Radical Conjugate Addition of Aryl-Tethered β-Alkoxyacrylates: Formal Synthesis of (±)-Frenolicin B and (±)-*epi*-Frenolicin B

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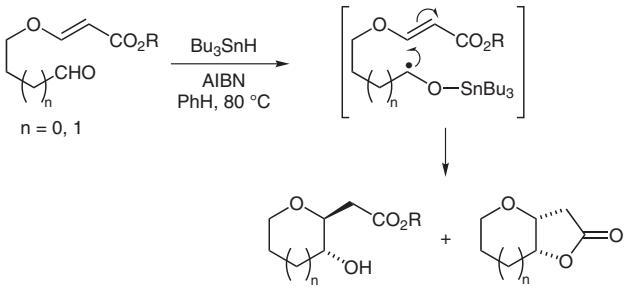
Abstract: The radical conjugate addition of aromatic-tethered *O*-stannyl ketyl radicals to β-alkoxyacrylates is demonstrated for the preparation of benzopyran-γ-lactone-fused tricyclic systems. This method is then applied to the stereodivergent formal synthesis of the kinase inhibitor (±)-frenolicin B and (±)-*epi*-frenolicin B.

Key words: radical conjugate addition, *O*-stannyl ketyl, frenolicin B, pyranonaphthoquinone

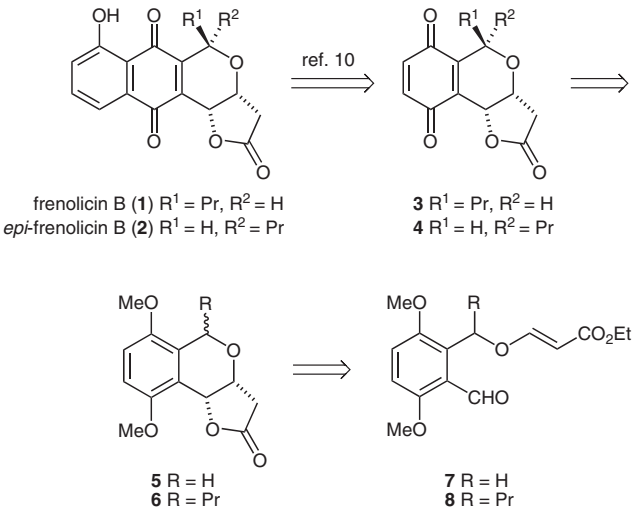
Radical conjugate addition reactions have emerged as a useful tool in synthetic organic chemistry with many variations on this general technique having been explored.[1] Along with the advantages usually associated with radical reactions (e.g., mild neutral conditions and compatibility with unprotected functional groups), radical conjugate addition reactions display exclusive preference for 1,4- over 1,2-addition, in contrast to related anionic processes. However, the reductive nature of most radical processes has been seen as a shortcoming of this technique. To alleviate this deficiency, Enholm has demonstrated that ketyl radicals, generated from the corresponding aldehyde (or ketone), cyclise efficiently onto α,β-unsaturated esters to generate products that retain an alcohol group at the site of the initially formed radical.[2] A variation on this general process is the inclusion of a heteroatom into the tether, giving access to tetrahydropyrans and tetrahydrofurans (Scheme 1).[3] Such a strategy has been employed regularly towards the preparation of a variety of natural products that incorporate cyclic ether motifs.[1b,4]



Scheme 1 Radical conjugate addition of *O*-stannyl ketyl radicals to β-alkoxyacrylates[3]

Few examples of aryl-tethered ketyl radical conjugate addition reactions have been reported[3,5] and notably, the ketyl radical cyclisation to a β-alkoxyacrylate that includes an aryl tether appears to have been unexplored. Given our ongoing interest in developing methodology for the preparation of pyranoquinone natural products,[6] we sought to explore the possibility of applying the radical conjugate addition approach towards these systems using an aryl-linked β-alkoxyacrylate as the cyclisation substrate. Herein we describe the application of this approach to a formal synthesis of (±)-frenolicin B (**1**), a pyranonaphthoquinone antibiotic first isolated from a strain of *Streptomyces roseofulvus*,[7] which exhibits excellent anticoccidial activity[8] and has recently been shown to be a potent inhibitor of the serine/threonine kinase AKT (AKT1 IC_{50} = 0.313 μM).[9]

Both frenolicin B (**1**) and *epi*-frenolicin B (**2**) have previously been prepared by the regioselective Diels–Alder reaction of 1-(trimethylsiloxy)butadiene with the pyranobenzoquinones **3** and **4**, respectively (Scheme 2).[10] We planned to prepare benzoquinone **3** and/or **4** by either alkylation and oxidation of benzopyran **5**, or more directly by oxidation of **6**. It was anticipated that the key γ-lactone-fused benzopyran tricyclic intermediates **5** and **6** may each be formed in a single step by an intramolecular radical conjugate addition of the ketyl radical formed from benzaldehydes **7** and **8**, respectively.



