Photoinduced Molecular Transformations. Part 135.[1] New Synthesis of Taiwanin C and Justicidin E based on a Radical Cascade Process involving β-Scission of Alkoxyl Radicals generated from 3- and 8-Aryl-1-ethyl-1,2-dihydrocyclobuta[*b*]naphthalen-1-ols prepared by Thermolysis of (*Z*)-*tert*-Butyl 3-Amino-3-(bicyclo[4.2.0]octa-1,3,5-trien-7-yl)propenoates[2]

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A new general synthesis of naturally occurring phthalide lignans, based on a radical cascade process triggered by a regioselective β-scission of the alkoxyl radicals generated by photolysis of the hypoiodites of 8-aryl-1-ethyl-1,2-dihydrocyclobuta[*b*]naphthalen-1-ols, is described. Two phases are involved in the present synthesis of phthalide lignans; the first is a new general synthesis of *tert*-butyl 4-aryl-3- and 4-aryl-8-aminonaphthalene-2-carboxylates by an electrocyclic reaction of *o*-quinonedimethides thermally generated from (*Z*)-*tert*-butyl 3-amino-3-(bicyclo[4.2.0]octa-1,3,5-trien-7-yl)propenoates; the second is a transformation of the protected 4-aryl-3-aminonaphthalene-2-carboxylic acids into the phthalide lignans. This latter phase involves their successive conversions into 3- and 8-arylcyclobuta[*b*]naphthalen-1(2*H*)-ones *via* the formation of a benzyne intermediate, and then into 3- and 8-aryl-1-ethyl-1,2-dihydrocyclobuta[*b*]naphthalen-1-ols, followed by β-scission of the alkoxyl radicals generated by photolysis of their hypoiodites, generated *in situ* with the mercury(II) oxide–iodine reagent in benzene. Simultaneous syntheses of the naturally occurring phthalide lignans taiwanin C and justicidin E were thus achieved.

We recently reported[3] on a new, short step, general synthesis of isobenzofuran-1(3*H*)-ones (phthalides) based on a regioselective single or double β-scission of the alkoxyl radicals generated by photolysis of the hypoiodites of 1-ethylbenzocyclobuten-1-ols or 1,2-catacondensed benzocyclobuten-1-ols. Thus, for example, irradiation of 1-ethylbenzocyclobuten-1-ols **1** in benzene containing mercury(II) oxide and iodine (3 mol equiv. each) with a 100 W high-pressure Hg arc through a Pyrex filter at room temperature gave phthalides **2** in 54–64% yields.[3]

The principal reaction pathway from cyclobutenols **1** into phthalides **2**, which is essentially parallel to that leading to the hypoiodites of steroidal 17-β-ols upon irradiation previously reported,[4] is outlined in Scheme 1; the regioselective β-scission of alkoxyl radicals **B** generated by photolysis of the hypoiodites **A** gives rise to benzyl radicals **C**, which cascade to give phthalides **2** *via* successive intermediates **D**, **E**, **F** and **G** by interaction with the metal ions and diiodine monoxide present in the solution.[3]

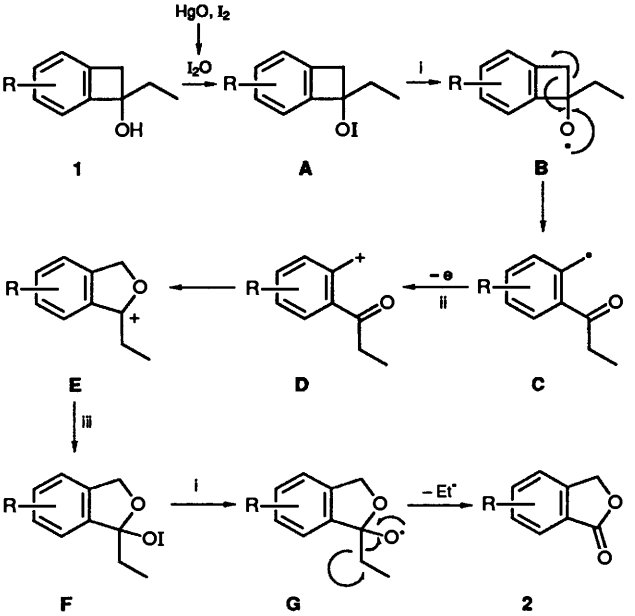
In a previous paper we reported on the applications of this process to new syntheses of some simple natural products.[3]

In this paper we report on an additional application of this reaction to a new synthesis of phthalide lignans: taiwanin C, isolated from the heartwood of *Taiwania cryptomerioides* Hayata,[5] and justididin E, isolated as a piscicidal constituent from *Justicia procumbenes*.[6]

Since the pioneering work by Haworth[7] a number of phthalide lignans have been found in Nature and their synthesis under varying degrees of sophistication have been reported. For example, taiwanin C and justicidin E were first synthesized by Haworth and Kelly long before they were found as natural products; since their discovery as natural products the synthesis of either or both of them by different approaches has been reported by several groups of investigators.[8]

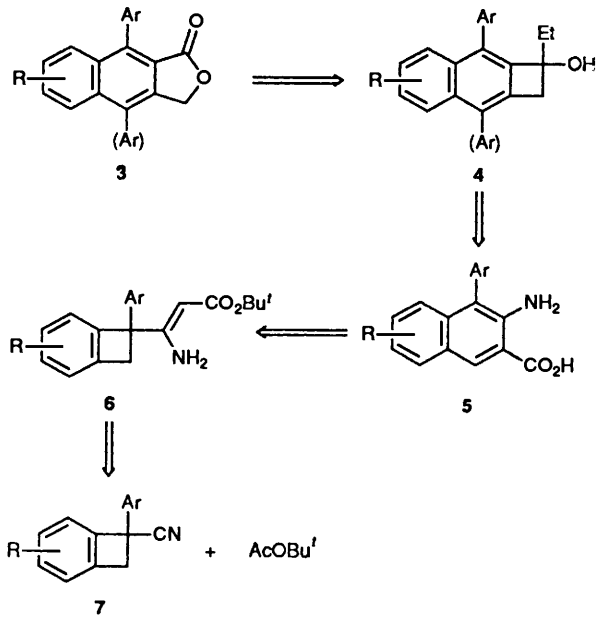
A retrosynthetic Scheme including our phthalide synthesis suggests that naphthalide **3** can be obtained from 1-cyanobenzocyclobutenes **7** *via* 3-amino-4-arylnaphthalene-2-carboxylic acids **5** (Scheme 2).

The present new synthesis of phthalide lignans thus comprises two phases; the first phase involves the synthesis of



Scheme 1 *Reagents and conditions:* i, *hν*; ii, Hg^{2+}; iii, I_2O

protected 4-aryl-3-aminonaphthalene-2-carboxylic acids **5** by the new general method *via* the aminopropenoates **6**. These protected 3-aminonaphthalene-2-carboxylic acids **5** are then transformed into phthalide lignans **3** during the second phase of the synthesis; *tert*-butyl 4-aryl-3-aminonaphthalene-2-carboxylate is converted into 3- and 8-arylcyclobuta[*b*]naphthalen-1(2*H*)-ones *via* the formation of the benzyne intermediate, and then into 3- and 8-aryl-1,2-dihydrocyclobuta[*b*]naphthalen-1-ols **4** with ethylmagnesium bromide; the generation of alkoxyl radicals by photolysis of the hypoiodites of the cyclobutanaphthalen-1-ols **4** results in rearrangements to benzyl radicals which cascade to give phthalide lignans **3**, following the pathway outlined in Scheme 1.

