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A new benzannulation reaction and its application in the multiple parallel synthesis of arylnaphthalene lignans

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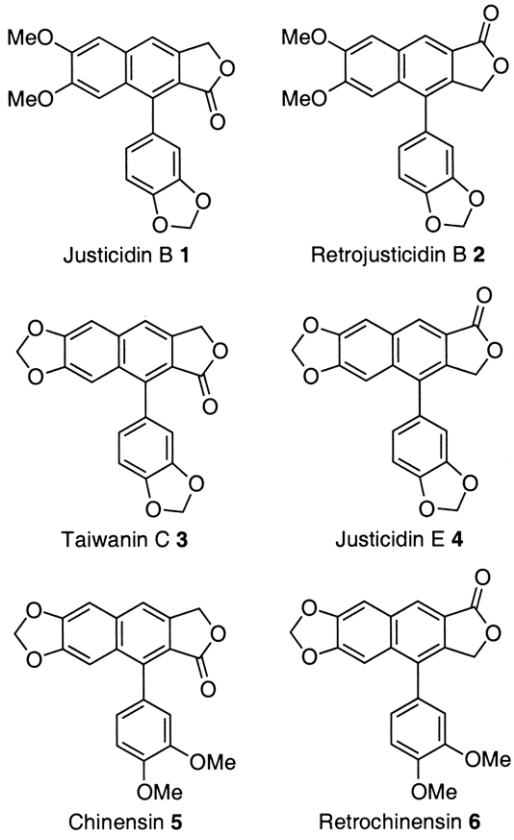
Abstract—A new aromatic annulation reaction based on sequential Horner–Emmons and Claisen condensation reactions is described. The method is high yielding and provides a rapid entry to arylnaphthalenes. The lignan natural products justicidin B **1**, retrojusticidin B **2**, taiwanin C **3**, justicidin E **4**, chinensin **5** and retrochinensin **6** have all been synthesised in good overall yield using this protocol, demonstrating its potential in multiple parallel synthesis. The selective oxidation of diols **34**–**36** to the corresponding retrolactones with barium manganate(VI) is also noteworthy.

1. Introduction

1.1. Background

Arylnaphthalene lignans occur widely in nature and have frequently been identified as constituents of tree barks and plants with folkloric medicinal usage.[1,2] Numerous biological assays have been conducted on lignans in this subgroup.[3] For example, the lactones justicidin B **1**, taiwanin C **3** and chinensin **5** have recently been shown to inhibit calcium release from a fetal long-bone culture,[4] while justicidin B **1** has been reported to have significant antiviral activity.[5] The corresponding retrolactones, **2**, **4** and **6** are less common in nature and have been less well studied.[6] Nonetheless, antimicrobial and anti-platelet activating factor activity have been reported in this series and retrojusticidin B **2** has been shown to inhibit HIV-1 reverse transcriptase.[7–9]

Most of the aforementioned studies have been conducted on individual natural products or on small groups isolated from the same plant source.[3–9] As a consequence, it is difficult to draw meaningful structural activity relationships from the data presently available. A synthetic entry to the arylnaphthalenes that is amenable to multiple parallel synthesis would therefore be desirable in order to probe biological function in a systematic way. Though several ingenious routes to arylnaphthalenes have been reported,[10–12] we wished to approach the problem from a new direction.



1.2. Our retrosynthetic analysis

The route we envisioned targeted diesters akin to **9** as these could be readily transformed into lactones **7** and retrolactones **8** using known procedures.[11,12] An opportunity to construct the central arene ring through sequential

Keywords: annulation; Claisen condensation; combinatorial chemistry; Horner–Emmons; lignans; natural products.

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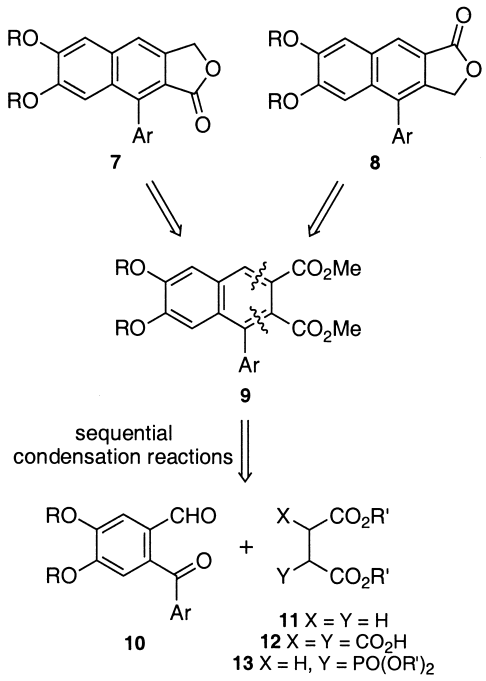


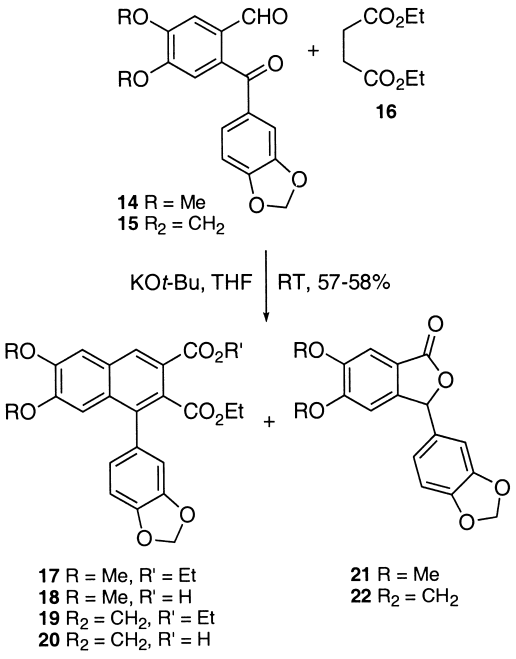
Scheme 1.

condensation reactions between a ketoaldehyde **10** and a succinate derivative then presented itself (Scheme 1); the requisite ketoaldehydes **10** being easily synthesised in four steps as outlined in Section 4 (Scheme 5).

2. Results and discussion

2.1. Sequential Stobbe/Claisen condensations

Initially, we sought to construct the central aromatic ring using sequential Stobbe and Claisen condensation reactions.[13,14] The approach was blessed with limited success. While it was possible to synthesise arylnaphthalene **17** through base promoted union of ketoaldehyde **14** and diethyl succinate **16**, the reaction led to a complex product mixture. One complication was the formation of both diester **17** and its half acid **18** which, though useful, had to be isolated and purified separately. More importantly, an intramolecular Cannizzaro reaction leading to lactone **21** was a significant side reaction.[15] Many parameters were examined in an attempt to bias the reaction in favour of the desired cyclisation pathway, but to little avail. Indeed, the best conditions we were able to establish employed potassium *tert*-butoxide in THF and gave rise to a separable mixture of diester **17** (15%), half acid **18** (26%) and γ-lactone **21** (16%).



Scheme 2.

When the same conditions were applied to ketoaldehyde **15**, a similar product mixture resulted. The desired diester **19** was again produced in low yield (9%), with the half acid **20** (34%) and γ-lactone **22** (15%) accounting for much of the outstanding mass balance (Scheme 2). As it was clear that the reaction's inefficiency stemmed in part from an inability to enhance the rate of the initial Stobbe condensation relative to the Cannizzaro reaction, we decided to explore alternative methods of effecting the union of an ester enolate and an aldehyde.

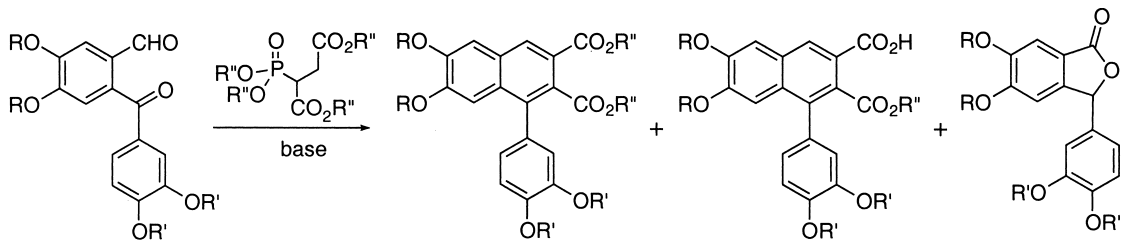
2.2. Arene annulation by sequential Horner–Emmons and Claisen condensation reactions

Following unsuccessful attempts to effect a tandem Knovenagel condensation between diacid **12** (R′=Me)[16] and ketoaldehyde **23** (a reaction giving γ-lactone **33** in 51% yield), we decided to see if the desired aromatic annulation could be accomplished by means of a tandem Horner–Emmons–Claisen condensation sequence. Pleasingly, simply stirring a solution of ketoaldehyde **14** and phosphonosuccinate **25** with sodium ethoxide at 0°C in ethanolic THF provided the corresponding arylnaphthalene **17** in 68% yield and half acid **18** in 5% yield.[17]

The annulation was then extended to ketoaldehydes **15** and **23** and phosphonosuccinate **24**.[18] In each case, the desired aromatic annulation proceded in good yield, with the respective half acids and γ-lactones being given as minor byproducts in most cases. These were easily separated from the diester as they remained in the aqueous phase whilst it was basic. Later, we found that the reaction could also be mediated by a combination of DBU and LiCl in acetonitrile, though yields were compromised in some cases (Scheme 3).

2.3. Completing the total syntheses

Completing the total syntheses from this juncture was straightforward.[11,12] Taking advantage of a procedure developed by Padwa et al. the diesters **17**, **19** and **26** were each saponified with potassium trimethylsilanoate to the corresponding half acids **18**, **20** and **30**.[11] Each was then reduced with borane–dimethyl sulfide to give lactones justicidin B **1**, taiwanin C **3** and chinensin **5**, respectively after acidification.[12] Likewise, it was possible to access the corresponding retrolactones by sequential deprotonation of the half acids (**18**, **20** and **30**) with sodium hydride, ester



14 R = Me, R'$_2$ = CH_2
15 R_2 = R'$_2$ = CH_2
23 R_2 = CH_2, R' = Me

24 R" = Me
25 R" = Et

17 R = Me, R'$_2$ = CH_2, R" = Et
19 R_2 = R'$_2$ = CH_2, R" = Et
26 R_2 = CH_2, R' = Me, R" = Et
27 R = R" = Me, R'$_2$ = CH_2
28 R_2 = R'$_2$ = CH_2, R" = Me
29 R_2 = CH_2, R' = R" = Me

18 R = Me, R'$_2$ = CH_2, R" = Et
20 R_2 = R'$_2$ = CH_2, R" = Et
30 R_2 = CH_2, R' = Me, R" = Et
31 R = R" = Me, R'$_2$ = CH_2
32 R_2 = R'$_2$ = CH_2, R" = Me

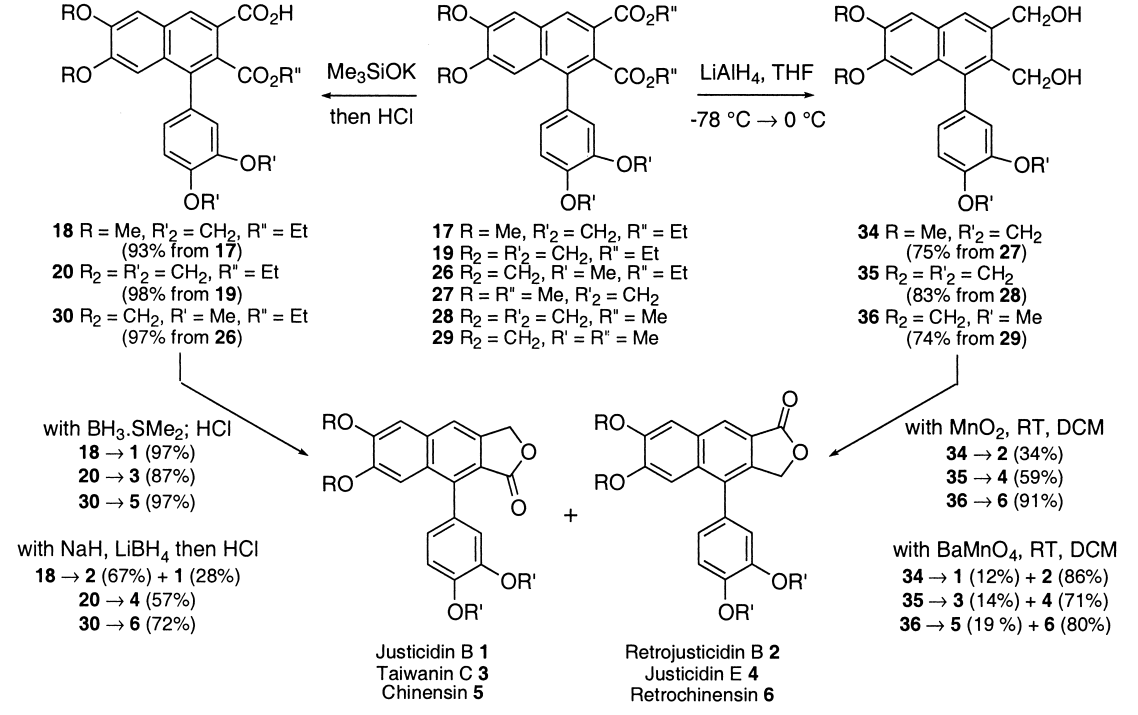
21 R = Me, R'$_2$ = CH_2
22 R_2 = R'$_2$ = CH_2
33 R_2 = CH_2, R' = Me

Ketoaldehyde	Phosphonate	Reaction Conditions	Products (Yields)
14	**24**	NaOMe, MeOH, THF, 0 °C, 3 h	**27** (56%), **31** (15%), **21** (11%)
		DBU, LiCl, MeCN, RT, 16 h	**27** (70%)
	25	NaOEt, EtOH, THF, 0 °C, 5 h	**17** (68%), **18** (5%)
15	**24**	NaOMe, MeOH, THF, 0 °C, 3 h	**28** (84%), **32** (5%), **22** (4%)
		DBU, LiCl, MeCN, RT, 16 h	**28** (60%)
	25	NaOEt, EtOH, THF, 0 °C, 3 h	**19** (67%), **20** (3%), **22** (5%)
23	**24**	NaOMe, MeOH, THF, 0 °C, 3 h	**29** (65%)
		DBU, LiCl, MeCN, RT, 16 h	**29** (49%)
	25	NaOEt, EtOH, THF, 0 °C, 2 h	**26** (46%), **30** (19%), **33** (9%)

Scheme 3.

reduction with lithium borohydride and acid mediated lactonisation.[11] In this way synthetic samples of retrojusticidin B **2**, justicidin E **4** and retrochinensin **6** were generated (Scheme 4).

