Experimental Procedures

General details
All reactions were carried out in flame or oven-dried glassware under a dry nitrogen atmosphere. Tetrahydrofuran and diethyl ether were dried over sodium wire and dichloromethane was dried over calcium hydride. All solvents were distilled prior to use. Flash chromatography was carried out using 0.063-0.1 mm silica gel with the desired solvent. Thin layer chromatography (TLC) was performed using 0.2 mm Kieselgel F254 (Merck) silica plates and compounds were visualised using UV irradiation at 365 nM and/or staining with: vanillin in methanolic sulfuric acid, a solution of ammonium heptamolybdate and cerium sulphate in aqueous sulfuric acid or a solution of potassium permanganate and potassium carbonate in aqueous sodium hydroxide. Preparatory TLC was carried out on 500 μm Uniplate™ (Analtech) silica gel (20 x 20 cm) thin layer chromatography plates. Infrared spectra were obtained as indicated using a Perkin-Elmer Spectrum 1000 series Fourier Transform IR (FTIR) spectrometer as a thin film between sodium chloride plates or Perkin-Elmer Spectrum One FTIR spectrometer on a diamond ATR sampling accessory. Absorption maxima are expressed in wave numbers (cm⁻¹). Optical rotations were measured using a Perkin-Elmer 341 polarimeter at λ = 598 nm and are given in 10⁻¹ deg cm² g⁻¹.

Zoe E. Wilson and Margaret A. Brimble

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Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded as indicated on either the Bruker Avance 300 spectrometer operating at 300 MHz for \(^1\)H nuclei and 75 MHz for \(^{13}\)C nuclei or using the Bruker DRX-400 spectrometer operating at 400 MHz for \(^1\)H nuclei, 100 MHz for \(^{13}\)C nuclei and 162 MHz for \(^{31}\)P nuclei. All chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (\(^1\)H) or CDCl\(_3\) (\(^1\)H and \(^{13}\)C). \(^1\)H NMR data is reported as chemical shift, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; dd, doublet of doublets, coupling constant (J Hz) and assignment. Assignments were made with the aid of DEPT 135, COSY, NOESY and HSQC experiments where required. High resolution mass spectra were recorded on a VG-70SE at a nominal accelerating voltage of 70 eV.

**Synthesis of \(N\)-methoxy-\(N\)-methylhexamide, 10**

Oxalyl chloride (12.2 mL, 143.4 mmol) was added to a stirred solution of hexanoic acid (3.00 mL, 23.9 mmol) in dichloromethane (50 mL). DMF (2 drops) was added resulting in vigorous gaseous evolution for 30 minutes after which the reaction mixture was stirred at rt for a further 30 min then the solvent and residual oxalyl chloride were removed \textit{in vacuo}. Chloroform (200 mL) and the hydrochloric acid salt of \(N, O\)-dimethylhydroxylamine (5.13 g, 52.6 mmol) were added to the crude yellow oil before cooling to 0 °C. Pyridine (4.33 mL, 52.6 mmol) was added and the reaction mixture warmed to rt for 1 h then the solvent was removed \textit{in vacuo}. Saturated sodium chloride (50 mL), diethyl ether (25 mL) and dichloromethane (25 mL) were added and the layers separated. The aqueous layer was extracted with dichloromethane (3 x 50 mL) then diethyl ether (2 x 50 mL) and the combined organic extracts were dried over magnesium sulfate and the solvent removed \textit{in vacuo}. Purification via flash chromatography eluting with hexanes-ethyl acetate (4:1, \(R_f = 0.17\)) gave the \textit{title compound} 10 (3.78 g, 99%) as a colourless oil.

**Synthesis of benzyl 4-(benzyloxy)butanoate, 14**

A mixture of \(\gamma\)-butyrolactone (2.29 mL, 30.0 mmol), benzyl bromide (17.4 mL, 147.0 mmol) and potassium hydroxide (5.89 g, 105.0 mmol) in toluene (60 mL) was heated to reflux under Dean-Stark conditions for 50 h. The reaction mixture was cooled to rt, water (50 mL) was added and the reaction mixture extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated sodium bicarbonate (50 mL) and saturated sodium chloride (50 mL) before drying over magnesium sulfate and concentration \textit{in vacuo}. The resultant crude oil was purified \textit{via} flash chromatography using hexanes-ethyl acetate as eluent (19:1, \(R_f = 0.17\)) to afford the \textit{title compound} 14 (7.14 g, 88%) as a pale yellow oil; \(v_{\text{max}}\) (diamond/cm\(^{-1}\)) 3032 (C-H Ar str.), 2932 (C-H str.), 2859 (C-H (CH\(_2\)O) str.), 1732 (C=O str.), 1495, 1454, 1162 (C-O str.), 1083; \(\delta_{\text{H}}\) (300 MHz, CDCl\(_3\)) 1.23-1.30 (4H, m, CH\(_2\)CH\(_2\)CH\(_2\)), 1.53-1.63 (2H, m, CH\(_2\)CH\(_2\)CO), 2.36 (2H, t, \(J = 7.6\) Hz, CH\(_2\)CO), 3.12 (3H, s, NCH\(_3\)), 3.63 (3H, s, OCH\(_3\)). The \(^1\)H NMR data obtained was in agreement with that reported in the literature.\(^1\)