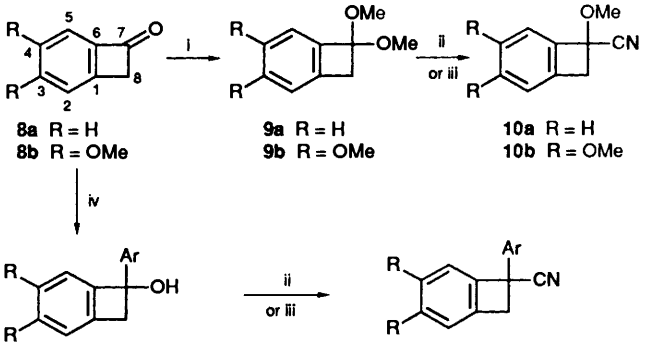


Scheme 2

New General Synthesis of tert-*Butyl* 3-*Aminonaphthalene*-2-*carboxylates.*[2]—As described in the foregoing part, an efficient synthesis of 3-aminonaphthalene-2-carboxylic acids was required for the synthesis of 8- and 3-arylcyclobuta[*b*]naphthalen-1-ones, from which 1,2-dihydrocyclobutanaphthalen-1-ols **4** can be derived. 3-Aminonaphthalene-2-carboxylic acids, useful intermediates as precursors for the generation of benzynes,[9] have been exploited as precursors for the synthesis of polyaromatic[10] and heteroaromatic compounds.[11] There has been, however, little work[12] on a general method for preparing this group of molecules, particularly those having substituents which are required in the present work and which may have considerable potential in general organic synthesis.

We therefore devised a new general method for the synthesis of *tert*-butyl 3-aminonaphthalene-2-carboxylates by an electrocyclic reaction of *o*-quinonedimethides generated from (*Z*)-*tert*-butyl 3-amino-3-(bicyclo[4.2.0]octa-1,3,5-trien-7-yl)propenoates.

Bicyclo[4.2.0]octa-1,3,5-trien-7-one **8a**[13] or its 3,4-dimethoxy derivative **8b** was transformed into the 7,7-dimethyl ketal **9a**[14] or **9b**, respectively, with trimethyl orthoformate and toluene-*p*-sulfonic acid (PTSA) in refluxing methanol in 87 and 83% yield (Scheme 3). Dimethyl ketals **9a** and **9b** were then converted into the corresponding 7-methoxy 7-carbonitriles **10a** and **10b** with cyanotrimethylsilane and either boron trifluoride–diethyl ether or zinc iodide in dichloromethane at 0 °C in 88 and 58% yield. On the other hand, treatment of bicyclo[4.2.0]-octa-1,3,5-trien-7-one **8a** with phenylmagnesium bromide in tetrahydrofuran (THF) at −78 °C gave 7-phenylbicyclo-[4.2.0]octa-1,3,5-trien-7-ol **11a**[15] in 77% yield. Similar reactions of benzocyclobutenone **8a** and its 3,4-dimethoxy derivative **8b** with *p*-methoxyphenylmagnesium bromide and with 3,4-dimethoxyphenylmagnesium bromide gave the corresponding 7-aryl alcohols, **11b**, **11c** and **11d**, in 93, 60 and 54% yield. These 7-aryl 7-ols **11b**–**11d** were then transformed into the corresponding 7-carbonitriles, **12a**–**12d**, in 57–79% yield according to the procedure described for the transformation of 7,7-dimethyl ketals **9a** and **9b** into 7-carbonitriles **10a** and **10b**. The 7-carbonitriles, **10a**, **10b** and **12a**–**12d**, were next transformed into the corresponding (*Z*)-*tert*-butyl 3-amino-3-(bicyclo[4.2.0]octa-1,3,5-trien-7-yl)propenoates **13a**–**13f** with magnesium bis(diisopropylamide)



8a R = H
8b R = OMe
9a R = H
9b R = OMe
10a R = H
10b R = OMe

11a Ar = Ph, R = H
11b Ar = 4-MeOC$_6$H$_4$, R = H
11c Ar = 3, 4-(MeO)$_2$C$_6$H$_3$, R = H
11d Ar = 3, 4-(MeO)$_2$C$_6$H$_3$, R = OMe
12a Ar = Ph, R = H
12b Ar = 4-MeOC$_6$H$_4$, R = H
12c Ar = 3, 4-(MeO)$_2$C$_6$H$_3$, R = H
12d Ar = 3, 4-(MeO)$_2$C$_6$H$_3$, R = OMe

Scheme 3 *Reagents and conditions:* i, $CH(OMe)_3$–PTSA–MeOH, reflux; ii, Me_3SiCN–BF_3·OEt–CH_2Cl_2, 0 °C; iii, Me_3SiCN–ZnI_2–CH_2Cl_2, 0 °C; iv, ArMgBr–THF, −78 °C or 0°C.

and *tert*-butyl acetate in diethyl ether at 0 °C in 53–75% yield.[16]

The thermal generation of *o*-quinonedimethides (H in Scheme 4) from propenoates **13a** and **13b** with exclusion of molecular oxygen in solution gave protected 3-aminonaphthalene-2-carboxylic acid esters **14a** and **14b**, while thermolysis of a solution saturated with molecular oxygen gave their 4-methoxy derivative **15a**; a solution of (*Z*)-*tert*-butyl 3-amino-3-(7′-methoxybicyclo[4.2.0]octa-1′,3′,5′-trien-7′-yl)propenoate **13a** or its 3′,4′-dimethoxy derivative **13b** in *o*-dichlorobenzene was heated under reflux for 30 min under nitrogen to give *tert*-butyl 3-aminonaphthalene-2-carboxylate **14a** or its 6,7-dimethoxy derivative **14b** through intermediates H, I and J in 58 and 64% yield, respectively, as outlined in Scheme 4. The analogous thermolysis of 3-aminopropenoates **13a** and **13c**–**13f**, in *o*-dichlorobenzene saturated with oxygen gave 3-aminonaphthalene-2-carboxylates **15a**–**15e** in 33–72% yield.

