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Process research on arylnaphthalene lignan aza-analogues: a new palladium-catalyzed benzannulation of α,β-bisbenzylidenesuccinic acid derivatives

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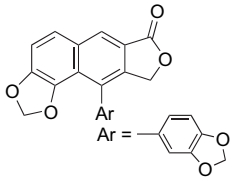
Abstract—The discovery of a new Pd-catalyzed benzannulation reaction of bisbenzylidenesuccinimide during process research on arylnaphthalene lignan aza-analogues is described. An extension of the Pd-catalyzed benzannulation to the regiospecific synthesis of various arylnaphthalene lignan aza-analogues utilizing classical Stobbe condensation is included.

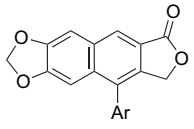
1. Introduction

The objective of process chemistry in the pharmaceutical industry is to develop an efficient synthetic process for a new drug candidate that is cost effective, safe and easy to apply, environmentally friendly, and robust enough for large-scale preparation, to support both preclinical and clinical studies and also commercial purpose. In order to realize such a process, chemists utilize state-of-the-art methods of organic synthesis. In addition, a new method of synthesis discovered during process chemistry research can contribute to organic synthesis. This relationship is mutually beneficial to both fields of chemistry. In this paper, we disclose a new Pd-catalyzed benzannulation reaction[1] of α,β-bisbenzylidenesuccinic acid derivatives discovered during process research on 1-arylnaphthalene lignan aza-analogues.[2]

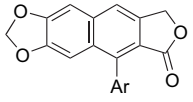
1-Arylnaphthalene lignans[3] occur widely in nature and have several regioisomers as a structural feature. Helioxanthin **1**, Justicidin E **2**, and Taiwanin C **3** are representative, bearing a 'curved' 7,8-methylenedioxynaphthalene or 'straight' 6,7-methylenedioxynaphthalene and 'up' 3-lactone or 'down' 2-lactone carbonyl moiety. Since each regioisomer varies in its bioactivities,[3b–d] analogues, particularly nitrogen-containing types, have been studied as potent candidates. For example, hydrazide compound **4** of antiviral activity,[4a] cyanonaphthalene **5** as a 5-lipoxygenase inhibitor,[4b] and amide analogue **7** for PDE-V inhibitor[4c] have been reported to date.



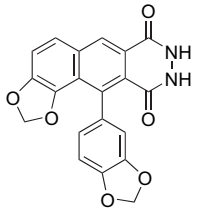
1 (Helioxanthin)



2 (Justicidin E)



3 (Taiwanin C)



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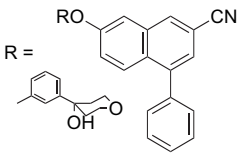

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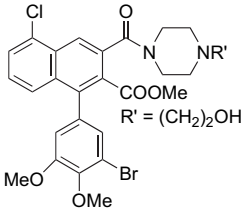

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Keywords: Lignans; Palladium and compounds; Naphthalenes; Biaryls.
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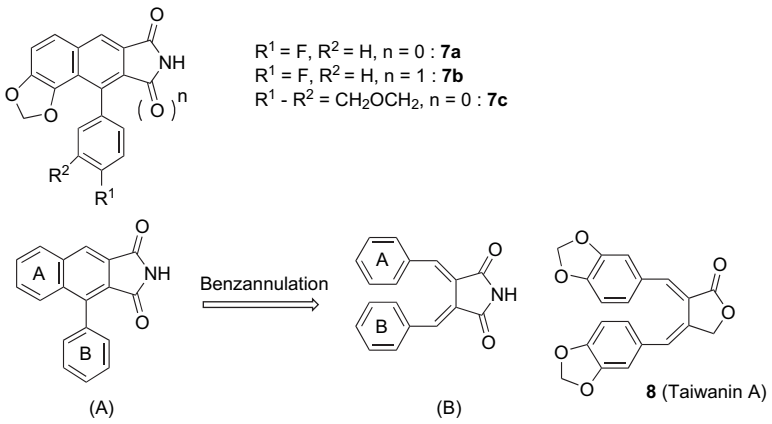


Scheme 1.

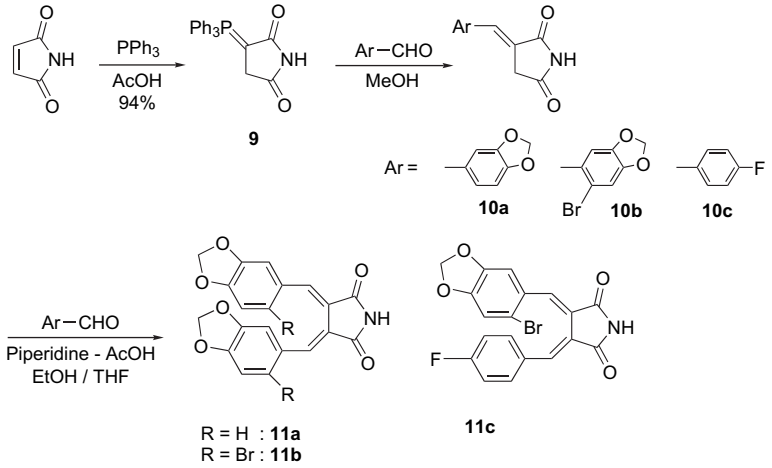
1-Arylnaphthalene lignan analogues[2] **7a–c**, with a 'curved' 7,8-methylenedioxynaphthalene and 'up' lactam or imide moiety, have been studied in Takeda Pharmaceutical Co. as new drug candidates. A number of methods have been developed to construct the arylnaphthalene lignan skeleton, represented by the key reaction of the strategy, intermolecular[5] or intramolecular Diels–Alder reactions,[6] conjugate addition reactions,[7] biaryl coupling reactions,[8] and a benzannulation reaction.[9] However, to achieve the regiospecific synthesis of the target compounds **7a–c**, we decided to explore a new method based on the strategy shown in Scheme 1, in which the target arylnaphthalene (A) would be prepared via the benzannulation[10] of bisbenzylidenesuccinimide (B). The substrate (B) is also of interest as an aza-analogue of the natural lignan Taiwanin A **8**, having antithrombotic activity.[11]

2. Results and discussion

2.1. Discovery of a Pd-catalyzed benzannulation reaction of α,β-bisbenzylidenesuccinimide during process research on arylnaphthalene lignan analogues

Initially, the cyclization of bisbenzylidenesuccinimide was studied under various conditions. As shown in Scheme 2, bisbenzylidenesuccinimide **11a–c** were prepared by the Wittig reaction[12] using a stable phosphorane **9** with a benzaldehyde and the Knoevenagel reaction of monobenzylidenesuccinimide **10a–c** with a benzaldehyde. In the process, as well as symmetrical type **11a–b**, unsymmetrical bisbenzylidenesuccinimide **11c** was prepared as a single isomer (Table 1) independent of the order in which 6-bromopiperonal and 4-fluorobenzaldehyde were used in the two condensation reactions. Since the Wittig reaction using a stable phosphorane gives the product of the (*E*)-configuration, this result supports the notion that a bisbenzylidenesuccinic acid derivative usually forms an (*E*)/(*E*)-type isomer.[13]

Next, the thermal cyclization of symmetrical bisbenzylidenesuccinimide **11a** in DMF was studied. While the heating of the DMF solution at 140 °C under an atmosphere of nitrogen gave dihydronaphthalene **12**, the corresponding conditions under ambient atmosphere provided naphthalene **13** with dehydrogenation. To avoid the reaction at the 6-position of the 3,4-piperonyl group, we investigated the thermal cyclization of unsymmetrical bisbenzylidenesuccinimide **11c** bearing bromine as a protective group. A complex reaction mixture with a small amount of the desired naphthalene **14** was given under a higher temperature (190 °C in NMP) condition. On the other hand, to



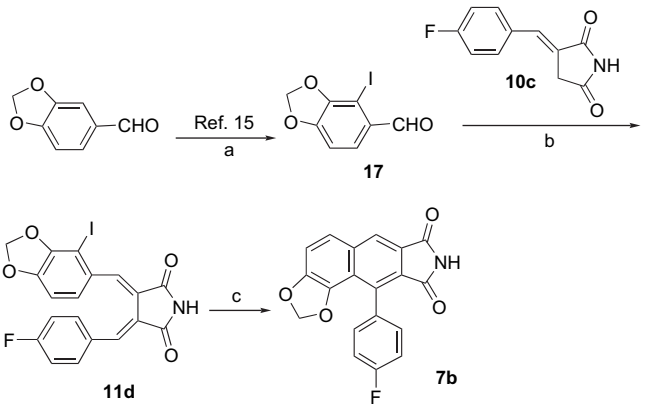
Scheme 2.