Scheme 2 Retrosynthetic analysis of frenolicin B (**1**) and *epi*-frenolicin B (**2**)

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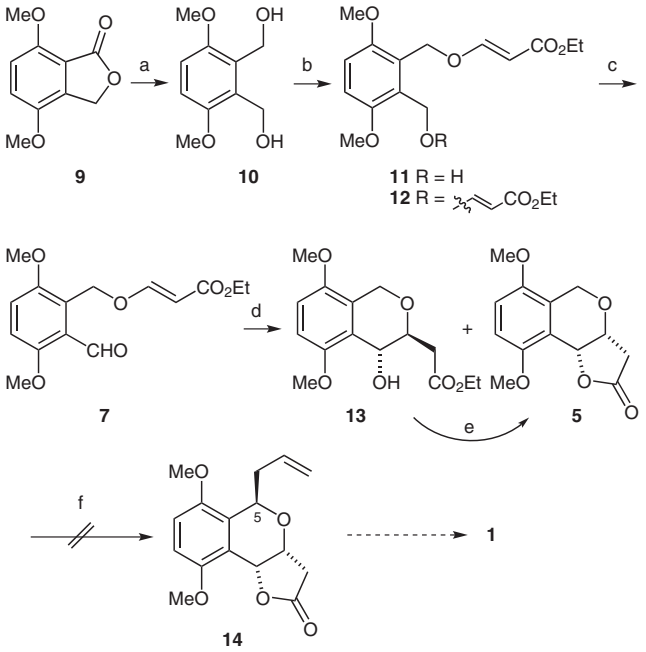
With the expectation of being able to introduce the propyl group in **3** at a late stage via the reported diastereoselective allylation of benzopyrans,[11] the benzaldehyde **7** became the first target as a potential radical cyclisation substrate. Thus, the synthesis began with reduction of 4,7-dimethoxyphthalide (**9**)[12] using lithium aluminium hydride in tetrahydrofuran to give the symmetrical diol **10**[13] in 93% yield (Scheme 3). Slow addition of ethyl propiolate to diol **10** in the presence of *N*-methylmorpholine gave the alkoxyacrylate **11** in 80% yield, exclusively as the *E*-isomer. A small amount of the dialkylated product **12** (8% yield) and unreacted diol **10** (10% yield) were also obtained. Oxidation of benzyl alcohol **11** [TEMPO, $PhI(OAc)_2$] gave the corresponding benzaldehyde **7** in 78% yield.



Scheme 3 *Reagents and conditions:* (a) $LiAlH_4$, THF, 0 °C, 1.5 h (93%); (b) ethyl propiolate, NMM, CH_2Cl_2, 1.5 h (**11** 80%, **12** 8%); (c) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 5 h (78%); (d) Bu_3SnH, AIBN, benzene, reflux, 5 h (**13** 46%, **5** 13%, **11** 15%); (e) K_2CO_3, 18-crown-6, DMF, 100 °C, 12 h (66%); (f) $Ph_3SnCH_2CH{=}CH_2$, DDQ, CH_2Cl_2.

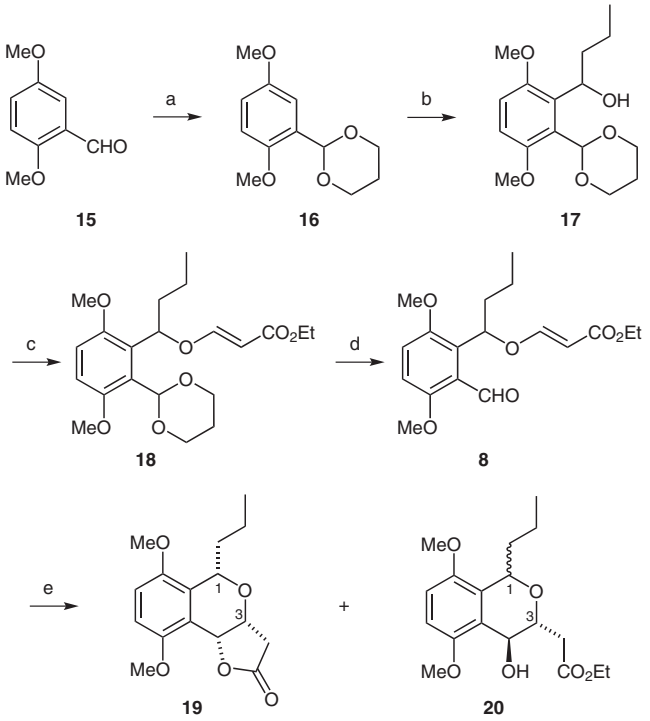
With the cyclisation substrate prepared, the propensity of **7** to undergo an intramolecular radical conjugate addition was explored. A solution of the aldehyde **7** (0.05 M in benzene) and tributyltin hydride (1.5 equiv) was heated at reflux with 2,2′-azobis(isobutyronitrile) added in portions over six hours. Under these conditions the cyclised product **13** was isolated in 37% yield with the major product being the benzyl alcohol **11** (51% yield), formed by competitive reduction of the ketyl radical generated from aldehyde **7**. Despite the concentration of tributyltin hydride being lower than that originally described by Enholm,[2] cyclisation could not compete efficiently with reduction. However, at lower concentration (0.017 M) the cyclised products **13** and **5** were formed in a 3.5:1 ratio (combined yield of 59%) with the reduction product **11** being isolated in only 15% yield. Although the ratio of cyclised products favours the *trans*-isomer **13**, conversion of the *trans*-isomer **13** into the required lactone **5** could be effected in moderate yield by heating **13** in *N*,*N*-dimethylformamide with potassium carbonate.[14]

At this point we anticipated being able to install the C5 alkyl group using conditions reported for the stereoselective allylation of benzopyrans using allyltriphenyltin and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[11] Unfortunately, these conditions failed to give any of the anticipated product **14**, with only recovery of starting material **5** being observed.