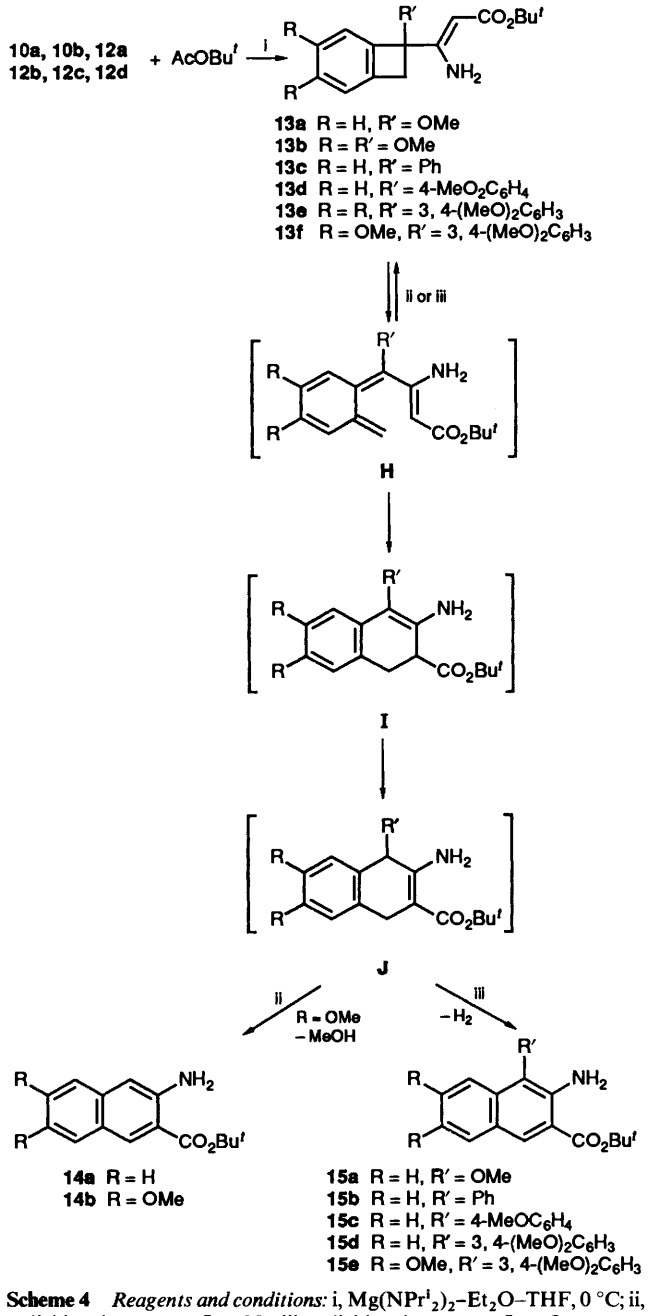
Although a number of syntheses by intramolecular electrocyclic reactions of *o*-quinonedimethides[17] have been reported,[18,19] the synthesis reported here is the first one in which an enamino group is involved as an internal dienophile.

Transformation of 1,1-*Dimethylethyl* 3-*Amino*-4-(3,4-*dimethoxyphenyl*)-6,7-*dimethoxynaphthalene*-2-*carboxylate* **15e** *into the Phthalide Lignans Taiwanin C and Justicidin E.*—The synthesis of naturally occurring phthalide lignans **19a** and **19b** from the *tert*-butyl aminonaphthoate **15e** was achieved according to the retrosynthetic Scheme 2 in which our new general method for the synthesis of phthalides[3] is the key step.

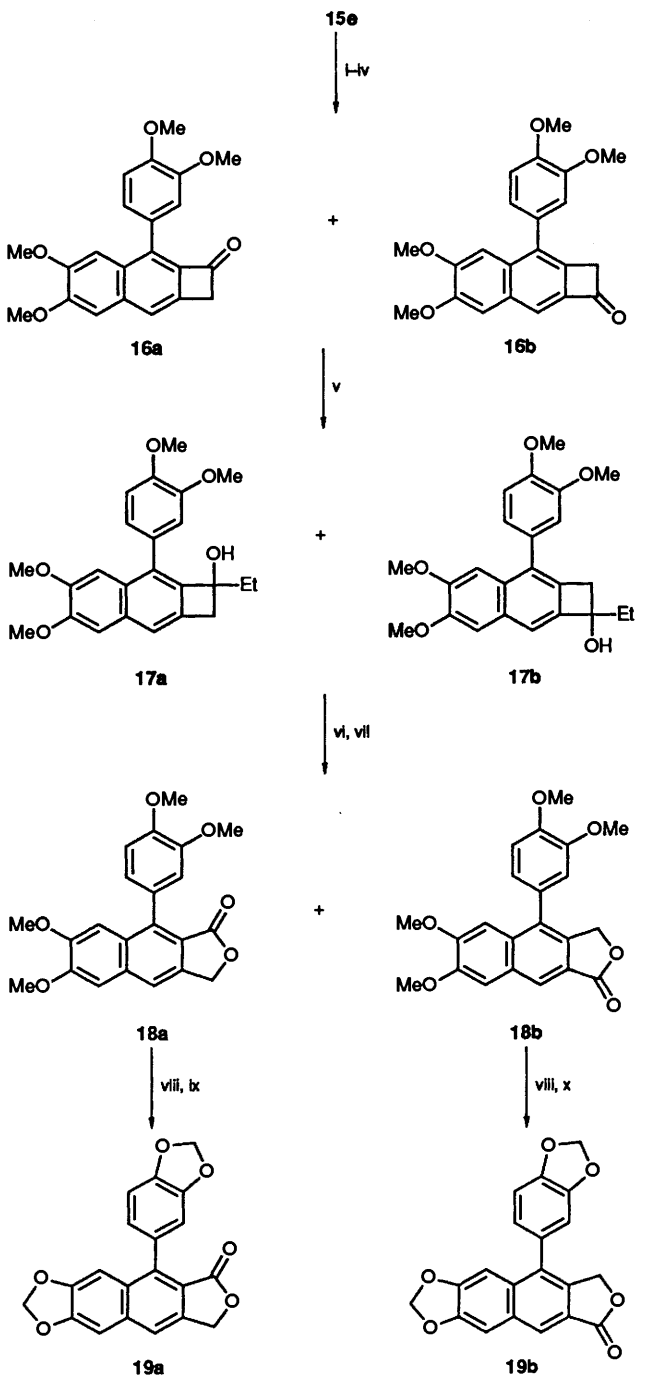
According to the procedure by Dürr *et al.*,[20] a diazonium salt of the *tert*-butyl aminonaphthoate **15e**, prepared as mentioned above, was treated with 1,1-dichloroethene and propylene oxide in 1,2-dichloroethane under reflux to give a mixture of isomeric dichloronaphthocyclobutenes, which was then heated under reflux with aq. sulfuric acid to give a mixture of 8- and 3-aryl-4,6-dimethoxycyclobuta[*b*]naphthalen-1-ones, **16a** and **16b**, in 31% yield.

The 8- and 3-arylcyclobutanaphthalen-1-ones **16a** and **16b** were then treated with ethylmagnesium bromide in THF to give a 1:1 mixture of the isomers of the 1-ethyl-1,2-dihydrocyclobuta[*b*]naphthalen-1-ols, **17a** and **17b**, in 83% yield.

