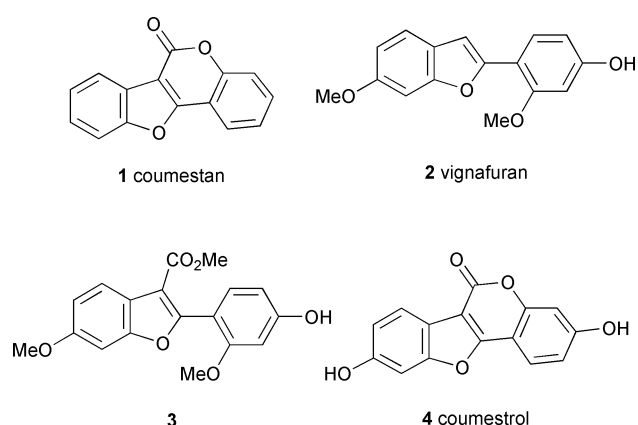
Scheme 3

1 coumestan   **2** vignafuran

3   **4** coumestrol
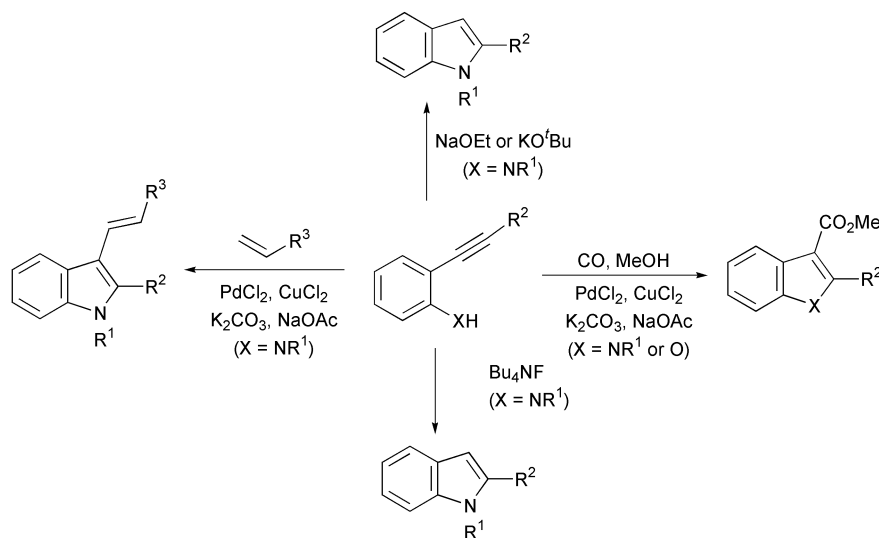
Fig. 1

with *Colletotrichum lindemuthianum*, has been shown to have strong antifungal activity (Fig. 1).[13] The biosynthetic pathway to vignafuran **2** has been elucidated by Martin and Dewick utilizing feeding experiments with labelled amino acids.[14] Kinoshita later showed the chemical mechanism by careful analysis.[15d] The total synthesis of vignafuran **2** was first reported at the same time as its isolation,[13a] after which four different synthetic methods were reported.[15]

In the meantime, 2-(4-hydroxy-2-methoxyphenyl)-6-methoxybenzofuran-3-carboxylic acid methyl ester **3** was isolated from exudates released by the roots of iron-deficient alfalfa (*Medicago sativa*) (Fig. 1).[16] However, not only the biological activities of **3**, but also both the biosynthetic pathway and its relationship to iron deficiency have yet to be determined.

Coumestrol **4** was isolated from alfalfa and ladino clover by Bickoff *et al.* in the 1950s (Fig. 1).[17] As the structure of **4** has some resemblance to the well known (*E*)-4,4′-dihydroxystilbene derivatives, which has potent pharmacological activity, coumestrol **4** shows estrogenic activity.[18] Total syntheses of **4** have been reported by several groups using different approaches;[17d,18,19] however, most of the reported methods required multiple steps and it appears that the overall yield could be improved.

Before the synthesis of the natural products, we planned to apply our carbonylative cyclization strategy[10a] toward constructing the coumestan ring system **1** (Fig 1). Namely, the intramolecular carbonylative cyclization reaction of the diphenylacetylene **5**, which would be prepared from a 2-halogenophenol **6** and acetylene, could produce the coumestan ring system **1** in one step.

For the synthesis of three benzo[*b*]furan natural products, we planned the following strategy. Coumestrol **4** could be synthesized from **3** by successive deprotection and lactonization reactions. Compounds **2** and **3** could be synthesized from diphenylacetylene **7** either by a cyclization reaction to benzo[*b*]furan or *via* our method involving the carbonylative cyclization reaction[10a] to methyl benzo[*b*]furan-3-carboxylates. Compound **7** could be synthesized by the Sonogashira coupling reaction between **8** and **9**. Both **8** and **9** could be constructed from the same starting material **10** (Fig. 2).

(b) Synthesis of the coumestan ring system

2-Iodophenol **11** was used as the starting material for the synthesis of the coumestan ring system. Pal and Kundu reported that the Pd-catalyzed cross-coupling reaction of aryl iodides under an acetylene atmosphere gave the corresponding diarylacetylene.[20] Thus, by using their conditions, **13** was afforded in one step using the reaction of the acetate **12** under acetylene gas with aryl iodides in the presence of PdCl$_2$(PPh$_3$)$_2$, CuI, and Et$_3$N (75%). Deacetylation of **13** under basic conditions, followed by the intramolecular carbonylative cyclization reaction of **5** as catalyzed by PdCl$_2$ under carbon monoxide atmosphere,[10a] afforded **1** in one step (35%) (Scheme 4). The synthesized product was identified based on a comparison with previously reported data.[18,19c,d,21]

(c) Synthesis of the substituted phenylacetylene derivatives

Commercially available 4-bromoresorcinol **14a** was selectively tosylated and the resulting monohydroxy compound was converted into both the methyl ether **15a** and the methoxymethyl ether **16a** under standard conditions, respectively. The Sonogashira coupling reaction[22] of the bromide **15a** with trimethylsilylacetylene catalyzed by PdCl$_2$(PPh$_3$)$_2$ in the presence of CuI and Et$_3$N in DMF, followed by the detrimethylsilylation reaction, gave **9** in 87% yield (2 steps). On the other hand, the tosyl ester **16a** was converted into the methyl ether **17** by alkaline hydrolysis followed by the standard methylation reaction. The methoxymethyl group of **17** was removed under acidic conditions, then the resulting hydroxy group was acetylated to afford the acetate **8a** (Scheme 5).