With access to the benzopyran **14**, and hence potentially frenolicin B (**1**), via a late-stage introduction of the C5 propyl group being unsuccessful, instead we resorted to incorporating the required propyl group early in the synthetic sequence. Beginning from 2,5-dimethoxybenzaldehyde (**15**) (Scheme 4), conversion into the acetal **16** proceeded smoothly upon treatment with propane-1,3-diol.[15] Metallation of the acetal followed by addition of butyraldehyde gave the *ortho*-substituted product **17** in 64% yield as the predominant product with a minor amount of the *para*-substituted isomer also formed (14% yield). Alkylation of the sterically hindered secondary alcohol in **17** proceeded reluctantly with significant decomposition of ethyl propiolate occurring before alkylation was complete. The addition of further portions of ethyl propiolate and *N*-methylmorpholine during the course of the reaction allowed further conversion of alcohol **17** into the required product **18**. Although complete conversion of **17** into **18** was not effected, adequate quantities of the β-alkoxyacrylate **18** could be obtained for further use. Hydrolysis of the acetal in **18** proceeded by exposure to dilute hydrochloric acid in acetone to give benzaldehyde **8** (90% yield) in preparation for the radical cyclisation.

Cyclisation of the ketyl radical derived from benzaldehyde **8** may lead to the formation of four possible (racemic) diastereoisomeric products. Treatment of benzaldehyde **8** under the conditions described earlier led to the isolation of three products. The major product (66% yield) was identified as the lactone **19**. The 1,3/3,4-*cis*/*cis* relative stereochemistry in **19** was established from the presence of NOE correlations between the H1/H3 and H3/H4 methine protons on the pyran ring.[16] The chromatographically inseparable minor products from the radical conjugate addition reaction (combined yield of 26%) were shown to have a 3,4-*trans*-relationship by analysis of the ^{1}H NMR spectrum, being consistent with epimeric structures **20**. The preferential formation of **19** from the radical conjugate addition of benzaldehyde **8** is in accord with the known preference for β-alkoxyacrylates, as with related hept-1-enyl radical systems, to give 1,3-*cis*-products via a 6-*exo* radical cyclisation process.[17]

Completion of the formal synthesis of frenolicin B (**1**) and *epi*-frenolicin B (**2**) was undertaken by the stereodivergent conversion of **19** into the benzoquinones **3** and **4**, as outlined in Scheme 5. Firstly, oxidation of **19** using ceri-

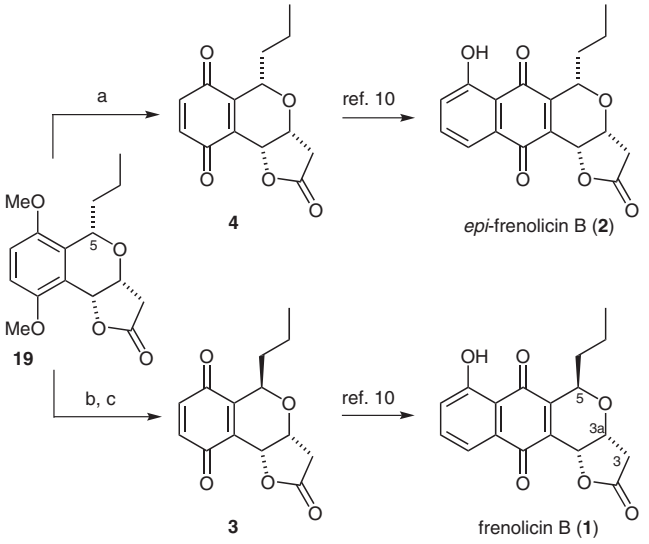


Scheme 4 *Reagents and conditions:* (a) propane-1,3-diol, $(MeO)_3CH$, Bu_4NBr_3, 45 min (100%); (b) 1. BuLi, Et_2O–hexane, 0 °C, 1.5 h; 2. PrCHO, 0 °C to r.t., 1.5 h (64%); (c) ethyl propiolate, NMM, CH_2Cl_2, 22 h (75%); (d) 2 M HCl, acetone, 16 h (90%); (e) Bu_3SnH, AIBN, benzene, reflux, 3 h (**19** 66%, **20** 26%).

um(IV) ammonium nitrate gave the benzoquinone **4** in 71% yield. The spectroscopic data for **4** was in agreement with data reported by Kraus,[10] thus confirming both the structure and relative stereochemistry of the pyranobenzoquinone **4**. Access to the natural product frenolicin B (**1**) requires epimerisation of the C5 asymmetric centre in **19**. This was achieved by exposure of **19** to boron tribromide in dichloromethane leading to formation of a mixture of products (due to partial cleavage of the methyl ethers) that were subsequently treated with cerium(IV) ammonium nitrate to give the pyranobenzoquinone **3** as the exclusive product in 69% yield, with the spectroscopic data for **3** being consistent with that previously reported.[10] Since the benzoquinones **3** and **4** have previously been converted into the pyranonaphthoquinones **1** and **2**, respectively, using a Diels–Alder/oxidation procedure,[10] this constitutes a formal synthesis of both (±)-frenolicin B (**1**) and (±)-*epi*-frenolicin B (**2**).