A complimentary end game for the synthesis of these retrolactones has also been developed. First, the diesters **27**–**29** were reduced with lithium aluminium hydride to the corresponding diols **34**–**36**. Oxidation of these materials



18 R = Me, R'$_2$ = CH_2, R" = Et (93% from **17**)
20 R_2 = R'$_2$ = CH_2, R" = Et (98% from **19**)
30 R_2 = CH_2, R' = Me, R" = Et (97% from **26**)

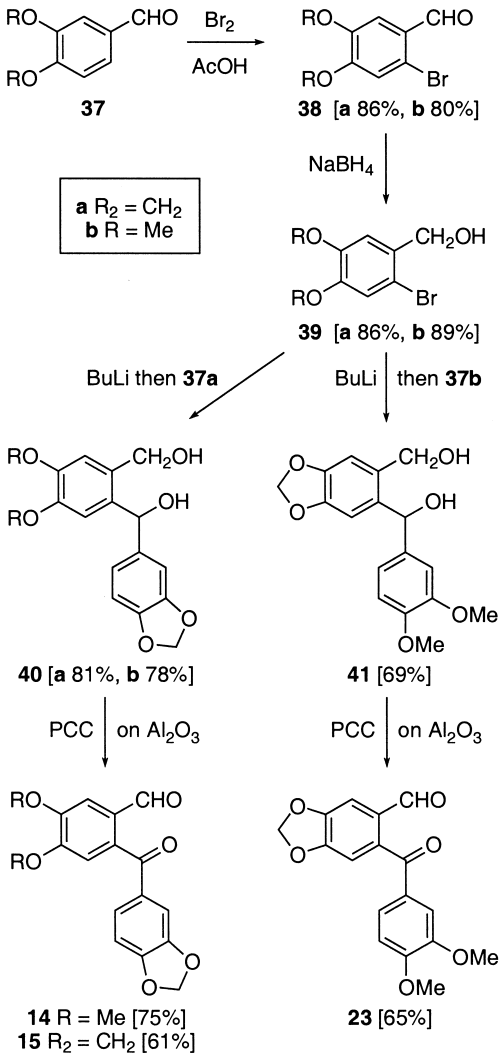
17 R = Me, R'$_2$ = CH_2, R" = Et
19 R_2 = R'$_2$ = CH_2, R" = Et
26 R_2 = CH_2, R' = Me, R" = Et
27 R = R" = Me, R'$_2$ = CH_2
28 R_2 = R'$_2$ = CH_2, R" = Me
29 R_2 = CH_2, R' = R" = Me

34 R = Me, R'$_2$ = CH_2 (75% from **27**)
35 R_2 = R'$_2$ = CH_2 (83% from **28**)
36 R_2 = CH_2, R' = Me (74% from **29**)

Justicidin B **1**
Taiwanin C **3**
Chinensin **5**

Retrojusticidin B **2**
Justicidin E **4**
Retrochinensin **6**

Scheme 4.



Scheme 5.

to retrolactones **2**, **4** and **6** was then achieved using either manganese(IV) oxide or barium manganate(VI). Product yields were always higher with $BaMnO_4$, though these were sometimes compromised by the formation of the regioisomeric lactones in significant quantity (Scheme 4).

3. Conclusion

In conclusion, we have developed a new aromatic annulation reaction based on sequential Horner–Emmons and Claisen condensation reactions. The method has been exploited in efficient and robust syntheses of six arylnaphthalene lignans: the natural products justicidin B **1**, retrojusticidin B **2**, taiwanin C **3**, justicidin E **4**, chinensin **5** and retrochinensin **6**. The selective oxidation of diols **34**–**36** to the corresponding retrolactones **2**, **4** and **6** with barium manganate(VI) is also notable as it provides a means of converting the more common 'lactone' natural products into retrolactones via the corresponding diol.[19]

4. Experimental

4.1. General remarks

Melting points were recorded on a Griffin melting point apparatus and are uncorrected. UV spectra were recorded on either a Pye Unicam SP8-400 or a Shimadzu UV-240 Graphicord spectrophotometer as solutions in dichloromethane or methanol. IR spectra were recorded using a Bio-Rad FTS 135 Fourier transform infrared spectrometer equipped with a Golden Gate Single Reflection Diamond ATR or a Nicolet Impact 400 spectrometer equipped with a SpectraTech Thunderdome attachment (n.b. IR data was attained directly from solid samples). NMR spectra were recorded on a Bruker AC300 operating at 300 MHz for ^{1}H, 75 MHz for ^{13}C and 121.5 MHz for ^{31}P. Chemical shifts are reported as values in parts per million relative to tetramethylsilane (δ_H 0.00, δ_C 0.00), $CDCl_3$ (δ_C 77.2) or residual $CHCl_3$ (δ_H 7.27). Mass spectra were attained using chemical ionisation (CI) or electron ionisation (EI) on a Thermoquest Trace GCMS spectrometer whilst electrospray (ES) experiments were performed on a Micromass Platform (MP) spectrometer. High resolution mass spectra (HRMS) were recorded on a VG Analytical 70-250-SE normal geometry double focusing mass spectrometer using 70 eV ionisation energy and a 200°C source temperature.

All reactions were magnetically stirred under nitrogen, unless stated otherwise. Reactions were monitored by thin layer chromatography using Macherey–Nagel Alugram Sil G/UV_{254} precoated aluminium foil plates of layer thickness 0.25 mm. Compounds were visualised first by UV irradiation then heating plates exposed to solutions of phosphomolybdic acid in ethanol or basified aqueous potassium permanganate. Column chromatography was performed on Sorbsil 60 silica (230–400 mesh), slurry packed and run under slight positive pressure.

Tetrahydrofuran was dried by distillation over sodium and benzophenone. Dichloromethane was dried by distillation over calcium hydride. Ether refers to diethyl ether and petrol refers to the fraction of petroleum ether in the boiling point range 40–60°C.

4.2. Preparation of the precursors (Scheme 5)

6-Bromopiperonal (**38a**) [white crystalline solid, mp 129–130°C (ethanol/H_2O), lit.[20] 127–128.5°C] and 6-bromoveratraldehyde (**38b**) [white needles, mp 151–152°C (aq. ethanol), lit.[20] 149–151°C] were prepared following the procedure of Orr et al.[20] (6-Bromo-benzo[1,3]dioxol-5-yl)-methanol (**39a**) [white needles, mp 87–89°C (ether/petrol), lit.[21] 90°C (petrol)] was prepared following the procedure of Mann et al.[21] (2-Bromo-4,5-dimethoxyphenyl)-methanol (**39b**) [white solid, mp 95–96°C (Et_2O/petrol), lit. 97–98°C] was prepared following the procedure of Crombie and Josephs.[22] 2,3-Bis-methoxycarbonyl-succinic acid (**12**) [white solid, mp 204–205°C, lit.[16] not reported] was prepared following the procedure of Walker and Appleyard.[16] Dimethyl 2-(dimethoxyphosphoryl)-succinate (**24**) [viscous colourless oil] was prepared following the procedure of Trost and Melvin.[18] Diethyl

2-(diethoxyphosphoryl)-succinate (**25**) [viscous pale yellow oil] was prepared following the procedure of Harvey.[17]

4.2.1. Benzo[1,3]dioxol-5-yl-(6-hydroxymethyl-benzo-[1,3]dioxol-5-yl)-methanol (40a). To a stirred solution of **39a** (10.00 g, 43.3 mmol) in THF (100 mL) at −78°C was added *n*-butyllithium (2.26 M in hexanes, 40.2 mL, 90.9 mmol) via cannula over 30 min at a rate sufficient to maintain the reaction temperature below −70°C. After 30 min, a solution of piperonal (6.823 g, 45.4 mmol) in THF (30 mL) was added via cannula over 10 min. After a further 30 min, saturated ammonium chloride solution (40 mL) was added and the reaction mixture was warmed to room temperature and partitioned between ether (140 mL) and water (100 mL). The aqueous phase was washed with ether (2×100 mL) and the combined ether phases were dried ($MgSO_4$) and concentrated in vacuo to a pale orange oil. Purification by column chromatography (gradient elution—60% Et_2O in petrol to neat Et_2O) afforded first piperonyl alcohol as a colourless solid (1.25 g, 8.22 mmol, 19%) then diol **40a** as a pale yellow oil (10.61 g, 35.1 mmol, 81%); IR (neat, cm^{-1}) ν_{max} 3428 br w, 1501 w, 1476 s, 1444 w, 1341 w, 1280 m, 1243 s, 1035 vs, 933 m, 805 w, 787 w; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 292 (5900); ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.81 (1H, d, *J*=1.8 Hz, Ar*H*), 6.80 (1H, dd, *J*=8.0, 1.8 Hz, Ar*H*), 6.79 (1H, s, Ar*H*), 6.78 (1H, d, *J*=8.0 Hz, Ar*H*), 6.71 (1H, s, Ar*H*), 5.92–5.98 (4H, m, OCH_2O), 5.88 (1H, br s, C*H*OH), 4.60 (1H, br d, *J*=12.3 Hz, C*H*HOH), 4.40 (1H, br d, *J*=12.3 Hz, CH*H*OH), 3.70 (1H, br s, O*H*), 2.97 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 147.9 (*C*), 147.5 (*C*), 147.0 (2×*C*), 136.8 (*C*), 136.6 (*C*), 132.4 (*C*), 119.9 (*C*H), 110.4 (*C*H), 109.1 (*C*H), 108.2 (*C*H), 107.3 (*C*H), 101.4 (*C*H_2), 101.2 (*C*H_2), 73.1 (*C*H), 63.5 (*C*H_2); LRMS (CI) 285 ([MH−H_2O]$^+$, 100%), 149 ([M−$C_8H_9O_3$]$^+$, 47%); HRMS (EI) *m/z* Found: M^+, 302.0801, $C_{16}H_{14}O_6$ requires 302.0790.