The iodides **15b** and **16b** also could be synthesized in exactly the same way as described above from the known 4-iodoresorcinol **14b** which was synthesized from resorcinol and iodine monochloride.[23] However, as the overall yields of both **15b** and **16b** from **14b** were quite low due to the lack of regioselectivity during the monotosylation reaction, we have to improve the synthesis of these compounds.
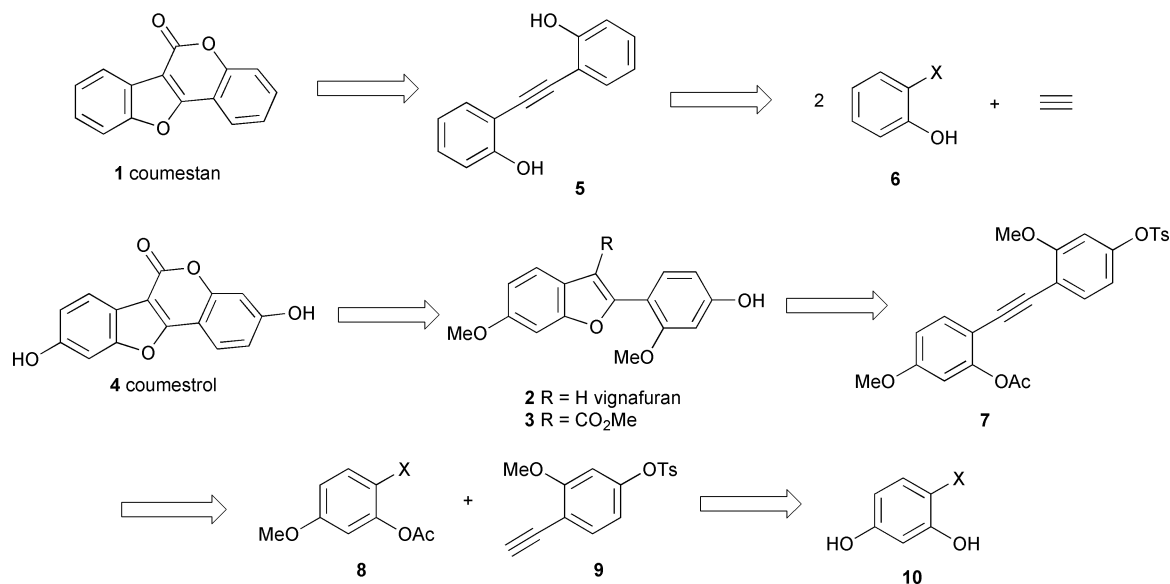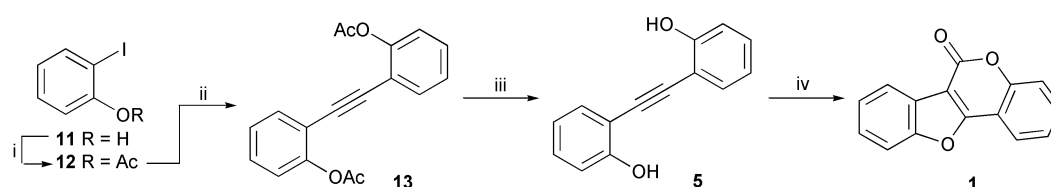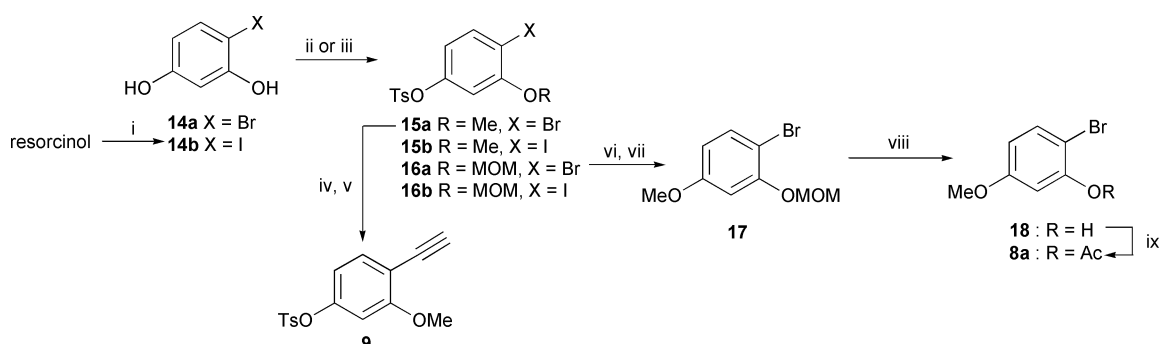
Fig. 2

Scheme 4 *Reagents, conditions and yields*: i, Ac$_2$O, pyridine; ii, acetylene (1 atm), PdCl$_2$(PPh$_3$)$_2$, CuI, Et$_3$N, DMF, 60 °C, 75% from **11**; iii, NaOH, aq. MeOH, RT, 90%; iv, CO (1 atm), PdCl$_2$, CuCl$_2$, AcONa, K$_2$CO$_3$, MeCN, 35%.

Scheme 5 *Reagents, conditions and yields*: i, ICl, Et$_2$O, RT, 70%; ii, TsCl, K$_2$CO$_3$, acetone, reflux; then MeI, reflux, 79% (**14a** ⟶ **15a**), 56% (**14b** ⟶ **15b**); iii, TsCl, K$_2$CO$_3$, acetone, reflux; then MOMCl, reflux, 82% (**14a** ⟶ **16a**), 56% (**14b** ⟶ **16b**); iv, trimethylsilylacetylene, PdCl$_2$(PPh$_3$)$_2$, CuI, Et$_3$N, DMF, 100 °C; v, K$_2$CO$_3$, MeOH, RT, 87% from **15a**; vi, KOH, aq. EtOH, reflux; vii, K$_2$CO$_3$, MeI, acetone, reflux, 74% from **16a**; viii, (COOH)$_2$·2H$_2$O, aq. MeOH, reflux, 96%; ix, AcCl, K$_2$CO$_3$, acetone, reflux, 90%.

This problem has been solved by conversion of the bromides into the iodides by employing Suzuki's method.[24] Thus, reaction of the bromides **15a** and **8a** with KI and CuI in warm HMPA gave the iodides **15b** and **8b**, each in 94% yield, respectively. Also, the Sonogashira coupling reaction was carried out using the iodide **15b** as the starting material under milder conditions to give **9** in a much higher overall yield (91% from **15a**) (Scheme 6).

(d) Coupling and cyclization reaction

When the acetylenic compound **9** and the bromide **8a** were heated at 100 °C in the presence of PdCl$_2$(PPh$_3$)$_2$, CuI and Et$_3$N in DMF, only the homocoupled product **20** was isolated (Table 1, entry 1). However, under almost the same reaction conditions but using the more reactive iodide **8b** as the counterpart, the desired heterocoupled product **7** was obtained in 41% yield at room temperature and 68% yield under reflux (Table 1, entries 2 and 3).
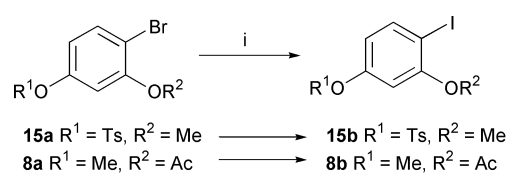
Scheme 6 *Reagents, conditions and yields*: i, KI, CuI, HMPA, 150 °C, 94% (**15a** ⟶ **15b**), 94% (**8a** ⟶ **8b**); ii, trimethylsilylacetylene, PdCl$_2$(PPh$_3$)$_2$, CuI, Et$_3$N, DMF, RT, 98%; iii, TBAF, THF, RT, 99%.

Table 1 Sonogashira coupling reaction of terminal alkyne **9** and halides **8a** and **8b**

Reagents and solvent: i, PdCl$_2$(PPh$_3$)$_2$, CuI, base, DMF.
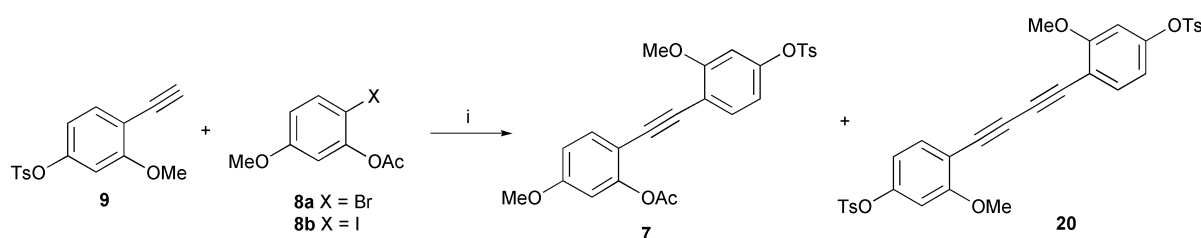
					Yield (%)	
Entry	X	Base	Temperature	Time (*t*/h)	**7**	**20**
1	Br	Et$_3$N	100 °C	1	0	39
2	I	Et$_3$N	RT	1.5	41	0
3	I	Et$_3$N	Reflux	1.5	68	0
4	I	^{i}Pr$_2$NH	RT	1.5	53	0
5	I	^{i}Pr$_2$NH	Reflux	1.5	Decomposition	0
6	I	^{i}Pr$_2$NH	60 °C	1.5	96	0

In 1997, Miller and Johnson reported the acceleration of the Sonogashira reaction by employing ^{i}Pr$_2$NH as the base.[25] In our case, an improvement in the yield was observed using their reaction conditions (Table 1, entry 2 *vs.* entry 4). However, when the reaction mixture was refluxed, the desired product could not be isolated at all. Presumably the instability of the coupled compound **7** causes a decrease in the yield. Finally, the coupled compound **7** was obtained in 96% yield when the reaction mixture was heated at 60 °C for 1.5 h (Table 1, entry 6).