In summary, the potential for aromatic-tethered ketyl radicals to undergo cyclisation to β-alkoxyacrylates has been demonstrated. The radical cyclisation of acrylate **8** occurs with good diastereoselectivity to give the *cis*/*cis*-benzopyran **19** as the major product, thus providing rapid access to the epimeric pyranobenzoquinones **3** and **4** and completing a formal synthesis of both (±)-frenolicin B (**1**) and (±)-*epi*-frenolicin B (**2**).

^1H and ^{13}C NMR spectra were recorded using a Varian-500 spectrometer operating at 500 MHz and 125 MHz, respectively; residual



Scheme 5 *Reagents and conditions:* (a) CAN, MeCN, H_2O, 20 min (71%); (b) BBr_3, CH_2Cl_2, –60 °C to r.t., 1 h; (c) CAN, MeCN, H_2O, 5 min (69% 2 steps).

$CHCl_3$ (δ = 7.26 for ^1H and 77.0 for ^{13}C) was used as internal standard. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrophotometer. GC-MS spectra were recorded on an Agilent 7890A GC system using a HP-5MS column (30 m, i.d. 0.25 mm, film thickness 0.25 μm) and 5975C MS system (EI, 70 eV). GC heat program: $100_5 \rightarrow 250_5$, heating rate 5 °C min^{-1}. The retention time (t_R) and selected fragment ions as their mass/charge ratio (*m*/*z*) are reported. HRMS (ESI) were recorded on a Thermo-Finnigan LTQ-FT ICR hybrid mass spectrometer. All moisture sensitive reactions were performed under a dry N_2 or argon atmosphere in oven-dried or flame-dried glassware. Anhyd THF and CH_2Cl_2 were pre-dried over activated alumina under argon. Benzene was distilled from Na/benzophenone ketyl prior to use. TLC was performed on pre-coated silica plates (Merck $60GF_{254}$) and compounds were visualised at 254 nm and 365 nm or stained with 20% w/v phosphomolybdic acid in EtOH. Flash column chromatography (silica gel, Kieselgel 60, 230–400 mesh) was performed using the indicated solvent system; PE = petroleum ether. Melting points were measured using a Bausch and Lomb hot-stage melting point apparatus and are uncorrected.

2,3-Bis(hydroxymethyl)-1,4-dimethoxybenzene (10)

To a soln of 4,7-dimethoxyphthalide[12] (**9**, 460 mg, 2.37 mmol) in THF (20 mL) at 0 °C was added $LiAlH_4$ (200 mg, 5.27 mmol) in portions over 10 min. Stirring was continued at 0 °C for a further 90 min at which time the reaction was quenched by the dropwise addition of sat. NH_4Cl (20 mL). The resultant suspension was diluted with $CHCl_3$ (15 mL) and filtered through Celite and the filter cake was washed with $CHCl_3$ (10 mL); the filtrate was further extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give **10** (436 mg, 93%) as a white crystalline solid; mp 139–140 °C [Lit.[13] 145 °C (toluene–MeOH)]. ^1H and ^{13}C NMR data are in agreement with the literature.[13]

IR (neat): 3311, 2932, 1488, 1440, 1265, 1232, 1088, 987 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.75 (br s, 2 H), 3.82 (s, 6 H), 4.83 (s, 4 H), 6.84 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 56.2, 56.5, 111.1, 129.5, 151.9.

GC-MS: *m*/*z* (%) = 198.1 (M^+, 49), 180.1 (100), 165.1 (47), 151.1 (47), 137.1 (40), 121.1 (36), 107.1 (20), 91.1 (29), 77.1 (33); t_R = 22.51 min.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{14}NaO_4$: 221.0784; found: 221.0785.

Ethyl (*E*)-3-[2-(Hydroxymethyl)-3,6-dimethoxybenzyloxy]acrylate (11) and Diethyl (2*E*,2′*E*)-3,3′-(3,6-Dimethoxy-1,2-phenylene)bis(methylene)bis(oxy)diacrylate (12)

To a suspension of **10** (400 mg, 2.02 mmol) in CH_2Cl_2 (10 mL) was added NMM (225 mg, 2.22 mmol) followed by the addition of ethyl propiolate (225 μL, 2.22 mmol) over 20 min and stirring was continued for a further 90 min. The soln was diluted 0.5 M HCl and extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography (gradient elution, EtOAc–PE, 1:1 to 4:1) gave, in order of elution, **12** (60 mg, 8%), **11** (480 mg, 80%), and starting diol **10** (40 mg, 10%).

Monoacrylate 11

Colourless solid.

IR (neat): 3451, 2941, 1701, 1619, 1484, 1258, 1124, 1091, 1008 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3 H), 2.37 (t, *J* = 6.7 Hz, 1 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.72 (d, *J* = 6.7 Hz, 2 H), 5.10 (s, 2 H), 5.36 (d, *J* = 12.7 Hz, 1 H), 6.85 (d, *J* = 9.0 Hz, 1 H), 6.91 (d, *J* = 9.0 Hz, 1 H), 7.67 (d, *J* = 12.7 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4, 56.1, 56.3, 57.1, 59.7, 63.9, 97.3, 111.1, 112.4, 123.1, 130.5, 152.1, 152.2, 162.2, 167.8.