4.2.2. Benzo[1,3]dioxol-5-yl-(2-hydroxymethyl-4,5-dimethoxyphenyl)-methanol (40b). To a stirred suspension of petrol washed sodium hydride (1.77 g of a 60% dispersion in mineral oil, 26.6 mmol) in THF (25 mL) at 0°C was added a solution of 6-bromo-3,4-dimethoxybenzyl alcohol **39b** (5.47 g, 22.1 mmol) in THF (50 mL) via cannula over 10 min. Further THF (75 mL) was added and the reaction mixture was allowed to warm to room temperature and stirred until effervescence ceased (30 min). The resulting white suspension was then cooled to −78°C and *n*-butyllithium (1.40 M in hexanes, 16.6 mL, 23.3 mmol) was added dropwise via syringe over 10 min. After 30 min, a solution of piperonal (3.491 g, 23.3 mmol) in THF (30 mL) was added via cannula over 10 min. After a further 30 min, saturated ammonium chloride solution (50 mL) and ether (100 mL) were added, the mixture was warmed to room temperature and the two phases separated. The aqueous phase was extracted with ether (2×100 mL) and the combined ether phases were dried ($MgSO_4$) and concentrated in vacuo to yield a yellow oil. Purification by column chromatography (gradient elution—90% Et_2O in petrol to Et_2O with 5% MeOH) afforded **40b** as a clear viscous oil (5.48 g, 17.2 mmol, 78%); IR (neat, cm^{-1}) ν_{max} 3374 br w, 2915 br w, 1608 w, 1504 m, 1487 m, 1441 m, 1337 w, 1241 s, 1099 s, 1036 s, 929 m, 871 w; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 290 (6900), 242 (10,400); ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.82 (1H, d, *J*=8.1 Hz, Ar*H*), 6.81 (1H, s, Ar*H*), 6.80 (1H, s, Ar*H*), 6.79 (1H, dd, *J*=8.1, 1.1 Hz, Ar*H*), 6.77 (1H, d, *J*=1.1 Hz, Ar*H*), 6.01 (2H, s, OCH_2O), 5.86 (1H, s, C*H*OH), 4.55 (1H, br d, *J*=12.1 Hz, C*H*HOH), 4.41 (1H, br d, *J*=12.1 Hz, CH*H*OH), 3.85 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.07 (1H, br s, O*H*), 1.86 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 148.5 (*C*), 148.3 (*C*), 147.8 (*C*), 146.9 (*C*), 137.1 (*C*), 134.9 (*C*), 130.9 (*C*) 119.8 (*C*H), 113.4 (*C*H), 111.9 (*C*H), 108.2 (*C*H), 107.3 (*C*H), 101.2 (*C*H_2), 73.4 (*C*H), 63.4 (*C*H_2), 56.2 (*C*H_3), 56.1 (*C*H_3); LRMS (CI) 301 ([MH−H_2O]$^+$, 100%); HRMS (EI) *m/z* Found: M^+, 318.1101, $C_{17}H_{18}O_6$ requires 318.1103.

4.2.3. (3,4-Dimethoxyphenyl)-(6-hydroxymethylbenzo-[1,3]dioxol-5-yl)-methanol (41). To a stirred solution of **39a** (10.00 g, 43.3 mmol) in THF (100 mL) at −78°C was added *n*-butyllithium (2.25 M in hexanes, 40.4 mL, 90.9 mmol) via cannula over 30 min at a rate sufficient to maintain the reaction temperature below −60°C. After 30 min, a solution of veratraldehyde (7.55 g, 45.4 mmol) in THF (30 mL) was added via cannula over 10 min. After a further 30 min, saturated ammonium chloride solution (50 mL) was added and the reaction mixture was warmed to room temperature and partitioned between ether (100 mL) and water (100 mL). The aqueous phase was washed with ether (2×100 mL) and the combined ether phases were dried ($MgSO_4$) and concentrated in vacuo to a viscous orange oil. Purification by column chromatography (gradient elution—50% Et_2O in petrol to Et_2O with 5% MeOH) afforded first piperonyl alcohol as a colourless solid (1.98 g, 13.0 mmol, 30%) then diol **41** as a white solid (9.49 g, 29.8 mmol, 69%): mp 41–43°C; IR (neat, cm^{-1}) ν_{max} 2943 w, 2834 w, 1514 m, 1475 m, 1340 w, 1279 m, 1259 s, 1234 m, 1159 w, 1138 s, 1028 vs, 938 w, 844 w, 806 m; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 285 (6500), 236 (11,400); ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.92 (1H, br s, Ar*H*), 6.85 (1H, dd, *J*=8.0, 2.0 Hz, Ar*H*), 6.85 (1H, d, *J*=8.0 Hz, Ar*H*), 6.80 (1H, s, Ar*H*), 6.67 (1H, s, Ar*H*), 5.96 (1H, s, C*H*OH), 5.91–5.95 (2H, m, OCH_2O), 4.65 (1H, br d, *J*=11.8 Hz, C*H*HOH), 4.42 (1H, br d, *J*=11.8 Hz, CH*H*OH), 3.88 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.71 (1H, br s, O*H*), 2.98 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 149.1 (*C*), 148.5 (*C*), 147.5 (*C*), 147.0 (*C*), 136.7 (*C*), 135.3 (*C*), 132.6 (*C*), 118.8 (*C*H), 111.1 (*C*H), 110.4 (*C*H), 109.9 (*C*H), 109.2 (*C*H), 101.5 (*C*H_2), 73.0 (*C*H), 63.4 (*C*H_2), 55.9 (*C*H_3), 55.8 (*C*H_3); LRMS (CI) 301 ([MH−H_2O]$^+$, 100%); HRMS (EI) *m/z* Found: M^+, 318.1111, $C_{17}H_{18}O_6$ requires 318.1103.

4.2.4. Benzo[1,3]dioxol-5-yl-(6-formyl-3,4-dimethoxybenzyl)-methanone (14). Diol **40b** (5.48 g, 17.2 mmol) in dichloromethane (50 mL) was added via syringe to a suspension of PCC (12.4 g, 40.5 mmol) on alumina (45 g) in dichloromethane (400 mL) at room temperature. After 30 min, the reaction mixture was filtered through florisil and the solids were washed with dichloromethane (400 mL). The combined organic phases were concentrated in vacuo to a brown solid. Purification by column chromatography (gradient elution—80% chloroform in petrol to neat chloroform) gave ketoaldehyde **14** (4.057 g, 12.9 mmol, 75%) as a pale yellow solid: mp 157–160°C

[lit. 162–163°C];[23] IR (solid, cm^{-1}) ν_{max} 1751 m, 1681 m, 1591 m, 1521 m, 1500 m, 1490 m, 1445 s, 1352 m, 1285 vs, 1270 vs, 1218 s, 1141 m, 1116 s, 1071 w, 1034 vs, 923 m, 869 w; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 318 (10,400), 270 (11,500), 240 (20,100); ^1H NMR (300 MHz, $CDCl_3$) δ_H 9.88 (1H, s, C*H*O), 7.54 (1H, s, Ar*H*), 7.41 (1H, d, *J*=1.8 Hz, Ar*H*), 7.30 (1H, dd, *J*=8.1, 1.8 Hz, Ar*H*), 6.97 (1H, s, Ar*H*), 6.84 (1H, d, *J*=8.1 Hz, Ar*H*), 6.10 (2H, s, OCH_2O), 4.02 (3H, s, OCH_3), 3.96 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 194.0 (*C*), 189.2 (*C*H), 153.1 (*C*), 152.7 (*C*), 150.7 (*C*), 148.6 (*C*), 137.0 (*C*), 132.8 (*C*), 129.1 (*C*) 127.7 (*C*H), 111.2 (*C*H), 109.8 (*C*H), 109.2 (*C*H), 108.1 (*C*H), 102.3 (*C*H_2), 56.6 (*C*H_3), 56.4 (*C*H_3); LRMS (CI) 315 (MH^+, 88%), 301 (100%), 299 ($[M-CH_3]^+$, 46%). Anal. found: C, 64.59; H, 4.49; $C_{17}H_{14}O_6$ requires C, 64.97; H, 4.49.

4.2.5. Benzo[1,3]dioxol-5-yl-(6-formylbenzo[1,3]dioxol-5-yl)-methanone (15). Diol **40a** (1.00 g, 3.31 mmol) in dichloromethane (50 mL) was added via syringe to a suspension of PCC (2.85 g, 13.24 mmol) on alumina (11.5 g) in dichloromethane (100 mL) at room temperature. After 2 h, the reaction mixture was filtered through florisil and the solids were washed with dichloromethane (300 mL). The combined organic phases were concentrated in vacuo to a viscous brown oil. Purification by column chromatography (gradient elution—60% Et_2O in petrol to neat Et_2O) gave ketoaldehyde **15** as a cream solid (0.606 g, 2.03 mmol, 61%): mp 126–130°C [lit. 133–134°C];[24] IR (solid, cm^{-1}) ν_{max} 1680 m, 1601 m, 1504 m, 1493 m, 1367 m, 1286 m, 1267 vs, 1098 m, 1035 s, 764 m; UV (MeOH, nm) λ_{max} (ε_{max}) 317 (10,900), 294 (8800); ^1H NMR (300 MHz, $CDCl_3$) δ_H 9.82 (1H, s, C*H*O), 7.48 (1H, s, Ar*H*), 7.39 (1H, d, *J*=1.7 Hz, Ar*H*), 7.30 (1H, dd, *J*=8.2, 1.7 Hz, Ar*H*), 6.92 (1H, s, Ar*H*), 6.84 (1H, d, *J*=8.2 Hz, Ar*H*), 6.15 (2H, s, OCH_2O), 6.09 (2H, s, OCH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 193.5 (*C*), 188.7 (*C*H), 152.8 (*C*), 151.8 (*C*), 149.8 (*C*), 148.6 (*C*), 139.2 (*C*), 132.2 (*C*), 131.2 (*C*), 127.8 (*C*H), 109.2 (*C*H), 108.9 (*C*H), 108.1 (*C*H), 107.8 (*C*H), 102.8 (*C*H_2), 102.3 (*C*H_2); LRMS (ES^+) 317 ($[M+NH_4]^+$, 85%), 299 (MH^+, 100%); HRMS (ES^+) *m/z* Found: $[M+Na]^+$, 321.0365, $C_{16}H_{10}O_6Na$ requires 321.0369.

4.2.6. 3,4-Dimethoxybenzyl-(6-formylbenzo[1,3]dioxol-5-yl)-methanone (23). Diol **41** (5.15 g, 16.2 mmol) in dichloromethane (50 mL) was added via syringe to a suspension of PCC (8.73 g, 40.5 mmol) on alumina (35 g) in dichloromethane (200 mL) at room temperature. After 30 min, the reaction mixture was filtered through florisil and the solids were washed with dichloromethane (500 mL). The combined organic phases were concentrated in vacuo to a brown solid. Purification by column chromatography (chloroform) gave ketoaldehyde **23** (3.33 g, 10.6 mmol, 65%) as a pale yellow solid: mp 171–173°C (MeOH); IR (solid, cm^{-1}) ν_{max} 1680 w, 1649 w, 1586 w, 1488 w, 1361 w, 1267 vs, 1228 w, 1126 m, 1037 s, 1022 s, 928 w; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 314 (10,200), 280 (10,000), 262 (11,300), 233 (20,400); ^1H NMR (300 MHz, $CDCl_3$) δ_H 9.83 (1H, s, C*H*O), 7.57 (1H, d, *J*=2.0 Hz, Ar*H*), 7.50 (1H, s, Ar*H*), 7.23 (1H, dd, *J*=8.4, 2.0 Hz, Ar*H*), 6.95 (1H, s, Ar*H*), 6.85 (1H, d, *J*=8.4 Hz, Ar*H*), 6.16 (2H, s, OCH_2O), 3.97 (3H, s, OCH_3), 3.96 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 193.0 (*C*), 188.7 (*C*H), 154.2 (*C*), 151.8 (*C*), 149.8 (*C*), 149.5 (*C*), 139.4 (*C*), 131.4 (*C*), 130.6 (*C*) 126.5 (*C*H), 111.1 (*C*H), 110.1 (*C*H), 109.0 (*C*H), 107.6 (*C*H), 102.8 (*C*H_2), 56.4 (*C*H_3), 56.3 (*C*H_3); LRMS (CI) 315 (MH^+, 62%), 301 (65%), 299 ($[M-CH_3]^+$, 100%). Anal. found: C, 64.68; H, 4.48; $C_{17}H_{14}O_6$ requires C, 64.97; H, 4.49.

4.3. Cyclisation reactions

4.3.1. Diethyl 6,7-dimethoxy-1-(benzo[1,3]dioxol-5-yl)-naphthalene-2,3-dicarboxylate (17), 6,7-dimethoxy-1-(benzo[1,3]dioxol-5-yl)-naphthalene-2,3-dicarboxylic acid 2-ethyl ester (18) and 3-benzo[1,3]dioxol-5-yl-5,6-dimethoxy-3*H*-isobenzofuran-1-one (21). To a stirred solution of potassium *tert*-butoxide (225 mg, 2.00 mmol) in THF (20 mL) at room temperature was added a solution of ketoaldehyde **14** (300 mg, 0.96 mmol) and diethyl succinate **16** (0.17 mL, 1.00 mmol) in THF (20 mL), dropwise over 20 min. After 30 min, the dark brown reaction mixture was diluted with water (20 mL) and extracted with ether (3×50 mL). The combined ether phases were dried ($MgSO_4$) and concentrated in vacuo to an orange semi-solid. Purification by column chromatography (50–60% Et_2O in petrol) yielded diester **17** as an off-white solid (64 mg, 0.14 mmol, 15%): mp 192–194°C [lit. 195–197°C].[12] The aqueous phase was acidified with 6 M HCl (10 mL) and extracted with chloroform (3×50 mL). The combined chloroform phases were dried ($MgSO_4$), concentrated in vacuo and purified by column chromatography (40–50% EtOAc in petrol with 0.5% acetic acid) to yield γ-lactone **21** as an off-white solid (49 mg, 0.16 mmol, 16%): mp 156–158°C [lit. 157.5–158°C],[25] then mono-ester **18** as a cream solid (106 mg, 0.25 mmol, 26%): mp 200–202°C [lit. not reported];[12] IR (solid, cm^{-1}) ν_{max} 2961 w, 2918 w, 2844 w, 1723 m, 1678 m, 1504 m, 1475 m, 1431 s, 1236 vs, 1207 s, 1163 m, 1111 m, 1097 m, 1037 s, 1008 m; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 290 (14,000), 259 (47,500), 216 (25,000); ^1H NMR (300 MHz, $CDCl_3$) δ_H 9.50 (1H, br s, COO*H*), 8.54 (1H, s, Ar*H*), 7.25 (1H, s, Ar*H*), 6.91 (1H, d, *J*=7.9 Hz, Ar*H*), 6.88 (1H, s, Ar*H*), 6.86 (1H, d, *J*=1.0 Hz, Ar*H*), 6.82 (1H, dd, *J*=7.9, 1.0 Hz, Ar*H*), 6.07 (1H, s, OC*H*HO), 6.03 (1H, s, OCH*H*O), 4.14 (2H, q, *J*=7.2 Hz, OCH_2CH$_3$), 4.02 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 1.15 (3H, t, *J*=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 171.5 (*C*), 169.1 (*C*), 152.2 (*C*), 150.7 (*C*), 147.5 (*C*), 147.5 (*C*), 136.6 (*C*), 131.3 (*C*), 130.8 (*C*), 130.7 (*C*H), 130.5 (*C*), 128.5 (*C*), 124.0 (*C*H), 121.8 (*C*), 111.0 (*C*H), 108.3 (*C*H), 107.6 (*C*H), 105.5 (*C*H), 101.4 (*C*H_2), 61.4 (*C*H_2), 56.2 (*C*H_3), 56.0 (*C*H_3), 14.0 (*C*H_3); LRMS (ES^-) 537 ($[M+CF_3CO_2]^-$, 97%), 356 (100%); HRMS (ES^+) *m/z* Found: $[M+Na]^+$, 447.1056, $C_{23}H_{20}O_8Na$ requires 447.1050.