(e) Synthesis of vignafuran, 2-(4-hydroxy-2-methoxyphenyl)-6-methoxybenzo[*b*]furan-3-carboxylic acid methyl ester, and coumestrol

The availability of **7** described above prompted us to attempt to use it for the syntheses of the three kinds of benzo[*b*]furan natural products.

Thus, the acetyl group of **7** was reductively removed by DIBAL-H to give the phenol **21**, which was cyclized by applying the TBAF-promoted reaction[12] to afford the benzo[*b*]furan **22** in 53% overall yield from **7**. Finally, the detosylation of **22** with sodium methoxide afforded vignafuran **2** in 78% yield (Scheme 7). The ^{1}H NMR and mass spectral data of the synthesized vignafuran **2** were identical with those of the reported natural product.[13]

For the synthesis of **3**, the methoxycarbonyl analogue of vignafuran **2**, the acetate **7** was allowed to react with carbon monoxide in MeOH in the presence of PdCl$_2$(PPh$_3$)$_2$, Cu-Cl$_2$·2H$_2$O, AcONa, and K$_2$CO$_3$ at room temperature for 2 days. Deacetylation, cyclization, and trapping reactions of the C3-Pd species by carbon monoxide proceeded successively and the desired methyl 2-arylbenzo[*b*]furan-3-carboxylate **23** was obtained in 71% yield (Scheme 7). The structure of **23** was confirmed by the molecular-ion peak (*m/z* 482) from EI mass spectrometry, the absorption at 1720 cm^{-1} from IR spectroscopy, and the three methoxy peaks (δ 3.71, 3.80, 3.87) and two typical 1,2,4-trisubstituted benzene ring patterns [δ 6.63 (1H, dd, *J* 8.5, 2.2), 6.71 (1H, d, *J* 2.2), 6.98 (1H, dd, *J* 8.5, 2.2), 7.03 (1H, dd, *J* 8.5, 2.2), 7.44 (1H, d, *J* 8.5), 7.87 (1H, d, *J* 8.5)] in the ^{1}H NMR spectrum. Finally, the tosyl group of **23** was removed by treatment with sodium methoxide in MeOH to afford quantitatively the target benzo[*b*]furan natural product **3** (Scheme 7).

For the coumestrol **4** synthesis, we first tried to cleave the two methoxy group of **3**. However, in our hands, it was not possible to remove the two methyl groups at the same time (BBr$_3$, CH$_2$Cl$_2$, −78 °C or AlCl$_3$, MeCN, 70 °C). The only isolated product was a monodemethylated compound. Therefore, we

changed the order of the reactions based on the assumption that the unreactivity of the second demethylation reaction will be due to the higher electron density on the aromatic ring. When the tosyl ester **23** was treated with BBr$_3$ at from −78 to −40 °C, as we expected, the double demethylation reaction smoothly proceeded to afford the dihydroxy compound **24** in 72% yield. Alkaline hydrolysis of the tosyl compound **24** (3 M KOH, THF, reflux), followed by acid-catalyzed lactonization (cat. TsOH, THF, 60 °C) gave coumestrol **4** in 53% yield from **24**. The spectral data of the synthesized **4** were identified with those of the reported compound (Scheme 7).[16,19d]

Experimental

2,2′-Diacetoxydiphenylacetylene 13

Acetic anhydride (0.89 ml, 10 mmol) was added to a solution of 2-iodophenol **11** (2.2 g, 10 mmol) in pyridine (50 ml) at 0 °C. After the solution had been stirred for 1 h at room temperature, pyridine was evaporated off and 3 M HCl (50 ml) was added to the residue. The aqueous solution was extracted by CHCl$_3$ and the organic solution was washed with water, dried over MgSO$_4$ and evaporated. Crude **12** was used in the next reaction without further purification.

A mixture of **12** (0.52 g, 2 mmol), PdCl$_2$(PPh$_3$)$_2$ (50 mg, 0.07 mmol), CuI (40 mg, 0.23 mmol) and Et$_3$N (0.59 ml, 10 mmol) in DMF (20 ml) was stirred at 60 °C under dried acetylene gas. After the mixture had been stirred for 16 h, the mixture was filtered through a Celite® pad and the filtrate was extracted with Et$_2$O. The combined organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (7:1) as eluent to give **13** (0.45 g, 75%) as a *white powder*, mp 143–145 °C (Found: C, 73.44; H, 4.84. C$_{18}$H$_{14}$O$_4$ requires C, 73.46; H, 4.79%); ν_{max} (KBr)/cm^{-1} 1760, 1220, 1180; δ_H (500 MHz) 2.36 (6H, s), 7.12 (2H, d, *J* 8.0), 7.22–7.26 (2H, m), 7.38 (2H, dt, *J* 8.0, 1.8), 7.54 (2H, dd, *J* 8.0, 1.8);
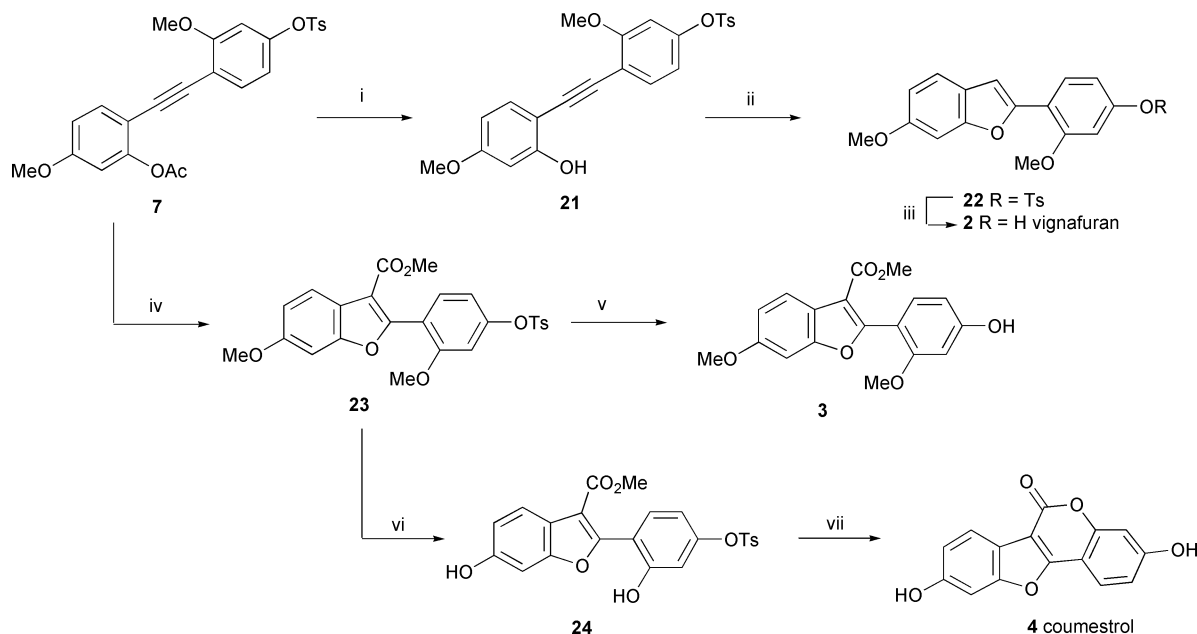
Scheme 7 *Reagents, conditions and yields*; i, DIBAL-H, PhMe, −78 °C, 81%; ii, TBAF, THF, reflux, 67%; iii, NaOMe, MeOH, reflux, 78 °C; iv, PdCl$_2$(PPh$_3$)$_2$, CuCl$_2$·2H$_2$O, AcONa, K$_2$CO$_3$, MeOH, CO, RT, 71%; v, NaOMe, MeOH, reflux, 100%; vi, BBr$_3$, CH$_2$Cl$_2$, −78 to 40 °C, 72%; vii, 3 M KOH, THF, reflux; then cat. TsOH, THF, 60 °C, 53%.