Irradiation of the mixture of 1,2-dihydrocyclobutanaphthalen-1-ols **17a** and **17b** in benzene containing mercury(II) oxide and iodine (3 mol equiv. each) with a 100 W high-pressure mercury arc through a Pyrex filter under nitrogen at room



Scheme 4 *Reagents and conditions:* i, $Mg(NPr^i_2)_2$–Et_2O–THF, 0 °C; ii, *o*-dichlorobenzene, reflux, N_2; iii, *o*-dichlorobenzene, reflux, O_2



Scheme 5 *Reagents and conditions:* i, conc. HCl, 50 °C; ii, Am^{i}ONO–EtOH, 0 °C; iii, CH_2=CCl_2, propylene oxide, $ClCH_2CH_2Cl$, reflux; iv, 10% aq. H_2SO_4, reflux; v, EtMgBr–THF, 0 °C; vi, HgO–I_2–benzene; vii, *hv*; viii, BBr_3–CH_2Cl_2; ix, CsF–CH_2Cl_2–DMF; x, KF–CH_2Br_2–DMF

temperature[3] gave a mixture of isomeric phthalides. These phthalides were separated by preparative TLC (PLC) to give 9- and 4-(3,4-dimethoxyphenyl)-6,7-dimethoxynaphtho[2,3-*c*]-furan-1(3*H*)-one, **18a** and **18b**, synthesized by Haworth and Sheldrick by a different route in 1935.[7b]

Replacement of a pair of dimethoxy groups of the methoxynaphthofuranones **18a** and **18b** by a methylenedioxy group was accomplished according to the procedure of Clark *et al.*;[21] treatment of tetramethoxynaphthofuranone **18a** with boron tribromide in dichloromethane at −10 °C gave the corresponding crude phenol, which reacted with dichloromethane in the presence of caesium fluoride in dimethylformamide (DMF) to give taiwanin C **19a** in 59% yield. Similarly, treatment of the isomeric tetramethoxynaphthofuranone **18b** with boron tribromide followed by reaction of the resulting crude phenol with dibromomethane in the presence of potassium fluoride gave justicidine E **19b** in 41% yield (Scheme 5).

Experimental

General Methods.—M.p.s were determined with a Yanagimoto m.p. apparatus and are uncorrected. The IR spectra were determined for Nujol mulls with a Hitachi Model 285 infrared spectrometer. The ^{1}H NMR spectra were determined in $CDCl_3$ ($SiMe_4$ as internal reference) with a Hitachi R-90H FT NMR spectrometer operating at 90 MHz. High- and low-resolution mass spectra were recorded with a JEOL JMS-DX303 spectrometer (70 eV). TLC was carried out on Merck Kieselgel 60 PF_{254}. Photolysis of the hypoiodites was carried out by irradiation of a stirred solution of each substrate in a Pyrex

vessel with light generated by a 100 W EIKOSHA PIH-100 high-pressure Hg arc lamp.

Bicyclo[4.2.0]*octa*-1,3,5-*trien*-7-*one* **8a**.—This compound[13] was prepared according to a procedure by Dürr *et al.*[20]

3,4-*Dimethoxybicyclo*[4.2.0]*octa*-1,3,5-*trien*-7-*one* **8b**.—This *compound* was similarly prepared from 2-amino-4,5-dimethoxybenzoic acid in 45% yield by the procedure of Dürr *et al.*[20] M.p. 133–134 °C (from hexane–diethyl ether); ν_{max}/cm^{-1} 1734; δ 3.86 (6 H, s, 2 × OMe), 4.00 (2 H, s, 8-H), 6.82 (1 H, s, 2-H) and 7.01 (1 H, s, 5-H); *m*/*z* 178 (M^+, 82%) and 150 [$(M - CO)^+$, 100] (Found: M^+, 178.0633. $C_{10}H_{10}O_3$ requires *M*, 178.0630).

7,7-*Dimethoxybicyclo*[4.2.0]*octa*-1,3,5-*triene* **9a**.[14]—A solution of benzocyclobutenone **8a** (0.45 g, 3.8 mmol), PTSA (30 mg) and trimethyl orthoformate (0.7 cm^3) in methanol (5 cm^3) was heated under reflux for 6 h. After cooling, the resulting mixture was diluted with diethyl ether, washed successively with saturated aq. sodium hydrogen carbonate and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a product, which was distilled by Kugelrohr to give ketal **9a** (0.54 g, 87%), b.p. 72–73 °C (bath temp.)/0.05 mmHg.

3,4,7,7-*Tetramethoxybicyclo*[4.2.0]*octa*-1,3,5-*triene* **9b**.—*Ketal* **9b** was prepared (83%) in a similar manner as described for the preparation of compound **9a** (reflux for 3.5 h), and had b.p. 114–115 °C (bath temp.)/0.2 mmHg; ν_{max}(neat)/cm^{-1} no C=O group; δ 3.28 (2 H, s, 8-H_2), 3.43 (6 H, s), 3.86 (6 H, s), 6.80 (1 H, s) and 6.87 (1 H, s); *m*/*z* 224 (M^+, 2.7%) and 91 (100) (Found: M^+, 224.1070. $C_{12}H_{16}O$ requires *M*, 224.1048.

7-*Phenylbicyclo*[4.2.0]*octa*-1,3,5-*trien*-7-*ol* **11a**.[15]—To phenylmagnesium bromide, prepared *in situ* by the reaction of magnesium (61 mg, 2.5 mmol), in THF (15 cm^3), was added **8a** (0.26 g, 2.2 mmol) in THF (20 cm^3) at −78 °C. After the solution had been stirred for 30 min, it was poured into 5% hydrochloric acid and extracted with diethyl ether. The ether layer was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crude alcohol which was purified by PLC to give the cyclobutanol **11a** (0.33 g, 77%); R_f 0.42 (1:3 ethyl acetate–hexane), m.p. 70–73 °C (from hexane) (lit.,[15] 72–73 °C).

7-(4-*Methoxyphenyl*)*bicyclo*[4.2.0]*octa*-1,3,5-*trien*-7-*ol* **11b**.—The conversion of benzocyclobutenone **8a** into the cyclobutenol **11b** was carried out in 93% yield at 0 °C under otherwise the same conditions as mentioned above; *compound* **11b** had R_f 0.39 [(1:3) ethyl acetate–hexane]; ν_{max}(neat)/cm^{-1} 3360; δ 3.58 (2 H, s, 8-H_2), 3.78 (3 H, s, OMe), 6.84 (2 H, d, *J* 8.57, 3′, 5′-H) and 7.1–7.5 (6 H, m); *m*/*z* 226 (M^+, 21%), 225 [$(M - 1)^+$, 69] and 195 [$(M - OMe)^+$, 100) (Found: M^+, 226.0976. $C_{15}H_{14}O_2$ requires *M*, 226.0994).

7-(3,4-*Dimethoxyphenyl*)*bicyclo*[4.2.0]*octa*-1,3,5-*trien*-7-*ol* **11c**.—This preparation was carried out similarly to that described for compound **11b**, at −40 °C but otherwise under the same conditions as described above (60% yield). *Compound* **11c** had R_f 0.18 [(1:3) ethyl acetate–hexane]; ν_{max}/cm^{-1} 3452; δ 3.59 (2 H, s, 8-H_2), 3.86 (6 H, s, OMe) and 6.7–7.4 (7 H, m); *m*/*z* 256 (M^+, 18%) and 225 [$(M - 1)^+$, 100] (Found: M^+, 256.1092. $C_{16}H_{16}O_3$ requires *M*, 256.1100).