\(^1\)H NMR data obtained was in agreement with that reported in the literature.\(^1\)
Synthesis of dimethyl 5-(benzyloxy)-2-oxopentylphosphonate, 5

\[
\text{BrO} \quad \supseteq \quad \text{P} \quad \supseteq \quad \text{O}
\]

n-Butyllithium (3.47 mL, 1.6 M in hexane, 5.6 mmol) was added dropwise to a solution of dimethyl methylphosphonate (0.60 mL, 5.6 mmol) in THF (20 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 30 min before addition of 14 (0.5 g, 1.9 mmol). After 1 h at -78 °C saturated ammonium chloride (20 mL) was added and the reaction mixture warmed to rt then extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with water (20 mL), saturated sodium chloride (20 mL), dried over magnesium sulfate and concentrated in vacuo. The resulting oil was purified via flash chromatography using ethyl acetate as eluent (RF = 0.18) to afford the title compound 5 (0.49 g, 88%) as a colourless oil; \(\nu_{\text{max}}\) (NaCl/cm\(^{-1}\)) 3029 (ArCH str.), 2956 (CH str.), 2856 (CH str.), 1715 (C=O str.), 1454 (Ar C-C str.), 1253 (P=O str.), 1096 (C-O-C str.), 1029 (P-O str.), \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 1.90 (2H, q, \(J = 6.6\) Hz, CH\(_2\CH_2\)), 2.72 (2H, t, \(J = 7.1\) Hz, COCH\(_2\CH_2\)), 3.08 (2H, d, \(J = 22.6\) Hz, POCH\(_2\CO\)), 3.48 (2H, t, \(J = 6.1\) Hz, CH\(_2\)OBn), 4.46 (2H, s, CH\(_2\)C\(_6\)H\(_5\)), 7.36-7.23 (5H, m, C\(_6\)H\(_5\)); \(\delta_{\text{C}}\) (100 MHz; CDCl\(_3\)) 23.5 (CH\(_2\), CH\(_2\)C\(_6\)H\(_5\)CH\(_2\)), 40.6 (CH\(_2\), COCH\(_2\)CH\(_3\)), 41.1 (CH\(_2\), \(J = 127.5\) Hz, POCH\(_2\)CO), 52.7, 52.8 (2 x CH\(_3\), 2 x OC\(_3\)H\(_3\)), 68.8 (CH\(_2\), CH\(_2\)OBn), 72.6 (CH\(_2\), CH\(_2\)C\(_6\)H\(_5\)), 127.3, 127.4, 128.1 (5 x ArCH, Bn), 138.1 (quat., from BnO), 201.4 (quat., \(J = 6.1\) Hz, C=O); \(\delta_{\text{p}}\) (162 MHz) 22.760; \(m/z\) (FAB+, %) 301 (MH\(^+\), 2), 282 (3), 209 (5), 194 (30), 191 (25), 179 (10), 166 (100, MH\(^+\)-C\(_9\)H\(_{11}\)O), 151 (50), 124 (50), 109 (26), 94 (10), 91 (100, C\(_7\)H\(_7\)), 81 (17), 65 (16); Found MH\(^+\), 301.12049. C\(_{14}\)H\(_{22}\)O\(_5\)P requires 301.12049.

Synthesis of methyl 2,4-dihydroxy-6-methylbenzoate (methyl orsellinate), 8

8 was synthesized according to the procedure of Chiarello and Joullié. Methyl acetoacetate (18.6 mL, 0.17 mol) was added dropwise over 15 min to a suspension of sodium hydride (10.3 g, 60% in paraffin, 0.24 mol) in THF (100 mL) at 0 °C. The reaction mixture was cooled to -78 °C and n-butyllithium (100 mL, 1.6 M in hexane, 0.16 mol) added dropwise over 15 min. The reaction mixture was warmed to rt for 17 h, heated at reflux for a further 24 h before cooling to 0 °C and acidifying to pH 1 using concentrated hydrochloric acid (30 mL, 36%). After 2 h at rt, water (50 mL) was added and the mixture extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate and the solvent removed in vacuo to afford a brown oil which was purified via flash chromatography using hexanes-ethyl acetate as eluent (3:1, \(R_F = 0.38\)) to afford the title compound 8 (11.36 g, 72%) as a pale yellow solid, m.p. = 137-138.5 °C (lit 136-138 °C\(^2\)). \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 2.49 (3H, s, CH\(_3\)), 3.92 (3H, s, OCH\(_3\)), 5.41 (1H, br. s, C\(_4\)O\(_\text{H}\)), 6.23 (1H, d, \(J = 2.5\) Hz, C\(_3\)H\(_2\)), 6.28 (1H, d, \(J = 2.5\) Hz, C\(_5\)H\(_2\)), 11.74 (1H, s, 1H, s, C\(_2\)O\(_\text{H}\)). The \(^1\)H NMR data obtained was in agreement with that reported in the literature.\(^2\)
**Synthesis of methyl 2,4-dibenzyloxy-6-methylbenzoate, 15**

\[
\text{BnO} \quad \text{O} \\
\text{O} \quad \text{Bn}
\]

A solution of benzyl bromide (3.26 mL, 27.4 mmol), 8 (2.00 g, 10.8 mmol) and potassium carbonate (6.00 g, 43.2 mmol) in acetone (50 mL) was heated to reflux for 17 h. The solvent was removed in vacuo and water (50 mL) added. The resulting mixture was extracted with diethyl ether (3 x 70 mL), the combined organic layers dried over magnesium sulfate and the solvent removed in vacuo. The crude oil was purified via flash chromatography using hexanes-ethyl acetate as eluent (4:1, R_f = 0.41) to afford the title compound 15 (3.78 g, 96%) as a pale yellow solid, m.p. = 66 - 67.5 °C (lit 67-68 °C). δH (400 MHz, CDCl3) 2.32 (3H, s, CH₃), 3.89 (3H, s, OCH₃), 5.03, 5.07 (2 x 2H, s, 2 x CH₂C₆H₅), 6.45 (2H, s, 2 x ArH), 7.20-7.42 (10H, m, C₆H₅CH₂). The ¹H NMR data obtained was in agreement with that reported in the literature.