Alternatively, sodium (75 mg, 3.26 g atom) was added portionwise at room temperature to vigorously stirred anhydrous ethanol (5 mL). On consumption of the metal the solution was cooled to 0°C and ketoaldehyde **14** (250 mg, 0.80 mmol) and phosphonate **25** (493 mg, 1.60 mmol) in THF (20 mL) and ethanol (7 mL) were added via a dropping funnel over 20 min. After 5 h, the reaction mixture was warmed to room temperature, concentrated in vacuo and partitioned between water (50 mL) and

1:1 THF/ether (100 mL). The aqueous layer was washed with 1:1 THF/ether (2×50 mL), then the combined organic phases were washed with saturated sodium bicarbonate solution (2×30 mL), dried ($MgSO_4$) and concentrated in vacuo to a yellow solid. Purification by column chromatography (50% Et_2O in petrol) yielded diester **17** (246 mg, 0.54 mmol, 68%) as a white solid. The combined aqueous phases were acidified with 6 M HCl (25 mL) and extracted with chloroform (3×50 mL). The combined chloroform phases were then dried ($MgSO_4$) and concentrated in vacuo to an oily yellow solid. Purification by column chromatography (40% ethyl acetate in petrol+0.5% acetic acid) yielded half-acid **18** (16 mg, 0.038 mmol, 5%) as a pale yellow solid. Data as stated above.

4.3.2. Diethyl 5-benzo[1,3]dioxol-5-yl-naphtho[2,3-*d*]-[1,3]dioxole-6,7-dicarboxylate (19), 5-benzo[1,3]dioxol-5-yl-naphtho[2,3-*d*][1,3]dioxole-6,7-dicarboxylic acid-7-ethyl ester (20) and 7-benzo[1,3]dioxol-5-yl-7*H*-furo-[3′,4′:4,5]benzo[1,2-*d*][1,3]dioxol-5-one (22). To a stirred solution of potassium *tert*-butoxide (236 mg, 2.10 mmol) in THF (20 mL) at room temperature was added a solution of ketoaldehyde **15** (300 mg, 1.00 mmol) and diethyl succinate **16** (0.175 mL, 1.05 mmol) in THF (20 mL), dropwise over 20 min. After 30 min the dark brown reaction mixture was diluted with water (25 mL) and extracted with ether (3×50 mL). The combined ether phases were dried ($MgSO_4$) and concentrated in vacuo to a dark orange oil. Purification by column chromatography (40–50% Et_2O in petrol) yielded diester **19** as an off-white solid (39 mg, 0.089 mmol, 9%): mp 169–172°C, [lit. 171–172°C].[12] The aqueous phase was acidified with 6 M HCl (15 mL) and extracted with chloroform (3×50 mL). The combined chloroform phases were dried ($MgSO_4$), concentrated in vacuo and purified by column chromatography (40–50% EtOAc in petrol with 0.5% acetic acid) to yield γ-lactone **22** as an off-white solid (46 mg, 0.15 mmol, 15%): mp 139–142°C (benzene/petrol) [lit. 146–147°C];[26] then mono-ester **20** as a cream solid (140 mg, 0.34 mmol, 34%): mp 223–226°C [lit. not reported];[12] IR (solid, cm^{-1}) ν_{max} 1689 w, 1487 w, 1457 s, 1238 s, 1106 w, 1039 s, 941 w, 753 w; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 292 (12,200); ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.34 (1H, s, Ar*H*), 7.15 (1H, s, Ar*H*), 6.81 (1H, d, *J*=7.9 Hz, Ar*H*), 6.79 (1H, s, Ar*H*), 6.73 (1H, d, *J*=1.5 Hz, Ar*H*), 6.70 (1H, dd, *J*=7.9, 1.5 Hz, Ar*H*), 5.994 (1H, d, *J*=1.0 Hz, OC*H*HO), 5.988 (1H, d, *J*=1.0 Hz, OCH*H*O), 5.97 (1H, d, *J*=1.5 Hz, OC*H*HO), 5.95 (1H, d, *J*=1.5 Hz, OCH*H*O), 4.03 (2H, q, *J*=7.2 Hz, OCH_2), 1.03 (3H, t, *J*=7.2 Hz, CH_3); ^{13}C NMR (75 MHz, D_6-DMSO) δ_C 168.0 (*C*), 167.0 (*C*), 150.2 (*C*), 148.6 (*C*), 147.1 (*C*), 147.0 (*C*), 136.2 (*C*), 131.3 (*C*), 130.4 (*C*), 130.2 (*C*), 129.6 (*C*), 129.6 (*C*H), 124.0 (*C*), 123.5 (*C*H), 110.6 (*C*H), 108.1 (*C*H), 105.0 (*C*H), 102.2 (CH_2), 102.1 (*C*H), 101.3 (CH_2), 60.4 (CH_2), 13.7 (CH_3); LRMS (ES^-) 521 ($[M+CF_3COO]^-$, 9%), 407 ($[M-H]^-$, 10%); HRMS (ES^+) *m/z* Found: $[M+Na]^+$, 431.0746, $C_{22}H_{16}O_8Na$ requires 431.0737.

Alternatively, sodium (126 mg, 5.5 g atom) was added portionwise at room temperature to vigorously stirred anhydrous ethanol (8 mL). On consumption of the metal, the solution was cooled to 0°C and ketoaldehyde **15** (400 mg, 1.34 mmol) and phosphonate **25** (832 mg, 2.68 mmol) in THF (32 mL) and ethanol (10 mL) were added via a dropping funnel over 20 min. After 3 h the reaction mixture was warmed to room temperature and partitioned between water (50 mL) and 1:1 THF/ether (100 mL). The aqueous layer was washed with 1:1 THF/ether (2×100 mL), then the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to a viscous oil. Purification by column chromatography (40–50% Et_2O in petrol) yielded diester **19** (394 mg, 0.90 mmol, 67%) as an off-white solid. The aqueous phase was acidified with 6 M HCl (50 mL) and extracted with chloroform (3×50 mL). The combined chloroform phases were then dried ($MgSO_4$) and concentrated in vacuo to a brown solid. Purification by column chromatography (40% ethyl acetate in petrol+0.5% acetic acid) yielded first γ-lactone **22** (18 mg, 0.06 mmol, 5%) then mono-ester **20** (14 mg, 34 mmol, 3%). Data as stated above.

4.3.3. Diethyl 6,7-methylenedioxy-1-(3,4-dimethoxyphenyl)-naphthalene-2,3-dicarboxylate (26), 6,7-methylenedioxy-1-(3,4-dimethoxyphenyl)-naphthalene-2,3-dicarboxylic acid 2-ethyl ester (30) and 7-(3,4-dimethoxyphenyl)-7*H*-furo[3′,4′:4,5]benzo[1,2-*d*][1,3]dioxol-5-one (33). Sodium (150 mg, 6.52 g atom) was added portionwise at room temperature to vigorously stirred anhydrous ethanol (10 mL). On consumption of the metal, the solution was cooled to 0°C and ketoaldehyde **23** (500 mg, 1.59 mmol) and phosphonate **25** (987 mg, 3.18 mmol) in THF (50 mL) and ethanol (12 mL) were added via a dropping funnel over 20 min. After 2 h, the reaction mixture was warmed to room temperature, concentrated in vacuo and partitioned between water (50 mL) and 1:1 THF/ether (200 mL). The aqueous layer was washed with 1:1 THF/ether (2×100 mL), then the combined organic phases were washed with saturated sodium bicarbonate solution (2×50 mL), dried ($MgSO_4$) and concentrated in vacuo to an orange oil. Purification by column chromatography (50% Et_2O in petrol) yielded diester **26** (332 mg, 0.73 mmol, 46%) as a pale yellow solid: mp 159–162°C [lit. not reported];[12] IR (solid, cm^{-1}) ν_{max} 1727 m, 1710 m, 1460 s, 1256 s, 1235 vs, 1207 s, 1157 m, 1144 m, 1030 s, 811 m; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 300 (14,800), 258 (59,600); ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.39 (1H, s, Ar*H*), 7.23 (1H, s, Ar*H*), 6.95 (1H, d, *J*=8.2 Hz, Ar*H*), 6.88 (1H, dd, *J*=8.2, 2.0 Hz, Ar*H*), 6.87 (1H, s, Ar*H*), 6.85 (1H, d, *J*=2.0 Hz, Ar*H*), 6.05 (2H, s, OCH_2O), 4.39 (2H, q, *J*=7.2 Hz, OCH_2), 4.08 (2H, m, OCH_2), 3.95 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 1.40 (3H, t, *J*=7.2 Hz, CH_3), 1.04 (3H, t, *J*=7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.3 (*C*), 166.1 (*C*), 150.3 (*C*), 148.8 (2×*C*), 148.6 (*C*), 137.3 (*C*), 132.5 (*C*), 130.7 (*C*), 130.0 (*C*H), 130.0 (*C*), 129.6 (*C*), 123.4 (*C*), 122.9 (*C*H), 113.7 (*C*H), 110.8 (*C*H), 105.0 (*C*H), 103.5 (*C*H), 101.9 (CH_2), 61.6 (CH_2), 61.2 (CH_2), 56.1 (2×CH_3), 14.4 (CH_3), 14.0 (CH_3); LRMS (CI) 452 (M^+, 100%), 407 ($[MH-EtOH]^+$, 84%), 379 ($[M-CO_2Et]^+$, 31%); HRMS (ES^+) *m/z* Found: $[2M+Na]^+$, 927.2828, $C_{50}H_{48}O_{16}Na$ requires 927.2835. The combined aqueous phases were acidified with 6 M HCl (50 mL) and extracted with chloroform (3×100 mL). The combined chloroform phases were then dried ($MgSO_4$) and concentrated in vacuo to a yellow oil. Purification by column chromatography (40% ethyl acetate in petrol+0.5% acetic acid) yielded γ-lactone **33** (45 mg, 0.14 mmol, 9%) as a white solid: mp 173–174°C; IR (solid, cm^{-1}) ν_{max} 1733 s,

1518 w, 1475 w, 1460 w, 1323 m, 1256 m, 1234 w, 1142 w, 1102 m, 1023 vs, 954 w, 935 m, 878 w; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 300 (4500), 285 (4700), 229 (10,600); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.25 (1H, s, Ar*H*), 6.87 (1H, d, *J*=1.0 Hz, Ar*H*), 6.86 (1H, s, Ar*H*), 6.68–6.64 (2H, m, Ar*H*), 6.21 (1H, s, OC*H*), 6.12 (1H, d, *J*=1.2 Hz, OC*H*HO), 6.11 (1H, d, *J*=1.2 Hz, OCH*H*O), 3.89 (3H, s, OCH_3), 3.82 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 170.2 (*C*), 154.0 (*C*), 150.1 (*C*), 149.6 (*C*), 149.6 (*C*), 146.6 (*C*), 128.8 (*C*), 120.2 (*C*H), 119.6 (*C*), 111.2 (*C*H), 109.8 (*C*H), 104.2 (*C*H), 102.9 (*C*H_2), 102.7 (*C*H), 82.4 (*C*H), 56.1 (*C*H_3), 56.1 (*C*H_3); LRMS (CI) 332 ([M+NH_4]$^+$, 13%), 315 (MH^+, 100%); HRMS (EI^+) *m*/*z* Found: [2M+Na]$^+$, 651.1473, $C_{34}H_{28}O_{12}Na$ requires 651.1493; then mono-ester **30** (125 mg, 0.30 mmol, 19%) as a white solid: mp 200–203°C [lit. not reported];[12] IR (solid, cm^{-1}) ν_{max} 1743 m, 1687 m, 1460 s, 1236 vs, 1037 m; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 304 (17,600), 254 (73,400); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.24 (1H, s, Ar*H*), 7.05 (1H, s, Ar*H*), 6.79 (1H, d, *J*=8.0 Hz, Ar*H*), 6.70 (1H, dd, *J*=8.0, 1.7 Hz, Ar*H*), 6.69 (1H, s, Ar*H*), 6.68 (1H, d, *J*=1.7 Hz, Ar*H*), 5.89 (2H, s, OCH_2O), 3.90 (2H, m, OCH_2), 3.78 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 0.90 (3H, t, *J*=7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 174.0 (*C*), 172.4 (*C*), 154.9 (*C*), 153.4 (2×*C*), 153.2 (*C*), 141.7 (*C*), 137.0 (*C*), 135.6 (*C*), 134.9 (*C*H), 134.6 (*C*), 134.4 (*C*), 128.7 (*C*), 127.6 (*C*H), 118.4 (*C*H), 115.6 (*C*H), 109.6 (*C*H), 108.0 (*C*H), 106.6 (*C*H_2), 65.8 (*C*H_2), 60.7 (2×*C*H_3), 18.7 (*C*H_3); LRMS (CI) 537 ([M+CF_3COO]$^-$, 100%); HRMS (ES^+) *m*/*z* Found: [M+Na]$^+$, 447.1048, $C_{23}H_{20}O_8Na$ requires 447.1050.