GC-MS: *m*/*z* (%) = 296.1 (M$^+$, 3), 181.1 (100), 180.1 (58), 165.1 (28), 151.0 (34); t_R = 33.50 min.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}NaO_6$: 319.1152; found: 319.1153.

Diacrylate 12

Colourless solid.

IR (neat): 2997, 1702, 1629, 1488, 1263, 1231, 1185, 1136, 1095, 1042 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 6 H), 3.82 (s, 6 H), 4.16 (q, *J* = 7.1 Hz, 4 H), 5.03 (s, 4 H), 5.33 (d, *J* = 12.4 Hz, 2 H), 6.93 (s, 2 H), 7.66 (d, *J* = 12.4 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4, 56.3, 59.7, 63.9, 97.2, 112.9, 124.5, 152.3, 162.3, 167.8.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{26}NaO_8$: 417.1520; found: 417.1521.

Ethyl (*E*)-3-(2-Formyl-3,6-dimethoxybenzyloxy)acrylate (7)

To a soln of **11** (450 mg, 1.52 mmol) in CH_2Cl_2 (10 mL) was added $PhI(OAc)_2$ (587 mg, 1.82 mmol) and TEMPO (24 mg, 0.15 mmol) and the mixture was stirred at r.t. for 5 h. After removal of the solvent in vacuo the remaining residue was purified by column chromatography (EtOAc–PE, 1:2) to give **7** (350 mg, 78%) as a colourless crystalline solid; mp 96–97 °C.

IR (neat): 2982, 1709, 1682, 1618, 1483, 1271, 1130, 1006 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3 H), 3.82 (s, 3 H), 3.87 (s, 3 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 5.29 (s, 2 H), 5.29 (d, *J* = 12.7 Hz, 1 H), 7.02 (d, *J* = 9.1 Hz, 1 H), 7.13 (d, *J* = 9.1 Hz, 1 H), 7.69 (d, *J* = 12.7 Hz, 1 H), 10.55 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 56.3, 56.7, 59.6, 63.0, 96.7, 113.6, 117.9, 124.0, 124.4, 152.3, 156.9, 162.9, 168.0, 191.9.

GC-MS: *m*/*z* (%) = 294.1 (M$^+$, 3), 179.1 (100); t_R = 33.17 min.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{18}NaO_6$: 317.0996; found: 317.0996.

Ethyl 2-[(3*S,4*R**)-4-Hydroxy-5,8-dimethoxyisochroman-3-yl]acetate (13) and (3a*R**,9b*R**)-6,9-Dimethoxy-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*]isochromen-2-one (5)**

A soln of **7** (100 mg, 0.34 mmol), Bu_3SnH (148 mg, 0.51 mmol), and AIBN (6 mg, 0.037 mmol) in benzene (20 mL) was flushed with argon for 1 h after which the soln was heated at reflux for 5 h during which further portions of AIBN (6 mg) were added after 1 h and 2 h of heating. After cooling and removal of the solvent in vacuo the remaining residue was purified by column chromatography (gradient elution, EtOAc–PE, 1:2 to 1:1) to give, in order of elution, **13** (46 mg, 46%), **5** (11 mg, 13%), and reduction product **11** (15 mg, 15%).

***trans*-Product 13**

Colourless oil.

IR (neat): 3461, 2927, 1735, 1486, 1257, 1164, 1055, 1026 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H), 2.60 (dd, *J* = 15.4, 9.0 Hz, 1 H), 2.95 (dd, *J* = 15.4, 3.4 Hz, 1 H), 3.75 (s, 3 H), 3.84 (s, 3 H), 4.00 (m, 1 H), 4.19 (m, 2 H), 4.62 (d, *J* = 16.0 Hz, 1 H), 4.72 (d, *J* = 8.3 Hz, 1 H), 4.82 (d, *J* = 16.0 Hz, 1 H), 6.68 (d, *J* = 8.8 Hz, 1 H), 6.72 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 38.1, 55.5, 55.7, 60.5, 64.2, 66.2, 75.3, 108.6, 108.8, 125.4, 125.5, 149.3, 151.6, 171.3.

GC-MS: *m*/*z* (%) = 296.1 (M$^+$, 9), 278.1 (86), 250.1 (54), 206.1 (29), 205.1 (100), 191.1 (46), 180.1 (31), 179.1 (46), 165.1 (44), 91.1 (23); t_R = 32.35 min.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}NaO_6$: 319.1152; found: 319.1149.

***cis*-Lactone 5**

Colourless solid; mp 162–165 °C.

IR (neat): 2923, 1770, 1489, 1263, 1153, 1092, 1070, 1056, 964 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.72 (d, *J* = 17.5 Hz, 1 H), 2.90 (dd, *J* = 17.5, 4.9 Hz, 1 H), 3.79 (s, 3 H), 3.85 (s, 3 H), 4.34 (dd, *J* = 4.9, 2.8 Hz, 1 H), 4.47 (d, *J* = 16.1 Hz, 1 H), 4.98 (d, *J* = 16.1 Hz, 1 H), 5.33 (d, *J* = 2.8 Hz, 1 H), 6.78 (d, *J* = 8.9 Hz, 1 H), 6.84 (d, *J* = 8.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.6, 55.7, 56.1, 62.7, 71.8, 72.6, 109.0, 111.2, 117.7, 125.7, 148.8, 152.8, 175.1.