m/z 294 (M$^+$, 13.6%) and 210 (100) (Found: M$^+$, 294.0909. C$_{18}$H$_{14}$O$_4$ requires *M*, 294.0892).

2,2′-Dihydroxydiphenylacetylene 5

A mixture of **13** (0.21 g, 0.78 mmol) and 3 M NaOH (0.57 ml, 1.7 mmol) in MeOH (12 ml) was stirred at room temperature. After the mixture had been stirred for 30 min, the mixture was concentrated under reduced pressure and the residue was extracted with CHCl$_3$. The combined organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was purified by column chromatography and elution with hexane–AcOEt (7:1) to afford the *bisphenol* **5** (0.15 g, 90%) as a white powder, mp 95–97 °C (Found: C, 80.22; H, 5.06. C$_{14}$H$_{10}$O$_2$ requires C, 79.98; H, 4.79%); ν_{max} (KBr)/cm^{-1} 3300; δ_H (300 MHz) 5.87 (2H, s), 6.92–7.00 (4H, m), 7.30 (2H, ddd, *J* 8.8, 7.4, 1.4), 7.44 (2H, dd, *J* 7.7, 1.4); *m/z* 210 (M$^+$, 100%) and 181 (73.3) (Found: M$^+$, 210.0725. C$_{14}$H$_{10}$O$_2$ requires *M*, 210.0681).

6H-[1]Benzofuro[3,2-c]chromen-6-one (coumestan ring system) 1

A mixture of **5** (0.12 g, 0.56 mmol), PdCl$_2$ (10 mg, 0.06 mmol), CuCl$_2$ (0.16 g, 1.23 mmol), AcONa (0.09 g, 0.56 mmol) and K$_2$CO$_3$ (0.15 g, 1.1 mmol) in MeCN (5 ml) was stirred at room temperature for 20 h. The reaction mixture was concentrated under reduced pressure, then the residue was extracted with CHCl$_3$. The combined extracts were washed successively with water and saturated aq. NaCl. The organic solution was dried over MgSO$_4$ and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (10:1) as eluent to give coumestan **1**[18,19c,d,21] (0.046 g, 35%) as a white powder, mp 178–181 °C (lit.,[19c] mp 182–183 °C, mp 179–180 °C[19d]) (Found: C, 76.09; H, 3.57. Calc. for C$_{15}$H$_8$O$_3$: C, 76.27; H, 3.41%); δ_H (300 MHz) 7.40–7.53 (4H, m), 7.60–7.70 (2H, m), 8.05 (1H, d, *J* 7.7), 8.15 (1H, dd, *J* 6.3, 4.1); *m/z* 236 (M$^+$, 100%) (Found: M$^+$, 236.0457. Calc. for C$_{15}$H$_8$O$_3$: *M*, 236.0473).

4-Iodoresorcinol 14b

A solution of resorcinol (2.75 g, 25.0 mmol) and ICl (4.0 g, 25.0 mmol) in dry Et$_2$O (25 ml) was stirred at room temperature for 1 h. Water (50 ml) and Na$_2$SO$_3$ (1.0 g) were added to the mixture, then the aqueous phase was extracted with Et$_2$O. The

combined organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was successively purified with silica gel chromatography [AcOH–CHCl$_3$ (1:9)] and alumina chromatography [hexane–AcOEt (2:1)] to afford **14b**[23] as a colorless solid (4.13 g, 70%), δ_H (300 MHz) 5.21 (2H, br), 6.27 (1H, dd, *J* 8.6, 2.8), 6.54 (1H, d, *J* 2.8), 7.46 (1H, d, *J* 8.6); *m/z* 236 (M$^+$, 100%) (Found: M$^+$, 235.9356. Calc. for C$_6$H$_5$IO$_2$: *M*, 235.9327).

1-Bromo-2-methoxy-4-(tosyloxy)benzene 15a

A mixture of 4-bromoresorcinol **14a** (10.0 g, 53.0 mmol), K$_2$CO$_3$ (22.0 g, 159 mmol) and TsCl (11.1 g, 58.0 mmol) in acetone (150 ml) was refluxed for 21 h. MeI (15.0 g, 106 mmol) was added to the mixture, which was further refluxed for 3 h. The inorganic precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with AcOEt. The combined organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (3:1) as eluent to give **15a** (15.0 g, 79%) as a white powder. An analytical sample was recrystallized from AcOEt–hexane to give *colorless needles*, mp 69–72 °C (Found: C, 47.17; H, 3.76; S, 8.90. C$_{14}$H$_{13}$BrO$_4$S requires C, 47.07; H, 3.67; S, 8.97%); ν_{max} (CHCl$_3$)/cm^{-1} 1380, 1280, 1180, 1030; δ_H (300 MHz) 2.46 (3H, s), 3.79 (3H, s), 6.41 (1H, dd, *J* 8.5, 2.5), 6.60 (1H, d, *J* 2.5), 7.33 (2H, d, *J* 8.5), 7.41 (1H, d, *J* 8.5), 7.72 (2H, d, *J* 8.5).

1-Bromo-2-methoxymethoxy-4-(tosyloxy)benzene 16a

A mixture of 4-bromoresorcinol **14a** (5.00 g, 26.5 mmol), K$_2$CO$_3$ (11.0 g, 79.4 mmol) and TsCl (5.56 g, 29.2 mmol) in acetone (100 ml) was refluxed for 21 h. MOMCl (4.27 g, 53.0 mmol) was added to the mixture, which was further refluxed for 3 h. The inorganic precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with AcOEt. The combined organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (3:1) as eluent to give **16a** (8.45 g, 82%) as a white powder. An analytical sample was recrystallized from AcOEt–hexane to give *colorless needles*, mp 70–72 °C (Found: C, 46.54; H,

3.82; S, 8.25. $C_{15}H_{15}BrO_5S$ requires C, 46.52; H, 3.90; S, 8.28%); ν_{max} (CHCl$_3$)/cm^{-1} 1380, 1280, 1180, 1040; δ_H (300 MHz) 2.47 (3H, s), 3.43 (3H, s), 5.10 (2H, s), 6.57 (1H, dd, J 8.8, 2.7), 6.77 (1H, d, J 8.8), 7.33 (2H, d, J 8.2), 7.44 (1H, d, J 8.8), 7.72 (2H, d, J 8.2).