4.3.4. 7-(3,4-Dimethoxyphenyl)-7*H*-furo[3′,4′:4,5]benzo-[1,2-*d*][1,3]dioxol-5-one (33). To a solution of ketoaldehyde **23** (200 mg, 0.64 mmol) and diacid **12** (297 mg, 1.27 mmol) in pyridine (5 mL) was added via syringe piperidine (0.130 mL, 1.31 mmol). The reaction was heated at 100°C for 48 h then cooled to room temperature and added carefully to conc. hydrochloric acid (10 mL) on ice (20 g) resulting in a yellow suspension. After extraction with ether (3×50 mL), the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to a viscous brown oil. Purification by column chromatography (gradient elution—60 to 80% ether in petrol) gave **33** as a white solid (101 mg, 0.32 mmol, 51%). Data as stated above.

4.3.5. Dimethyl 6,7-dimethoxy-1-(benzo[1,3]dioxol-5-yl)-naphthalene-2,3-dicarboxylate (27) 6,7-dimethoxy-1-(benzo[1,3]dioxol-5-yl)-naphthalene-2,3-dicarboxylic acid 2-methyl ester (31) and 3-benzo[1,3]dioxol-5-yl-5,6-dimethoxy-3*H*-isobenzofuran-1-one (21). Sodium (150 mg, 6.52 g atom) was added portionwise at room temperature to vigorously stirred anhydrous methanol (10 mL). On consumption of the metal, the solution was cooled to 0°C and ketoaldehyde **14** (500 mg, 1.59 mmol) and phosphonate **24** (810 mg, 3.18 mmol) in THF (50 mL) and methanol (12 mL) were added via a dropping funnel over 20 min. After 3 h, the reaction mixture was warmed to room temperature, concentrated in vacuo and partitioned between water (50 mL) and 1:1 THF/ether (200 mL). The aqueous layer was washed with 1:1 THF/ether (2×100 mL), then the combined organic phases were washed with saturated sodium bicarbonate solution (2×50 mL), dried ($MgSO_4$) and concentrated in vacuo to an orange oil. Purification by column chromatography (40% Et_2O in petrol) yielded diester **27** (376 mg, 0.89 mmol, 56%) as a white solid, mp 169–171°C [lit. 169–170°C].[27] The combined aqueous phases were acidified with 6 M HCl (50 mL) and extracted with chloroform (3×100 mL). The combined chloroform phases were dried ($MgSO_4$) and concentrated in vacuo to a yellow oil. Purification by column chromatography (gradient elution—30 to 50% ethyl acetate in petrol+0.5% acetic acid) yielded first γ-lactone **21** (53 mg, 0.17 mmol, 11%) as a white solid: mp 156–158°C [lit. 157.5–158°C];[25] then mono-ester **31** (98 mg, 0.24 mmol, 15%) as a white solid: mp 251–253°C [lit. 255–256°C];[27] IR (solid, cm^{-1}) ν_{max} 1730 m, 1679 m, 1474 m, 1436 m, 1239 s, 1209 m, 1047 m, 850 m; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 288 (13,000), 258 (51,300), 214 (23,600); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.42 (1H, s, Ar*H*), 7.18 (1H, s, Ar*H*), 6.85 (1H, d, *J*=8.0 Hz, Ar*H*), 6.81 (1H, s, Ar*H*), 6.79 (1H, d, *J*=1.0 Hz, Ar*H*), 6.76 (1H, dd, *J*=8.0, 1.0 Hz, Ar*H*), 6.02 (1H, s, OC*H*HO), 5.98 (1H, s, OCH*H*O), 3.97 (3H, s, COOCH_3), 3.74 (3H, s, OCH_3), 3.60 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 174.7 (*C*), 172.7 (*C*), 156.4 (*C*), 155.2 (*C*), 152.2 (*C*), 152.0 (*C*), 141.0 (*C*), 135.4 (*C*), 135.3 (*C*), 135.1 (*C*), 134.7 (*C*H), 133.3 (*C*), 128.5 (*C*H), 128.4 (*C*), 115.5 (*C*H), 112.9 (*C*H), 112.1 (*C*H), 110.1 (*C*H), 106.0 (*C*H_2), 60.8 (*C*H_3), 60.6 (*C*H_3), 57.0 (*C*H_3); LRMS (ES^-) 523 ([M+CF_3COO]$^-$, 100%); HRMS (ES^+) *m*/*z* Found: [M+Na]$^+$, 433.0896, $C_{22}H_{18}O_8Na$ requires 433.0894.

4.3.6. Dimethyl 6,7-dimethoxy-1-(benzo[1,3]dioxol-5-yl)-naphthalene-2,3-dicarboxylate (27). To a stirred suspension of lithium chloride (166 mg, 3.92 mmol) in acetonitrile (30 mL) was added ketoaldehyde **14** (300 mg, 0.96 mmol). A solution of phosphonate **24** (486 mg, 1.91 mmol) in acetonitrile (10 mL) was then added via cannula immediately followed by DBU (0.60 mL, 3.92 mmol) in one portion via syringe. After 16 h at room temperature the reaction mixture was diluted with water (20 mL) and extracted with ether (2×50 mL) and 1:1 THF/ether (50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to an orange oil. Purification by column chromatography (50–60% Et_2O in petrol) gave **27** as a white solid (284 mg, 0.67 mmol, 70%). Data as stated above.

4.3.7. Dimethyl 5-benzo[1,3]dioxol-5-yl-naphtho[2,3-*d*]-[1,3]dioxole-6,7-dicarboxylate (28), 5-benzo[1,3]dioxol-5-yl-naphtho[2,3-*d*][1,3]dioxole-6,7-dicarboxylic acid-7-methyl ester (32) and 7-benzo[1,3]dioxol-5-yl-7*H*-furo-[3′,4′:4,5]benzo[1,2-*d*][1,3]dioxol-5-one (22). Sodium (126 mg, 5.5 g atom) was added portionwise at room temperature to vigorously stirred anhydrous methanol (8 mL). On consumption of the metal the solution was cooled to 0°C and ketoaldehyde **15** (400 mg, 1.34 mmol) and phosphonate **24** (680 mg, 2.68 mmol) in THF (32 mL) and methanol (10 mL) were added via a dropping funnel over 20 min. After 3 h the reaction mixture was warmed to room temperature and partitioned between water (50 mL) and 1:1 THF/ether (100 mL). The aqueous layer was washed with 1:1 THF/ether (2×100 mL), then the combined organic phases were dried ($MgSO_4$) and

concentrated in vacuo to a viscous yellow oil. Purification by column chromatography (40–60% Et_2O in petrol) yielded diester **28** (462 mg, 1.13 mmol, 84%) as a white solid: mp 217–219°C, [lit. 218–219°C].[11] The aqueous phase was acidified with 6 M HCl (50 mL) and extracted with chloroform (3×50 mL). The combined chloroform phases were then dried ($MgSO_4$) and concentrated in vacuo to a yellow solid. Purification by column chromatography (40% ethyl acetate in petrol+0.5% acetic acid) yielded first γ-lactone **22** (14 mg, 0.05 mmol, 4%),[26] then mono-ester **32** (26 mg, 0.07 mmol, 5%): mp 234–237°C [lit. 243–244°C].[11]

4.3.8. Dimethyl 6,7-methylenedioxy-1-(3,4-dimethoxyphenyl)-naphthalene-2,3-dicarboxylate (29). To a stirred suspension of lithium chloride (166 mg, 3.92 mmol) in acetonitrile (30 mL) was added ketoaldehyde **23** (300 mg, 0.96 mmol). A solution of phosphonate **24** (486 mg, 1.91 mmol) in acetonitrile (10 mL) was then added via cannula, followed immediately by DBU (0.60 mL, 3.92 mmol) in one portion via syringe. After 16 h at room temperature the reaction mixture was diluted with water (50 mL) and extracted with 1:1 THF/ether (50 mL) and dichloromethane (2×50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to a dark orange oil. Purification by column chromatography (gradient elution—60–80% Et_2O in petrol) gave **29** as an off-white solid (199 mg, 0.47 mmol, 49%): mp 252–254°C, [lit. 248–250°C ($CHCl_3$/hexane)];[28] IR (solid, cm^{-1}) ν_{max} 1731 w, 1716 m, 1457 s, 1256 m, 1235 s, 1212 m, 1130 m, 1024 s, 929 m, 849 m, 835 s; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 300 (10,700), 254 (50,400); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.39 (1H, s, Ar*H*), 7.22 (1H, s, Ar*H*), 6.96 (1H, d, *J*=7.9 Hz, Ar*H*), 6.88 (1H, s, Ar*H*), 6.87 (1H, dd, *J*=7.9, 1.0 Hz, Ar*H*), 6.85 (1H, d, *J*=1.0 Hz, Ar*H*), 6.06 (2H, s, OCH_2O), 3.95 (3H, s, $COOCH_3$), 3.93 (3H, s, $COOCH_3$), 3.85 (3H, s, OCH_3), 3.63 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.8 (*C*), 166.5 (*C*), 150.4 (*C*), 148.9 (*C*), 148.8 (*C*), 148.6 (*C*), 137.4 (*C*), 132.5 (*C*), 130.5 (*C*), 130.0 (*C*H), 129.4 (*C*), 125.7 (*C*), 122.9 (*C*), 122.8 (*C*H), 113.5 (*C*H), 110.8 (*C*H), 105.0 (*C*H), 103.5 (*C*H), 101.9 (CH_2), 56.1 (CH_3), 56.0 (CH_3), 52.6 (CH_3), 52.4 (CH_3); LRMS (CI) 424 (M^+, 100%), 393 ($[MH-MeOH]^+$, 91%); HRMS (ES^+) *m/z* Found: $[2M+Na]^+$, 871.2249, $C_{46}H_{40}O_{16}Na$ requires 871.2209.

Alternatively, sodium (150 mg, 6.52 g atom) was added portionwise at room temperature to vigorously stirred anhydrous methanol (12 mL). On consumption of the metal the solution was cooled to 0°C and ketoaldehyde **23** (500 mg, 1.59 mmol) and phosphonate **24** (810 mg, 3.18 mmol) in THF (50 mL) and methanol (12 mL) were added via a dropping funnel over 20 min. After 3 h the reaction mixture was warmed to room temperature, concentrated in vacuo and partitioned between water (50 mL) and 1:1 THF/ether (200 mL). The aqueous layer was washed with 1:1 THF/ether (2×100 mL), then the combined organic phases were washed with saturated sodium bicarbonate solution (2×50 mL), dried ($MgSO_4$) and concentrated in vacuo to an orange semi-solid. Purification by column chromatography (50% Et_2O in petrol) yielded diester **29** (84 mg, 0.20 mmol, 12%) as a sparingly soluble pale yellow solid. The combined aqueous phases were acidified with 6 M HCl (50 mL) and extracted with chloroform (3×100 mL). The combined chloroform phases were dried ($MgSO_4$) and concentrated in vacuo to a yellow solid. Column chromatography (30% ethyl acetate in petrol+0.5% acetic acid) yielded a further quantity of diester **29** (355 mg, 0.79 mmol, 53%). Data as stated above.

4.4. Completion of the total syntheses

4.4.1. 6,7-Dimethoxy-1-(benzo[1,3]dioxol-5-yl)-naphthalene-2,3-dicarboxylic acid 2-ethyl ester (18). The procedure of Padwa et al.[11b] is followed. To a stirred solution of diester **17** (246 mg, 0.54 mmol) in THF (30 mL) at room temperature was added potassium trimethylsilanolate (308 mg, 2.40 mmol). After 5 h, the solution was acidified with 5% HCl (50 mL) and extracted with chloroform (3×50 mL). The combined chloroform extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to yield the half-acid **18** as an off-white solid (215 mg, 0.51 mmol, 93%). Data as stated above.