**Synthesis of 2,4-bis(benzyloxy)-N,N-diethyl-6-methylbenzamide, 9**

\[
\text{BnO} \quad \text{N} \\
\text{O} \quad \text{N} \\
\text{O}
\]

A solution of trimethylaluminium (9.3 mL, 2.0 M in hexanes, 18.6 mmol) in toluene (20 mL) was cooled to -6 °C, diethylamine (1.9 mL, 18.7 mmol) added, and the reaction mixture stirred for 10 min at -6 °C before warming to rt for 25 min. A solution of 15 (1.68 g, 4.6 mmol) in toluene (6 mL) was added and the resulting reaction mixture heated to reflux for 16 h before cooling to 0 °C and addition of aqueous hydrochloric acid (20 mL, 10%). The layers were separated and the organic layer was washed with aqueous hydrochloric acid (40 mL, 10%). The combined aqueous layers were extracted with ethyl acetate (2 x 60 mL), the combined organic layers were dried over magnesium sulfate and the solvent was removed in vacuo. The resultant crude oil was purified via flash chromatography utilizing hexane-ethyl acetate as eluent (3:2, R_f = 0.32) to afford the title compound 9 (1.75 g, 94%) as a pale yellow solid, m.p. = 83.8 - 84.0 °C. \(\nu_{\text{max}}\) (NaCl/cm⁻¹) 2973 (C-H str.), 2934, 1602 (C=O str.), 1151, 733, 696; δH (400 MHz, CDCl₃) 1.01 (3H, t, \(J = 7.1\) Hz, CH₃CH₂), 1.19 (3H, t, \(J = 7.1\) Hz, CH₂CH₃), 2.27 (3H, s, CH₃), 3.10 – 3.24 (2H, m, CH₂CH₃), 3.49 (1H, qd, \(J = 14.2, 7.1\) Hz, CHHCH₃), 3.66 (1H, qd, \(J = 14.2, 7.1\) Hz, CHHCH₃), 4.98-5.05 (4H, m, 2 x CH₂C₆H₅), 6.47 (2H, s, 2 x ArH), 7.26-7.44 (10H, m, 2 x C₆H₅), δC (100 MHz; CDCl₃) 12.5, 13.8 (2 x CH₃, 2 x CH₂CH₃), 19.0 (CH₃, ArCH₃), 38.5, 42.4 (2 x CH₂, 2 x CH₂CH₃), 69.8, 69.9 (2 x CH₂, 2 x CH₂C₆H₅), 97.9 (CH, C₃), 107.8 (CH, C₅), 119.9 (quat., C₁), 126.8, 127.3, 127.5, 127.8, 128.1, 128.4 (10 x CH, from 2 x OBn), 136.5 (quat., from 2 x OBn), 136.6 (quat., C₆), 155.4 (quat., C₂), 159.3 (quat., C₄), 168.1 (quat., C=O); \(m/z\) (EI+, %) 403 (M+, 24), 331 (22), 241 (8), 181 (9), 151 (5), 100 (4), 91 (C₆H₅CH₂, 100), 72 (N(CH₂CH₃)₂), 12, 65 (9), 58 (4), 39 (4); Found M+, 403.21487. C₂₆H₃₉NO₃ requires 403.21474.
tert-Butyllithium (3.00 mL, 1.5 M in pentane, 4.5 mmol) and \(N,N\)-tetramethylenediamine (0.75 mL, 4.46 mmol) were added dropwise simultaneously to a stirred solution of 9 (1.5 g, 3.72 mmol) in THF (60 mL) at -78 °C and the mixture stirred for 15 min. 10 (1.24 g, 7.81 mmol) was then added dropwise and the resultant mixture stirred at -78 °C for 1 h. Aqueous hydrochloric acid (60 mL, 10%) was added and the reaction mixture allowed to warm to rt. Ethyl acetate (50 mL) was added, the layers separated and the aqueous layer extracted with dichloromethane (3 x 60 mL). The combined organic extracts were dried over magnesium sulfate and the solvent removed \textit{in vacuo}. The resulting crude oil was purified via flash chromatography using hexanes-ethyl acetate as eluent (4:1, \(R_F = 0.09\)) to afford the title compound 11 (1.70 g, 91%) as a viscous colourless oil. \(v_{\text{max}}\) (diamond/cm\(^{-1}\)) 2931 (C-H str.), 1713 (C=O str. ketone), 1602 (C=O str. amide), 1432, 1154, 698; \(\delta_H\) (400 MHz, CDCl\(_3\)) 0.87 (3H, t, \(J = 7.0\) Hz, CH\(_2\)CH\(_2\)CH\(_3\)), 0.97 (3H, t, \(J = 7.1\) Hz, CH\(_2\)CH\(_2\)N), 1.11 (3H, t, \(J = 7.1\) Hz, CH\(_2\)CH\(_2\)N), 1.19-1.33 (4H, m, CH\(_2\)CH\(_2\)CH\(_3\)), 1.54 (2H, quint., \(J = 7.4\) Hz, COCH\(_2\)CH\(_3\)), 2.46 (2H, t, \(J = 7.4\) Hz, COCH\(_2\)CH\(_3\)), 3.14 (2H, q, \(J = 7.1\) Hz, NCH\(_2\)CH\(_3\)), 3.37-3.45 (1H, m, NCH\(_2\)CH\(_3\)), 3.74-3.55 (3H, m, NCH\(_2\)CH\(_3\) and ArCH\(_2\)), 4.96-5.07 (4H, m, 2 x CH\(_2\)C\(_6\)H\(_5\)), 6.44 (1H, d, \(J = 2.1\) Hz, C3H), 6.52 (1H, d, \(J = 2.1\) Hz, C5H), 7.26-7.41 (10H, m, 2 x C\(_6\)H\(_5\)); \(\delta_C\) (100 MHz; CDCl\(_3\)) 12.5, 13.6 (2 x CH\(_3\)), 13.8 (CH\(_3\)), 22.4 (CH\(_2\)), 23.3 (CH\(_2\)), 31.2 (CH\(_3\)), 38.5 (CH\(_2\)), 42.3, 42.8 (2 x CH\(_2\)), 70.1, 70.2 (2 x CH\(_2\)), 99.2 (CH, C\(_3\)), 108.1 (CH, C\(_5\)), 120.3 (quat., C\(_1\)), 128.50, 128.29, 127.99, 127.76, 127.49, 127.06 (10 x CH, from 2 x OBn), 133.9 (quat., C\(_6\)), 136.3, 136.4 (2 x quat., from 2 x OBn), 155.7 (quat., C\(_2\)), 157.6 (quat., C\(_4\)), 167.7 (quat., CONEt\(_2\)), 208.1 (quat., COC\(_3\)H\(_2\)); \(m/z\) (El+, %) 501 (M+, 9), 429 (6), 388 (14), 256 (5), 122 (13), 105 (41), 91 (C\(_3\)H\(_4\)CH\(_2\), 100), 77 (39), 58 (32), 44 (64); Found M\(^+\), 501.28603. C\(_{32}\)H\(_{39}\)NO\(_4\) requires M\(^+\), 501.28791.
Synthesis of 6,8-bis(benzyloxy)-3-pentyl-1H-isochromen-1-one, 12