1-Iodo-2-methoxy-4-(tosyloxy)benzene 15b

(a) **Synthesis from 4-iodoresorcinol 14b.** A mixture of 4-iodoresorcinol **14b** (1.60 g, 6.78 mmol), K$_2$CO$_3$ (2.82 g, 20.4 mmol) and TsCl (1.40 g, 7.40 mmol) in acetone (30 ml) was refluxed for 15 h. MeI (2.89 g, 20.4 mmol) was added to the mixture, which was further refluxed for 3 h. The inorganic precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with AcOEt. The combined organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (4:1) as eluent to give **15b** (1.53 g, 56%) as a *yellow viscous oil*, ν_{max} (CHCl$_3$)/cm^{-1} 1380, 1280, 1180, 1040; δ_H (300 MHz) 2.46 (3H, s), 3.77 (3H, s), 6.30 (1H, dd, J 8.3, 2.5), 6.52 (1H, d, J 2.5), 7.30 (2H, d, J 8.3), 7.63 (1H, d, J 8.4), 7.72 (2H, d, J 8.4); *m/z* 404 (M$^+$, 76.2%) and 91(100) (Found: M$^+$, 403.9555. $C_{14}H_{13}IO_4S$ requires *M*, 403.9579).

(b) **Synthesis from 15a.** A mixture of **15a** (0.36 g, 1.00 mmol), KI (2.46 g, 15.0 mmol) and CuI (0.95 g, 5.00 mmol) in HMPA (3 ml) was stirred under an Ar atmosphere at 150 °C for 3 h. The reaction mixture was acidified by 3 M HCl and extracted with Et$_2$O. The organic solution was washed successively with aq. Na$_2$SO$_3$, water, and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was purified by silica gel column chromatography with hexane–AcOEt (2:1) as eluent to afford **15b** (0.38 g, 94%) as a yellow viscous oil.

1-Iodo-2-methoxymethoxy-4-(tosyloxy)benzene 16b

A mixture of 4-iodoresorcinol **14b** (3.25 g, 13.8 mmol), K$_2$CO$_3$ (9.54 g, 67.0 mmol) and TsCl (2.86 g, 15.0 mmol) in acetone (50 ml) was refluxed for 5 h. MOMCl (2.20 g, 27.4 mmol) was added to the mixture, which was further refluxed for 3 h. The inorganic precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with AcOEt. The combined organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (2:1) as eluent to give **16b** (3.67 g, 56%) as a *yellow viscous oil*, δ_H (300 MHz) 2.45 (3H, s), 3.43 (3H, s), 5.10 (2H, s), 6.46 (1H, dd, J 8.5, 2.6), 6.69 (1H, d, J 2.6), 7.33 (2H, d, J 8.5), 7.67 (1H, d, J 8.5), 7.72 (2H, d, J 8.5); *m/z* 434 (M$^+$, 13.6%) and 45 (100) (Found: M$^+$, 433.9680. $C_{15}H_{15}IO_5S$ requires *M*, 433.9685).

1-Bromo-4-methoxy-2-(methoxymethoxy)benzene 17

A solution of **16a** (7.51 g, 19.4 mmol) and KOH (5.88 g, 105 mmol) in a mixture of EtOH (315 ml) and water (35 ml) was heated under reflux for 2 h. 3 M HCl was added to the mixture at room temperature until pH 4. The aqueous phase was extracted with Et$_2$O and the extracts were washed successively with water and saturated aq. NaCl. The organic solution was dried over MgSO$_4$ and evaporated to give the crude phenol, which was used to the next reaction without further purification.

A mixture of the crude phenol, K$_2$CO$_3$ (14.0 g, 101 mmol) and MeI (19.0 g, 134 mmol) in acetone (1 l) was refluxed for 2.5 h. The inorganic precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted with Et$_2$O and the combined extract was washed

successively with water and saturated aq. NaCl. The organic solution was dried over MgSO$_4$ and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (4:1) as eluent to give **17** (3.56 g, 74%) as a *colorless oil*, bp 95 °C/3 mmHg (Found: C, 44.02; H, 4.62. $C_9H_{11}BrO_3$ requires C, 43.75; H, 4.49%); ν_{max} (CHCl$_3$)/cm^{-1} 1310, 1280, 1060, 1030; δ_H (300 MHz) 3.52 (3H, s), 3.78 (3H, s), 5.20 (2H, s), 6.48 (1H, dd, J 8.8, 2.7), 6.77 (1H, d, J 2.7), 7.41 (1H, d, J 8.8).

2-Bromo-5-methoxyphenol 18

A solution of **17** (3.56 g, 14.4 mmol) and oxalic acid dihydrate (3.66 g, 29.0 mmol) in MeOH–water (1:1; 80 ml) was refluxed for 2.5 h. The reaction mixture was extracted with Et$_2$O and the combined extract was washed successively with water and saturated aq. NaCl. The organic solution was dried over MgSO$_4$ and evaporated. The residue was purified by silica gel column chromatography and elution with hexane–AcOEt (7:1) to give **18**[26] (2.82 g, 96%) as a colorless oil, bp 90 °C/3 mmHg (Found: C, 41.39; H, 3.55. Calc. for $C_7H_7BrO_2$: C, 41.41; H, 3.47%); δ_H (300 MHz) 3.77 (3H, s), 5.53 (1H, br), 6.41 (1H, dd, J 8.8, 2.9), 6.60 (1H, d, J 2.9), 7.30 (1H, d, J 8.8).

2-Acetoxy-1-bromo-4-methoxybenzene 8a

A mixture of **18** (2.30 g, 11.3 mmol), K$_2$CO$_3$ (3.10 g, 22.4 mmol) and AcCl (2.21 g, 28.1 mmol) in acetone (60 ml) was refluxed for 2 h. Water (200 ml) was added to the mixture, which was extracted with AcOEt. The combined extract was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (5:1) as eluent to give **8a** (2.50 g, 90%) as a colorless oil, bp 110 °C/4 mmHg (Found: C, 44.30; H, 3.79. $C_9H_9BrO_3$ requires C, 44.11; H, 3.70%); ν_{max} (CHCl$_3$)/cm^{-1} 1780, 1290, 1200, 1020; δ_H (300 MHz) 2.30 (3H, s), 3.71 (3H, s), 6.66 (1H, dd, J 8.5, 2.7), 6.68 (1H, d, J 2.7), 7.43 (1H, d, J 8.5).

2-Acetoxy-1-iodo-4-methoxybenzene 8b

A mixture of **8a** (0.38 g, 1.55 mmol), KI (3.86 g, 23.3 mmol) and CuI (1.48 g, 7.75 mmol) in HMPA (3 ml) was stirred under an Ar atmosphere at 150 °C for 3 h. The reaction mixture was acidified by 3 M HCl and extracted with Et$_2$O. The organic solution was washed successively with aq. Na$_2$SO$_3$, water, and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was purified by silica gel column chromatography and elution with hexane–AcOEt (2:1) to afford **8b**[27] (0.43 g, 94%) as a colorless oil; ν_{max} (film)/cm^{-1} 1780, 1240, 1200, 1040; δ_H (300 MHz) 2.36 (3H, s), 3.78 (3H, s), 6.60 (1H, dd, J 8.8, 3.0), 6.69 (1H, d, J 3.0), 7.66 (1H, d, J 8.8); *m/z* 292 (M$^+$, 76.2%) and 250 (100) (Found: M$^+$, 291.9587. $C_9H_9IO_3$ requires *M*, 291.9595).

2-Methoxy-4-(tosyloxy)phenylacetylene 9

(a) **Synthesis from 15a.** A mixture of **15a** (0.20 g, 0.56 mmol), trimethylsilylacetylene (0.33 g, 3.36 mmol), CuI (13.0 mg, 0.06 mmol) and PdCl$_2$(PPh$_3$)$_2$ (23.0 mg, 0.03 mmol) in a mixture of Et$_3$N (1.0 ml) and DMF (0.5 ml) was heated at 100 °C for 24 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted with Et$_2$O and the combined extracts were washed successively with water and saturated aq. NaCl. The organic solution was dried over MgSO$_4$ and evaporated to afford **19** as a colorless solid, which was used to the next reaction without further purification.