Table 1. Syntheses of mono- or bisbenzylidenesuccinimide **10a–c**, **11a–c**

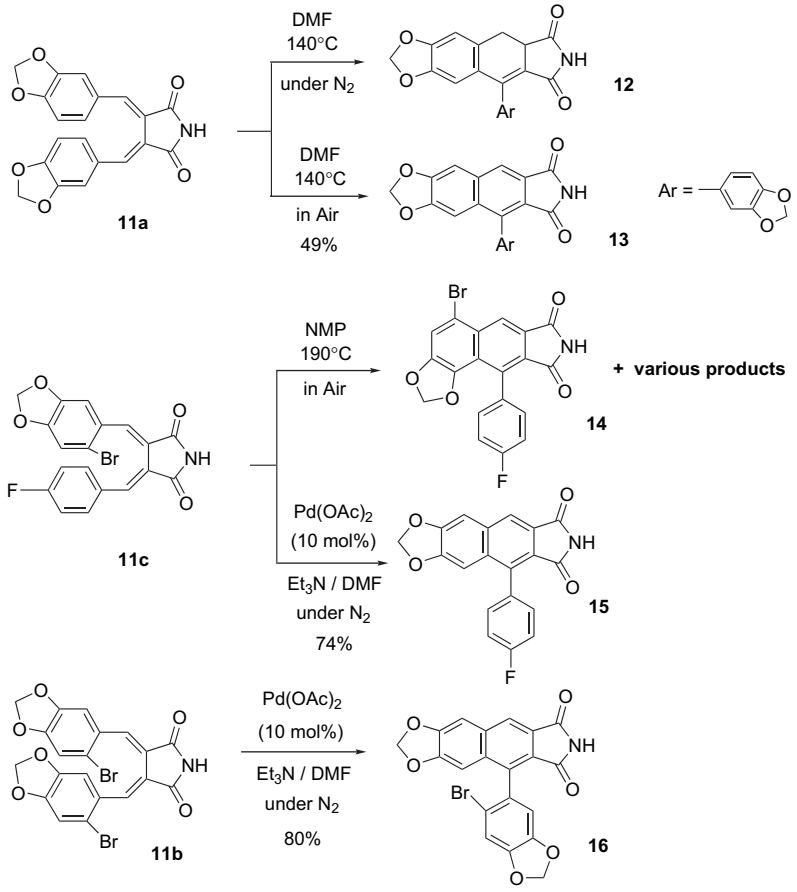
Compound	Yield (%)	Purity (%) by HPLC	^{1}H NMR signal of benzylidene moiety
10a	88	99.8	7.31 (1H, t, J=2.3 Hz)
10b	82	99.4	7.53 (1H, t, J=2.3 Hz)
10c	83	99.9	7.39 (1H, t, J=2.2 Hz)
11a	83	98.9	7.49 (2H, s)
11b	82	94.2	7.43 (2H, s)
11c (via **10b**)	80	93.4	7.44 (1H, s) and 7.59 (1H, s)
11c (via **10c**)	81	98.1	The same as above

accelerate the dehydrogenation, stoichiometric use of $Pd(OAc)_2$ in AcOH for the cyclization afforded naphthalene **15** with dehydrobromination. This surprising result inspired us to try a catalytic Heck reaction with $Pd(OAc)_2$ (10 mol %)/Et_3N in DMF at 100 °C, for the cyclization of **11c** to give naphthalene **15** in 74% yield. In addition, the Pd-catalyzed reaction of the symmetrical bisbenzylidene form **11b** provided naphthalene **16** with only monodehydrobromination. To our knowledge, there had been no report regarding the generation of benzene ring using the intramolecular Heck reaction of an arylhalide or a vinylhalide with the conjugated 1,3-diene system before our preliminary report[1a] for the synthesis of Helioxanthin based on the discovery of a Pd-catalyzed benzannulation of bisbenzylidensuccimide derivatives. Therefore, our discovery will contribute to general synthesis[14] of naphthalene derivatives (Scheme 3).

Based on the discovery of the Pd-catalyzed benzannulation reaction, we have achieved the regiospecific synthesis of 'curved' 7,8-methylenedioxy-substituted naphthalene **7b** in combination with directed ortho metalation. Thus, a key intermediate, 2-iodopiperonal **17**, prepared by Young's metalation synthesis[15] was condensed with monobenzylidenesuccinimide **10c** to give bisbenzylidenesuccinimide **11d**, which was then converted to naphthalene **7b** by the Pd-catalyzed benzannulation. In the process, each product was easily isolated in high purity only by crystallization suitable for a large-scale preparation (Scheme 4).



Scheme 4. Reagents and conditions: (a) *n*-BuLi, *N*,*N*,*N*′-trimethylethylenediamine, DME–THF then *n*-BuLi, I_2, 46%; (b) piperidine, AcOH, EtOH, 79%; (c) $Pd(OAc)_2$ (10 mol %), Et_3N (2.2 equiv), DMF, 110 °C; 80 min, 78%.

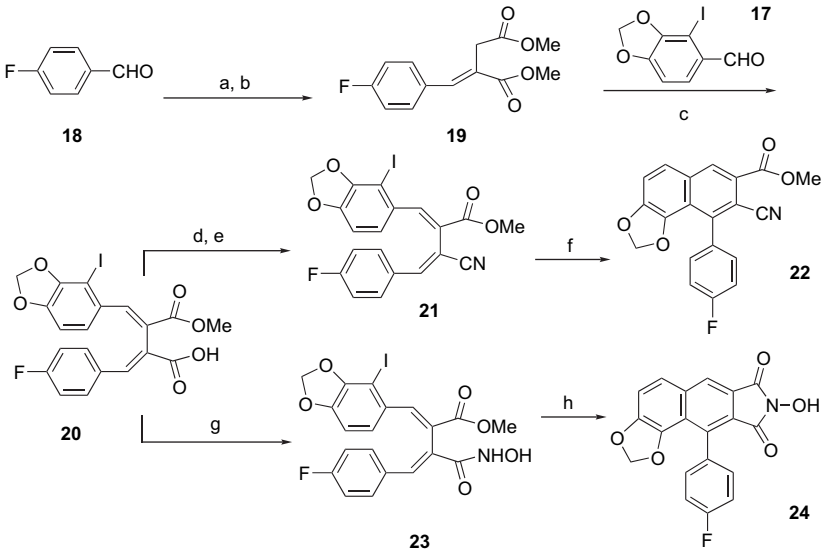


Scheme 3.

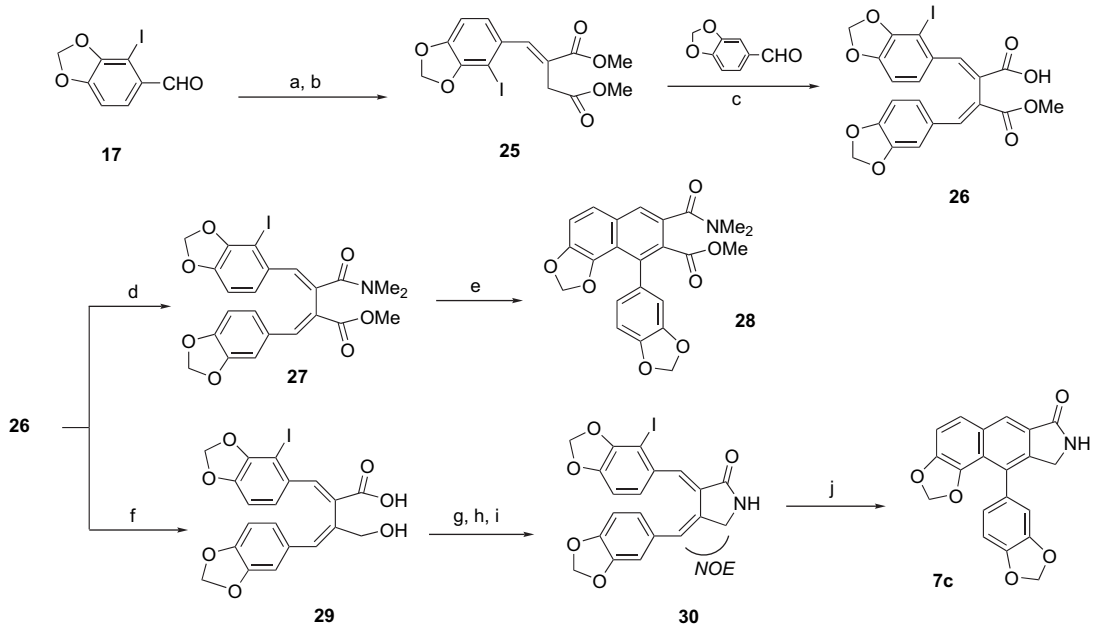
2.2. Extension of the new Pd-catalyzed benzannulation to the regiospecific synthesis of various arylnaphthalene lignan analogues