A solution of 11 (0.3 g, 0.6 mmol) in acetic acid (3 mL) was heated to 170 °C in a sealed tube for 49 h. Silica (~0.5 g) was added, the acetic acid removed in vacuo, and the resultant pre-loaded silica purified by flash chromatography using hexanes-ethyl acetate as eluent (4:1, Rf = 0.34) to afford the title compound 12 (0.206 g, 80%) as a white solid, m.p. = 83.9 °C.

\[ v_{\text{max}} (\text{diamond/cm}^{-1}) 3061 (\text{=C-H str.}), 2956 (\text{C-H str.}), 2857 (\text{C-H (CH}_2\text{O) str.}), 1708 (\text{C=O str.}), 1596 (\text{C=C-O str.}), 1564, 1166 (\text{C-O str.}), 739, 694; \delta_{\text{H}} (300 \text{ MHz; CDCl}_3) 0.89-0.94 (3H, m, \text{CH}_2\text{CH}_3), 1.32-1.37 (4H, \text{CH}_2\text{CH}_2\text{CH}_3), 1.64-1.74 (2H, m, \text{CH}_2\text{CH}_3), 2.45 (2H, t, J = Hz, \text{COCH}_2\text{CH}_2), 5.08, 5.23 (2 x 2H, s, 2 x \text{CH}_2\text{C}_6\text{H}_5), 6.06 (1H, s, \text{C}_4\text{H}), 6.40 (1H, d, J = 2.1 Hz, \text{C}_7\text{H}), 6.54 (1H, d, J = 2.1 Hz, \text{C}_5\text{H}), 7.26-7.59 (10H, m, 2 x \text{CH}_2\text{C}_6\text{H}_5); \delta_{\text{C}} (75 \text{ MHz; CDCl}_3) 13.9 (\text{CH}_3, \text{CH}_2\text{C}_6\text{H}_3), 22.3 (\text{CH}_2, \text{CH}_2\text{CH}_2\text{CH}_3), 26.4 (\text{CH}_2, \text{COCH}_2\text{CH}_3), 31.1 (\text{CH}_2, \text{CH}_2\text{CH}_2\text{CH}_3), 33.2 (\text{CH}_2, \text{COCH}_2\text{CH}_3), 70.2, 70.4 (2 x \text{CH}_2, 2 x \text{CH}_2\text{C}_6\text{H}_5), 100.3 (\text{CH}, \text{C}_7), 100.8 (\text{CH}, \text{C}_5), 102.8 (\text{CH}, \text{C}_4), 103.6 (\text{quat.}, \text{C}_8\text{a}), 126.5, 127.5, 127.6, 128.3, 128.5, 128.6 (10 \text{ ox C}, \text{from 2 x OBn}), 135.7, 136.2 (2 \text{ ox C}, \text{from 2 x OBn}), 142.3 (\text{quat.}, \text{C}_4\text{a}), 159.2 (\text{quat.}, \text{C}_8), 159.3 (\text{quat.}, \text{CHCOCH}_2), 162.0 (\text{quat.}, \text{C}_6), 164.2 (\text{quat.}, \text{C}=\text{O}); m/z (\text{ESi+}, \%) 429 (\text{MH}^+, 15), 337 (7), 261 (22), 249 (12), 181 (100), 91 (75); Found \text{MH}^+, 429.2063 \text{C}_{28}\text{H}_{29}\text{O}_4 \text{requires} 429.2060.

Synthesis of methyl 2,4-bis(benzyloxy)-6-(2-oxoheptyl)benzoate, 13

A solution of potassium hydroxide (1.00 g, 17.8 mmol) and 12 (0.62 g, 1.4 mmol) in ethanol (20 mL) and water (20 mL) was heated to reflux for 14 h. The solvent was removed in vacuo and the reaction mixture acidified using aqueous hydrochloric acid (~ 5 mL, 10%) before extracting with ethyl acetate (3 x 10 mL). The combined organic layers were dried over magnesium sulfate and the solvent removed in vacuo. The resulting crude oil was dissolved in acetone (40 mL) and anhydrous potassium carbonate (0.774 g, 5.6 mmol) and methyl iodide (0.26 mL, 4.2 mmol) were added. The resulting mixture was heated to reflux for 2 h at which point the warm reaction mixture was filtered through a plug of basic alumina, washed with warm acetone (100 mL) and the solvent removed in vacuo. The resultant crude oil was dry loaded onto basic alumina and purified via flash chromatography, utilizing hexanes-ethyl acetate as eluent (4:1, Rf = 0.47) to afford the title compound 11 (0.583 g, 87%) as a white solid, m.p. = 62.7 – 63.0 °C. 