4.4.2. 5-Benzo[1,3]dioxol-5-yl-naphtho[2,3-*d*][1,3]dioxole-6,7-dicarboxylic acid 7-ethyl ester (20). The procedure of Padwa et al.[11b] is followed. To a stirred solution of diester **19** (200 mg, 0.46 mmol) in THF (20 mL) at room temperature was added potassium trimethylsilanolate (260 mg, 2.00 mmol). After 4 h, the solution was acidified with 5% HCl (35 mL) and extracted with chloroform (3×50 mL). The combined chloroform extracts were dried ($MgSO_4$) and reduced in vacuo to yield a pale green solid. Column chromatography (40% EtOAc in petrol with 0.5% acetic acid) gave **20** as a light cream solid (185 mg, 0.45 mmol, 98%). Data as stated above.

4.4.3. 6,7-Methylenedioxy-1-(3,4-dimethoxyphenyl)-naphthalene-2,3-dicarboxylic acid 2-ethyl ester (30). The procedure of Padwa et al.[11b] is followed. To a stirred solution of diester **26** (205 mg, 0.45 mmol) in THF (20 mL) at room temperature was added potassium trimethylsilanolate (260 mg, 2.00 mmol). After 5 h the solution was acidified with 5% HCl (50 mL) and extracted with chloroform (3×50 mL). The combined chloroform extracts were dried ($MgSO_4$) and concentrated in vacuo to a pale green solid. Purification by column chromatography (40% ethyl acetate in petrol+0.5% acetic acid) gave **30** as a white solid (227 mg, 0.55 mmol, 94%). Data as stated above.

4.4.4. 6,7-Dimethoxy-1-(3,4-methylenedioxyphenyl)-naphthalene-2,3-dimethanol (34). To a stirred solution of diester **27** (275 mg, 0.65 mmol) in THF (20 mL) at −78°C was added lithium aluminium hydride (100 mg, 2.66 mmol) in one portion. The reaction mixture was allowed to warm to 0°C over 1 h then water (1 mL) was added dropwise via syringe. Once effervescence had ceased, 15% NaOH (1 mL) and water (1 mL) were added. After stirring vigorously at room temperature for 16 h, anhydrous $MgSO_4$ (10 g) was added. After stirring for 150 min the reaction mixture was filtered, concentrated in vacuo and purified by column chromatography (gradient elution—90% Et_2O in petrol to 5% MeOH in Et_2O) to give diol **34** (180 mg, 0.49 mmol, 75%) as a white solid: mp 191–193°C (benzene/petrol), [lit. 191°C];[10r] IR (solid, cm^{-1}) ν_{max} 3320 br w, 2768 w, 1509 m, 1434 m, 1233 s, 1155 m, 1037 m,

1005 m, 984 m, 851 vs; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 331 (6100), 289 (14,600), 246 (78,500); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.64 (1H, s, Ar*H*), 7.09 (1H, s, Ar*H*), 6.93 (1H, d, *J*=7.7 Hz, Ar*H*), 6.80 (1H, d, *J*=1.7 Hz, Ar*H*), 6.75 (1H, dd, *J*=7.7, 1.7 Hz, Ar*H*), 6.72 (1H, s, Ar*H*), 6.08 (1H, d, *J*=1.5 Hz, OC*H*HO), 6.03 (1H, d, *J*=1.5 Hz, OCH*H*O), 4.83 (2H, s, CH_2OH), 4.57 (2H, s, CH_2OH), 3.98 (3H, s, OCH_3), 3.73 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 150.2 (*C*), 150.0 (*C*), 148.1 (*C*), 147.3 (*C*), 139.2 (*C*), 136.1 (*C*), 133.6 (*C*), 132.9 (*C*), 129.2 (*C*), 129.0 (*C*), 127.7 (*C*H), 123.9 (*C*H), 111.2 (*C*H), 108.7 (*C*H), 106.7 (*C*H), 106.4 (*C*H), 101.6 (CH_2), 65.6 (CH_2), 61.1 (CH_2), 56.4 (CH_3), 56.3 (CH_3); LRMS (CI) ([MH−H_2O]$^+$, 100%), 350 ([M−H_2O]$^+$, 79%); HRMS (ES$^+$) *m*/*z* Found: [2M+Na]$^+$, 759.2444, $C_{42}H_{40}O_{12}Na$ requires 759.2412.

4.4.5. 6,7-Methylenedioxy-1-(3,4-methylenedioxy)naphthalene-2,3-dimethanol (35). To a stirred solution of diester **28** (250 mg, 0.61 mmol) in THF (50 mL) at −78°C was added lithium aluminium hydride (95 mg, 2.51 mmol) in one portion. The reaction mixture was then warmed to 0°C over 1 h then water (1 mL) was added dropwise via syringe. Once effervescence had ceased, 15% NaOH (1 mL) and water (1 mL) were added. After stirring vigorously at room temperature for 16 h, anhydrous $MgSO_4$ (10 g) was added. After stirring for 150 min the reaction mixture was filtered, concentrated in vacuo and purified by column chromatography (gradient elution—90% Et_2O in petrol to 5% MeOH in Et_2O) to yield **35** (179 mg, 0.51 mmol, 83%) as a white solid: mp 176–179°C [lit. 181–183°C];[29] IR (solid, cm^{-1}) ν_{max} 3349 br w, 1504 w, 1486 m, 1459 s, 1234 s, 1038 s, 1013 m, 939 m, 885 w; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 332 (3300), 294 (12,400); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.65 (1H, s, Ar*H*), 7.10 (1H, s, Ar*H*), 6.93 (1H, d, *J*=8.1 Hz, Ar*H*), 6.70–6.85 (3H, m, Ar*H*), 5.89–6.13 (4H, m, OCH_2O), 4.87 (2H, s, CH_2OH), 4.61 (2H, s, CH_2OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 148.2 (*C*), 147.9 (*C*), 147.8 (*C*), 147.1 (*C*), 139.6 (*C*), 135.9 (*C*), 133.6 (*C*), 132.6 (*C*), 130.2 (2×*C*), 128.2 (*C*H), 123.6 (*C*H), 110.9 (*C*H), 108.5 (*C*H), 103.9 (*C*H), 103.8 (*C*H), 101.3 (2×CH_2), 65.4 (CH_2), 60.8 (CH_2); LRMS (CI) 321 ([MH−MeOH]$^+$, 100%); HRMS (ES$^+$) *m*/*z* Found: [2M+Na]$^+$, 727.1798, $C_{40}H_{32}O_{12}Na$ requires 727.1786.

4.4.6. 6,7-Methylenedioxy-1-(3,4-dimethoxyphenyl)-naphthalene-2,3-dimethanol (36). To a stirred solution of diester **29** (100 mg, 0.24 mmol) in THF (50 mL) at −78°C under argon was added lithium aluminium hydride (37 mg, 0.97 mmol) in one portion. After 30 min, the reaction mixture was warmed to 0°C, stirred for a further 1 h then water (0.4 mL) was added. Once effervescence had ceased, 15% NaOH (0.4 mL) and water (0.4 mL) were added, the reaction was warmed to room temperature and vigorously stirred for 16 h. Anhydrous $MgSO_4$ (5 g) was then added and after 150 min the resulting suspension was filtered and concentrated in vacuo to a pale yellow solid. Purification by column chromatography (gradient elution—90% Et_2O in petrol to 5% MeOH in Et_2O) yielded **36** as a white solid (64 mg, 0.17 mmol, 74%): mp 179–182°C [lit. 183°C];[10r] IR (solid, cm^{-1}) ν_{max} 3430 br w, 2943 w, 1515 w, 1462 s, 1248 s, 1229 m, 1139 m, 1025 s, 941 m, 763 m; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 314 (2000), 274 (12,800), 238 (60,400); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.68 (1H, s, Ar*H*), 7.13 (1H, s, Ar*H*), 7.00 (1H, d, *J*=7.7 Hz, Ar*H*), 6.85 (1H, dd, *J*=7.7, 2.0 Hz, Ar*H*), 6.84 (1H, d, *J*=2.0 Hz, Ar*H*), 6.76 (1H, s, Ar*H*), 6.01 (2H, s, OCH_2O), 4.91 (2H, s, CH_2OH), 4.62 (2H, s, CH_2OH), 3.98 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 2.64 (2H, br s, 2×CH$_2$O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 148.8 (*C*), 148.3 (*C*), 148.0 (*C*), 147.8 (*C*), 139.8 (*C*), 135.8 (*C*), 133.5 (*C*), 131.3 (*C*), 128.0 (*C*), 128.0 (*C*H), 122.3 (*C*), 122.3 (*C*H), 113.3 (*C*H), 111.1 (*C*H), 103.8 (*C*H), 103.7 (*C*H), 101.2 (CH_2), 65.5 (CH_2), 61.0 (CH_2), 56.1 (CH_3), 56.1 (CH_3); LRMS (CI) 368 (M$^+$, 4%), 351 ([MH−H_2O]$^+$, 62%), 350 ([M−H_2O]$^+$, 100%); HRMS (ES$^+$) *m*/*z* Found: [2M+Na]$^+$, 759.2427, $C_{42}H_{40}O_{12}Na$ requires 759.2412.

4.4.7. Justicidin B (1) and retrojusticidin B (2). *Method I—using a borane reduction*. The procedure of Cow et al.[12] is followed. To a stirred solution of half-acid **18** (30 mg, 0.17 mmol) in THF (1.5 mL) at room temperature was added borane–dimethyl sulfide complex (10.0 M solution in dimethylsulfide, 0.080 mL, 0.80 mmol) dropwise via syringe. After 3 h, 3% HCl in ethanol (5 mL) was added. Once effervescence had ceased, the solvent was removed in vacuo. The residue was dissolved in anhydrous ethanol (3 mL), concentrated in vacuo to a yellow solid and dissolved in chloroform (25 mL). Washing with saturated sodium bicarbonate solution (3×25 mL) and water (25 mL), drying ($MgSO_4$) and concentrating in vacuo, gave a white solid. Purification by column chromatography (10% ethyl acetate in toluene) gave justicidin B **1** (25 mg, 0.069 mmol, 97%) as a white solid, mp 237–239°C [lit. 235–238°C];[1g] IR (solid, cm^{-1}) ν_{max} 1759 s, 1506 s, 1481 m, 1439 m, 1387 w, 1343 w, 1262 s, 1239 s, 1217 s, 1198 s, 1158 m, 1044 s, 1021 m, 1002 m, 932 w, 876 m; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 340 (3100), 286 (8300), 252 (38,000); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.71 (1H, s, Ar*H*), 7.19 (1H, s, Ar*H*), 7.12 (1H, s, Ar*H*), 6.98 (1H, d, *J*=7.7 Hz, Ar*H*), 6.86 (1H, d, *J*=1.2 Hz, Ar*H*), 6.84 (1H, dd, *J*=7.7, 1.2 Hz, Ar*H*), 6.10 (1H, d, *J*=1.0 Hz, OC*H*HO), 6.05 (1H, d, *J*=1.0 Hz, OCH*H*O), 5.39 (2H, s, CH_2OCO), 4.06 (3H, s, OCH_3), 3.82 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.9 (*C*), 151.9 (*C*), 150.2 (*C*), 147.7 (2×*C*), 139.7 (2×*C*), 133.3 (*C*), 129.0 (*C*), 128.5 (*C*), 123.6 (*C*H), 118.6 (*C*), 118.5 (*C*H), 110.7 (*C*H), 108.4 (*C*H), 106.1 (*C*H), 105.9 (*C*H), 101.4 (CH_2), 68.2 (CH_2), 56.2 (CH_3), 56.0 (CH_3); LRMS (CI) 365 (MH$^+$, 100%); HRMS (ES$^+$) *m*/*z* Found: [M+Na]$^+$, 387.0842, $C_{21}H_{16}O_6Na$ requires 387.0839.