7-(3,4-*Dimethoxyphenyl*)-3,4-*dimethoxybicyclo*[4.2.0]*octa*-1,3,5-*trien*-7-*ol* **11d**.—To a stirred solution of 3,4-dimethoxyphenylmagnesium bromide, prepared from 1-bromo-3,4-dimethoxybenzene (3.6 g, 18 mmol) and magnesium (0.48 g, 20 mg), in THF (15 cm^3) at 0 °C under argon was added dropwise a solution of 3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-one **8b** (2.9 g, 17 mmol) in THF (30 cm^3). The mixture was stirred for 2 h at the same temperature, and then was treated with diethyl ether (150 cm^3) and washed successively with aq. ammonium chloride, aq. sodium hydrogen carbonate and brine. After drying over anhydrous sodium sulfate the solvent was removed and the residue was purified by PLC on silica gel [(1:3) ethyl acetate–hexane] to give *compound* **11d** (2.9 g, 54%), m.p. 132–133 °C (from hexane–acetone); ν_{max}/cm^{-1} 3370; δ 3.49 (2 H, s, 8-H_2), 3.86 (12 H, s, 4 × OMe) and 6.7–7.1 (5 H, m, ArH); *m*/*z* 316 (M^+, 45%) and 285 [$(M - OMe)^+$, 100] (Found: M^+, 316.1321. $C_{18}H_{20}O_5$ requires *M*, 316.1311).

7-*Methoxybicyclo*[4.2.0]*octa*-1,3,5-*triene*-7-*carbonitrile* **10a**.—To a stirred solution of the ketal **9a** (0.54 g, 3.3 mmol) and cyanotrimethylsilane (0.35 g, 3.5 mmol) in dichloromethane (3 cm^3) at 0 °C was added dropwise boron trifluoride–diethyl ether (57 mg, 0.40 mmol). The solution was stirred for 25 h at that temperature before being diluted with diethyl ether, washed successively with saturated aq. sodium hydrogen carbonate and brine, and dried over anhydrous sodium sulfate. After removal of the solvent the product was distilled by Kugelrohr to afford the *nitrile* **10a** (0.46 g, 88%), b.p. 85–86 °C (bath temp.)/10.5 mmHg; ν_{max}/cm^{-1} 2230; δ 3.50 (1 H, d, *J* 14.50, 8-H), 3.61 (3 H, s, OMe), 3.83 (1 H, d, *J* 4.50, 8-H) and 7.1–7.5 (4 H, m); *m*/*z* 159 (M^+, 4.6%), 158 [$(M - 1)^+$, 24], 144 [$(M - Me)^+$, 93] and 116 (100) (Found: M^+, 159.0670. $C_{10}H_9NO$ requires *M*, 159.0684).

3,4,7-*Trimethoxybicyclo*[4.2.0]*octa*-1,3,5-*triene*-7-*carbonitrile* **10b**.—Conversion of ketal **9b** into nitrile **10b** was carried out by the same procedure as mentioned above but using zinc iodide in the place of boron trifluoride–diethyl ether (58% yield). *Compound* **10b** had R_f 0.26 [(1:3) ethyl acetate–hexane]; ν_{max}/cm^{-1} 2228; δ 3.41 (1 H, d, *J* 13.63, 8-H), 3.60 (3 H, s, 7-OMe), 3.73 (1 H, d, *J* 13.63, 8-H), 3.87 (6 H, s, 3-, 4-OMe), 6.76 (1 H, s) and 6.87 (1 H, s); *m*/*z* 219 (M^+, 25%) and 204 [$(M - 1)^+$, 100] (Found: M^+, 219.0884. $C_{12}H_{13}NO_3$ requires *M*, 219.0896).

7-*Phenylbicyclo*[4.2.0]*octa*-1,3,5-*triene*-7-*carbonitrile* **12a**.—This nitrile was prepared in 71% yield from the alcohol **11a** according to the procedure described for the preparation of nitrile **10a**. *Compound* **12a** had R_f 0.55 [(1:3) ethyl acetate–hexane]; ν_{max}(neat)/cm^{-1} 2232; δ 3.54 (1 H, d, *J* 14.07, 8-H), 4.15 (1 H, d, *J* 14.07, 8-H) and 7.2–7.5 (9 H, m); *m*/*z* 205 (M^+, 81%) and 204 [$(M - 1)$, 100] (Found: M^+, 205.0873. $C_{15}N_{11}N$ requires *M*, 205.0892).

7-(4-*Methoxyphenyl*)*bicyclo*[4.2.0]*octa*-1,3,5-*triene*-7-*carbonitrile* **12b**.—This compound was prepared from the alcohol **11b** according to the procedure described for the preparation of compound **10b**, in 73% yield. *Nitrile* **12b** had R_f 0.46 [(1:3) ethyl acetate–hexane]; ν_{max}/cm^{-1} 2230; δ 3.50 (1 H, d, *J* 14.06, 8-H), 3.80 (3 H, s, OMe), 4.12 (1 H, d, *J* 14.06, 8-H), 688 (2 H, d, *J* 8.79, 3′-, 5′-H) and 7.1–7.5 (6 H, m); *m*/*z* 235 (M^+, 97%) and 204 [$(M - OMe)^+$, 100] (Found: M^+, 235.0995. $C_{16}H_{13}NO$ requires *M*, 235.0997).

7-(3,4-*Dimethoxyphenyl*)*bicyclo*[4.2.0]*octa*-1,3,5-*triene*-7-*carbonitrile* **12c**.—This compound was prepared from the alcohol **11c** according to the procedure described for the preparation of nitrile **10b**, in 57% yield. For *nitrile* **12c**: m.p. 126–127 °C (from hexane–diethyl ether); ν_{max}/cm^{-1} 2230; δ 3.52 (1 H, d, *J* 13.85, 8-H), 3.85 (3 H, s, OMe), 3.87 (3 H, s, OMe), 4.13 (1 H, d, *J* 13.85, 8-H), 6.7–7.0 (3 H, m) and 7.1–7.5 (4 H, m); *m*/*z* 265 (M^+, 20%) and 234 [$(M - OMe)^+$, 100] (Found: M^+, 265.1080. $C_{17}H_{15}NO_2$ requires *M*, 265.1103).

7-(3,4-*Dimethoxyphenyl*)-3,4-*dimethoxybicyclo*[4.2.0]*octa*-1,-3,5-*triene*-7-*carbonitrile* **12d**.—To a stirred solution of the benzocyclobutenol **11d** (2.1 g, 6.6 mmol) and cyanotrimethylsilane (1.1 g, 11 mmol) in dichloromethane (24 cm^3) at 0°C under argon was added zinc iodide (0.28 g, 0.9 mmol) and the mixture was stirred for 1.5 h at the same temperature. The solution was diluted by addition of diethyl ether (60 cm^3) and was then washed successively with aq. sodium hydrogen carbonate and brine. After drying over anhydrous sodium sulfate the solvent was evaporated to give a residue, which was subjected to PLC on silica gel [(1:1) ethyl acetate–hexane] to give *nitrile* **12d** (1.7 g, 79%); m.p. 126–127 °C (from hexane–acetone); ν_{max}/cm^{-1} 2264; δ 3.39 (1 H, d, *J* 13.18, 8-H), 3.85, 3.87 and 3.90 (12 H, each s, 4 × OMe), 4.03 (1 H, d, *J* 13.18, 8-H) and 6.75–6.9 (5 H, m, ArH); *m/z* 325 (M^+, 17%) and 294 [$(M - OMe)^+$, 100] (Found: M^+, 325.1327. $C_{19}H_{19}NO_4$ requires *M*, 325.1314).

