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A Flexible Approach to 6,5-Benzannulated Spiroketals

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A novel route to simple 6,5-benzannulated spiroketal analogues has been developed. A convergent Horner–Wadsworth–Emmons olefination enabled ready assembly of the spiroketal precursors. Use of a benzyl protecting group strategy enabled an efficient one-pot hydrogenation/deprotection/spiroketalisation process to be employed providing a robust method to access a range of substituted aromatic monobenzannulated spiroketals.

Introduction

Spiroketals are privileged scaffolds that are present in a range of natural products that exhibit interesting biological activity.[1] 6,5-Benzannulated spiroketals comprise a relatively small subgroup of spiroketal-containing natural products; however, they have attracted considerable research interest due to their significant biological activity and structural diversity.[2]

Examples of 6,5-benzannulated natural products include berkelic acid (**1**), paecilospirone (**2**), and γ-rubromycin (**3**) (Figure 1). Berkelic acid (**1**) exhibits selective activity against the ovarian cancer cell line OVCAR3, as well as activity against caspase 1 and matrix metalloproteinase 3 (MMP3).[3] Paecilospirone (**2**) is an antibiotic exhibiting weak inhibition of microtubule assembly.[4] γ-Rubromycin (**3**) exhibits antibacterial properties as well as inhibitory effects on human telomerase, HIV-1 reverse transcriptase and moloney murine leukaemia viruses.[5] Efficient access to these natural products, as well as simplified analogues is therefore desirable in order to probe the promising bioactivity that these compounds exhibit.

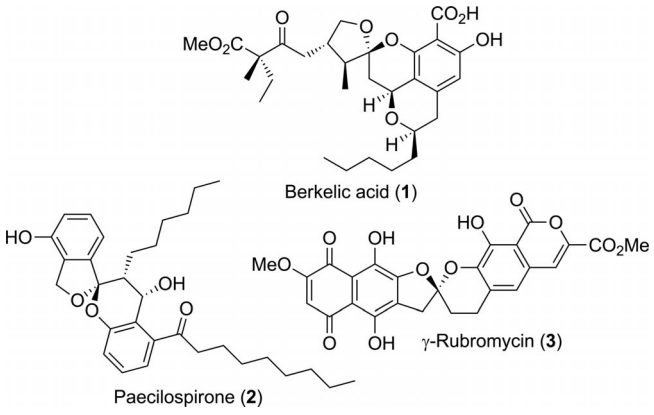
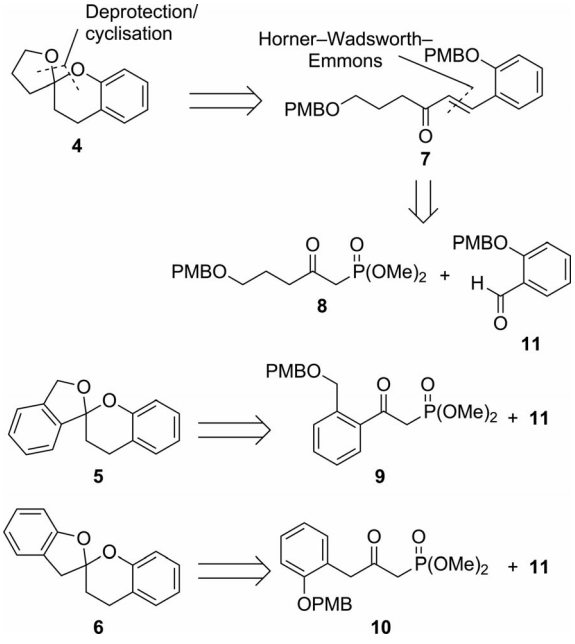


Figure 1. 6,5-Benzannulated spiroketal-containing natural products.

Results and Discussion

It was envisaged that 6,5-benzannulated spiroketals **4**–**6**, the cyclic cores of natural products **1**–**3**, respectively, could be accessed from *p*-methoxybenzyl (PMB) protected dihydroxy ketone precursors by using a global deprotection/cyclisation process. These precursors can be accessed by hydrogenation of the corresponding enones such as **7**. In turn, a range of enones are available by Horner–Wadsworth–Emmons (HWE) olefination[6] of phosphonates **8**–**10** with PMB-protected salicylaldehyde **11** (Scheme 1).