Next our objective is to extend the Pd-catalyzed benzannulation to the synthesis of other aza-analogues utilizing classical Stobbe condensation in two stages. The first Stobbe condensation of diethyl succinate with 4-fluorobenzaldehyde **18** gave the monobenzylidene form **19**. The second reaction of **19** with 2-iodopiperonal **17** provided bisbenzylidene halfester **20** as a key intermediate, in which the ester moiety of **19** distant from the reacting carbon was selectively saponified in a typical Stobbe condensation manner.[10a–c] Conversion of the carboxyl moiety of halfester **20** to a cyano group via dehydration of the corresponding amide yielded the bisbenzylidene form **21**, which was then converted into 2-cyanonaphthalene **22** by subsequent Pd-catalyzed benzannulation. Halfester **20** was also transformed to the corresponding hydroxamic acid derivative **23**, which was cyclized to furnish naphthoimide **24** by sequential hydroxyimide formation and the Pd-catalyzed benzannulation (Scheme 5).

By changing the order in which the 2-iodopieronylidene moiety is installed into Stobbe's halfester, the regiospecific synthesis of different substituted aza-analogues can be achieved. Indeed, as shown in Scheme 6, the first Stobbe's condensation of diethyl succinate with 2-iodopiperonal **17**



Scheme 5. Reagents and conditions: (a) $(CH_2COOEt)_2$, NaOMe, MeOH then aq NaOH, 36%; (b) MeOH, H_2SO_4, 94%; (c) NaOMe, MeOH, 74%; (d) $(COCl)_2$, cat. DMF, THF then aq NH_3, 91%; (e) $(COCl)_2$, cat. DMF, THF, 91%; (f) $Pd(OAc)_2$ (10 mol %), K_2CO_3 (2.2 equiv), NMP, 110 °C, 50 min, 32%; (g) $(COCl)_2$, cat. DMF, THF then NH_2OH, 68%; (h) $Pd(OAc)_2$ (10 mol %), Et_3N (2.2 equiv), DMF, 110 °C, 45 min, 69%.



Scheme 6. Reagents and conditions: (a) $(CH_2COOEt)_2$, NaOMe, MeOH, aq NaOH, 62%; (b) MeOH, H_2SO_4, 84%; (c) NaOMe, MeOH, 82%; (d) $(COCl)_2$, cat. DMF, THF then Me_2NH, 67%; (e) $Pd(OAc)_2$ (20 mol %), AcOK (2.2 equiv), NMP, 9%; (f) $LiEt_3BH$, THF, 67%; (g) EtI, K_2CO_3, DMF; (h) PBr_3, MePh; (i) aq NH_3, THF–MeOH, 35% based on **29**; (j) $Pd(OAc)_2$ (10 mol %), AcOK (2.2 equiv), NMP, 110 °C, 40 min, 48% (HPLC yield 72%).

gave the monobenzylidene **25**, which was then converted into bisbenzylidene halfester **26** by the second condensation with piperonal. Since halfester **26** bore a carboxyl moiety the near 2-iodopieronylidene group, conversion of the carboxyl into a *N*,*N*-dimethylamide group and subsequent Pd-catalyzed benzannulation introduced the amide moiety as a nitrogen-containing substituent to the 3-position of naphthalene derivative **28**. As well as compound **21**, the acyclic bisbenzylidene **27** gave lower yield of the Pd-catalyzed benzannulation than the bisbenzylidenesuccinimides. Moreover, the super-hydride reduction[16] of an ester moiety of halfester **26** afforded the hydroxy form **29**, which was transformed into lactam **30** by a sequence of esterization, bromination, and amination. The geometrical configuration of α,β-bisbenzylidene-γ-lactam **30** was confirmed as (*E*,*E*)-configuration, on the basis of the NOESY spectrum study focusing on a relationship between benzylidene and lactone protone. The bisbenzylidenelactam **30** was cyclized by a Pd catalyst to provide the lactam analogue **7c** bearing an 'up' carbonyl moiety.

Discussion about the possible mechanism of the novel benzannulation reaction of (*E*,*E*)-α,β-bisbenzylidene-γ-lactam **30** inspired us to recognize the role of its 1,3-diene system. The following reaction mechanism including two conceivable processes is proposed in Scheme 7. In the first process, the oxidative addition of palladium(0) into the C–I bond of **30** generates σ-arylpalladium complex **31** based on the (*E*,*E*)-type isomer. Despite the steric hindrance of the other aryl group, the stable palladium(II) complex with the 1,3-diene system (square planar complex) accelerates *syn* insertion of an intramolecular alkenyl double bond into the C–Pd bond, to give δ-dihydronaphthalenylpalladium complex **32**. Then, the palladium(II) species **32** smoothly undergoes *syn* β-hydride elimination to yield the naphthalene product **7a**. In the other process, (*E*,*E*)-type σ-arylpalladium complex **31** is isomerized to (*E*,*Z*)-type σ-arylpalladium complex **33** due to the delocalized π-electron system on the 1,3-diene complex with the palladium(II) species. The subsequent *syn* insertion of an intramolecular alkenyl double bond to the C–Pd bond provides σ-dihydronaphthalenylpalladium complex **34**. Although the reaction intermediate **34** does not undergo *syn* β-hydride elimination to yield the naphthalene **7a**, **34** is converted into π-allylpalladium complex **35**, which isomerizes into σ-dihydronaphthalenylpalladium complex **32** allowing *syn* β-hydride elimination.

3. Conclusion

In conclusion, a new Pd-catalyzed benzannulation of bisbenzylidenesuccinimides has been discovered during process research on arylnaphthalene lignan analogues. Furthermore, an extension of the benzannulation to the regiospecific synthesis of various arylnaphthalene lignan analogues has been achieved utilizing classical Stobbe condensation.

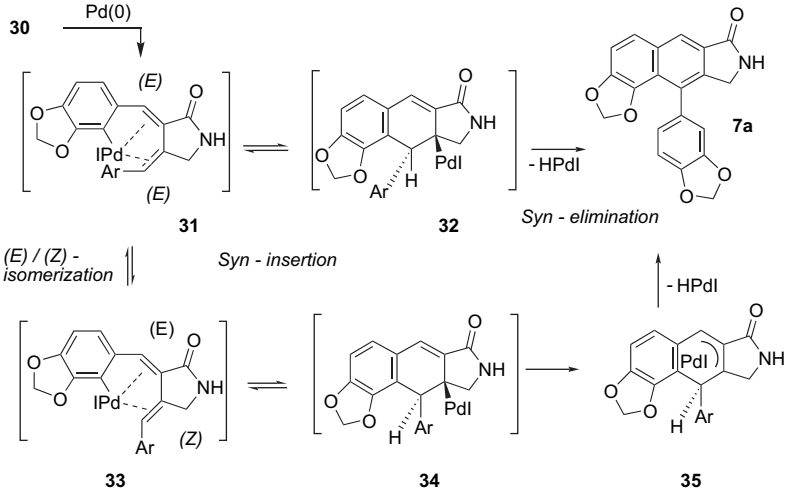
4. Experimental

4.1. General remarks

Melting points were recorded on a Yanagimoto micro melting apparatus and are uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DPX-300 spectrometer. Elemental analyses and mass spectra were analyzed by Takeda Analytical Research Ltd. HPLC was performed on a YMC-Pack ODS-A302 column (150 mm×4.6 mm I.D.) with 0.05 M KH_2PO_4 in water and acetonitrile (50:50) at 25 °C. Detection was effected with a Hitachi spectrophotometric detector at 254 nm.

4.2. Pd-catalyzed benzannulation reaction of α,β-bisbenzylidenesuccinimide

4.2.1. 3-(Triphenylphosphoranylidene)pyrrolidine-2,5-dione 9. A mixture of maleimide (66.6 g, 688 mmol), triphenylphosphine (180 g, 686 mmol), and acetone (670 ml) was heated under reflux for 1 h. After cooling, the resulting precipitate was filtered, washed with acetone (200 ml), and dried in vacuo at 40 °C to give **9** (233 g, yield 94%) as a colorless solid, which was used for the next step without further purification.



Scheme 7.