Method II—using a lithium borohydride reduction. The procedure of Padwa et al.[11b] is followed. To a cooled (0°C) solution of half-acid **18** (140 mg, 0.33 mmol) and sodium hydride (105 mg of a 60% dispersion in mineral oil and washed with petrol, 2.62 mmol) in 1,4-dioxane (6.25 mL) was added lithium borohydride (2.0 M solution in THF, 0.94 mL, 1.88 mmol) dropwise via syringe. Once effervescence had ceased, the reaction mixture was heated to reflux for 28 h then cooled to 0°C and acidified with 5% HCl (15 mL). The resulting biphasic mixture was extracted with dichloromethane (4×20 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to a white solid. Purification by column chromatography (gradient elution—5 to 15% ethyl acetate in toluene)

yielded firstly retrojusticidin B **2** (80 mg, 0.22 mmol, 67%) as a white solid mp 216–220°C [lit. 218–220°C];[10t] IR (solid, cm^{-1}) ν_{max} 2948 w, 2919 w, 2849 w, 1750 s, 1505 m, 1483 m, 1457 m, 1435 m, 1263 m, 1240 s, 1230 s, 1154 m, 1037 s, 1006 m, 832 m, 761 m; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 310 (8000), 252 (65,600); ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.30 (1H, s, Ar*H*), 7.30 (1H, s, Ar*H*), 7.10 (1H, s, Ar*H*), 6.99 (1H, d, *J*=8.4 Hz, Ar*H*), 6.85 (1H, d, *J*=1.7 Hz, Ar*H*), 6.84 (1H, dd, *J*=8.4, 1.7 Hz, Ar*H*), 6.11 (1H, d, *J*=1.2 Hz, OC*H*HO), 6.08 (1H, d, *J*=1.2 Hz, OCH*H*O), 5.21 (2H, s, CH_2OCO), 4.05 (3H, s, OCH_3), 3.86 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 171.8 (*C*), 152.2 (*C*), 150.3 (*C*), 148.5 (*C*), 147.8 (*C*), 138.1 (*C*), 132.1 (*C*), 131.8 (*C*), 130.0 (*C*), 129.9 (*C*), 124.4 (*C*H), 122.9 (*C*H), 121.5 (*C*), 109.7 (*C*H), 109.2 (*C*H), 107.8 (*C*H), 104.1 (*C*H), 101.6 (CH_2), 69.7 (CH_2), 56.2 (CH_3), 56.1 (CH_3); LRMS (CI) 364 (M^+, 100%); HRMS (ES^+) *m/z* Found: $[M+Na]^+$, 387.0842, $C_{21}H_{16}O_6Na$ requires 387.0839; then justicidin B **1** (34 mg, 0.09 mmol, 28%) as a white solid.

Method III—using a manganese dioxide oxidation. To a stirred solution of diol **34** (25 mg, 0.068 mmol) in dichloromethane (10 mL) at room temperature was added activated manganese dioxide (354 mg, 4.1 mmol) in one portion. After 24 h the suspension was filtered through celite and the solids were washed with chloroform (150 mL). The combined solutions were concentrated in vacuo and purified by column chromatography (5–10% EtOAc in toluene) to give retrojusticidin B **2** (8.3 mg, 0.023 mmol, 34%) as a white solid.

Method IV—using a barium manganate oxidation. To a stirred solution of diol **34** (25 mg, 0.068 mmol) in dichloromethane (10 mL) at room temperature was added barium manganate (174 mg, 0.68 mmol) in one portion. After 16 h the suspension was filtered through celite and the solids were washed with chloroform (150 mL). The combined solutions were concentrated in vacuo to a white solid which was purified by column chromatography (5–10% EtOAc in toluene) to give firstly retrojusticidin B **2** (21.2 mg, 0.058 mmol, 86%) as a white solid, then justicidin B **1** (3.0 mg, 0.008 mmol, 12%) as a white solid.

4.4.8. Taiwanin C (3) and justicidin E (4). *Method I—using a borane reduction*. The procedure of Cow et al.[12] is followed. To a stirred solution of half-acid **20** (50 mg, 0.12 mmol) in THF (4 mL) at room temperature was added borane–dimethyl sulfide complex (10.0 M solution in dimethylsulfide, 0.12 mL, 0.80 mmol) dropwise via syringe. After 2 h, 3% HCl in ethanol (5 mL) was added. Once effervescence had ceased, the solvent was removed in vacuo. The residue was dissolved in anhydrous ethanol (5 mL), concentrated in vacuo to a yellow solid and dissolved in chloroform (25 mL). Washing with saturated sodium bicarbonate solution (3×25 mL) and water (25 mL), drying ($MgSO_4$) and concentrating in vacuo, gave a yellow solid. Purification by column chromatography (5–10% ethyl acetate in toluene) gave taiwanin C **3** (37 mg, 0.11 mmol, 87%) as a white solid: mp 270–272°C, [lit. 270–272°C];[1c,10o] IR (solid, cm^{-1}) ν_{max} 2919 w, 2850 w, 1763 s, 1612 w, 1489 m, 1469 s, 1457 m, 1257 m, 1234 m, 1203 m, 1152 m, 1033 s, 1012 s, 930 m, 874 m, 797 m; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 340 (4700), 288 (12,400), 251 (50,300); ^1H NMR (300 MHz, D_6-DMSO) δ_H 7.93 (1H, s, Ar*H*), 7.52 (1H, s, Ar*H*), 7.03 (1H, d, *J*=7.7 Hz, Ar*H*), 6.88 (1H, s, Ar*H*), 6.87 (1H, d, *J*=1.5 Hz, Ar*H*), 6.73 (1H, dd, *J*=7.7, 1.5 Hz, Ar*H*), 6.18 (1H, d, *J*=2.6 Hz, OC*H*HO), 6.17 (1H, d, *J*=2.6 Hz, OCH*H*O), 6.13 (1H, d, *J*=1.1 Hz, OC*H*HO), 6.12 (1H, d, *J*=1.1 Hz, OCH*H*O), 5.42 (2H, s, CH_2OCO); ^{13}C NMR (75 MHz, D_6-DMSO) δ_C 169.1 (*C*), 149.5 (*C*), 148.3 (*C*), 146.9 (2×*C*), 140.2 (*C*), 138.6 (*C*), 134.2 (*C*), 129.3 (*C*), 128.3 (*C*), 123.2 (*C*H), 119.5 (*C*H), 118.4 (*C*), 110.4 (*C*H), 107.9 (*C*H), 103.7 (*C*H), 102.1 (*C*H), 102.1 (CH_2), 101.1 (CH_2), 67.9 (CH_2); LRMS (CI) 349 (MH^+, 100%); HRMS (ES^+) *m/z* Found: $[M+Na]^+$, 371.0527, $C_{20}H_{12}O_6Na$ requires 371.0526.

Method II—using a lithium borohydride reduction. The procedure of Padwa et al.[11b] is followed. To a solution of half-acid **20** (50 mg, 0.12 mmol) and sodium hydride (39 mg of a 60% dispersion in mineral oil and washed with petrol, 0.97 mmol) in 1,4-dioxane (2.3 mL) at room temperature was added lithium borohydride (0.49 mL, 0.97 mmol, 2.0 M solution in THF) dropwise via syringe. Once effervescence had ceased, the reaction mixture was heated to reflux for 28 h then cooled to 0°C and acidified with 5% HCl (10 mL). The resulting biphasic mixture was extracted with dichloromethane (3×25 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to a white solid. Purification by column chromatography (5–10% ethyl acetate in toluene) yielded justicidin E **4** (24 mg, 0.07 mmol, 57%) as a white solid: mp 264–268°C, [lit. 265–269°C];[10w] IR (solid, cm^{-1}) ν_{max} 2920 w, 1757 s, 1498 w, 1458 vs, 1245 s), 1207 m, 1025 s, 1007 m, 931 m; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 300 (9500), 244 (33,800); ^1H NMR (300 MHz, D_6-DMSO) δ_H 8.34 (1H, s, Ar*H*), 7.62 (1H, s, Ar*H*), 7.08 (1H, d, *J*=8.1 Hz, Ar*H*), 7.03 (1H, d, *J*=1.5 Hz, Ar*H*), 6.99 (1H, s, Ar*H*), 6.89 (1H, dd, *J*=8.1, 1.5 Hz, Ar*H*), 6.18 (2H, s, OCH_2O), 6.12 (2H, s, OCH_2O), 5.32 (1H, d, *J*=14.7 Hz, OC*H*H), 5.25 (1H, d, *J*=14.7 Hz, OCH*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 170.8 (*C*), 150.4 (*C*), 148.0 (*C*), 147.9 (*C*), 147.3 (*C*), 138.7 (*C*), 132.6 (*C*), 132.1 (*C*), 131.0 (*C*), 129.1 (*C*), 124.1 (*C*H), 123.0 (*C*H), 121.2 (*C*), 109.7 (*C*H), 108.9 (*C*H), 105.2 (*C*H), 102.3 (CH_2), 101.4 (CH_2), 100.9 (*C*H), 69.3 (CH_2); LRMS (CI) 349 (MH^+, 100%); HRMS (ES^+) *m/z* Found: $[M+Na]^+$, 371.0525, $C_{20}H_{12}O_6Na$ requires 371.0526.

Method III—using a manganese dioxide oxidation. To a stirred solution of diol **35** (175 mg, 0.50 mmol) in dichloromethane (25 mL) at room temperature was added activated manganese dioxide (2.59 g, 29.8 mmol) in one portion. After 16 h the suspension was filtered through celite and the solids were washed with chloroform (250 mL). The combined solutions were concentrated in vacuo and purified by column chromatography (5% EtOAc in toluene) to give justicidin E **4** (102 mg, 0.29 mmol, 59%) as a white solid.

Method IV—using a barium manganate oxidation. To a stirred solution of diol **35** (50 mg, 0.14 mmol) in dichloromethane (10 mL) at room temperature was added barium manganate (364 mg, 1.42 mmol) in one portion. After 16 h the suspension was filtered through celite and the solids were washed with chloroform (150 mL). The combined

solutions were concentrated in vacuo and purified by column chromatography (5–10% EtOAc in toluene) to give firstly justicidin E **4** (35 mg, 0.10 mmol, 71%) as a white solid, then taiwanin C **3** (7.0 mg, 0.02 mmol, 14%) as a white solid.

4.4.9. Chinensin (5) and retrochinensin (6). *Method I—using a borane reduction*. The procedure of Cow et al.[12] is followed. To a stirred solution of half-acid **30** (60 mg, 0.14 mmol) in THF (3 mL) at room temperature was added borane–dimethyl sulfide complex (10.0 M solution in dimethylsulfide, 0.14 mL, 1.40 mmol) dropwise via syringe. After 3 h, 3% HCl in ethanol (5 mL) was added. Once effervescence had ceased, the solvent was removed in vacuo. The residue was dissolved in anhydrous ethanol (5 mL), concentrated in vacuo to a white solid and dissolved in chloroform (25 mL). Washing with saturated sodium bicarbonate solution (3×25 mL) and water (25 mL), drying ($MgSO_4$) and concentrating in vacuo, gave a white solid. Purification by column chromatography (10% ethyl acetate in toluene) gave chinensin **5** (50 mg, 0.134 mmol, 97%) as a white solid: mp 224–226°C [lit. 224–225°C];[10o] IR (solid, cm^{-1}) ν_{max} 1762 s, 1738 s, 1462 m, 1366 m, 1245 m, 1229 s, 1217 s, 1202 s, 1032 m, 1018 m; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 340 (5500), 300 (10,600), 250 (46,600); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.70 (1H, s, Ar*H*), 7.21 (1H, s, Ar*H*), 7.12 (1H, s, Ar*H*), 7.03 (1H, d, *J*=8.1 Hz, Ar*H*), 6.91 (1H, dd, *J*=8.1, 1.8 Hz, Ar*H*), 6.87 (1H, d, *J*=1.8 Hz, Ar*H*), 6.08 (2H, s, OCH_2O), 5.38 (2H, s, CH_2OCO), 3.98 (3H, s, OCH_3), 3.87 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 170.0 (*C*), 150.1 (*C*), 149.0 (*C*), 148.8 (*C*), 148.7 (*C*), 140.6 (*C*), 140.0 (*C*), 134.8 (*C*), 130.6 (*C*), 127.3 (*C*), 122.6 (*C*H), 119.1 (*C*H), 118.9 (*C*), 113.5 (*C*H), 110.9 (*C*H), 103.9 (*C*H), 103.8 (*C*H), 102.0 (*C*H_2), 68.1 (*C*H_2), 56.1 (*C*H_3), 56.0 (*C*H_3); LRMS (CI) 365 (MH^+, 65%), 364 (M^+, 100%); HRMS (ES^+) *m/z* Found: $[M+Na]^+$, 387.0843, $C_{21}H_{16}O_6Na$ requires 387.0839.