A mixture of the crude silyl compound **19** and K$_2$CO$_3$ (0.35 g, 2.52 mmol) in MeOH (100 ml) was stirred at room temperature for 1.5 h. The excess of K$_2$CO$_3$ was filtered off and the residue was concentrated under reduced pressure. The

residue was extracted with Et$_2$O and the combined organic solution was washed successively with water and saturated aq. NaCl. The organic solution was dried over MgSO$_4$ and evaporated. The residue was purified by silica gel column chromatography and elution with hexane–AcOEt (3:1) to give **9** (0.44 g, 87%) as a yellow viscous oil, v_{max} (film)/cm^{-1} 3300, 1380, 1280, 1180, 1040; δ_H (300 MHz) 2.45 (3H, s), 3.30 (1H, s), 3.79 (3H, s), 6.48 (1H, dd, J 8.2, 2.2), 6.59 (1H, d, J 2.2), 7.32 (2H, d, J 8.3), 7.33 (1H, d, J 8.5), 7.72 (2H, d, J 8.3); m/z 302 (M$^+$, 17.3%) and 91 (100) (Found: M$^+$, 302.0611. C$_{16}$H$_{14}$O$_4$S requires M, 302.0613).

(b) Synthesis from 15b. A mixture of **15b** (1.05 g, 2.60 mmol), trimethylsilylacetylene (1.78 g, 18.2 mmol), CuI (50 mg, 0.26 mmol) and PdCl$_2$(PPh$_3$)$_2$ (92 mg, 0.13 mmol) in a mixture of Et$_3$N (4.0 ml) and DMF (6.0 ml) was stirred at room temperature for 1 h. Water was added to the mixture and extracted with Et$_2$O. The combined extracts were washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (5:1) as eluent to give the *TMS-acetylene* **19** (0.95 g, 98%) as a colorless solid. The analytical sample was further purified by recrystallization from AcOEt–hexane to afford colorless needles, mp 105–107 °C (Found: C, 61.02; H, 5.96; S, 8.46. C$_{19}$H$_{22}$O$_4$SSi requires C, 60.93; H, 5.92; S, 8.56%); v_{max} (CHCl$_3$)/cm^{-1} 1380, 1280, 1180, 1040; δ_H (300 MHz) 0.24 (9H, s), 2.44 (3H, s), 3.75 (3H, s), 6.45 (1H, dd, J 8.4, 2.2), 6.53 (1H, d, J 2.2), 7.30 (3H, d, J 8.4), 7.69 (2H, d, J 8.4).

A solution of **19** (0.56 g, 1.50 mmol) and TBAF (1.0 M solution in THF; 1.50 ml, 1.50 mmol) in THF (30 ml) was stirred at room temperature for 10 min. Water was added to the mixture, which was extracted with Et$_2$O. The organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (3:1) as eluent to give **9** (0.45 g, 99%) as a yellow viscous oil.

2-Acetoxy-2′,4-dimethoxy-4′-(tosyloxy)diphenylacetylene 7. Typical procedure (Table 1, entry 6)

A mixture of **8b** (148 mg, 0.51 mmol), **9** (200 mg, 0.66 mmol), CuI (10.0 mg, 0.05 mmol), PdCl$_2$(PPh$_3$)$_2$ (18.0 mg, 0.03 mmol) and ^{i}Pr$_2$NH (0.11 ml, 0.77 mmol) in DMF (3.0 ml) was stirred at 60 °C for 1.5 h. Water was added to the mixture, which was extracted with CHCl$_3$. The organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was purified by silica gel column chromatography with hexane–AcOEt (2:1) as eluent to give **7** (230 mg, 96%) as a *yellow viscous oil*, v_{max} (CHCl$_3$)/cm^{-1} 1770, 1380, 1280, 1180, 1040; δ_H (300 MHz) 2.35 (3H, s), 2.45 (3H, s), 3.78 (3H, s), 3.82 (3H, s), 6.48 (1H, dd, J 8.5, 2.2), 6.59 (1H, d, J 2.2), 6.66 (1H, d, J 2.2), 6.77 (1H, dd, J 8.5, 2.2), 7.30 (1H, d, J 8.5), 7.32 (2H, d, J 8.5), 7.47 (1H, d, J 8.5), 7.72 (2H, d, J 8.5); m/z 466 (29.9%, M$^+$) and 269 (100) (Found: M$^+$, 466.1091. C$_{25}$H$_{22}$O$_7$S requires M, 466.1087).

2-Hydroxy-2′,4-dimethoxy-4′-(tosyloxy)diphenylacetylene 21

DIBAL-H (1.0 M solution in PhMe; 1.56 ml, 1.56 mmol) was added to a solution of **7** (240 mg, 0.52 mmol) in CH$_2$Cl$_2$ (3 ml) at −78 °C. After the solution had been stirred at the same temperature for 3 h, Et$_2$O and saturated aq. NH$_4$Cl were successively added to the mixture, which was then extracted with CHCl$_3$. The combined organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was chromatographed on silica gel and eluted with hexane–AcOEt (6:1) to afford **21** (180 mg, 81%) as a *viscous yellow oil*, v_{max} (CHCl$_3$)/cm^{-1} 3400, 1380, 1280, 1180, 1040; δ_H (300 MHz) 2.45 (3H, s), 3.80 (3H, s), 3.85 (3H, s), 6.46 (1H, dd, J 8.5, 2.2), 6.53 (1H, dd, J 8.5, 2.2),

6.55 (1H, d, J 2.2), 6.63 (1H, d, J 2.2), 6.74 (1H, s), 7.27 (1H, d, J 8.5), 7.30 (1H, d, J 8.5), 7.33 (2H, d, J 8.0), 7.73 (2H, d, J 8.0); m/z 424 (39.3%, M$^+$) and 269 (100) (Found: M$^+$, 424.0932. C$_{23}$H$_{20}$O$_6$S requires M, 424.0981).

6-Methoxy-2-[2-methoxy-4-(tosyloxy)phenyl]benzo[b]furan 22

A solution of **21** (120 mg, 0.28 mmol) and TBAF (1.0 M solution in THF; 0.56 ml, 0.56 mmol) in THF (7 ml) was refluxed for 3 h. The reaction mixture was diluted with water and the precipitate was filtered off. The filtrate was concentrated *in vacuo*, then the residue was extracted with CHCl$_3$. The combined organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was purified by silica gel column chromatography and eluted with hexane–AcOEt (6:1) to afford **22** (80 mg, 67%) as a *colorless solid*, mp 89–91 °C; v_{max} (CHCl$_3$)/cm^{-1} 3400, 1270, 1040; δ_H (300 MHz) 2.45 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 6.58 (1H, dd, J 8.5, 2.2), 6.71 (1H, d, J 2.2), 6.86 (1H, dd, J 8.5, 2.2), 7.02 (1H, d, J 2.2), 7.25 (1H, s), 7.33 (2H, d, J 8.0), 7.44 (1H, d, J 8.5), 7.75 (2H, d, J 8.0), 7.87 (1H, d, J 8.5); m/z 424 (33.6%, M$^+$) and 269 (100) (Found: M$^+$, 424.1011. C$_{23}$H$_{20}$O$_6$S requires M, 424.0981).