(Z)-1,1-*Dimethylethyl* 3-*Amino*-3-(7-*methoxybicyclo*[4.2.0]-*octa*-1,3,5-*trien*-7-*yl*)*propenoate* **13a**.—To a stirred solution of ethylmagnesium bromide (5.4 mmol) in diethyl ether (4.7 cm^3) at 0 °C was added diisopropylamine (0.63 g, 11 mmol). The mixture was then stirred at that temperature for 1 h. To the resulting turbid solution were added successively *tert*-butyl acetate (0.31 g, 2.7 mmol) and a solution of the cyanide **10a** (0.43 g, 2.7 mmol) in THF (2 cm^3). The solution was stirred for an additional 1.5 h and aq. ammonium chloride was then added. The solution was extracted with diethyl ether, washed with brine, and dried over anhydrous sodium sulfate. After removal of solvent under reduced pressure, solid residue was purified by recrystallization from hexane to afford ester **13a** (0.56 g, 75%), m.p. 135–136 °C; ν_{max}/cm^{-1} 3412, 3306, 1674, 1625 and 1563; δ 1.44 (9 H, s, Bu^t), 3.38 (3 H, s, OMe), 3.41 (2 H, s, 8′-H_2), 4.44 (1 H, s, 2-H), 5.4–6.9 (2 H, br, NH_2) and 7.1–7.4 (4 H, m); *m/z* 275 (M^+, 0.91%), 219 [$(M - CH_2{=}CMe_2)^+$, 60] and 204 (100) (Found: M^+, 275.1534. $C_{16}H_{21}NO_3$ requires *M*, 275.1523).

(Z)-1,1-*Dimethylethyl* 3-*Amino*-3-(3′,4′,7′-*trimethoxybicyclo*-[4.2.0]*octa*-1′,3′,5′-*trien*-7′-*yl*)*propenoate* **13b**.—This enamino ester was prepared from nitrile **10b** in 67% yield by the same procedure as that described for the preceding experiment. For *ester* **13b**: m.p. 122–144 °C (from hexane–diethyl ether–dichloromethane); ν_{max}/cm^{-1} 3466, 3340, 1655, 1613 and 1547; δ 1.44 (9 H, s, Bu^t), 3.32 (2 H, s, 8′-H_2), 3.37 (3 H, s, 7′-OMe), 3.88 (3 H, s), 3.89 (3 H, s), 4.43 (1 H, s, 2-H), 5.2–6.7 (2 H, br s, NH_2), 6.77 (1 H, s) and 6.83 (1 H, s); *m/z* 335 (M^+, 3.4%), 279 [$(M - CH_2CMe_2)^+$, 72] and 264 (100) (Found: M^+, 335.1718. $C_{18}H_{25}NO_5$ requires *M*, 335.1733).

(Z)-1,1-*Dimethylethyl* 3-*Amino*-3-(7′-*phenylbicyclo*[4.2.0]-*octa*-1′,3′,5′-*trien*-7′-*yl*)*propenoate* **13c**.—3-Aminopropenoate **13c** was obtained from nitrile **12a** by the same procedure as that described for ester **13a**, in 72% yield. *Ester* **13c** had m.p. 150–151 °C (from hexane); ν_{max}/cm^{-1} 3492, 3346, 1663, 1611 and 1538; δ 1.44 (9 H, s, Bu^t), 3.75 (2 H, s, 8′-H_2), 4.67 (1 H, s, 2-H), 5.7–6.6 (2 H, br, NH_2) and 7.1–7.5 (9 H, m); *m/z* 321 (M^+, 2.8%), 265 [$(M - CH_2CMe_2)^+$, 77] and 220 (100) (Found: M^+, 321.1739. $C_{21}H_{23}NO_2$ requires *M*, 321.1729).

(Z)-1,1-*Dimethylethyl* 3-*Amino*-3-{7′-(4″-*methoxyphenyl*)*bicyclo*[4.2.0]*octa*-1′,3′,5′-*trien*-7′-*yl*}*propenoate* **13d**.—Enamino ester **13d** was obtained in 53% yield from nitrile **12b** in a similar manner as described for the enimino ester **13a**. *Ester* **13d** had m.p. 142–143 °C (from hexane–diethyl ether); ν_{max}/cm^{-1} 3474, 3322, 1663, 1611, 1544 and 1512; δ 1.44 (9 H, s, Bu^t), 3.71 (2 H, s, 8′-H_2), 3.78 (3 H, s, OMe), 4.65 (1 H, s, 2-H), 5.7–6.4 (2 H, br, NH_2), 6.85 (2 H, d, *J* 8.79, 3″-, 5″-H) and 7.0–7.5 (6 H, m); *m/z* 351 (M^+, 2.8%) and 295 [$(M - CH_2CMe_2)^+$, 100] (Found: M^+, 351.1833. $C_{22}H_{25}NO_3$ requires *M*, 351.1834).

(Z)-1,1-*Dimethylethyl* 3-*Amino*-3-{7′-(3″,4″-*dimethoxyphenyl*]*bicyclo*[4.2.0]*octa*-1′,3′,5′-*trien*-7′-*yl*}*propenoate* **13e**.—This enamino ester was prepared from cyanide **12c** in 69% yield as described for the enamino ester **13a**. For ester **13e**: m.p. 158–159 °C (from hexane–diethyl ether); ν_{max}/cm^{-1} 3468, 3324, 1658, 1612, 1543 and 1517; δ 1.44 (9 H, s, Bu^t), 3.72 (2 H, s, 8′-H_2), 3.85 (3 H, s, OMe), 3.87 (3 H, s, OMe), 4.65 (1 H, s, 2-H), 5.6–6.5 (2 H, br, NH_2), 6.80 (1 H, d, *J* 8.13, 5″-H), 6.96 (1 H, d, 2″-H) and 7.0–7.4 (5 H, m); *m/z* 381 (M^+, 7.1%) and 325 [$(M - CH_2CMe_2)^+$, 100] (Found: M^+, 381.1949. $C_{23}H_{27}NO_4$ requires *M*, 381.1940).

(Z)-1,1-*Dimethylethyl* 3-*Amino*-3-{7′-(3,4-*dimethoxyphenyl*)-3′,4′-*dimethoxybicyclo*[4.2.0]*octa*-1′,3′,5′-*trien*-7′-*yl*}*propenoate* **13f**.—To a stirred solution of ethylmagnesium bromide (6.8 mmol) in diethyl ether (10.4 cm^3) at 0 °C under argon was added diisopropylamine (1.4 g, 14 mmol). The mixture was stirred for 1 h at the same temperature. *tert*-Butyl acetate (0.40 g, 3.4 mmol) and then a solution of nitrile **12d** (1.1 g, 3.4 mmol) in THF (32 cm^3) were added successively, and the resulting mixture was stirred for an additional 1 h. The reaction was quenched with aq. ammonium chloride and products were extracted with diethyl ether. The extract was washed with brine, dried over anhydrous sodium sulfate, and finally evaporated to give a product, which was recrystallized from hexane–diethyl ether to afford pure *ester* **13f** (1.0 g, 67%), m.p. 161–162 °C; ν_{max}/cm^{-1} 3450, 3320, 1695 and 1607; δ 1.45 (9 H, s, Bu^t), 3.53 (1 H, d, *J* 13.63, 8′-H), 3.70 (1 H, d, *J* 13.63, 8′-H), 3.86 and 3.89 (12 H, 2 s, 4 × OMe), 4.62 (1 H, s, vinylic H), 5.9–6.5 (2 H, br, NH_2) and 6.7–7.05 (5 H, m, ArH); *m/z* 441 (M^+, 17%) and 385 [$(M - CH_2CMe_2)^+$, 100] (Found: M^+, 441.2178. $C_{25}H_{31}NO_6$ requires *M*, 441.2151).