4.2.2. 3-(1,3-Benzodioxol-5-ylmethylene)pyrrolidine-2,5-dione 10a (method A). A mixture of phosphorane **9** (2.35 g, 6.66 mmol), piperonal (1.00 g, 6.66 mmol), and methanol (20 ml) was heated under reflux for 1 h and 10 min, then cooled at room temperature. The resulting crystal was filtered, washed with methanol (5 ml), and dried in vacuo at 40 °C to give **10a** (1.36 g, yield 88%) as a colorless crystalline powder: mp 230 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.61 (2H, d, J=2.3 Hz), 6.10 (2H, s), 7.01 (1H, d, J=8.1 Hz), 7.1–7.2 (2H, m), 7.30 (1H, t, J=2.3 Hz), 11.4 (1H, br), IR (ATR, cm^{-1}): 1695, 1645, 1498, 1180, 1027, MS (EI, m/z): (M^+) 231; Elemental analysis: calcd for $C_{12}H_9NO_4$, C: 62.34, H: 3.92, N: 6.06, found C: 62.15, H: 3.78, N: 6.07.

4.2.3. 3-[(6-Bromo-1,3-benzodioxol-5-yl)methylene]pyrrolidine-2,5-dione 10b. Following the method A, phosphorane **9** (4.71 g, 13.1 mmol) was treated with 6-bromo-3,4-methylenedioxybenzaldehyde (3.00 g, 13.1 mmol) in methanol (60 ml) for 1.5 h under reflux to give **10b** (3.34 g, yield 82%) as a pale yellow powder: mp 265 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.65 (2H, d, J=2.3 Hz), 6.16 (2H, s), 7.25 (1H, s), 7.39 (1H, s), 7.53 (1H, t, J=2.3 Hz), 11.5 (1H, br), IR (ATR, cm^{-1}): 1765, 1695, 1501, 1348, 1205, 1038, MS (EI, m/z): (M+1) 311, (M) 309; Elemental analysis: calcd for $C_{12}H_8BrNO_4$, C: 46.48, H: 2.60, N: 4.52, found C: 46.56, H: 2.67, N: 4.27.

4.2.4. 3-(4-Fluorobenzylidene)pyrrolidine-2,5-dione 10c. Following the method A, phosphorane **9** (29.0 g, 80.6 mmol) was treated with 4-fluorobenzaldehyde (10.0 g, 80.6 mmol) in methanol (100 ml) for 1.5 h under reflux to give **10c** (13.9 g, yield 83%) as a colorless crystalline powder: mp 210 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.64 (2H, d, J=2.2 Hz), 7.28–7.34 (2H, m), 7.39 (1H, t, J=2.2 Hz), 7.67–7.72 (2H, m), 11.4 (1H, br), IR (ATR, cm^{-1}): 1765, 1707, 1650, 1510, 1350, 1184, MS (EI, m/z): (M^+) 205; Elemental analysis: calcd for $C_{11}H_8NO_2F$, C: 64.39, H: 3.93, N: 6.83, found C: 64.28, H: 3.95, N: 6.86.

4.2.5. 3,4-Bis(1,3-benzodioxol-5-ylmethylene)pyrrolidine-2,5-dione 11a (method B). A mixture of compound **10a** (350 mg, 1.51 mmol), piperonal (227 mg, 1.51 mmol), and piperidine (129 mg, 1.51 mmol) in ethanol (3.5 ml) and tetrahydrofuran (3.5 ml) was heated under reflux for 18 h. The reaction mixture was then allowed to stand at room temperature, and the resulting crystals were filtered and washed with ethanol/tetrahydrofuran (1:1, 1.2 ml) and dried in vacuo at 40 °C to give **11a** (456 mg, yield 83%) as a yellow crystalline powder: mp 249 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 5.90 (4H, s), 6.30 (2H, d, J=1.2 Hz), 6.62 (2H, d, J=8.1 Hz), 6.65 (2H, dd, J=8.1 and 1.2 Hz), 7.49 (2H, s), 11.5 (1H, br), IR (ATR, cm^{-1}): 1692, 1485, 1246, 1037, 925, MS (EI, m/z): (M^+) 363; Elemental analysis: calcd for $C_{20}H_{13}NO_6$, C: 66.12, H: 3.61, N: 3.86, found C: 65.89, H: 3.76, N: 3.87.

4.2.6. 3,4-Bis[(6-bromo-1,3-benzodioxol-5-yl)methylene]pyrrolidine-2,5-dione 11b. Following the method B, compound **10b** (1.50 g, 4.84 mmol) was treated with 6-bromo-3,4-methylenedioxybenzaldehyde (1.11 g, 4.83 mmol), piperidine (411 mg, 4.83 mmol), acetic acid (290 mg, 4.83 mmol), and ethanol (30 ml) for 11 h under reflux to give **11b** (2.07 g, yield 82%) as a yellow crystalline powder: mp 245 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 5.96 (4H, s), 5.97 (2H, s), 7.24 (2H, s), 7.38 (2H, s), 11.7 (1H, br), IR (ATR, cm^{-1}): 1755, 1702, 1471, 1263, 1116, 1034, MS (EI, m/z): (M+2) 521, (M) 519; Elemental analysis: calcd for $C_{20}H_{11}NO_6Br_2$, C: 46.10, H: 2.13, N: 2.69, found C: 45.86, H: 2.13, N: 2.72.

4.2.7. 3-[(6-Bromo-1,3-benzodioxol-5-yl)methylene]-4-(4-fluorobenzylidene)pyrrolidine-2,5-dione 11c. Following the method B, compound **10b** (1.50 g, 4.84 mmol) was treated with 4-fluorobenzaldehyde (0.813 g, 6.55 mmol), piperidine (0.558 g, 6.55 mmol), acetic acid (0.393 g, 6.55 mmol), and ethanol (30 ml) for 6 h under reflux to give the title compound (1.60 g, yield 80%) as a yellow crystalline powder: mp 244 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 5.84 (2H, s), 6.07 (2H, s), 6.77–6.83 (2H, m), 6.94–6.99 (2H, m), 7.18 (2H, s), 7.44 (1H, s), 7.59 (1H, s), 11.72 (1H, br), IR (KBr, cm^{-1}): 1760, 1706, 1473, 1421, 1238, 833, 648, MS (EI, m/z): (M+2) 417, (M) 415; Elemental analysis: calcd for $C_{19}H_{11}NO_4BrF$, C: 54.83, H: 2.66, N: 3.37, found C: 54.53, H: 2.55, N: 3.25.

Following the method B, compound **10c** (2.69 g, 13.1 mmol) was treated with 6-bromo-3,4-methylenedioxybenzaldehyde (3.00 g, 13.1 mmol), piperidine (1.12 g, 13.1 mmol), acetic acid (0.787 g, 13.1 mmol), and ethanol (53.8 ml) to give the title compound (4.41 g, yield 81%).

4.2.8. 9-(1,3-Benzodioxol-5-yl)-5*H*-[1,3]benzodioxolo[5,6-*f*]isoindole-6,8(5a*H*,7*H*)-dione 12. A mixture of compound **11a** (6.00 g, 16.5 mmol) and *N*,*N*-dimethylformamide (120 ml) was heated at 140 °C for 96 h under a nitrogen atmosphere. The reaction mixture was allowed to stand at room temperature, and then ethyl acetate (180 ml), tetrahydrofuran (60 ml), and H_2O (180 ml) were added. The aqueous layer was separated and extracted with ethyl acetate (2×60 ml). The combined organic layer was washed with H_2O and concentrated in vacuo to give crude compound **12**, which indicated a 66% peak area on HPLC analysis. The residue was purified with silica-gel column chromatography (eluent: hexane/acetate) and washed with ethanol and ethyl acetate to give the title compound (0.63 g, yield 16%) as a pale yellow crystalline powder: mp 261–263 °C, ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 2.79 (1H, t, J=15.7 Hz), 3.07 (1H, dd, J=15.3 and 6.5 Hz), 3.66 (1H, dd, J=16.6 and 6.5 Hz), 5.9–6.1 (2H, m), 6.09 (2H, d, J=3.9 Hz), 6.33 (1H, s), 6.5–7.0 (2H, m), 6.96 (1H, d, J=8.0 Hz), 7.05 (1H, s), 11.2 (1H, br), ^{13}C NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 28.03, 40.79, 101.11, 101.51, 107.57, 108.28, 109.05, 122.58, 128.38, 129.19, 131.63, 142.58, 146.08, 146.52, 147.41, 148.04, 167.65, 176.43, IR (ATR, cm^{-1}): 1759, 1702, 1484, 1236, 1032, 639, MS (EI, m/z): (M^+) 363; Elemental analysis: calcd for $C_{20}H_{13}NO_6$, C: 66.12, H: 3.61, N: 3.86, found C: 65.91, H: 3.55, N: 3.90, HPLC purity: 98.5%.