Vignafuran 2

A solution of **22** (80 mg, 0.19 mmol) and NaOMe (21 mg, 0.38 mmol) in MeOH (20 ml) was refluxed for 20 h. MeOH was evaporated off and the residue was extracted with CHCl$_3$. The combined organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and concentrated. The residue was chromatographed on silica gel and eluted with hexane–AcOEt (6:1) to afford **2**[13–15] (40 mg, 78%) as a viscous oil; v_{max} (CHCl$_3$)/cm^{-1} 3400, 1270, 1040; δ_H (500 MHz) 3.86 (3H, s), 3.91 (3H, s), 5.36 (1H, br), 6.49–6.51 (2H, m), 6.84 (1H, dd, J 8.5, 2.4), 7.04 (1H, d, J 2.4), 7.10 (1H, s), 7.84 (1H, d, J 8.5); m/z 270 (100%, M$^+$) and 255 (64.8) (Found: M$^+$, 270.0845. Calc. for C$_{16}$H$_{14}$O$_4$: M, 270.0891).

Methyl 6-methoxy-2-[2-methoxy-4-(tosyloxy)phenyl]benzo[b]-furan-3-carboxylate 23

A mixture of **7** (440 mg, 0.94 mmol), K$_2$CO$_3$ (260 mg, 1.88 mmol), PdCl$_2$(PPh$_3$)$_2$ (33.0 mg, 0.19 mmol), CuCl$_2$·2H$_2$O (480 mg, 2.82 mmol) and AcONa (154 mg, 1.88 mmol) in MeOH (20 ml) was stirred under CO at room temperature. After 2 days, the inorganic precipitate was filtered off and the filtrate was extracted with CHCl$_3$. The organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was purified by silica gel column chromatography with hexane–AcOEt (5:1) as eluent to afford **23** (370 mg, 71%) as a *colorless solid*, mp 124–126 °C (Found: C, 62.31; H, 4.41; S, 6.87. C$_{25}$H$_{22}$O$_8$S requires C, 62.23; H, 4.60; S, 6.65%); v_{max} (CHCl$_3$)/cm^{-1} 1720, 1380, 1280, 1180, 1040; δ_H (300 MHz) 2.46 (3H, s), 3.71 (3H, s), 3.80 (3H, s), 3.87 (3H, s), 6.63 (1H, dd, J 8.5, 2.2), 6.71 (1H, d, J 2.2), 6.98 (1H, dd, J 8.5, 2.2), 7.03 (1H, dd, J 8.5, 2.2), 7.35 (2H, d, J 8.5), 7.44 (1H, d, J 8.5), 7.79 (2H, d, J 8.5), 7.87 (1H, d, J 8.5); m/z 482 (58.6%, M$^+$) and 327 (100) (Found: M$^+$, 482.1021. C$_{25}$H$_{22}$O$_8$S requires M, 482.1034).

Methyl 2-(4-hydroxy-2-methoxyphenyl)-6-methoxybenzo[b]-furan-3-carboxylate 3

A solution of **23** (60 mg, 0.12 mmol) and NaOMe (9.60 mg, 0.24 mmol) in MeOH (15 ml) was heated under reflux for 4 h. The mixture was acidified by 3 M HCl and extracted with CHCl$_3$. The organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was chromatographed on silica gel

and eluted with hexane–AcOEt (4:1) to give **3**[16] (40 mg, 100%) as a colorless solid; mp 153–155 °C (Found: C, 65.95; H, 4.95. Calc. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91%); ν_{max} (CHCl$_3$)/cm^{-1} 3400, 1720, 1280, 1040; δ_H (500 MHz; CD$_3$OD) 3.75 (3H, s), 3.78 (3H, s), 3.84 (3H, s), 6.48 (1H, dd, J 8.6, 1.8), 6.52 (1H, d, J 1.8), 6.94 (1H, dd, J 8.6, 1.8), 7.08 (1H, d, J 1.8), 7.32 (1H, d, J 8.6), 7.77 (1H, d, J 8.6); m/z 328 (100%, M$^+$) (Found: M$^+$, 328.0941. Calc. for $C_{18}H_{16}O_6$: M, 328.0947).

Methyl 6-hydroxy-2-[2-hydroxy-4-(tosyloxy)phenyl]benzo[*b*]-furan-3-carboxylate 24

A solution of BBr$_3$ (1 M solution in CH$_2$Cl$_2$; 0.64 ml, 0.64 mmol) was added to a solution of **23** (40 mg, 0.08 mmol) in CH$_2$Cl$_2$ (5 ml) at −78 °C. After the mixture had been stirred at the same temperature for 30 min, the mixture was allowed to warm at −40 °C and was further stirred for 30 h. The mixture was acidified by 3 M HCl and extracted with CHCl$_3$. The organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was chromatographed on silica gel and eluted with hexane–AcOEt (6:1) to give **24** (26 mg, 72%) as a *colorless solid*; mp 95–97 °C; ν_{max} (CHCl$_3$)/cm^{-1} 3350, 1700, 1380, 1260, 1180, 1040; δ_H (300 MHz) 2.45 (3H, s), 4.01 (3H, s), 5.88 (1H, br), 6.76 (1H, d, J 2.2), 6.81 (1H, dd, J 8.5, 2.2), 6.91 (1H, dd, J 8.5, 2.2), 6.98 (1H, d, J 2.2), 7.34 (1H, d, J 8.5), 7.56 (1H, d, J 8.5), 7.78 (2H, d, J 8.5), 7.80 (1H, d, J 8.5), 8.59 (1H, s); m/z 454 (3.6%, M$^+$) and 267 (100) (Found: M$^+$, 454.0675. $C_{23}H_{18}O_8S$ requires M, 454.0721).

Coumestrol 4

A mixture of **24** (30 mg, 0.07 mmol) and 3 M KOH (0.14 ml) in THF (20 ml) was refluxed for 2 h. The mixture was acidified by 3 M HCl and extracted with AcOEt. The organic solution was washed successively with water and saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The crude acid was used in the next reaction without further purification.

A solution of the crude acid and TsOH·H$_2$O (10 mg, 0.06 mmol) in THF (20 ml) was stirred at 60 °C for 5 h. The reaction mixture was extracted with AcOEt. The organic solution was washed with saturated aq. NaCl, dried over MgSO$_4$ and evaporated. The residue was purified by silica gel column chromatography and elution with hexane–AcOEt (5:1) to afford **4**[17,19] (10 mg, 53%) as a colorless solid; mp >360 °C (lit.[17a] mp 385 °C); δ_H (500 MHz; DMSO-D$_6$) 6.90 (1H, d, J 1.9), 6.92 (1H, dd, J 8.8, 1.9), 6.94 (1H, dd, J 8.8, 1.9), 7.16 (1H, d, J 1.9), 7.68 (1H, d, J 8.8), 7.84 (1H, d, J 8.8); δ_H (500 MHz; CD$_3$OD) 6.84 (1H, d, J 2.4), 6.88–6.90 (2H, m), 7.04 (1H, d, J 2.4), 7.70 (1H, d, J 8.5), 7.81 (1H, d, J 8.5); m/z 268 (100%, M$^+$) (Found: M$^+$, 268.0357. Calc. for $C_{15}H_8O_5$: M, 268.0371).