1,1-*Dimethylethyl* 3-*Aminonaphthalene*-2-*carboxylate* **14a**.—A solution of ester **13a** (83 mg, 0.30 mmol) in *o*-dichlorobenzene (15 cm^3) was heated under reflux for 30 min under nitrogen. TLC [(1:10) ethyl acetate–hexane] indicated the complete disappearance of the starting material. The solvent was then removed under reduced pressure and the residue was chromatographed on silica gel [(1:10) ethyl acetate–hexane]. The isolated product was identified as the *naphthoate* **14a** (42 mg, 58%), m.p. 105–106 °C (from hexane–diethyl ether); ν_{max}/cm^{-1} 3476, 3362, 1693, 1634, 1602 and 1570; δ 1.64 (9 H, s, Bu^t), 5.2–5.9 (2 H, br, NH_2), 7.0–7.9 (5 H, m) and 8.40 (1 H, s, 1-H); *m/z* 243 (M^+, 21%), 187 [$(M - CH_2CMe_2)^+$, 84] and 169 (100) (Found: M^+, 243.1268. $C_{15}H_{17}NO_2$ requires *M*, 243.1259).

1,1-*Dimethyl* 3-*Amino*-6,7-*dimethoxynaphthalene*-2-*carboxylate* **14b**.—This aminonaphthalene-2-carboxylate was prepared in a similar manner from propenoate **13b** in 64% yield as described above. *Naphthoate* **14b** had m.p. 187–189 °C (from hexane–diethyl ether); ν_{max}/cm^{-1} 3476, 3364, 1686, 1634, 1613 and 1575; δ 1.65 (9 H, s, Bu^t), 3.94 (3 H, d, OMe), 3.96 (3 H, s, OMe), 4.5–6.0 (2 H, br, NH_2), 6.80 (1 H, s), 6.83 (1 H, s), 7.00 (1 H, s) and 8.23 (1 H, s, 1-H); *m/z* 303 (M^+, 26%) and 247 [$(M - CH_2CMe_2)^+$, 100] (Found: M^+, 303.1471. $C_{17}H_{21}NO_4$ requires *M*, 303.1471).

1,1-*Dimethylethyl* 3-*Amino*-4-*methoxynaphthalene*-2-*carboxylate* **15a**.—A solution of propenoate **13a** (83 mg, 0.30 mmol) in *o*-dichlorobenzene (15 cm^3) was heated under reflux for 15 min while oxygen was bubbled through. After cooling, the solvent was removed under reduced pressure. Purification of the product by PLC on silica gel [(1:5) ethyl acetate–hexane] gave the *title naphthoate* **15a** (27 mg, 33%) as a yellow solid, m.p. 131–132 °C (from hexane); ν_{max}/cm^{-1} 3484, 3376, 1693, 1634, 1602, 1574 and 1559; δ 1.64 (9 H, s, Bu^t), 3.87 (3 H, s, OMe), 5.7 (2 H, br s, NH_2), 7.0–7.9 (4 H, m) and 8.24 (1 H, s, 1-H); *m/z*

273 (M^+, 34%), 217 [$(M - CH_2CMe_2)^+$, 66] and 202 (100) (Found: M^+, 273.1368. $C_{10}H_{19}NO_3$ requires *M*, 273.1365).

1,1-*Dimethylethyl* 3-*Amino*-4-*phenylnaphthalene*-2-*carboxylate* **15b**.—Aminonaphthalene-2-carboxylate **15b** was prepared in 66% yield from propenoate **13c** in a similar manner to that described for the preparation of its analogue **15a**. *Compound* **15b** had m.p. 151–152 °C (from hexane); ν_{max}/cm^{-1} 3480, 1697, 1624, 1598 and 1562; δ 1.66 (9 H, s, Bu^t), 4.9–6.5 (2 H, br, NH_2), 7.0–7.8 (9 H, m) and 8.47 (1 H, s, 1-H); *m/z* 319 (M^+, 23%) and 263 [$(M - CH_2CMe_2)^+$, 100] (Found: M^+, 319.1577. $C_{21}H_{21}NO_2$ requires *M*, 319.1572).

1,1-*Dimethylethyl* 3-*Amino*-4-(4-*methoxyphenyl*)*naphthalene*-2-*carboxylate* **15c**.—The aminonaphthoate **15c** was prepared in 60% yield from propenoate **13d** by a similar method to that described for the preparation of compound **15a**; *compound* **15c** had m.p. 158–159 °C (from hexane–diethyl ether); ν_{max}/cm^{-1} 3484, 3366, 1688, 1625, 1612, 1594, 1556 and 1517; δ 1.65 (9 H, s, Bu^t), 3.89 (3 H, s, OMe), 5.0–5.8 (2 H, br, NH_2), 6.9–7.8 (8 H, m) and 8.45 (1 H, s, 1-H); *m/z* 349 (M^+, 25) and 293 [$(M - CH_2CMe_2)^+$, 100] (Found: M^+, 349.1693. $C_{22}H_{23}NO_3$ requires *M*, 349.1678).

1,1-*Dimethylethyl* 3-*Amino*-4-(3,4-*dimethoxyphenyl*)*naphthalene*-2-*carboxylate* **15d**.—Aminonaphthoate **15d** was prepared in 51% yield from propenoate **13e** in a similar manner to that described for compound **15a**; *compound* **15d** had m.p. 131–132 °C (from hexane); ν_{max}/cm^{-1} 3484, 3376, 1693, 1634, 1602, 1574 and 1559; δ 1.64 (9 H, s, Bu^t), 3.87 (6 H, s, OMe), 5.7 (2 H, br s, NH_2), 7.0–7.9 (4 H, m) and 8.24 (1 H, s, 1-H) (Found: M^+, 273.1368. $C_{16}H_{19}NO_3$ requires *M*, 273.1365).

1,1-*Dimethylethyl* 3-*Amino*-4-(3,4-*dimethoxyphenyl*)-6,7-*dimethoxynaphthalene*-2-*carboxylate* **15e**.—A solution of propenoate **13f** (0.75 g, 0.34 mmol) in *o*-dichlorobenzene (150 cm^3) was heated under reflux for 12 min, while oxygen was bubbled through the solution. The solvent was removed under reduced pressure and the residue was purified by PLC on silica gel [(1:1) ethyl acetate–hexane] to give the *title naphthoate* **15e** (0.54 g, 72%), m.p. 108–109 °C (from hexane–diethyl ether); ν_{max}/cm^{-1} 3474, 3372 and 1685; δ 1.65 (9 H, s, Bu^t), 3.71 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.96 and 3.98 (6 H, 2 s, 2 × OMe), 5.5 (2 H, br, NH_2), 6.48 (1 H, s, 2'-H), 6.8–7.1 (4 H, m) and 8.30 (1 H, s, 1-H); *m/z* 439 (M^+, 27%) and 383 [$(M - CH_2Me_2)^+$, 100] (Found: M^+, 439.2010. $C_{25}H_{29}NO_6$ requires *M*, 439.1195).