GC-MS: *m*/*z* (%) = 250.1 (M$^+$, 100), 191.1 (21), 175.1 (20); t_R = 31.51 min.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}O_5$: 251.0914; found: 251.0913.

(3a*R,9b*R**)-6,9-Dimethoxy-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*]isochromen-2-one (5)**

From Ester 13: A soln of **13** (9 mg, 0.03 mmol), K_2CO_3 (60 mg), and 18-crown-6 (1.8 mg, 6.8 μmol) in DMF (0.5 mL) was heated at 100 °C for 12 h. H_2O (5 mL) was added and the mixture extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with H_2O (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography (gradient elution, EtOAc–PE, 1:2 to 1:1) gave **5** (5 mg, 66%) identical to the material described above.

2-(2,5-Dimethoxyphenyl)-1,3-dioxane (16)

To 2,5-dimethoxybenzaldehyde (**15**, 1.0 g, 6.00 mmol) in propane-1,3-diol (1.75 mL, 24.1 mol) was added trimethyl orthoformate (0.75 mL, 6.86 mmol) and Bu_4NBr_3 (26 mg, 0.05 mmol). The mixture was stirred for 45 min at r.t. and then the reaction was quenched with sat. $NaHCO_3$ (5 mL) and H_2O (20 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic fractions

were washed sequentially with 10% $NaHCO_3$ (20 mL) and H_2O (3 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo to give **16** (1.35 g, 100%) as a colourless oil, which was used without further purification.

IR (neat): 2955, 1501, 1277, 1214, 1147, 1091, 1044, 992 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.43 (m, 1 H), 2.25 (m, 1 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 4.01 (m, 2 H), 4.25 (m, 2 H), 5.85 (s, 1 H), 6.81 (d, *J* = 8.9 Hz, 1 H), 6.85 (dd, *J* = 8.9, 3.1 Hz, 1 H), 7.20 (d, *J* = 3.1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.9, 55.8, 56.4, 67.6, 96.8, 111.9, 112.3, 115.9, 127.7, 150.6, 153.9.

GC-MS: *m*/*z* (%) = 224.2 (M^+, 100), 223.2 (29), 193.1 (37), 166.1 (62), 165.1 (54), 151.1 (32), 138.1 (38), 123.1 (25), 87.1 (40); t_R = 22.37 min.

1-[2-(1,3-Dioxan-2-yl)-3,6-dimethoxyphenyl]butan-1-ol (17) and 1-[4-(1,3-Dioxan-2-yl)-2,5-dimethoxyphenyl]butan-1-ol

To a soln of **16** (1.35 g, 6.02 mmol) in Et_2O (8 mL) and hexane (25 mL) maintained at 0 °C was added 2.2 M BuLi in hexane (5.5 mL, 12.1 mmol). The mixture was stirred for a further 1.5 h after which butyraldehyde (1.2 mL, 13.3 mmol) was added dropwise and stirring was continued at 0 °C for a further 30 min and then at r.t. for 1 h. H_2O (30 mL) and sat. NH_4Cl (20 mL) were added and the mixture extracted with EtOAc (2 × 10 mL). The aqueous layer was further acidified with 2 M HCl and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo and the residual oil was purified by column chromatography (gradient elution, EtOAc–PE, 1:2 to 1:1) to give, in order of elution, recovered **16** (460 mg, 34%), 1-[4-(1,3-dioxan-2-yl)-2,5-dimethoxyphenyl]butan-1-ol (165 mg, 9%, 14% based on recovered **16**), and **17** (755 mg, 42%, 64% based on recovered **16**).

***ortho*-Isomer 17**

Colourless solid mp 66–67 °C.

IR (neat): 3557, 2956, 1483, 1464, 1403, 1254, 1228, 1079, 988 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.2 Hz, 3 H), 1.39 (m, 1 H), 1.50 (m, 1 H), 1.68 (m, 2 H), 1.95 (m, 1 H), 2.25 (m, 1 H), 3.75 (s, 3 H), 3.81 (s, 3 H), 3.93 (m, 2 H), 4.19 (dd, *J* = 11.3, 5.0 Hz, 1 H), 4.25 (dd, *J* = 11.5, 4.9 Hz, 1 H), 5.77 (dd, *J* = 10.0, 2.4 Hz, 1 H), 6.18 (s, 1 H), 6.71 (d, *J* = 9.1 Hz, 1 H), 6.84 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 19.7, 25.8, 38.9, 55.6, 56.3, 67.7, 70.4, 97.4, 109.9, 112.6, 124.7, 134.3, 151.1, 152.6.

GC-MS: *m*/*z* (%) = 296.1 (M^+, 2), 221.1 (27), 220.2 (75), 205.1 (100), 191.1 (62); t_R = 29.76 min.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{24}NaO_5$: 319.1516; found: 319.1516.

1-[4-(1,3-Dioxan-2-yl)-2,5-dimethoxyphenyl]butan-1-ol

Colourless oil.