4.2.9. 5-(1,3-Benzodioxol-5-yl)-6*H*-[1,3]benzodioxolo[5,6-*f*]isoindole-6,8(7*H*)-dione 13. A mixture of compound **11a** (350 mg, 0.963 mol) and *N*,*N*-dimethylformamide (7 ml) was heated at 140 °C for 20 h under an

ambient atmosphere. The reaction mixture was then allowed to stand at room temperature, ethyl acetate (15 ml) and H_2O (15 ml) were added. The aqueous layer was separated and extracted with ethyl acetate. The combined organic layers were washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was washed with ethyl acetate and then ethanol to give the title compound (170 mg, yield 49%) as a colorless crystalline powder: mp 299 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 6.13 (2H, d, J=11.6 Hz), 6.22 (2H, d, J=1.6 Hz), 6.80 (1H, dd, J=7.9 and 1.6 Hz), 6.9–7.0 (2H, m), 7.05 (1H, d, J=7.9 Hz), 7.73 (1H, s), 8.22 (1H, s), 11.2 (1H, br), IR (ATR, cm^{-1}): 1767, 1722, 1469, 1253, 1039, MS (EI, *m*/*z*): (M^+) 361; Elemental analysis: calcd for $C_{20}H_{11}NO_6 \cdot 0.5H_2O$, C: 64.87, H: 3.27, N: 3.78, found C: 65.27, H: 3.20, N: 3.84.

4.2.10. 5-Bromo-10-(4-fluorophenyl)-7*H*-[1,3]benzodioxolo[4,5-*f*]isoindole-7,9(8*H*)-dione 14. A mixture of compound **11c** (2.00 g, 4.81 mmol) and *N*-methylpyrrolidone (20 ml) was heated at 190 °C for 9.5 h under an ambient atmosphere. The reaction mixture was then allowed to stand at room temperature, before ethyl acetate, tetrahydrofuran, and 1 M HCl were added to it. The aqueous layer was separated and extracted with ethyl acetate. The combined organic layers were washed with 1 M HCl and then H_2O, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give crude compound **14**, which indicated a 13% peak area on HPLC analysis. The residue was purified with silica-gel column chromatography (eluent: hexane/acetate) and recrystallized from hexane and ethyl acetate to give the title compound (36.3 mg, yield 1.8%) as a yellow crystalline powder: mp 305 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 5.98 (2H, s), 6.94–7.25 (2H, m), 7.39–7.44 (2H, m), 8.06 (1H, s), 8.43 (1H, s), 11.4 (1H, br), IR (ATR, cm^{-1}): 1712, 1278, 1134, 1061, 635, 499, MS (EI, *m*/*z*): (M+2) 415, (M) 413; Elemental analysis: calcd for $C_{19}H_9BrFNO_4$, C: 55.10, H: 2.19, N: 3.38, found C: 54.89, H: 2.29, N: 3.11, HPLC purity: 96.7%.

4.2.11. 5-(4-Fluorophenyl)-6*H*-[1,3]benzodioxolo[5,6-*f*]isoindole-6,8(7*H*)-dione 15 (method C). A mixture of compound **11b** (1.00 g, 2.40 ml), $Pd(OAc)_2$ (53.9 mg, 0.24 mmol), triethylamine (291 mg, 2.88 mmol), and *N*,*N*-dimethylformamide (20 ml) was stirred at room temperature under a nitrogen atmosphere for 1 h and the resulting mixture was heated at 100 °C for 1 h. After the reaction mixture had stood at room temperature, 1 M HCl (20 ml) was added to give a precipitate. The solid was filtered, washed with ethanol/tetrahydrofuran (1:1), and dried in vacuo at 40 °C to give the title compound (593 mg, yield 74%) as a colorless crystalline powder: mp 328 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 5.98 (2H, s), 6.59 (1H, s), 7.04–7.20 (4H, m), 7.47 (1H, s), 8.03 (1H, s), 11.2 (1H, br), IR (ATR, cm^{-1}): 1765, 1704, 1463, 1244, 1037, 750, 640, MS (EI, *m*/*z*): (M^+) 335; Elemental analysis: calcd for $C_{19}H_{10}FNO_4$, C: 68.06, H: 3.01, N: 4.18, found C: 67.93, H: 2.94, N: 4.09.

4.2.12. 5-(6-Bromo-1,3-benzodioxol-5-yl)-6*H*-[1,3]benzodioxolo[5,6-*f*]isoindole-6,8(7*H*)-dione 16. Following the method C, compound **11b** (1.56 g, 3 mmol) was treated with $Pd(OAc)_2$ (67.4 mg, 0.3 mmol), triethylamine (353 mg, 3.6 mmol), and *N*,*N*-dimethylformamide (31.2 ml) for 2 h at 100 °C to give the title compound (1.06 g, yield 80%) as a pale yellow crystalline powder: mp 301 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 6.19 (2H, d, J=13.0 Hz), 6.24 (2H, s), 6.76 (1H, s), 6.97 (1H, s), 7.39 (1H, s), 7.73 (1H, s), 8.31 (1H, s), 11.3 (1H, br), IR (ATR, cm^{-1}): 1706, 1464, 1231, 1024, 640, 437, MS (EI, *m*/*z*): (M+2) 441, (M) 439, HRMS: calcd for $C_{20}H_{10}NO_6Br$, 438.9691, found 438.9689.

4.2.13. 2-Iodo-3,4-methylenedioxybenzaldehyde (2-iodopiperonal) 17. (The following procedure is a modification of Young's 2-iodopiperonal synthesis.)

To a stirred mixture of *N*,*N*,*N*′-trimethylethyldiamine (29.4 g, 288 mmol) and 1,2-dimethoxyethane (DME) (180 ml) was added 1.6 M *n*-BuLi in hexanes (180 ml, 288 mmol) at 0–10 °C under a nitrogen atmosphere. After further stirring at the same temperature for 1 h, a DME (540 ml) solution of piperonal (35.1 g, 234 mmol) was added to the mixture. After more stirring at 0–10 °C for 1 h, the resulting mixture was diluted with tetrahydrofuran (360 ml), followed by 1.6 M *n*-BuLi in hexanes (225 ml, 360 mmol). The mixture was stirred at room temperature for 4.5 h, and iodine (107 g, 421 mmol) was added portionwise from −60 to −70 °C. The reaction mixture was then warmed up to room temperature for 22 h, and satd aq $Na_2S_2O_3$ (350 ml) was added to it. The aqueous layer was separated and extracted with ethyl acetate (175 ml+90 ml). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The concentrated residue was recrystallized from ethanol (320 ml) to give the title compound as the first crop (28.2 g). The second crop (1.7 g) was obtained from the mother liquor (yield 46%) as a colorless crystalline powder: ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 6.25 (2H, s), 7.07 (1H, d, J=8.2 Hz), 7.47 (1H, d, J=8.2 Hz), 9.80 (1H, s), MS (EI): (M^+) 276; Elemental analysis: calcd for $C_8H_5O_3I$, C: 34.81, H: 1.83, I: 45.98, found C: 34.85, H: 1.80, I: 46.01.

4.2.14. 3-(4-Fluorobenzylidene)-4-[(4-iodo-1,3-benzodioxol-5-yl)methylene]pyrrolidine-2,5-dione 11d. Following the method B, compound **10c** (4.15 g, 18.1 mmol) was treated with 2-iodopiperonal (5.00 g, 13.1 mmol), piperidine (1.54 g, 18.1 mmol), acetic acid (1.09 g, 18.1 mmol), and ethanol (83 ml) under reflux for 4.5 h to give the title compound (6.62 g, yield 79%) as a colorless crystalline powder: ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 6.03–6.13 (4H, m), 6.73–6.78 (2H, m), 6.88–6.92 (2H, m), 7.44 (1H, s), 7.56 (1H, s), 11.7 (1H, br), IR (ATR, cm^{-1}): 1701, 1453, 1227, 1173, 1038, 936, 446, MS (EI, *m*/*z*): (M^+) 463, HRMS: calcd for $C_{19}H_{11}NO_4FI$, 462.9717, found 462.9734; Elemental analysis: calcd for $C_{19}H_{11}FNO_4I \cdot 0.5H_2O$, C: 48.33, H: 2.56, N: 2.97, found C: 48.56, H: 2.34, N: 2.90.