\[ v_{\text{max}} (\text{diamond/cm}^{-1}) 2931 (\text{C-H str.}), 1707 (\text{C=O str.}), 1601, 1433, 1275, 1164 (\text{C-O str.}), 1029, 733; \delta_{\text{H}} (300 \text{ MHz; CDCl}_3) 0.92 (3H, t, J = 6.9 Hz, \text{CH}_2\text{CH}_3), 1.24-1.36 (4H, m, \text{CH}_2\text{CH}_2\text{CH}_3), 1.54-1.64 (2H, m, \text{COCH}_2\text{CH}_3), 2.46 (2H, t, J = 7.4 Hz, \text{COCH}_3), 3.73 (2H, s, \text{ArCH}_2\text{CO}), 3.85 (3H, s, \text{OCH}_3), 5.04 and 5.07 (2 x 2H, s, 2 x \text{CH}_2\text{C}_6\text{H}_5), 6.46 (1H, d, J = 2.1 Hz, \text{C}_3\text{H}), 6.56 (1H, d, J = 2.1 Hz, \text{C}_5\text{H}), 7.26-7.40 (10H, m, 2 x \text{CH}_2\text{C}_6\text{H}_5); \delta_{\text{C}} (75 \text{ MHz; CDCl}_3) 13.8 (\text{CH}_3, \text{CH}_2\text{CH}_3), 22.3 (\text{CH}_2, \text{CH}_2\text{CH}_3), 23.1 (\text{CH}_2,
COCH₂CH₃), 31.1 (CH₂, CH₂CH₂CH₃), 41.8 (CH₂, COCH₂CH₃), 48.0 (CH₂, ArCH₂CO), 51.8 (CH₃, OCH₃), 70.0, 70.5 (2 x CH₂, 2 x CH₂C₆H₅), 99.8 (CH, C₅), 108.8 (CH, C₃), 116.6 (quat., C₁), 126.8, 127.4, 127.7, 128.0, 128.3, 128.5 (10 x CH, from 2 x CH₂C₆H₅), 135.8, 136.1, 136.4 (3 x quat., C₆ and from 2 x BnO), 158.0 (quat., C₂), 160.6 (quat., C₄), 167.9 (quat., COOCH₃), 207.3 (quat., CH₂OCH₂); 

m/z (ESi+, %) 461 (MH⁺, 2), 429 (82), 337 (9), 261 (100), 181 (8), 91 (12); Found MH⁺, 461.2331 C₂₉H₃₃O₅ requires 461.2323.

Synthesis of (R)-6,8-bis(benzyloxy)-3-pentylisochroman-1-one, 7

METHOD A:

(S)-Me-CBS (0.43 mL, 1 M in THF, 0.43 mmol) was added to a solution of 11 (0.72 g, 1.44 mmol) in THF (22 mL) and the mixture stirred for 15 min at rt before BH₃.DMS (0.15 mL, 1.59 mmol) was added. The reaction mixture was stirred for 15 h at rt then methanol (0.5 mL) in diethyl ether (20 mL) was added followed by saturated sodium bicarbonate (20 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3 x 60 mL). The combined organics were dried over magnesium sulfate and the solvent removed in vacuo. The crude oil was partially purified via flash chromatography using hexanes-ethyl acetate as eluent (3:2) and the two rotameric alcohols (Rf = 0.27 and 0.35) were collected. The two combined rotamers (0.72 g) were heated to 90 °C for 19 h in a solution of anhydrous hydrochloric acid (40 mL, 2 M in dioxane). The reaction mixture was cooled to rt, diethyl ether (30 mL) and saturated sodium bicarbonate (30 mL) added and the layers separated. The organic layer was washed with water (30 mL) and the combined aqueous layers extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulfate and the solvent removed in vacuo to afford a crude oil consisting of the partially deprotected desired product 7. This oil was dissolved in dimethylformamide (20 mL), silver(I) oxide (1.67 g, 7.2 mmol) and benzyl bromide (0.86 mL, 7.2 mmol) were added and the mixture stirred at rt for 6 h. The reaction mixture was filtered through a pad of Celite that was washed with ethyl acetate (50 mL). The filtrate was washed with water (2 x 30 mL) and saturated sodium chloride (30 mL). The combined aqueous layers were extracted with ethyl acetate (3 x 20 mL), and the combined organic layers dried over magnesium sulfate and the solvent removed in vacuo. The resulting oil was purified via flash chromatography using hexane-ethyl acetate as eluent (4:1, Rf = 0.38) to afford the title compound 7 (0.36 g, 57%) as a colourless oil. e.e. = 51% (HPLC, Chiralpak® AD-H, hexanes/isopropanol (13/7), v = 0.5 mL.min⁻¹, λ = 254 nm, t(R) = 29.06 (75.53%), t(S) = 64.82 (24.47%); [α]D²⁰ = +32.6° (c 0.1 in CH₂Cl₂); v_max (diamond/cm⁻¹) 2930 (C-H str.), 1712 (C=O str.), 1600, 1579, 1161 (C-O str.), 733, 695; δH (400 MHz, CDCl₃) 0.89 (3H, t, J = 6.3 Hz, CH₃), 1.22-1.37 (4H, m, CH₂CH₂CH₃), 2.71–2.87 (2H, m, C₄H₂), 5.03 (2H, s, C₆H₅C₆H₅), 5.16 (2H, q, J = 14.0 Hz, CH₂C₆H₅), 5.30 (1H, s, C₇H), 5.40 (1H, s, C₅H), 5.47 (1H, s, C₇H), 7.24-7.39 (8H, m, from 2 x CH₂C₆H₅), 7.53 (2H, d, J = 7.6 Hz, from 2 ArH x CH₂C₆H₅); δC (100 MHz, CDCl₃) 13.9 (CH₃, C₅), 22.4 (CH₂, CHOCH₂CH₂), 24.6 (CH₂, CH₂CH₃), 31.5 (CH₂, CH₂CH₂CH₃), 34.6 (CH₂, CHOC₆H₅), 34.9 (CH₂, C₄), 70.1, 70.4 (2 x CH₂, 2 x CH₂C₆H₅), 77.1 (CH, CH₂CHOCH₂), 100.1 (CH, C₇), 105.1 (CH, C₅), 107.8 (quat., C₈a), 126.5, 127.4, 127.5, 128.2, 128.4, 128.6 (10 x CH, 2 x CH₂C₆H₅), 135.8, 136.3 (2 x quat., from 2 x BnO), 143.9 (quat., C₄a), 161.8 (quat., C₈), 162.4 (quat., C₄).
METOD B:

Freshly prepared\textsuperscript{4} (L)-TarB-\textsubscript{NO\textsubscript{2}} (1.44 mL, 0.5 M in THF) was added to 13 (0.167 g, 0.36 mmol) at rt and the mixture stirred for 10 min. The resulting complex was added to a suspension of sodium borohydride (0.027 g, 0.72 mmol) in THF (0.5 mL) at -78 °C. The reaction mixture was allowed to warm to rt in the dry ice bath for 13.5 h before aqueous hydrochloric acid (5 mL, 10%) was added. After gaseous evolution had ceased, the reaction mixture was basified to pH 12 using aqueous sodium hydroxide (~10 mL, 1 M) before extracting with ethyl acetate (3 x 10 mL). The combined organic layers were dried over magnesium sulfate and the solvent removed \textit{in vacuo}. The resultant crude oil was dissolved in dichloromethane (5 mL), Amberlyst 15\textsuperscript{®} (0.2 g, Aldrich) was added, and the reaction mixture stirred at rt for 2 h. The resin was removed by filtration, washed with dichloromethane (50 mL) and the solvent removed \textit{in vacuo}. The resultant crude oil was purified via flash chromatography utilizing hexanes-ethyl acetate (4:1, \textit{R\textsubscript{F} = 0.38}) as eluent to afford the \textit{title compound} 7 (0.15 g, 97%) as a colourless oil. e.e. = 73% (HPLC, Chiralpak® AD-H, hexanes/isopropanol (13/7), \(\nu = 0.5\) mL.min\(^{-1}\), \(\lambda = 254\) nm, \(t_1(R) = 24.31\) (86.38%), \(t_2(S) = 54.86\) (13.62%)); \([\alpha]_{D}^{22} = +45.5^\circ\) (c 0.2 in CH\(_2\)Cl\(_2\))

Preparatory HPLC separation of desired enantiomer:

7 (0.094 g, 0.22 mmol, 69% e.e. (HPLC)) was split into 4 batches and run on a Chiralpak® AD-H semiprep column (i.d. 10 mm) using hexanes/isopropanol (13/7), \(\nu = 4.7\) mL.min\(^{-1}\), \(\lambda = 254\) nm, \(t_1(R) = 9.0 - 14.0\), \(t_2(S) = 21.5 - 32.0\), to afford 7 ((R), 0.076 g, 0.18 mmol) and \textit{ent}-7 ((S), 0.014 g, 0.03 mmol) (96% recovery of product) which were determined to have e.e.'s of >99% \([\alpha]_{D}^{16.4} = +59.4^\circ\) (c 0.05 in CH\(_2\)Cl\(_2\)) and 90% \([\alpha]_{D}^{19.1} = -61.5^\circ\) (c 0.15 in CH\(_2\)Cl\(_2\)) respectively by analytical chiral HPLC as above.

Synthesis of (S)-6,8-bis(benzyloxy)-3-pentylisochroman-1-one, \textit{ent}-7

\textit{ent}-7 was synthesized in a similar manner to its enantiomer. (D)-TarB \textsubscript{NO\textsubscript{2}}\textsuperscript{4} (1.76 mL, 0.5 M in THF), was added to 13 (0.21 g, 0.44 mmol) and stirred at rt for 10 min. The resulting complex was added to a suspension of sodium borohydride (0.033 g, 0.88 mmol) in THF (0.5 mL) at -78 °C. The reaction mixture was allowed to warm to rt in the dry ice bath over 18 h before work up and Amberlyst 15\textsuperscript{®} catalyzed cyclization as for 7 to afford the \textit{title compound} \textit{ent}-7 (0.145 g, 77%) as a colourless oil. e.e. = 73% (HPLC, Chiralpak® AD-H, hexanes/isopropanol (13/7), \(\nu = 0.5\) mL.min\(^{-1}\), \(\lambda = 254\) nm, \(t_1(R) = 25.28\) (13.51%), \(t_2(S) = 50.07\) (86.49%)); \([\alpha]_{D}^{18} = -37.5^\circ\) (c 0.1 in CH\(_2\)Cl\(_2\)). The \(^1\text{H}\) NMR data obtained was in agreement with that reported above for 7.
Synthesis of 5-(benzyloxy)-1-((1S,3R)-6,8-bis(benzyloxy)-3-pentylisochroman-1-yl)pentan-2-one and 5-(benzyloxy)-1-((1R,3R)-6,8-bis(benzyloxy)-3-pentylisochroman-1-yl)pentan-2-one, cis and trans-3

Diisobutylaluminium hydride (0.12 mL, 1 M in toluene, 0.12 mmol) was added to a solution of 7 (0.05 g, 0.12 mmol) in toluene (1 mL) at -78 °C and the reaction mixture was stirred at this temperature for 3 h. Ethyl acetate (1 mL), methanol (0.1 mL) and water (1 mL) were added, the reaction mixture warmed to rt and the layers separated. The aqueous layer was extracted with ethyl acetate (5 mL), the combined organic layers dried over magnesium sulfate and the solvent removed in vacuo to afford the crude lactol.