Scheme 1. Retrosynthetic analysis for the synthesis of benzannulated spiroketals **4**–**6**.

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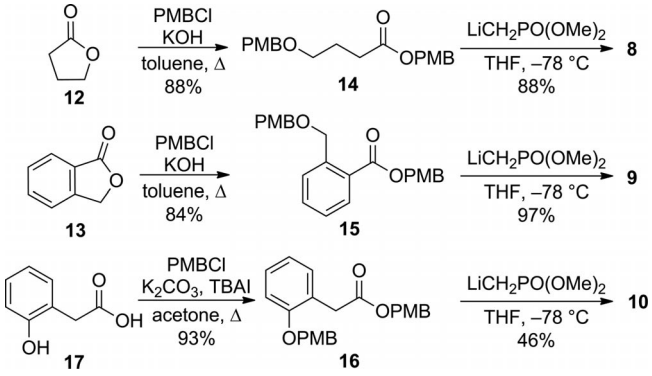
Phosphonates **8** and **9** were readily synthesised by facile ring opening of γ-butyrolactone (**12**) or phthalide (**13**), respectively, with potassium hydroxide and *p*-methoxybenzyl choride (PMBCl)[7] followed by displacement of the resultant PMB esters **14** and **15** with lithiated dimethyl methylphosphonate (Scheme 2). For the synthesis of ester **16**, bis(PMB) protection of acid **17** by using PMBCl, potassium carbonate and tetrabutylammonium iodide (TBAI) proved a more reliable method than ring opening of the corresponding lactone.



Scheme 2. Synthesis of phosphonates **8**–**10**.

Pleasingly, HWE olefination of phosophonates **8**–**10** with PMB-protected salicylaldehyde **11** proceeded smoothly, with complete diastereoselectivity in favour of the (*E*)-enones (Table 1). The resultant enones **7**, **18** and **19** were then subjected to chemoselective reduction[8] by employing Cp_2TiCl_2, zinc powder and triethylamine hydrochloride to yield protected dihydroxy ketones **20**–**22** in respectable yields (Table 1). Finally, attention turned to the simultaneous deprotection/cyclisation step. Treatment of dihydroxy ketones **20** and **22** with DDQ in dichloromethane/water (10:1) (Method A, Table 1) afforded spiroketals **4** and **6** in moderate 40% and 35% yield, respectively. When **21** was exposed to the same conditions, no spiroketal product resulted; rather an aldehyde by-product arising from oxidation of the benzylic alcohol formed after PMB cleavage.[9] Acid-catalysed PMB cleavage was therefore investigated. Spiroketalisation precursors **20**–**22** were stirred in a solution of anhydrous hydrogen chloride (1 M) in tetrahydrofuran and dioxane to afford the desired 6,5-benzannulated spiroketals **4** and **5** in moderate yield. However, only degradation and various elimination products were observed in the attempted synthesis of sensitive spiroketal **6** (Table 1).[5a,10]

Given the difficulties experienced with the synthesis of spiroketals **4**–**6**, attention next turned to fine-tuning of the reaction conditions by focusing on the monobenzannulated spiroketal core **4** of berkelic acid. Upon re-evaluation of our initial PMB protecting group strategy, it was noted that use of benzyl protecting groups would allow both the olefin hydrogenation and deprotection/spiroketalisation reactions to proceed in one pot. The potential of the established reaction conditions to accommodate various aromatic substitution patterns was also examined, with spiroketals **23**–**28** (Figure 2) chosen as targets for this purpose. A focused library of this important structural scaffold will be useful for further biological evaluation.