IR (neat): 3405, 2957, 1464, 1403, 1204, 1092, 1040 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.4 Hz, 3 H), 1.33 (m, 1 H), 1.44 (m, 2 H), 1.70 (m, 2 H), 2.25 (m, 1 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 4.01 (m, 2 H), 4.25 (m, 2 H), 4.87 (m, 1 H), 5.85 (s, 1 H), 6.89 (s, 1 H), 7.15 (s, 1 H).

GC-MS: *m*/*z* (%) = 296.1 (M^+, 29), 278.1 (26), 253.2 (100), 195.0 (20), 87.0 (47); t_R = 31.20 min.

Ethyl (*E*)-3-{1-[2-(1,3-Dioxan-2-yl)-3,6-dimethoxyphenyl]butoxy}acrylate (18)

To a soln of **17** (850 mg, 2.87 mmol) in CH_2Cl_2 (15 mL) was added NMM (345 μL, 3.15 mmol) followed by ethyl propiolate (321 μL, 3.15 mmol). Further portions of NMM (345 μL) and ethyl propiolate (321 μL) were added after 2 h and 5 h and stirring was continued for 22 h. The soln was diluted with brine (20 mL) and extracted with $CHCl_3$ (4 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography (gradient elution, EtOAc–PE, 1:3 to 1:1) gave, in order of elution, **18** (320 mg, 28%, 75% based on recovered **17**) and starting alcohol **17** (530 mg, 62%); colourless plates; mp 125–126 °C (CH_2Cl_2–hexane).

IR (neat): 2924, 1703, 1636, 1260, 1121, 1099, 1081, 1065, 986 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H), 1.37 (m, 1 H), 1.46 (m, 1 H), 1.57 (m, 1 H), 1.76 (m, 1 H), 2.27 (m, 1 H), 2.36 (m, 1 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 3.98 (m, 2 H), 4.08 (m, 2 H), 4.22 (dd, *J* = 11.2, 5.1 Hz, 1 H), 4.33 (dd, *J* = 11.4, 5.0 Hz, 1 H), 5.33 (d, *J* = 12.2 Hz, 1 H), 6.21 (m, 1 H), 6.23 (s, 1 H), 6.79 (d, *J* = 9.0 Hz, 1 H), 6.89 (d, *J* = 9.0 Hz, 1 H), 7.89 (d, *J* = 12.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 14.3, 19.7, 26.0, 35.5, 56.3, 57.0, 59.2, 67.7, 67.8, 81.5, 96.7, 97.3, 111.7, 115.1, 125.7, 130.0, 150.8, 153.5, 164.4, 168.6.

GC-MS: *m*/*z* (%) = 394.2 (M^+, 2), 279.1 (31), 221.1 (75), 205.1 (80), 203.1 (100), 191.1 (31); t_R = 37.47 min.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{30}NaO_7$: 417.1884; found: 417.1883.

Ethyl (*E*)-3-[1-(2-Formyl-3,6-dimethoxyphenyl)butoxy]acrylate (8)

To a soln of **18** (320 mg, 0.81 mmol) in acetone (5 mL) at 0 °C was added 2 M HCl (0.5 mL). The soln was allowed to warm to r.t. and stirred for 16 h. The soln was diluted with 5% $NaHCO_3$ (5 mL) and extracted with $CHCl_3$ (4 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography (EtOAc–PE, 1:3) gave **8** (246 mg, 90%) as a colourless oil.

IR (neat): 2961, 1704, 1638, 1620, 1477, 1258, 1189, 1123, 1048, 951 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.5 Hz, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.33 (m, 1 H), 1.50 (m, 1 H), 1.78 (m, 1 H), 2.12 (m, 1 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 4.07 (m, 2 H), 5.12 (d, *J* = 12.6 Hz, 1 H), 5.68 (dd, *J* = 8.8, 4.9 Hz, 1 H), 6.87 (d, *J* = 9.0 Hz, 1 H), 7.00 (d, *J* = 9.0 Hz, 1 H), 7.42 (d, *J* = 12.6 Hz, 1 H), 10.47 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6, 14.3, 19.2, 37.4, 56.2, 56.5, 59.6, 78.3, 97.8, 111.9, 116.2, 125.8, 129.6, 151.0, 154.2, 161.6, 167.9, 193.6.

GC-MS: *m*/*z* (%) = 336.2 (M^+, 1), 221.1 (100), 191.1 (33), 179.1 (26); t_R = 33.55 min.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}NaO_6$: 359.1465; found: 359.1465.

(3a*R,5*S**,9b*R**)-6,9-Dimethoxy-5-propyl-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*]isochromen-2-one (19)**

A soln of **8** (85 mg, 0.25 mmol), Bu_3SnH (92 mg, 0.32 mmol), and AIBN (4 mg, 0.02 mmol) in benzene (16 mL) was flushed with argon for 1 h after which the soln was heated at reflux for 3 h. After cooling and removal of the solvent in vacuo the remaining residue was purified by column chromatography (EtOAc–PE, 1:3) to give, in order of elution, a mixture of *trans*-epimers **20** (22 mg, 26%) as a colourless oil and the *cis*-lactone **19** (49 mg, 66%).