8-(3,4-*Dimethoxyphenyl*)-5,6-*dimethoxycyclobuta*[b]*naphthalen*-1(2H)-*one* **16a** *and* 3-(3,4-*Dimethoxyphenyl*)-5,6-*dimethoxycyclobuta*[b]*naphthalen*-1(2H)-*one* **16b**.—A mixture of aminonaphthoate **15e** (0.43 g, 0.98 mmol) and conc. hydrochloric acid (2.0 cm^3) was stirred at 50 °C for 1 h. After removal of hydrochloric acid under reduced pressure, ethanol (5 cm^3) and isoamyl(3-methylbutyl)nitrite (0.13 g, 1.1 mmol) were added to the residue at 0 °C, and the solution was stirred at room temperature overnight. Diethyl ether (10 cm^3) was then added to the mixture, and the solution was stirred for 1 h. The red precipitate was collected by filtration and washed with diethyl ether. A suspension of the obtained diazonium salt in 1,2-dichloroethane (5 cm^3) containing propylene oxide (22 mg, 0.38 mm^3) and 1,1-dichloroethene (0.27 g, 1.6 mmol) was heated under reflux for 12 h and the solvent was then evaporated off. To the residue was added 10% sulfuric acid (5 cm^3). The mixture was heated under reflux for 12 h. The product was extracted with dichloromethane, and the extract was washed with aq. sodium hydrogen carbonate and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue, which was purified by PLC on silica gel [(1:3) ethyl acetate–hexane] to afford a *mixture of ketones* **16a** and **16b** (the ratio was not determined) (0.11 g, 31%); R_f 0.10; ν_{max}/cm^{-1} 1756; δ 3.87, 3.90, 3.94, 3.97, 4.05 and 4.12 (14 H, 6 s, 4 × OMe and 2-H_2) and 6.95–7.7 (6 H, m, ArH); *m/z* (M^+, 85%) and 333 ([M − OMe]$^+$, 100] (Found: M^+, 364.1293. $C_{22}H_{20}O_5$ requires *M*, 364.1311).

8-(3,4-*Dimethoxyphenyl*)-1-*ethyl*-1,2-*dihydro*-5,6-*dimethoxycyclobuta*[b]*naphthalen*-1-*ol* **17a** *and* 3-(3,4-*Dimethoxyphenyl*)-1-*ethyl*-1,2-*dihydro*-5,6-*dimethoxycyclobuta*[b]*naphthalen*-1-*ol* **17b**.—To a stirred solution of a mixture of ketones **16a** and **16b** (82 mg, 0.23 mmol) in THF (5 cm^3) at 0 °C was added slowly ethylmagnesium bromide during 15 min at the same temperature. The resulting mixture was diluted with diethyl ether (20 cm^3) and washed successively with aq. ammonium chloride, aq. sodium hydrogen carbonate, and brine. The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue, which was purified by PLC on silica gel [(1:3) ethyl acetate–hexane] to afford a ~1:1 mixture of *alcohols* **17a** and **17b** (75 mg, 83%), R_f 0.27; ν_{max}(neat)/cm^{-1} 3500 and 3400; δ 0.78 (1.5 H, t, *J* 7.25, CH_2Me of **17a**), 1.14 (1.5 H, t, *J* 7.26, CH_2Me of **17b**), 1.5–2.6 (3 H, m, CH_2Me and OH), 3.15, 3.22, 3.45 and 3.52 (2 H, 4 d, *J* 14.72, 14.73, 14.72 and 14.73, 2-H_2), 3.82, 3.89, 3.96 and 4.00 (12 H, 4 s, 4 × OMe) and 6.9–7.5 (6 H, m); *m/z* 394 (M^+, 48%) and 365 [$(M - OMe)^+$, 100] (Found: M^+, 394.1786. $C_{24}H_{26}O_5$ requires *M*, 394.1780).

9-(3,4-*Dimethoxyphenyl*)-6,7-*dimethoxynaphtho*[2,3-c]*furan*-1(3H)-*one* **18a** *and* 4-(*Dimethoxyphenyl*)-6,7-*dimethoxynaphtho*[2,3-c]*furan*-1(3H)-*one* **18b**.—A stirred solution of alcohols **17a** and **17b** (~1:1; 50 mg, 0.13 mmol) in benzene (10 cm^3) containing red mercury(II) oxide (86 mg, 0.40 mmol) and iodine (102 mg, 0.40 mmol) was irradiated with a 100 W high-pressure mercury arc through a Pyrex filter under nitrogen for 4.5 h. The reaction mixture was filtered through a Celite pad. The filtrate was washed successively with aq. sodium thiosulfate and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue, which was subjected to PLC on silica gel [(1:1) ethyl acetate–hexane] to afford lactone **18a** [7b,8a] (14 mg, 29%), m.p. 252–254 °C (from chloroform–MeOH) (lit.,[7b] 254–255 °C) and lactone **18b** [7b,8a] (12 mg, 24%), m.p. 215–217 °C (from $CHCl_3$–MeOH) (lit.,[7b] 215–216 °C).

5-(1,3-*Benzodioxol*-5-*yl*)*furo*[3',4':6,7]*naphtho*[2,3-d]-1,3-*dioxol*-6(8H)-*one* (*Taiwanin C*) **19a**.—To a stirred solution of compound **18a** (11 mg, 0.029 mmol) in dichloromethane (2 cm^3) at −10 °C was added dropwise boron tribromide (0.30 g, 1.2 mmol). After being stirred for 2.5 h at the same temperature, the resulting mixture was washed with water several times and then with brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crude phenolic product, which was dissolved in DMF (8 cm^3). This solution was added to a solution of CsF (44 mg, 0.29 mmol) and dichloromethane (11 mg, 0.13 mmol) in DMF (2 cm^3), and the mixture was heated at 120 °C for 2 h under argon. The resulting mixture was cooled, diluted with diethyl ether (15 cm^3), washed successively with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue, which was subjected to PLC on silica gel [(1:1) ethyl acetate–hexane] to afford taiwanin C **19a** [7c,8b] (6.0 mg, 59%), m.p. 272–275 °C (from $CHCl_3$–MeOH) (lit.,[7c] 273–275 °C).

9-(1,3-*Benzodioxol*-5-*yl*)*furo*[3',4':6,7]*naphtho*[2,3-d]-1,3-*dioxol*-6(8H)-*one* (*Justicidin E*) **19b**.—A solution of compound **18b** (8.0 mg, 0.021 mmol) in dichloromethane (2 cm^3) was subjected to demethylation with boron tribromide (0.10 g, 0.40 mmol) and worked up in a similar manner to that mentioned above to give a crude phenol, which was dissolved in DMF (0.5 cm^3). To the solution was added KF (12 mg, 0.20 mmol) and a

solution of dibromomethane (7.9 mg, 0.046 mmol) in DMF (0.5 cm^3). The mixture was heated at 110 °C for 2 h and worked up in a similar manner as mentioned above. Purification by PLC on silica gel [(1:1) ethyl acetate–hexane] gave justicidin E **19b**,[6,7c] (3.0 mg, 41%), m.p. 267–270 °C (from $CHCl_3$) (lit.,[6] 264 °C; lit.,[8b] 271–272 °C; lit.,[7c] 265–269 °C).

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