Method II—using a lithium borohydride reduction. The procedure of Padwa et al.[11b] is followed. To a cooled (0°C) solution of half-acid **30** (68 mg, 0.16 mmol) and sodium hydride (51 mg of a 60% dispersion in mineral oil and washed with petrol, 1.27 mmol) in 1,4-dioxane (3 mL) was added lithium borohydride (2.0 M solution in THF, 0.64 mL, 1.28 mmol) dropwise via syringe. Once effervescence had ceased, the reaction mixture was heated to reflux for 28 h then cooled to 0°C and acidified with 5% HCl (10 mL). The resulting biphasic mixture was extracted with dichloromethane (4×20 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to a white solid. Purification by column chromatography (10% ethyl acetate in toluene) yielded retrochinensin **6** (42 mg, 0.12 mmol, 72%) as a white solid: mp 234–236°C [lit. 233–235°C];[10o] IR (solid, cm^{-1}) ν_{max} 1755 m, 1742 m, 1515 w, 1464 m, 1369 w, 1255 m, 1245 m, 1230 s, 1206 m, 1133 m, 1035 s, 1024 s, 942 w, 919 m, 831 m; UV (CH_2Cl_2, nm) λ_{max} (ε_{max}) 306 (9000), 248 (33,900), 224 (25,000); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.26 (1H, s, Ar*H*), 7.30 (1H, s, Ar*H*), 7.11 (1H, s, Ar*H*), 7.04 (1H, d, *J*=8.1 Hz, Ar*H*), 6.91 (1H, dd, *J*=8.1, 1.8 Hz, Ar*H*), 6.85 (1H, d, *J*=1.8 Hz, Ar*H*), 6.10 (2H, s, OCH_2O), 5.24 (1H, d, *J*=14.7 Hz, OC*H*H), 5.18 (1H, d, *J*=14.7 Hz, OCH*H*), 3.99 (3H, s, OCH_3), 3.89 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 171.7 (*C*), 150.6 (*C*), 149.5 (*C*), 149.2 (*C*), 148.5 (*C*), 138.5 (*C*), 133.6 (*C*), 133.1 (*C*), 131.4 (*C*), 128.7 (*C*), 124.7 (*C*H), 121.8 (*C*H), 121.8 (*C*), 112.3 (*C*H), 111.8 (*C*H), 105.4 (*C*H), 102.2 (*C*H), 102.0 (*C*H_2), 69.7 (*C*H_2), 56.2 (*C*H_3), 56.2 (*C*H_3); LRMS (CI) 365 (MH^+, 73%), 364 (M^+, 100%); HRMS (ES^+) *m/z* Found: $[M+Na]^+$, 387.0844, $C_{21}H_{16}O_6Na$ requires 387.0839.

Method III—using a manganese dioxide oxidation. To a stirred solution of diol **36** (20 mg, 0.054 mmol) in dichloromethane (10 mL) at room temperature was added activated manganese dioxide (284 mg, 3.26 mmol) in one portion. After 48 h the suspension was filtered through celite and the solids were washed with chloroform (100 mL). The combined solutions were concentrated in vacuo to yield retrochinensin **6** (18 mg, 49 μmol, 91%) as a white solid.

Method IV—using a barium manganate oxidation. To a stirred solution of diol **36** (20 mg, 0.054 mmol) in dichloromethane (5 mL) at room temperature was added barium manganate (140 mg, 0.54 mmol) in one portion. After 48 h the suspension was filtered through celite and the solids were washed with chloroform (100 mL). The combined solutions were concentrated in vacuo and purified by column chromatography (5–10% EtOAc in toluene) to give firstly retrochinensin **6** (15.7 mg, 0.043 mmol, 80%) as a white solid, then chinensin **5** (3.7 mg, 0.010 mmol, 19%) as a white solid.

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References

1. (a) Barrero, A. F.; Herrador, M. M.; Akssira, M.; Arteaga, P.; Romera, J. L. *J. Nat. Prod.* **1999**, *62*, 946. (b) Rajasekhar, D.; Vanisree, M.; Subbaraju, C. V. *Indian J. Chem. Sect. B* **1999**, *38*, 713. (c) Subbaraju, G. V.; Pillai, K. R. *Indian J. Chem. Sect. B* **1996**, *35*, 1233. (d) Asano, J.; Chiba, K.; Tada, M.; Yoshii, T. *Phytochemistry* **1996**, *42*, 713. (e) Goezler, B.; Arar, G.; Goezler, T.; Hesse, M. *Phytochemistry* **1992**, *31*, 2473. (f) Gonzalez, A. G.; Estevez-Reyes, R.; Mato, C.; Estevez-Braun, A. M. *Phytochemistry* **1990**, *29*, 1981. (g) Sheriha, G. M.; Amer, K. M. A. *Phytochemistry* **1984**, *23*, 151. (h) Pettit, G. R.; Cragg, G. M.; Suffness, M. I.; Gust, D.; Boettner, F. E.; Williams, M.; Saenz-Renauld, J. A.; Brown, P.; Schmidt, J. M.; Ellis, P. D. *J. Org. Chem.* **1984**, *49*, 4258. (i) Anjaneyulu, A. S. R.; Ramaiah, P. A.; Row, L. R.; Venkateswarlu, R.; Pelter, A.; Ward, R. S. *Tetrahedron* **1981**, *37*, 3641. (j) Gonzalez, A. G.; Trujillo, J. M.; Estevez, R.; Perez, J. P. *An. Quim.* **1975**, *71*, 109. (k) Okigawa, M.; Maeda, T.; Kawano, N. *Tetrahedron* **1970**, *26*, 4301. (l) Lin, Y.-T.; Lo, T. B.; Shih, E.-H. *J. Chin. Chem. Soc.* **1955**, *2*, 87.
2. For recent overviews of lignan natural products see (a) Ward, R. S. *Nat. Prod. Rep.* **1990**, *7*, 349. (b) Ward, R. S. *Nat. Prod. Rep.* **1993**, *10*, 1. (c) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183. (d) Ward, R. S. *Nat. Prod. Rep.* **1997**, *14*, 43. (e) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75.

3. (a) Bachmann, T. L.; Ghia, F.; Torssell, K. B. G. *Phytochemistry* **1993**, *33*, 189. (b) Kawazoe, K.; Yutani, A.; Tamemoto, K.; Yuasa, S.; Shibata, H.; Higuti, T.; Takaishi, Y. *J. Nat. Prod.* **2001**, *64*, 588. (c) Tanabe, Y.; Seko, S.; Nishii, Y.; Yoshida, T.; Utsumi, N.; Suzukamo, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2157. (d) Chang, S.-T.; Wang, D. S.-Y.; Wu, C.-L.; Shiah, S.-G.; Kuo, Y.-H.; Chang, C.-J. *Phytochemistry* **2000**, *55*, 227.
4. Asano, J.; Chiba, K.; Tada, M.; Yoshii, T. *Phytochemistry* **1996**, *42*, 713.
5. (a) Baba, A.; Oda, T.; Taketomi, S.; Notoya, K.; Nishimura, A.; Makino, H.; Sohoa, T. *Chem. Pharm. Bull.* **1999**, *47*, 369. (b) Baba, A.; Kawamura, N.; Makino, H.; Ohta, Y.; Taketomi, S.; Sohoa, T. *J. Med. Chem.* **1996**, *39*, 5176.
6. Subbaraju, G. V.; Pillai, K. R. *Indian J. Chem. Sect. B* **1996**, *35*, 1233.
7. Kawazoe, K.; Yutani, A.; Tamemoto, K.; Yuasa, S.; Shibata, H.; Higuti, T.; Takaishi, Y. *J. Nat. Prod.* **2001**, *64*, 588.
8. Tanabe, Y.; Seko, S.; Nishii, Y.; Yoshida, T.; Utsumi, N.; Suzukamo, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2157.
9. Chang, C. W.; Lin, M. T.; Lee, S. S.; Liu, K. C. S. C.; Hsu, F. L.; Lin, J. Y. *Antiviral Res.* **1995**, *27*, 367.
10. (a) Harrowven, D. C.; Bradley, M.; Castro, J. L.; Flanagan, S. R. *Tetrahedron Lett.* **2001**, *42*, 6973. (b) Rajasekhar, D.; Subbaraju, G.; Ravikumar, K.; Chandramohan, K. *Tetrahedron* **1998**, *54*, 13227. (c) Charlton, J. L.; Oleschuk, C. J.; Chee, G.-L. *J. Org. Chem.* **1996**, *61*, 3452. (d) Ogiku, T.; Yoshida, S.-i.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1995**, *60*, 4585. (e) Kobayashi, K.; Tokimatsu, J.; Maeda, K.; Morikawa, O.; Konishi, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 3013. (f) Hattori, T.; Tanaka, H.; Okaishi, Y.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 235. (g) Kamal, A.; Daneshtalab, M.; Micetich, R. G. *Tetrahedron Lett.* **1994**, *35*, 3879. (h) Harrowven, D. C. *Tetrahedron* **1993**, *49*, 9039. (i) Harrowven, D. C.; Dennison, S. T. *Tetrahedron Lett.* **1993**, *34*, 3323. (j) Kobayashi, K.; Kanno, Y.; Seko, S.; Suginome, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3111. (k) Harrowven, D. C. *Tetrahedron Lett.* **1991**, *32*, 3735. (l) Ogiku, T.; Seki, M.; Takahashi, M.; Ohmizu, H.; Iwasaki, T. *Tetrahedron Lett.* **1990**, *31*, 5487. (m) Pelter, A.; Ward, R. S.; Pritchard, M. C.; Kay, I. T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1603. (n) Anjaneyulu, A. S. R.; Sastry, Ch. V. M.; Umasundari, P.; Satyanarayana, P. *Indian J. Chem. Sect. B* **1987**, *26*, 305. (o) Ishii, Y.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *Tetrahedron Lett.* **1986**, *27*, 365. (p) Pelter, A.; Ward, R. S.; Pritchard, M. C.; Kay, I. T. *Tetrahedron Lett.* **1985**, *26*, 6377. (q) Takano, S.; Otaki, S.; Ogasawara, K. *Tetrahedron Lett.* **1985**, *26*, 1659. (r) Satyanarayana, P.; Rao, P. K. *Indian J. Chem. Sect. B* **1985**, *24*, 151. (s) Banerji, J.; Das, B.; Chatterjee, A.; Shoolery, J. N. *Phytochemistry* **1984**, *23*, 2323. (t) Pelter, A.; Ward, R. S.; Satyanarayana, P.; Collins, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 643. (u) Pelter, A.; Ward, R. S.; Satyanarayana, P.; Collins, P. *Tetrahedron Lett.* **1982**, *23*, 571. (v) de Silva, S. O.; St. Denis, C.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1980**, 995. (w) Wada, K.; Munakata, K. *Tetrahedron Lett.* **2017**, 1970.
11. (a) Cochran, J. E.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 3938. (b) Padwa, A.; Cochran, J. E.; Kappe, C. O. *J. Org. Chem.* **1996**, *61*, 3706. (c) Takano, S.; Otaki, S.; Ogasawara, K. *Tetrahedron Lett.* **1985**, *26*, 1659.
12. Cow, C.; Leung, C.; Charlton, J. L. *Can. J. Chem.* **2000**, *78*, 553.
13. Johnson, W. S.; Daub, G. H. *Org. React.* **1951**, *6*, 1.
14. For a related benzannulation reaction involving the condensation of succinate and phthalate esters see (a) Kelly, T. R.; Ohashi, N.; Armstrong-Chong, R. J.; Bell, S. H. *J. Am. Chem. Soc.* **1986**, *108*, 7100. (b) Kelly, T. R.; Bell, S. H.; Ohashi, N.; Armstrong-Chong, R. J. *J. Am. Chem. Soc.* **1988**, *110*, 6471. (c) Bird, C. W.; Wong, C. K.; Wong, D. Y.; Koh, F. L. H. *Tetrahedron* **1976**, *32*, 269. (d) Homeyer, A. H.; Wallingford, V. H. *J. Am. Chem. Soc.* **1942**, *64*, 798.
15. (a) Anvia, F.; Bowden, K. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2093. (b) Abbaszadeh, M. R.; Bowden, K. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2081.
16. Walker, J.; Appleyard, J. R. *J. Chem. Soc.* **1895**, 768.
17. Harvey, R. G. *Tetrahedron* **1966**, *22*, 2561.
18. Trost, B. M.; Melvin Jr., L. S. *J. Am. Chem. Soc.* **1976**, *98*, 1204.
19. (a) Iwasaki, T.; Kondo, K.; Kuroda, T.; Moritani, Y.; Yamagata, S.; Sugiura, M.; Kikkawa, H.; Kaminuma, O.; Ikezawa, K. *J. Med. Chem.* **1996**, *39*, 2696. (b) Batsuren, D.; Yagudaev, M. R.; Batirov, E. Kh.; Malikov, V. M. *Chem. Nat. Compd., Engl. Transl.* **1983**, *19*, 17.
20. Orr, A. M. B.; Robinson, R.; Williams, M. M. *J. Chem. Soc.* **1917**, 499.
21. Mann, J.; Piper, S. E.; Yeung, L. K. P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2081.
22. Crombie, L.; Josephs, J. L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2599.
23. Agurell, S.; Agurell, S.; Granelli, I.; Leander, K.; Rosenblom, J.; Lüning, B. *Acta Chem. Scand. Ser. B* **1974**, *28*, 239.
24. Patil, P. A.; Joshi, R. R.; Narasimhan, N. S. *Indian J. Chem. Sect. B* **1987**, *26*, 1025.
25. Iwao, M.; Inoue, H.; Kuraishi, T. *Chem. Lett.* **1984**, 1263.
26. Arnold, B. J.; Mellows, S. M.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1266.
27. Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Takahashi, M.; Kotera, J.; Ikeo, T. *J. Med. Chem.* **1999**, *42*, 1293.
28. Anjaneyulu, A. S. R.; Umasundari, P.; Sastry, Ch. V. M.; Satyanarayana, P. *Indian J. Chem. Sect. B* **1986**, *25*, 589.
29. Ganeshpure, P. A. *Indian J. Chem. Sect. B* **1979**, *17*, 202.