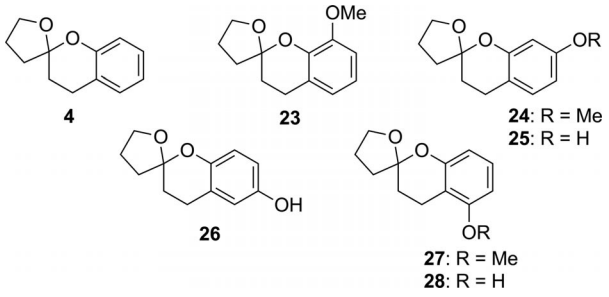
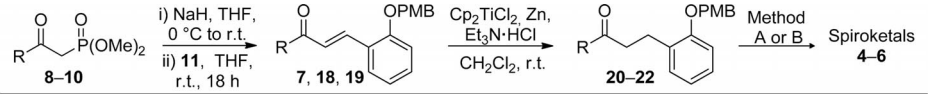
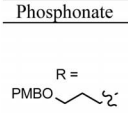
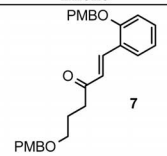
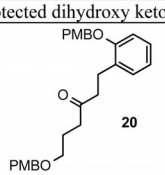
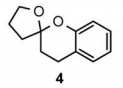
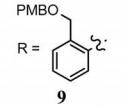
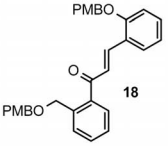
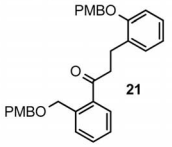
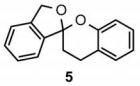
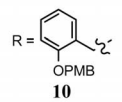
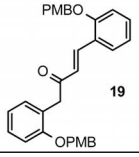
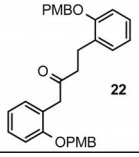
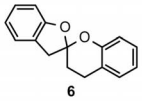


Figure 2. Target tricyclic analogues of berkelic acid.

Table 1. Synthesis of spiroketals **4**–**6** by HWE olefination, hydrogenation and concomitant deprotection/cyclisation.[a]



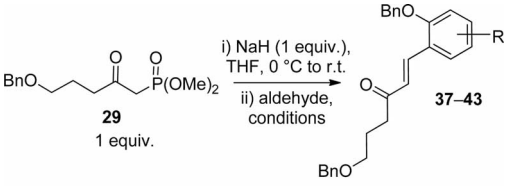
Phosphonate	Enone	Yield [%]	Protected dihydroxy ketone	Yield [%]	Spiroketal	Yield [%]
 **8**	 **7**	76	 **20**	79	 **4**	A: 40 B: 60
 **9**	 **18**	86	 **21**	83	 **5**	A: –[12] B: 58
 **10**	 **19**	88	 **22**	89	 **6**	A: 35 B: –

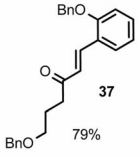
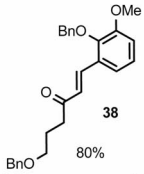
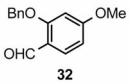
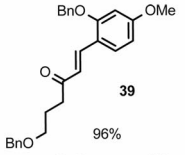
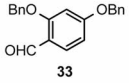
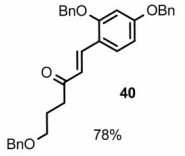
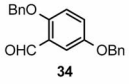
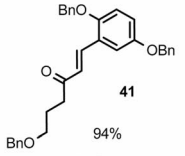
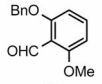
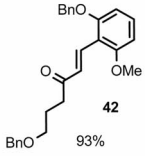
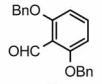
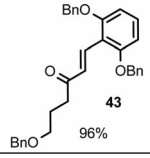
[a] Method A [DDQ, CH_2Cl_2/H_2O (10:1)] or Method B [HCl (1 M), THF/dioxane, room temp., 48 h].

With this idea in mind, the required benzyl-protected phosphonate **29** was synthesised as previously reported,[11] and aldehydes **30**–**36** were accessed from readily available salicylaldehyde starting materials by routine chemistry.[12]

HWE olefination of aldehydes **30**–**36** with phosphonate **29** proceeded without event to afford the spiroketal precursors **37**–**43** in 78–96% yield, with complete diastereoselectivity in favour of the (*E*)-enones (Table 2).

Table 2. HWE olefination of phosphonate **29** with benzaldehydes **30**–**36**.

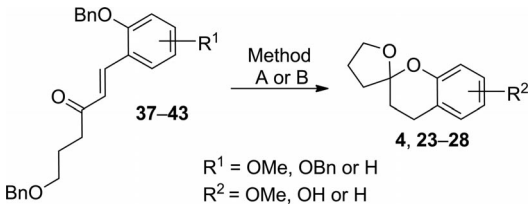


Entry	Aldehyde	Conditions	Product/Yield
1	 **30**	reflux, 2.5 h	 **37** 79%
2	 **31**	reflux/r.t., 1 h/1 h	 **38** 80%
3	 **32**	r.t., 23 h	 **39** 96%
4	 **33**	reflux, 2.5 h	 **40** 78%
5[a]	 **34**	r.t., 17 h	 **41** 94%
6	 **35**	r.t., 23 h	 **42** 93%
7	 **36**	r.t., 17.5 h	 **43** 96%

[a] 2 equiv. of **29** and NaH used.