4.2.15. 10-(4-Fluorophenyl)-7*H*-[1,3]benzodioxolo[4,5-*f*]isoindole-7,9(8*H*)-dione 7b. A mixture of compound **11d** (6.57 g, 14.2 ml), $Pd(OAc)_2$ (319 mg, 1.42 mmol), triethylamine (3.16 g, 31.2 mmol), and *N*,*N*-dimethylformamide (131 ml) was stirred at room temperature under a nitrogen atmosphere for 1 h and the resulting mixture was heated at 110 °C for 1 h and 20 min. After the reaction

mixture had stood at room temperature, its insoluble part was filtered out and washed with *N*,*N*-dimethylformamide (50 ml). To the combined filtrate and washing were added ethyl acetate (260 ml) and 5% aq $Na_2S_2O_3 \cdot 5H_2O$ (140 ml). The aqueous layer was separated and extracted with ethyl acetate (130 ml+65 ml). The combined organic layers were washed with H_2O (2×200 ml) and concentrated in vacuo. The residue was washed with tetrahydrofuran/EtOH (1:4, 25 ml) and dried in vacuo at 40 °C to give the title compound (3.70 g, yield 78%) as a yellow crystalline powder: mp 285 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 5.72 (2H, s), 6.95–7.01 (2H, m), 7.17–7.22 (2H, m), 7.35 (1H, d, J=8.6 Hz), 7.20 (1H, d, J=8.6 Hz), 8.17 (1H, s), 11.1 (1H, br), IR (ATR, cm^{-1}): 1756, 1716, 1284, 1348, 1057, 637, 447, MS (EI, *m*/*z*): (M^+) 335; Elemental analysis: calcd for $C_{19}H_{10}FNO_4 \cdot 0.5H_2O$, C: 66.28, H: 3.22, N: 4.07, found C: 66.49, H: 3.30, N: 4.08, HPLC purity: 96.8%.

4.3. Pd-catalyzed benzannualtion to regiospecific syntheses of various arylnaphthalene lignan analogues (Schemes 5 and 6)

4.3.1. Dimethyl 2-(4-fluorobenzylidene)succinate 19. To a stirred mixture of diethyl succinate (52.0 g, 299 ml), 28% NaOMe in methanol (43.4 g, 225 mmol), and methanol (87 ml) was added dropwise 4-fluorobenzaldehyde (18.6 g, 150 mmol) in methanol (46 ml) under reflux and the resulting mixture was heated for 2 h under reflux, then treated with 2 M-NaOH (298 ml) for 2 h at the same condition. After standing at room temperature, the reaction mixture was concentrated in vacuo and the resulting residue was recrystallized from ethyl acetate to give 2-(4-fluorobenzylidene)-succinic acid (8.16 g) as colorless crystals. The second crop (4.04 g) was obtained from the mother liquor of the first crystals (total yield 36%) as a colorless crystalline powder: ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.36 (2H, s), 7.26–7.31 (2H, m), 7.45–7.50 (2H, m), 7.73 (1H, s), 12.5 (2H, br), IR (ATR, cm^{-1}): 1673, 1309, 1218, 916, 829, 537, MS (EI, *m*/*z*): (M^+) 224; Elemental analysis: calcd for $C_{11}H_9O_4F$, C: 58.93, H: 4.05, found C: 59.14, H: 4.00.

To a stirred mixture of 2-(4-fluorobenzylidene)succinic acid (12.1 g, 54.0 mmol) and methanol (242 ml) was added concd H_2SO_4 (5.30 g, 54.0 mmol) and refluxed for 18 h. After cooling, the reaction mixture was concentrated in vacuo. To the residue was added H_2O (121 ml) and extracted with ethyl acetate (121 ml+61 ml). The combined organic layers were washed with H_2O (187 ml×2), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give the title compound as a pale yellow oil (12.8 g, yield 94%), which was used for the next step without further purification: ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.51 (2H, s), 3.64 (3H, s), 3.75 (3H, s), 7.26–7.32 (2H, m), 7.47–7.52 (2H, m), 7.81 (1H, s), IR (Neat, cm^{-1}): 2954, 1739, 1712, 1602, 1508, 1436.

4.3.2. 2-(4-Fluorobenzylidene)-4-(4-iodo-1,3-benzodioxol-5-yl)-3-(methoxycarbonyl)but-3-enoic acid 20. To a stirred mixture of compound **19** (12.7 g, 46.3 mmol), compound **17** (12.8 g, 46.3 mmol), and methanol (254 ml) was added 28% NaOMe in methanol (21.4 g, 111 mmol) and refluxed for 3.5 h. After the cooling of the reaction mixture, 6 M HCl (37 ml, 222 mmol) was added. The precipitate was filtered and washed with H_2O (254 ml) to give the title compound (18.1 g, yield 82%). The second crop (497 mg) was obtained from the mother liquor of the first crystals (total yield 74%) as a pale yellow crystalline powder: mp 209 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.70 (3H, s), 6.08 (2H, s), 6.8–6.9 (2H, m), 7.1–7.2 (2H, m), 7.3–7.4 (2H, m), 7.63 (1H, s), 7.68 (1H, s), 12.8 (1H, br), IR (KBr, cm^{-1}): 1700, 1683, 1600, 1232, 1047, 773, MS (EI, *m*/*z*): (M^+) 496; Elemental analysis: calcd for $C_{20}H_{14}O_6FI$, C: 48.41, H: 2.84, found C: 48.49, H: 2.87.

4.3.3. Methyl 3-cyano-4-(4-fluorophenyl)-2-[(4-iodo-1,3-benzodioxol-5-yl)methylene]but-3-enoate 21. To a stirred mixture of compound **20** (16.4 g, 33.0 mmol), tetrahydrofuran (328 ml), and *N*,*N*-dimethylformamide (3.3 ml), thionyl chloride (41 ml) was added dropwise at room temperature and the resulting mixture was heated for 2 h under reflux. After cooling, the reaction mixture was added dropwise to a stirred mixture of 28% aq NH_3 (328 ml) and tetrahydrofuran (164 ml) at ice-cold temperature. After further stirring at the same temperature for 2 h, concd HCl (250 ml) and water (400 ml) were added and the reaction mixture was extracted with ethyl acetate (100 ml×2 and 50 ml). The combined organic layers were concentrated in vacuo and the concentrated residue was washed with methanol (50 ml) to give methyl 3-(aminocarbonyl)-4-(4-fluorophenyl)-2-[(4-iodo-1,3-benzodioxol-5-yl)methylene]but-3-enoate (14.9 g, yield 91%) as a pale yellow crystalline powder: ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.67 (3H, s), 6.08 (2H, s), 6.87 (1H, d, J=8.8 Hz), 7.03 (1H, d, J=8.8 Hz), 7.0–7.3 (5H, m), 7.38 (1H, s), 7.46 (1H, br), 7.71 (1H, s), IR (ATR, cm^{-1}): 1702, 1674, 1460, 1228, 1047, 772, MS (EI, *m*/*z*): (M^+) 495; Elemental analysis: calcd for $C_{20}H_{15}FINO_5$, C: 48.50, H: 3.05, N: 2.83, found C: 48.49, H: 3.28, N: 2.68.

To a stirred mixture of the above amide (14.7 g, 29.6 mmol), tetrahydrofuran (294 ml), and *N*,*N*-dimethylformamide (4.4 ml), oxalyl chloride (14.7 ml) was added dropwise at room temperature and the resulting mixture was stirred at room temperature for 3 h. To the reaction mixture was added H_2O (394 ml) and extracted with ethyl acetate (149 ml×2). The combined organic layer was washed with H_2O (300 ml×2), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was washed with methanol to give the title compound **21** (12.8 g, yield 91%) as a pale yellow crystalline powder: mp 173–177 °C, ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.66 (3H, s), 6.16 (2H, s), 6.96 (1H, d, J=8.8 Hz), 7.04 (1H, d, J=8.8 Hz), 7.1–7.3 (2H, m), 7.4–7.5 (2H, m), 7.71 (1H, s), 7.84 (1H, s), IR (KBr, cm^{-1}): 2208, 1718, 1598, 1457, 1216, 925, MS (EI, *m*/*z*): (M^+) 477; Elemental analysis: calcd for $C_{20}H_{13}FINO_4$, C: 50.34, H: 2.75, N: 2.94, found C: 50.53, H: 2.84, N: 2.64.