References

1 G. W. Gribble, *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, Oxford, 1996, vol. 2, p. 207.
2 B. A. Keay, *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, Oxford, 1996, vol. 2, p. 395.
3 P. Cagniant and D. Cagniant, *Adv. Heterocycl. Chem.*, 1975, **18**, 343.
4 (*a*) R. J. Sundberg, *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, Oxford, 1996, vol. 2, p. 119; (*b*) G. W. Gribble, *J. Chem. Soc.*, *Perkin Trans. 1*, 2000, 1045 and references cited therein.
5 W. Friedrichsen, *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, Oxford, 1996, vol. 2, p. 351.
6 (*a*) C. E. Castro, E. J. Gaughan and D. C. Owsley, *J. Org. Chem.*, 1966, **31**, 4071; (*b*) C. E. Castro, R. Havlin, V. K. Honwad, A. Malte and S. Mojé, *J. Am. Chem. Soc.*, 1969, **91**, 6464; (*c*) G. J. S. Doad,

J. A. Barltrop, C. M. Petty and T. C. Owen, *Tetrahedron Lett.*, 1989, **30**, 1597; (*d*) O. Haglund and M. Nilsson, *Synlett*, 1991, 723.
7 K. Iritani, S. Matsubara and K. Utimoto, *Tetrahedron Lett.*, 1988, **29**, 1799.
8 (*a*) E. C. Taylor, A. H. Katz, H. Salgado-zomora and A. Mckillop, *Tetrahedron Lett.*, 1985, **26**, 5963; (*b*) A. Arcadi and F. Marinelli, *Synthesis*, 1986, 749; (*c*) N. G. Kundu, M. Pal, J. S. Mahanty and S. K. Dasgupta, *J. Chem. Soc.*, *Chem. Commun.*, 1992, 41; (*d*) S. Torii, L. H. Xu and H. Okumoto, *Synlett*, 1992, 515; (*e*) I. Candiani, S. DeBernardinis, W. Cabri, M. Marchi, A. Bedeschi and S. Penco, *Synlett*, 1993, 269; (*f*) M. C. Fagnola, I. Candiani, G. Visentin, W. Cabri and F. Zarini, *Tetrahedron Lett.*, 1997, **38**, 2307; (*g*) D. Fancelli, M. C. Fagnola, D. Severino and A. Bedeschi, *Tetrahedron Lett.*, 1997, **38**, 2311.
9 (*a*) R. C. Larock and E. K. Yum, *J. Am. Chem. Soc.*, 1991, **113**, 6689; (*b*) R. C. Larock, E. K. Yum, M. J. Doty and K. K. C. Sham, *J. Org. Chem.*, 1995, **60**, 3270; (*c*) R. C. Larock, E. K. Yum and M. D. Refvik, *J. Org. Chem.*, 1998, **63**, 7652.
10 (*a*) Y. Kondo, F. Shiga, N. Murata, T. Sakamoto and H. Yamanaka, *Tetrahedron*, 1994, **50**, 11803; (*b*) A. Arcadi, S. Cacchi, M. D. Rosario, G. Fabrizi and F. Marinelli, *J. Org. Chem.*, 1996, **61**, 9280; (*c*) S. Cacchi, G. Fabrizi, F. Marinelli, L. Moro and P. Pace, *Synlett*, 1997, 1363; (*d*) N. Monteiro and G. Balme, *Synlett*, 1998, 746; (*e*) S. Cacchi, G. Fabrizi and L. Moro, *Synlett*, 1998, 741; (*f*) N. Monteiro, A. Arnold and G. Balme, *Synlett*, 1998, 1111; (*g*) S. Cacchi, G. Fabrizi and L. Moro, *Tetrahedron Lett.*, 1998, **39**, 5101; (*h*) H. Lütjens and P. J. Scammells, *Tetrahedron Lett.*, 1998, **39**, 6581; (*i*) H. Lütjens and P. J. Scammells, *Synlett*, 1999, 1079; (*j*) Y. Nan, H. Miao and Z. Yang, *Org. Lett.*, 2000, **2**, 297; (*k*) A. Yasuhara, M. Kaneko and T. Sakamoto, *Heterocycles*, 1998, **48**, 1793.
11 (*a*) T. Sakamoto, Y. Kondo and H. Yamanaka, *Heterocycles*, 1986, **24**, 31; (*b*) T. Sakamoto, Y. Kondo, S. Iwashita and H. Yamanaka, *Chem. Pharm. Bull.*, 1987, **35**, 1823; (*c*) T. Sakamoto, Y. Kondo, S. Iwashita, T. Nagano and H. Yamanaka, *Chem. Pharm. Bull.*, 1988, **36**, 1305; (*d*) Y. Kondo, S. Kojima and T. Sakamoto, *Heterocycles*, 1996, **43**, 2741.
12 A. Yasuhara, Y. Kanamori, M. Kaneko, A. Numata, Y. Kondo and T. Sakamoto, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 529.
13 (*a*) N. W. Preston, K. Chamberlain and R. A. Skipp, *Phytochemistry*, 1975, **14**, 1843; (*b*) G. A. Carter, K. Chamberlain and R. L. Wain, *Ann. Appl. Biol.*, 1978, **88**, 57; (*c*) K. K. Dorr and D. I. Guest, *J. Chromatogr.*, 1987, **387**, 536.
14 M. Martin and P. M. Dewick, *Phytochemistry*, 1979, **18**, 1309.
15 (*a*) R. P. Duffley and R. Stevenson, *J. Chem. Soc.*, *Perkin Trans. 1*, 1977, 802; (*b*) M. Meyer, C. Deschamps and D. Molho, *Bull. Soc. Chim. Fr.*, 1991, 91; (*c*) M. Watanabe, K. Kawanishi and S. Furukawa, *Chem. Pharm. Bull.*, 1991, **39**, 579; (*d*) T. Kinoshita, *Tetrahedron Lett.*, 1997, **38**, 259.
16 H. Koshino, Y. Masaoka and A. Ichihara, *Phytochemistry*, 1993, **33**, 1075.
17 (*a*) E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson and F. DeEds, *Science*, 1957, **126**, 969; (*b*) E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson and G. O. Kohler, *J. Agric. Food Chem.*, 1958, **6**, 536; (*c*) E. M. Bickoff, R. L. Lyman, A. L. Livingston and A. N. Booth, *J. Am. Chem. Soc.*, 1958, **80**, 3969; (*d*) O. H. Emerson and E. M. Bickoff, *J. Am. Chem. Soc.*, 1958, **80**, 4381.
18 W. Stadlbauer and T. Kappe, *Heterocycles*, 1993, **35**, 1425.
19 (*a*) L. Jurd, *Tetrahedron Lett.*, 1963, 1151; (*b*) T. Kappe and A. Brandner, *Z. Naturforsch.*, *Teil B*, 1974, **29**, 292; (*c*) R. Laschober and T. Kappe, *Synthesis*, 1990, 387; (*d*) G. Kraus and N. Zhang, *J. Org. Chem.*, 2000, **65**, 5644.
20 M. Pal and N. G. Kundu, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 449.
21 (*a*) T. Kappe, G. Korbuly and W. Stadlbauer, *Chem. Ber.*, 1978, **111**, 3857; (*b*) R. C. Larock and L. W. Harrison, *J. Am. Chem. Soc.*, 1984, **106**, 4218; (*c*) R. P. Singh and D. Singh, *Heterocycles*, 1985, **23**, 903; (*d*) J. Maischein and E. Vilsmaier, *Liebigs Ann. Chem.*, 1988, 355; (*e*) S. B. Pandit and S. Y. Gadre, *Synth. Commun.*, 1988, **18**, 157; (*f*) R. S. Mali and S. G. Tilve, *Synth. Commun.*, 1990, **20**, 1781.
22 K. Sonogashira, Y. Ohda and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467.
23 I. Thomsen and K. B. G. Torssell, *Acta Chem. Scand.*, 1991, **45**, 539.
24 H. Suzuki, A. Kondo and T. Ogawa, *Chem. Lett.*, 1985, 441.
25 M. W. Miller and C. R. Johnson, *J. Org. Chem.*, 1997, **62**, 1582.
26 M. C. Carreño, J. L. G. Ruano, G. Snaz, M. A. Toledo and A. Urbano, *Synlett*, 1997, 1241.
27 H. Miao and Z. Yang, *Org. Lett.*, 2000, **2**, 1765.