With cyclisation precursors **37**–**43** in hand, attention turned to the final global deprotection/spiroketalisation step. Concomitant hydrogenation of the double bond and hydrogenolysis of the benzyl protecting groups by using hydrogen in the presence of palladium hydroxide or 10% palladium on carbon effected the unmasking of the dihydroxy ketones, which spontaneously cyclised to the desired spiroketals **4** and **23**–**28** in respectable yields. Through fine-tuning of the reaction conditions it was possible to synthesize tricyclic spiroketals **23**–**28** that were monosubstituted at each possible position around the aromatic ring, thereby demonstrating that this is an effective method for the synthesis for the spiroketal core of berkelic acid and analogues (Table 3).

Table 3. One-pot deprotection cyclisation of enones **37**–**43**.



Entry	Method[a]	Time [h]	Product	Yield [%]
1	A [$Pd(OH)_2$ or Pd/C]	72	**4**	88
2	B	–	**23**	68
3	A (Pd/C)	21	**24**	53
4	A [$Pd(OH)_2$]	72	**25**	76
5[b]	B	–	**26**	80
6	A (Pd/C)	70	**27**	62
7	A [$Pd(OH)_2$]	62	**28**	64

[a] Method A: $Pd(OH)_2$ or Pd/C, H_2 THF, room temp. Method B: H-Cube® HC-2 continuous hydrogenation equipment (THALES Nanotechnology Inc.) with $Pd(OH)_2$ catalyst, a column block temperature of 20 °C, pressure of 20 bar and flow rate of 1 mL/min, EtOAc/MeOH. [b] Required filtration through Amberlyst 15® acidic resin (Sigma–Aldrich).

Conclusions

We have developed a flexible route to a focused library of 6,5-benzannulated spiroketals. The key steps include HWE olefination followed by olefin hydrogenation and global deprotection/spiroketalisation. The benzannulated spiroketal cores of berkelic acid, γ-rubromycin and paecilospirone were synthesised by employing PMB protecting groups; however, separate hydrogenation and deprotection steps were required, and only moderate yields of the desired spiroketals were obtained. Monobenzannulated spiroketals analogous to berkelic acid were next targeted to optimise our synthetic strategy, and these spiroketals were readily prepared in good yield by using a one-pot hydrogenation/deprotection/cyclisation process. The methodology reported herein enabled the synthesis of a range of 6,5-monobenzannulated spiroketals containing a variety of aromatic substitution patterns.

Experimental Section

General Details: All reactions were carried out in flame- or oven-dried glassware under dry nitrogen. Tetrahydrofuran and diethyl

ether were dried with sodium wire, and dichloromethane was dried with calcium hydride. All solvents were distilled prior to use. Flash chromatography was carried out by using 0.063–0.1 mm silica gel with the appropriate solvent. Thin layer chromatography (TLC) was performed by using 0.2 mm Kieselgel F254 (Merck) silica plates, and compounds were visualised by using UV irradiation at 365 nm and/or staining with vanillin in methanolic sulfuric acid, a solution of ammonium heptamolybdate and cerium sulfate in aqueous sulfuric acid, or a solution of potassium permanganate and potassium carbonate in aqueous sodium hydroxide. Preparative TLC was carried out on 500 μm Uniplate™ (Analtech) silica gel (20 × 20 cm) thin layer chromatography plates. Infrared spectra were obtained as indicated by using a Perkin–Elmer Spectrum 1000 series Fourier Transform IR (FTIR) spectrometer as a thin film between sodium chloride plates or a Perkin–Elmer Spectrum One FTIR spectrometer with a film ATR sampling accessory. Absorption maxima are expressed in wavenumbers (cm^{-1}). Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded as indicated with either a Bruker Avance 300 spectrometer operating at 300 MHz for ^1H nuclei and 75 MHz for ^{13}C nuclei or by using a Bruker DRX-400 spectrometer operating at 400 MHz for ^1H 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 (^1H) or $CDCl_3$ (^1H and ^{13}C). ^1H NMR spectroscopic data is reported as chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; dd, doublet of doublets), coupling constant (J in Hz), relative integral, and assignment. High-resolution mass spectra were recorded with a VG-70SE at a nominal accelerating voltage of 70 eV or with a Bruker micrOTOF-Q II mass spectrometer.