A solution of 5 (0.1081 g, 0.36 mmol) in THF (0.5 mL) was added to a suspension of sodium hydride (0.1081 g, 0.36 mmol) in THF (0.5 mL) at 0 °C and the reaction mixture stirred at rt for 30 min. A solution of the crude lactol in THF (1 mL) was added to the reaction mixture heated to reflux and the solvent removed in vacuo. The resultant crude oil was purified via flash chromatography using hexanes-ethyl acetate as eluent (4:1, Rf = 0.57) to afford the title compound 3 (0.0581 g, 80%*) as a colourless solid, m.p. = 93.5-94.5 °C. e.e. > 99% (3a and 3b), d.r. = 1:1.48 (3a:3b) (HPLC, Chiralpak® IC, hexanes/isopropanol (9/1), v = 0.5 mL.min⁻¹, λ = 210 nm, tᵣ(1S, 3R) = 20.44 (40.33%), tᵣ(1R, 3R) = 37.56 (59.67%); [α]D²⁰ = +41.0° (c 0.01 in CH₂Cl₂); v_max (diamond/cm⁻¹) 2928 (C-H str.), 2856 (C-H str.), 1707 (C=O, str.), 1596, 1150, 1092 (C-O-C ring, str.), 1337, 733, 694; δH (400 MHz, CDCl₃) 0.86-0.90 (3H, m, CH₃), 1.24-1.51 (8H, m, 4 x CH₂ from C₅H₁₁), 1.78-1.89 (2H, m, C₄H₂), 2.46-2.66 (4.6H, m, C₃H₂, C₄H₂, C₁H(CIS)), 2.84 (0.6H, dd, J = 10.4, 14.8 Hz, C₁H(TRANS)), 3.00 (0.59H, dd, J = 3.0, 15.4H, C₁H(TRANS)), 3.27 (0.44H, dd, J = 2.8, 14.8 Hz, C₁H(CIS)), 3.40-3.50 (2.55H, m, C₃H(TRANS)), 4.45-4.46 (2H, m, CH₂OCH₂C₅H₃), 5.00-5.02 (4H, m, 2 x ArOCH₂C₅H₃), 5.34 (0.43H, br. d, J = 6.8 Hz, C₁H(CIS)), 5.51 (0.57H, dd, J = 3.0, 10.6 Hz, C₁H(TRANS)), 6.33 (1H, d, J = 2.0 Hz, C₇H), 6.44 (1H, dd, J = 2.4, 4.8 Hz, C₅H), 7.24-7.42 (15H, m, 3 x CH₂C₆H₅); δC (100 MHz; CDCl₃) 14.05 (CH₃, CH₃), 22.6 (CH₂, from C₃H₁₁), 23.65, 23.69 (CH₂, C₄(CIS) and TRANS), 25.08, 25.10 (2 x CH₂, from C₅H₁₁(CIS) and TRANS), 31.8, 31.9 (2 x CH₂, from C₅H₁₁(CIS) and TRANS), 34.5 (CH₂, C₃′ or C₄(CIS) or TRANS), 35.6 (CH₂, C₃′ or C₄(CIS) or TRANS), 35.8, 35.9 (2 x CH₂, from C₅H₁₁(CIS) and TRANS), 38.8 (CH₂, C₃′ or C₄(CIS) or TRANS), 39.7 (CH₂, C₃′ or C₄(CIS) or TRANS), 46.9 (CH₂, C₁′(TRANS)), 49.0 (CH₂, C₁′(CIS)), 67.3 (CH, C₃(TRANS)), 68.9 (CH, C₁(TRANS)), 69.5, 69.6 (CH₂, C₅′(CIS) and C₅′(TRANS)), 69.9, 70.0 (2 x CH₂, ArOCH₂C₅H₃(CIS) and TRANS), 70.10, 70.12 (2 x CH₂, ArOCH₂C₅H₃(CIS) and TRANS), 71.4 (CH, C₁(CIS)), 72.7, 72.8 (2 x CH₂, CH₂OCH₂C₅H₃(CIS) and TRANS), 73.3 (CH₂, C₃(CIS)), 98.3, 98.7 (2 x CH, C₅(CIS) and C₅(TRANS)), 105.7, 106.0 (2 x CH, C₇(CIS) and C₇(TRANS)), 118.69 and 119.73 (2 x quat., C₈a(CIS) and C₈a(TRANS)), 127.1, 127.5, 127.6, 127.9, 128.0, 128.3, 128.6 (15 x CH, from 3 x OBn), 135.8 (quat., from CH₂OBn), 136.6 (quat., C₄a), 136.9, 137.7 (2 xquat., from 2 x ArOBn), 155.2, 155.8 (2 x quat., C₆(CIS) and C₆(TRANS)), 158.2, 158.4 (2 x quat., C₆(CIS) and C₆(TRANS)), 208.6, 209.5 (2 x quat., C₂′(CIS) and C₂′(TRANS));
$m/z$ (FAB+, %) 606 (M$^+$, 2), 515 (10), 415 (36), 325 (5), 181 (3), 91 (100); Found M$^+$, 606.3345. 
C$_{40}$H$_{46}$O$_5$ requires 606.33452.

* upon repetition the yield for this step proved to be variable

**Synthesis (2R,3a’S,5’R)-5’-penty1-3’,3a’,4,5,5’,6’-hexahydro-3H-spiro[furan-2,2’-pyrano[2,3,4-de]chromen]-8’-ol, 2**

Palladium hydroxide (0.0098 g, 20% in carbon) and hydrochloric acid (2 drops, 4 M in dioxane) was added to a solution of 3 (0.045 g, 0.07 mmol) in tetrahydrofuran (1 mL) and the mixture stirred under a hydrogen atmosphere at rt for 18 h. The reaction mixture was loaded directly onto a preparatory thin layer plate and was eluted with hexanes-ethyl acetate (4:1, $R_f = 0.48$) to give the title compound 2 (0.0147 g, 72%) as a colourless solid, m.p. = 34.4-35.6 °C. e.e. >99%, d.r. = 14:1 (2(R):2(S)) (HPLC, Chiralpak® IC, hexanes/isopropanol (19/1), $v = 0.5$ mL.min$^{-1}$, $\lambda = 210$ nm, $t_1$(2R, 3’aS, 5’R) = 29.69 (93.57%), $t_2$(2S, 3’aS, 5’R) = 48.74 (6.43%); $[\alpha]_D^{19.9} = +72.7^\circ$ (c 0.045, CH$_2$Cl$_2$); $v_{\max}$ (diamond/cm$^{-1}$) 3346 (O-H str.), 2928 (C-H str.), 2859 (C-H (CH$_2$O) str.), 1600, 1456, 1316, 1151, 1078, 1016, 838; $\delta_H$ (400 MHz, CDCl$_3$) 0.90 (3H, t, $J = 6.8$ Hz, CH$_3$), 1.26-1.41 (6H, m, 3 x CH$_2$ from C$_5$H$_{11}$), 1.50-1.68 (4, m, 2 x CH$_2$ from C$_5$H$_{11}$), 1.91-2.06 (3H, m, C$_3$H$_{10}$ and C$_4$H$_2$), 2.23-2.29 (3H, m, C$_3$H$_{10}$ and C$_3$H$_2$), 2.59 (1H, dd, $J = 11.0$, 16.8 Hz, C$_6$H$_{12}$), 2.74 (1H, dd, $J = 4.4$, 16.8 Hz, C$_6$H$_{12}$), 3.80-3.87 (1H, m, H$_{5’}$), 3.98-4.00 (1H, m, C$_5$H$_{10}$), 4.02-4.09 (1H, m, C$_5$H$_{10}$), 4.68 (1H, s, OH$_2$), 4.81 (1H, dd, $J = 5.4$, 12.2 Hz, C$_3$’H$_2$), 6.10 (1H, d, $J = 2.4$ Hz, C$_9$’H$_2$), 6.16 (1H, d, $J = 1.6$ Hz, C’H$_2$); $\delta_C$ (75 MHz; CDCl$_3$) 14.1 (CH$_3$, C$_3$), 22.6 (CH$_2$, C$_2$CH$_3$), 23.8 (CH$_2$, C$_2$CH$_2$CH$_3$), 25.2 (CH$_2$, C$_4$), 31.8 (CH$_2$, C’), 34.1 (CH$_2$, CH$_2$CH$_2$CH$_3$), 36.3 (CH$_3$, CH$_2$(CH$_2$)CH$_3$), 36.5 (CH$_2$, C’), 37.8 (CH$_2$, C$_3$), 68.3 (CH$_2$, C’), 68.6 (CH, C’), 75.6 (CH, C’), 100.5 (CH, C’), 107.1 (CH, C’), 108.2 (quat., C$_2$), 113.9 (quat., central C), 135.0 (quat., C$_6$a’), 151.9 (quat., C’), 115.5 (quat., C$_9$a’); $m/z$ (EI+, %) 318 (M$^+$, 35), 259 (24), 234 (100), 163 (26), 73 (16); Found M$^+$, 318.1834 C$_{19}$H$_{26}$O$_4$ requires 318.1831.