***cis*-Lactone 19**

Colourless solid, mp 102–103 °C (CH_2Cl_2–hexane).

IR (neat): 2952, 1765, 1484, 1266, 1256, 1248, 1164, 1082, 976, 910 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.5 Hz, 3 H), 1.27 (m, 2 H), 1.96 (m, 2 H), 2.70 (d, *J* = 17.1 Hz, 1 H), 2.82 (dd, *J* = 17.1,

4.3 Hz, 1 H), 3.78 (s, 3 H), 3.84 (s, 3 H), 4.26 (dd, *J* = 4.3, 2.3 Hz, 1 H), 4.83 (m, 1 H), 5.33 (d, *J* = 2.3 Hz, 1 H), 6.77 (d, *J* = 8.9 Hz, 1 H), 6.86 (d, *J* = 8.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 17.8, 36.3, 38.3, 55.6, 56.1, 70.7, 72.6, 72.8, 108.8, 112.1, 118.4, 129.2, 149.7, 152.8, 175.9.

GC-MS: *m*/*z* (%) = 292.1 (M^+, 10), 249.1 (100), 205.1 (28); t_R = 32.88 min.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}O_5$: 293.1384; found: 293.1383.

(3a*R,5*S**,9b*R**)-5-Propyl-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*]isochromene-2,6,9-trione (4)**

To **19** (19 mg, 65 μmol) in MeCN (0.5 mL) was added CAN (89 mg, 0.16 mmol) in H_2O (0.2 mL). After stirring for 20 min the soln was diluted with H_2O (5 mL) and extracted with $CHCl_3$ (4 × 3 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography (EtOAc–$CHCl_3$, 2:1) gave **4** (12 mg, 71%) as a pale-yellow solid. The ^{1}H and ^{13}C NMR data are in agreement with the literature.[10b]

IR (neat): 2932, 1769, 1655, 1146, 1088, 1044, 907 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.4 Hz, 3 H), 1.26 (m, 1 H), 1.42 (m, 1 H), 1.82 (m, 1 H), 1.94 (m, 1 H), 2.71 (d, *J* = 17.5 Hz, 1 H), 2.86 (dd, *J* = 17.5, 4.6 Hz, 1 H), 4.29 (dd, *J* = 4.6, 2.5 Hz, 1 H), 4.61 (m, 1 H), 5.11 (m, 1 H), 6.80 (d, *J* = 10.2 Hz, 1 H), 6.86 (d, *J* = 10.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 18.1, 35.4, 37.2, 69.3, 70.9, 71.6, 133.4, 136.2, 137.2, 147.6, 174.3, 184.0, 185.8.

GC-MS: *m*/*z* (%) = 264.1 ([M + 2]$^+$, 13), 221.1 (100), 177.1 (91), 175.1 (30); t_R = 34.37 min.

GC-MS: *m*/*z* (%) = 264.1 ([M + 2]$^+$, 7), 262.1 (M^+, 8), 221.1 (57), 220.0 (66), 177.1 (33), 175.1 (100), 161.1 (40); t_R = 29.43 min.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}O_5$: 263.0914; found: 263.0913.

(3a*R,5*R**,9b*R**)-5-Propyl-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*]isochromene-2,6,9-trione (3)**

To **19** (4.0 mg, 13.7 μmol) in CH_2Cl_2 (0.5 mL) at –60 °C was added 1 M BBr_3 in CH_2Cl_2 (70 μL, 70 μmol). The soln was allowed to warm to r.t. then stirred for a further 1 h. H_2O (2 mL) was added and the mixture stirred vigorously for 30 min and extracted with $CHCl_3$ (3 × 3 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residual oil was dissolved in MeCN (0.5 mL), cooled to 0 °C and CAN (19 mg, 0.03 mmol) in H_2O (0.1 mL) was added. After stirring for 5 min the soln was diluted with brine (5 mL) and extracted with $CHCl_3$ (3 × 2 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography (EtOAc–$CHCl_3$ 2:1) gave **3** (2.5 mg, 69%) as a pale yellow solid. The ^{1}H and ^{13}C NMR data were in agreement with the literature.[10b]

IR (neat): 2930, 1781, 1659, 1197, 1150 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.4 Hz, 3 H), 1.63 (m, 4 H), 2.68 (d, *J* = 17.7 Hz, 1 H), 2.92 (dd, *J* = 17.7, 5.3 Hz, 1 H), 4.57 (dd, *J* = 5.3, 3.0 Hz, 1 H), 4.75 (m, 1 H), 5.09 (d, *J* = 3.0 Hz, 1 H), 6.81 (d, *J* = 10.3 Hz, 1 H), 6.86 (d, *J* = 10.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.5, 19.4, 33.6, 36.8, 66.2, 68.4, 69.6, 132.2, 136.5, 136.6, 146.9, 173.9, 184.3, 185.2.

GC-MS: *m*/*z* (%) = 264.1 ([M + 2]$^+$, 14), 221.1 (100), 177.1 (75), 175.1 (27); t_R = 35.09 min.

GC-MS: *m*/*z* (%) = 264.1 ([M + 2]$^+$, 13), 262.1 (M^+, 7), 221.1 (100), 220.0 (33), 177.1 (95), 175.1 (65); t_R = 30.51 min.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}O_5$: 263.0914; found: 263.0914.

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