4.3.4. Methyl 8-cyano-9-(4-fluorophenyl)naphtho[1,2-*d*][1,3]dioxole-7-carboxylate 22. A mixture of compound **21** (12.1 g, 25.4 mmol), $Pd(OAc)_2$ (570 mg, 2.54 mmol), potassium carbonate (7.73 g, 55.9 mmol), and *N*-methylpyrrolidone (242 ml) was stirred at room temperature under N_2 for 1 h and then heated at 110 °C for 4 h. The reaction mixture

was allowed to stand at room temperature, and any insoluble matter was filtered off and washed with *N*-methylpyrrolidone (30 ml). The filtrate and washing were combined, washed with satd $Na_2S_2O_3$ (300 ml) and H_2O (300 ml), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified with silica-gel column chromatography to give the title compound as a pale yellow crystalline powder (2.80 g, 32%): mp 224 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.58 (3H, s), 6.35 (2H, s), 7.3–7.4 (2H, m), 7.4–7.5 (2H, m), 7.62 (1H, d, J=8.8 Hz), 7.95 (1H, d, J=8.8 Hz), 8.76 (1H, s), IR (KBr, cm^{-1}): 2217, 1708, 1459, 1274, MS (EI, *m*/*z*): (M^+) 349; Elemental analysis: calcd for $C_{20}H_{12}FNO_4$, C: 68.77, H: 3.46, N: 4.01, found C: 68.56, H: 3.41, N: 3.93.

4.3.5. Methyl 4-(4-fluorophenyl)-3-[(hydroxyamino)carbonyl]-2-[(4-iodo-1,3-benzodioxol-5-yl)methylene]but-3-enoate 23 (method D). To a stirred mixture of compound **20** (2.00 g, 4.03 mmol), tetrahydrofuran (20 ml), chloroform (20 ml), and *N*,*N*-dimethylformamide (0.4 ml), oxalyl chloride (5 ml) was added dropwise at room temperature. After being stirred at room temperature for 5 h, the reaction mixture was concentrated in vacuo. A tetrahydrofuran (50 ml) solution of the above residue was added dropwise to a stirred mixture of hydroxylamine hydrochloride (2.44 g, 40.3 mmol), tetrahydrofuran (20 ml), and satd $NaHCO_3$ (20 ml) at ice-cold temperature. After further stirring for 1 h at the same temperature, 6 M HCl (20 ml) was added to the reaction mixture and extracted with ethyl acetate twice. The combined organic layer was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was washed with a mixture of ethyl acetate and *n*-hexane to give the title compound (1.40 g, yield 68.0%) as a pale yellow crystalline powder: mp 206 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.68 (3H, s), 6.08 (2H, s), 6.8–6.9 (1H, m), 7.0–7.3 (6H, m), 7.74 (1H, s), 8.94 (1H, br), 10.8 (1H, br), IR (KBr, cm^{-1}): 1695, 1656, 1506, 1461, 1226, MS (EI, *m*/*z*): (M^+) 511; Elemental analysis: calcd for $C_{20}H_{15}FINO_6$, C: 46.99, H: 2.96, N: 2.74, found C: 47.11, H: 2.91, N: 2.64.

4.3.6. 10-(4-Fluorophenyl)-8-hydroxy-7*H*-[1,3]benzodioxolo[4,5-*f*]isoindole-7,9(8*H*)-dione 24 (method E). A mixture of compound **23** (164 mg, 0.321 mmol), $Pd(OAc)_2$ (7.2 mg, 0.0321 mmol), triethylamine (71.4 mg, 0.706 mmol), and *N*,*N*-dimethylformamide (3.3 ml) was stirred for 1 h at room temperature and then at 110 °C for 45 min. The reaction mixture was allowed to stand at room temperature, and all insoluble matter was filtered off and washed with *N*,*N*-dimethylformamide. To the combined filtrate and washing was added aq $Na_2S_2O_3$ and extracted with ethyl acetate three times. The combined organic layers were washed with H_2O twice, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting residue was washed with methanol and dried in vacuo at 40 °C to give the title compound (78.1 mg, yield 69%) as a yellow crystalline powder: mp 256 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 5.95 (2H, s), 7.1–7.3 (2H, m), 7.4–7.5 (2H, m), 7.58 (1H, d, J=8.6 Hz), 7.93 (1H, d, J=8.6 Hz), 8.45 (1H, s), 10.8 (1H, br), IR (ATR, cm^{-1}): 1714, 1508, 1290, 1068, 880, 723, MS (EI, *m*/*z*): (M^+) 351, HRMS: calcd for $C_{19}H_{10}NO_5F$, 351.0543, found 351.0548.

4.3.7. Dimethyl 2-[(4-iodo-1,3-benzodioxol-5-yl)methylene]succinate 25. To a stirred mixture of compound **17** (26.7 g, 96.7 mmol), diethyl succinate (33.6 g, 193 mmol), and methanol (135 ml) was added 28% NaOMe in methanol (28.0 g, 145 mmol) and the resulting mixture was refluxed for 3 h and 25 min. NaOH (2 M, 267 ml) was then added and the mixture was refluxed for 3 h. After cooling, the reaction mixture was concentrated in vacuo. To the residue were added H_2O (134 ml) and concd HCl (134 ml) and the mixture was extracted with ethyl acetate (267 ml+134 ml×2). The combined organic layers were washed with water (300 ml×2), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was washed with ethyl acetate (67 ml) to give 2-[(4-iodo-1,3-benzodioxol-5-yl)methylene]succinic acid (22.6 g, 62%) as a colorless crystalline powder: ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.24 (2H, s), 6.14 (2H, s), 6.87 (1H, d, J=8.0 Hz), 7.00 (1H, d, J=8.0 Hz), 7.56 (1H, s), 12.6 (2H, br), IR (KBr, cm^{-1}): 2918, 1734, 1697, 1460, 1284, MS (FAB, *m*/*z*): ($M-H)^-$ 375.

To a stirred mixture of 2-[(4-iodo-1,3-benzodioxol-5-yl)-methylene]succinic acid (22.5 g, 59.8 mmol) and methanol (225 ml) was added concd H_2SO_4 (5.87 g, 59.8 mmol) and the resulting mixture was refluxed for 15 h and 40 min. After cooling, the reaction mixture was concentrated in vacuo. To the residue was added H_2O (200 ml) and extracted with ethyl acetate (300 ml+150 ml×2). The combined organic layers were washed with H_2O (300 ml×2), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was washed with methanol (170 ml) and dried in vacuo at 40 °C to give the title compound (20.2 g, 84%) as a colorless crystalline powder: mp 130–133 °C, ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.39 (2H, s), 3.62 (3H, s), 3.76 (3H, s), 6.15 (2H, s), 6.85 (1H, d, J=8.0 Hz), 6.98 (1H, d, J=8.0 Hz), 7.62 (1H, s), IR (KBr, cm^{-1}): 2958, 1718, 1460, 1429, 1373, 1333, 1230, 1180, MS (EI, *m*/*z*): (M^+) 404; Elemental analysis: calcd for $C_{14}H_{13}IO_6$, C: 41.61, H: 3.24, I: 31.40, found C: 41.45, H: 3.27, I: 31.55.

4.3.8. 4-(1,3-Benzodioxol-5-yl)-2-[(4-iodo-1,3-benzodioxol-5-yl)methylene]-3-(methoxycarbonyl)but-3-enoic acid 26. To a stirred mixture of compound **25** (15.0 g, 37.1 mmol), piperonal (6.13 g, 40.8 mmol), and methanol (150 ml) was added 28% NaOMe in methanol (17.2 g, 89.0 mmol) and refluxed for 5 h. After the mixture was cooled, concd HCl (14.8 ml, 178 mmol) was added. The precipitate was filtered and washed with H_2O (60 ml) to give the title compound (15.9 g, yield 82%) as a pale yellow crystalline powder: mp 207 °C (decomposed), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.66 (3H, s), 6.04 (2H, s), 6.08 (2H, d, J=2.7 Hz), 6.79 (1H, d, J=8.2 Hz), 6.83 (1H, d, J=8.2 Hz), 6.87–6.97 (3H, m), 7.58 (1H, s), 7.73 (1H, s), 12.9 (1H, br), IR (KBr, cm^{-1}): 1716, 1672, 1460, 1230, MS (EI, *m*/*z*): (M^+) 522; Elemental analysis: calcd for $C_{21}H_{15}IO_8 \cdot 0.5H_2O$, C: 47.48, H: 3.04, I: 23.89, found C: 47.64, H: 2.94, I: 23.80.