**References**


$^{13}$C NMR 100 MHz

$^3$P NMR 162 MHz
$\text{H NMR}$

400 MHz

$15$

$\text{H NMR}$

400 MHz
$^1$H NMR
300 MHz

$^{13}$C NMR
75 MHz
**METHOD A:**
Eluent = Hexanes-isopropanol (65:35)
Column = Chiralpak® AD-H, 4.6 mm i.d. x 250 mm
Packing = amylose tris(3,5-dimethyl phenyl carbamate) coated on silica gel
Particle size = 5 μm
Flow rate = 0.5 mL/min
Wavelength = 254 nM

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<th>Peak Name</th>
<th>Height mAU</th>
<th>Area mAU*min</th>
<th>Rel.Area %</th>
<th>Amount</th>
<th>Type</th>
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Total: 986.376 1016.042 100.00 0.000
e. e. = 75.53 - 24.47 = 51% (R)

**METHOD B:**
Eluent = Hexanes-isopropanol (65:35)
Column = Chiralpak® AD-H, 4.6 mm i.d. x 250 mm
Packing = amylose tris(3,5-dimethyl phenyl carbamate) coated on silica gel
Particle size = 5 μm
Flow rate = 0.5 mL/min
Wavelength = 254 nM

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<td>n.a.</td>
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Total: 1758.586 2559.146 100.00 0.000
e. e. = 86.38 - 13.62 = 73% (R)
After semi-prep
Eluent = Hexanes-isopropanol (65:35)
Column = Chiralpak® AD-H,
4.6 mm i.d x 250 mm
Packing = amylose tris(3,5-
-dimethyl phenyl carbamate)
coated on silica gel
Particle size = 5 μm
Flow rate = 0.5 mL/min
Wavelength = 254 nM

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<th>Area (mAU*min)</th>
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<td>1080.213</td>
<td>100.00</td>
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\(\text{e. e.} > 99\% \text{ (R)}\)

Eluent = Hexanes-isopropanol
Column = Chiralpak® AD-H,
4.6 mm i.d x 250 mm
Packing = amylose tris(3,5-
dimethyl phenyl carbamate)
coated on silica gel
Particle size = 5 μm
Flow rate = 0.5 mL/min
Wavelength = 254 nM

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<th>Area (mAU*min)</th>
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\(\text{e. e.} = 86.49 - 13.51 = 73\% \text{ (S)}\)
Eluent = Hexanes-isopropanol (90:10)
Column = Chiralpak® IC, 4.6 mm i.d. x 250 mm
Packing = cellulose tris(3,5-dichloro phenylcarbamate) immobilised on silica gel
Particle size = 5 μm
Flow rate = 0.5 mL/min
Wavelength = 210 nM

e. e. > 99% (3a and 3b)
d. r. (HPLC) = 1:1.48
d. r. (NMR) = 1:1.51
(cis 3a:trans 3b)

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<th>Area mAU min</th>
<th>Rel.Area %</th>
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Equilibration of isochroman 3 using anhydrous HCl in THF (50% e.e.)

Before equilibration (NMR)
400MHz
d. r. = 1 (trans) : 1.18 (cis)

After equilibration (NMR)
400MHz
d. r. = 1 (trans) : 0.33 (cis)

Desired Product

After equilibration (HPLC)
d. r. = 1 (trans) : 0.30 (cis)

d. e. = (17.17 + 60.01) - (14.93 + 7.89) = 50%

In THF in the presence of HCl overnight the cis isochroman equilibrates to the trans
$^1$H NMR
400 MHz

$^1$C NMR
75 MHz

E.S.I.26
Eluent = Hexanes-isopropanol (95:5)
Column = Chiralpak® IC, 4.6 mm i.d. x 250 mm
Packing = cellulose tris(3,5-dichloro phenylcarbamate) immobilised on silica gel
Particle size = 5 μm
Flow rate = 0.5 mL/min
Wavelength = 210 nM

e. e. >99%
d. r. = 14 : 1
(2(R):2(S))
$^1$H NMR comparison of 2 with Zhou and Snider’s related spiroketal

![Chemical Structure](image)


<table>
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<tr>
<th>assignment</th>
<th>shift</th>
<th>multiplicity / $J$ (Hz)</th>
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