4.3.9. Methyl 2-(1,3-benzodioxol-5-ylmethylene)-3-[(dimethylamino)carbonyl]-4-(4-iodo-1,3-benzodioxol-5-yl)-but-3-enoate 27. Following the method D, compound **26** (3.00 g, 5.74 mmol) was treated with tetrahydrofuran

(30 ml), *N*,*N*-dimethylformamide (0.6 ml), and oxalyl chloride (7.59 ml, 57.4 mmol) to give the corresponding acid chloride, which was treated with dimethylamine hydrochloride (4.68 g, 57.4 mmol), satd $NaHCO_3$ (60 ml), and tetrahydrofuran (45 ml) to provide the title compound (3.05 g, yield 97%) as a pale yellow crystalline powder: mp 190–191 °C, ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 2.8–3.2 (6H, br), 3.70 (3H, s), 6.01 (4H, s), 6.4–6.7 (2H, m), 6.7–6.9 (3H, m), 7.17 (1H, s), 7.48 (1H, s), IR (ATR, cm^{-1}): 1689, 1630, 1449, 1170, 1040, 932, MS (EI, *m*/*z*): (M^+) 549; Elemental analysis: calcd for $C_{23}H_{20}NO_7I$, C: 50.29, H: 3.67, N: 2.55, found C: 50.22, H: 3.58, N: 2.62.

4.3.10. Methyl 9-(1,3-benzodioxol-5-yl)-7-[(dimethylamino)-carbonyl]naphtho[1,2-*d*][1,3]dioxole-8-carboxylate 28. Following the method E, compound **27** (1.10 g, 2 mmol) was treated with $Pd(OAc)_2$ (89.8 mg, 0.4 mmol), AcOK (432 mg, 4.4 mmol), and *N*-methylpyrrolidone (22 ml) at 110 °C for 4 h, which was followed by purification with column chromatography (eluent: hexanes/AcOEt) and crystallization from aq methanol, to give the title compound (74.8 mg, yield 8.9%) as a pale yellow crystalline powder: ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 2.64 (3H, s), 2.85 (3H, s), 3.67 (3H, s), 6.00 (2H, s), 6.15 (2H, s), 6.8–7.0 (3H, s), 7.25 (1H, d, *J*=8.6 Hz), 7.47 (1H, d, *J*=8.6 Hz), 7.81 (1H, s), IR (ATR, cm^{-1}): 1737, 1617, 1459, 1223, 1200, 1111, MS (EI, *m*/*z*): (M^+) 421; Elemental analysis: calcd for $C_{23}H_{19}NO_7 \cdot 0.5H_2O$, C: 64.18, H: 4.68, N: 3.08, found C: 64.17, H: 4.82, N: 3.17, HPLC purity: 99.6%.

4.3.11. 4-(1,3-Benzodioxol-5-yl)-3-(hydroxymethyl)-2-[(4-iodo-1,3-benzodioxol-5-yl)methylene]-but-3-enoic acid 29. Under a nitrogen atmosphere, compound **29** (2.00 g, 3.83 mmol) was suspended in tetrahydrofuran (6 ml) and cooled at 0–10 °C. To the suspension was added dropwise 1.0 M $LiBHEt_3$ in tetrahydrofuran (25.2 ml, 25.2 mmol), maintaining the temperature below 10 °C, and stirred at this temperature for 1 h. To the reaction mixture were added 50% aq acetic acid (3 ml) and H_2O. The resultant mixture was extracted with ethyl acetate three times. The combined organic layers were washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was crystallized from ethyl acetate/*n*-hexane (2:1) to give the title compound (1.26 g, yield 67%) as a pale yellow crystalline powder: ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 3.8–4.0 (3H, m), 5.97 (2H, s), 6.10 (2H, s), 6.57 (1H, s), 6.69 (1H, dd, *J*=8.2 and 1.6 Hz), 6.7–6.9 (3H, m), 7.25 (1H, d, *J*=8.2 Hz), 7.63 (1H, s), IR (KBr, cm^{-1}): 3384, 1691, 1459, 1255, 1232, MS (FAB): (M−H) 493; Elemental analysis: calcd for $C_{20}H_{15}IO_7$, C: 48.60, H: 3.06, I: 25.68, found C: 48.38, H: 3.13, I: 25.31 and 25.42.

4.3.12. 4-(1,3-Benzodioxol-5-ylmethylene)-3-[(4-iodo-1,3-benzodioxol-5-yl)methylene]pyrrolidin-2-one 30. A mixture of compound **29** (1.2 g), iodoethane (2.83 g, 18.2 mmol), K_2CO_3 (1.26 g, 9.10 mmol), and *N*,*N*-dimethylformamide (8.18 ml) was stirred at room temperature for 2 h. To the reaction mixture was added H_2O (50 ml) and extracted with ethyl acetate (100 ml+50 ml+50 ml). The combined organic layers were washed with H_2O (50 ml), dried over anhydrous $MgSO_4$, and concentrated in vacuo to leave an oil.

To the residual oil was added toluene (24 ml), followed by PBr_3 (657 mg), and the resulting mixture was stirred at room temperature for 1 h. To the reaction mixture was added H_2O (50 ml) and extracted with ethyl acetate (50 ml) twice. The combined organic layers were washed with H_2O (50 ml), dried over anhydrous $MgSO_4$, and concentrated in vacuo to leave an oil.

To the residual oil were added tetrahydrofuran (12 ml), 28% aq NH_3 (24 ml), and methanol (12 ml) and the resulting mixture was stirred at room temperature for 11 h. After the reaction mixture was concentrated in vacuo, ethyl acetate (50 ml) and H_2O (50 ml) were added to the residue. The aqueous layer was separated and extracted with ethyl acetate (50 ml). The combined organic layers were washed with H_2O (50 ml), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified with silica-gel column chromatography (eluent: toluene/ethyl acetate) to give the title compound as a yellow solid (405 mg, yield 35%): ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 4.07 (2H, s), 5.84 (2H, s), 5.99 (1H, d, *J*=1.3 Hz), 6.02 (2H, s), 6.15 (1H, d, *J*=8.2 Hz), 6.19 (1H, d, *J*=8.2 Hz), 6.37 (1H, dd, *J*=1.3 and 8.1 Hz), 6.50 (1H, d, *J*=8.1 Hz), 6.53 (1H, s), 7.12 (1H, s), 8.41 (1H, br s), IR (KBr, cm^{-1}): 1697, 1454, 1249, 1037, MS (EI, *m*/*z*): (M+) 475, HRMS: calcd for $C_{20}H_{14}NO_5I$, 474.9914, found 474.9917, HPLC purity: 98.7%.

4.3.13. 10-(1,3-Benzodioxol-5-yl)-8,9-dihydro-7*H*-[1,3]benzodioxolo[4,5-*f*]isoindol-7-one 7c. A mixture of compound **30** (300 mg, 0.631 mmol), $Pd(OAc)_2$ (14.2 mg, 0.0631 mmol), AcOK (136 mg, 1.39 mmol), and *N*-methylpyrrolidone (6 ml) was stirred at room temperature for 1 h and the resulting mixture was heated at 110 °C for 40 min. After the reaction mixture had stood at room temperature, insoluble matter was filtered off and washed with *N*-methylpyrrolidone (3 ml) and ethyl acetate (10 ml). To the combined filtrate and washing was added aq $Na_2S_2O_3$ (35 ml) and extracted with ethyl acetate (20 ml+15 ml+15 ml). The combined organic layers were washed with 1 M HCl (2×30 ml) and brine (2×30 ml), and concentrated in vacuo. The residue was washed with tetrahydrofuran/ethanol (1:1, 0.5 ml) and dried in vacuo at 40 °C to give the title compound as yellow crystals (106 mg, yield 48%): mp: 250–251 °C (lit.[2] mp: 252–254 °C), ^{1}H NMR (DMSO-d_6, TMS, 300 MHz) δ (ppm): 4.20 (2H, s), 5.95 (2H, dd, *J*=6.3 and 0.9 Hz), 6.09 (2H, dd, *J*=14.1 and 0.8 Hz), 6.87 (1H, dd, *J*=7.9 and 1.6 Hz), 6.96 (1H, d, *J*=7.9 Hz), 7.00 (1H, d, *J*=1.6 Hz), 7.43 (1H, d, *J*=8.7 Hz), 7.95 (1H, d, *J*=8.7 Hz), 8.29 (1H, s), 8.58 (1H, br), IR (KBr, cm^{-1}): 1701, 1635, 1495, 1460, 1439, 1272, MS (EI, *m*/*z*): (M^+) 347; Elemental analysis: calcd for $C_{20}H_{13}NO_5 \cdot 0.75H_2O$, C: 66.57, H: 4.19, N: 3.88, found C: 66.65, H: 4.18, N: 4.16, HPLC purity: 96.9%.

The palladium-catalyzed reaction of compound **30** (25 mg) was carried out as before. The reaction mixture was assayed by HPLC under the following conditions to indicate a 72% yield of compound **7c**.

HPLC conditions: YMC-Pack ODS-A302 column (150 mm×4.6 mm I.D.) with 0.05 M KH_2PO_4 in water and acetonitrile (60:40) at 25 °C. Detection was effected with a Hitachi spectrophotometric detector at 254 nm.

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References and notes

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