4-Methoxybenzyl 4-(4-Methoxybenzyloxy)butanoate (14): A mixture of γ-butyrolactone (1.4 mL, 18.2 mmol), *p*-methoxybenzyl chloride (8.7 mL, 63.9 mmol) and potassium hydroxide (3.58 g, 63.9 mmol) in toluene (180 mL) was heated to reflux under Dean–Stark conditions for 48 h. The mixture was cooled to room temp., and water (150 mL) was added before extraction with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with aqueous saturated sodium hydrogen carbonate (150 mL) and brine (150 mL), dried with magnesium sulfate, and the solvent was removed in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (4:1) as eluent afforded **14** (5.55 g, 88%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.4 Hz, 2 H, OCH_2PhOCH_3), 7.21 (d, J = 8.8 Hz, 2 H, OCH_2PhOCH_3), 6.82–6.85 (m, 4 H, OCH_2PhOCH_3), 5.01 (s, 2 H, OCH_2PhOCH_3), 4.37 (s, 2 H, OCH_2PhOCH_3), 3.73 (s, 6 H, 2 OCH_2PhOCH_3), 3.43 (t, J = 6.4 Hz, 4-H), 2.42 (t, J = 7.2 Hz, 2 H, 2-H), 1.87–1.94 (m, 2 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 159.4, 158.9, 130.3, 129.8, 128.9, 128.0, 113.7, 113.5, 72.2, 68.6, 65.7, 54.9, 30.9, 24.9 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2931, 2837, 1731, 1512, 1243, 1162, 1032 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{24}NaO_5$ $[M + Na]^+$ 367.1516; found 367.1521.

4-Methoxybenzyl 2-[(4-Methoxybenzyloxy)methyl]benzoate (15): A mixture of phthalide (1.00 g, 7.5 mmol), *p*-methoxybenzyl chloride (5.7 mL, 41.8 mmol) and potassium hydroxide (1.46 g, 26.1 mmol) in toluene (60 mL) was heated to reflux under Dean–Stark conditions for 48 h. The mixture was cooled to room temp., and water (50 mL) was added before extraction with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with saturated sodium hydrogen carbonate (50 mL) and brine (50 mL), dried with magnesium sulfate, and the solvent was removed in vacuo. Purification by flash chromatography using hexanes/ethyl acetate (9:1) as eluent afforded **15** (2.50 g, 84%) as a colourless solid; m.p. 46–48 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.0 Hz, 1 H, 6-H), 7.80 (d, J = 8.0 Hz, 1 H, 3-H), 7.56 (t, J = 8.0 Hz, 1 H, 4-H), 7.44–7.33 (m, 5 H, 5-H and OCH_2PhOCH_3), 6.96 (d, J = 8.0 Hz, 4 H, OCH_2PhOCH_3), 5.33 (s, 2 H, OCH_2PhOCH_3), 5.04 (s, 2 H, CH_2OPMB), 4.62 (s, 2 H, OCH_2PhOCH_3), 3.81 (s, 6 H, 2 OCH_2PhOCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 159.4, 158.9, 140.7, 132.0, 130.2, 129.8, 129.1, 129.0, 128.0, 127.8, 127.4, 126.6, 113.7, 113.5, 72.3, 69.8, 66.2, 54.8 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2961, 2838, 1709, 1516, 1246, 739 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{18}NaO_5$ $[M + Na]^+$ 415.1516; found 415.1512.

4-Methoxybenzyl 2-{2-[(4-Methoxybenzyl)oxy]phenyl}acetate (16): *p*-Methoxybenzyl chloride (2.0 mL, 14.5 mmol) was added to a stirred solution of 2-(2-hydroxyphenyl)acetic acid (1.00 g, 6.6 mmol), potassium carbonate (1.91 g, 13.8 mmol) and tetrabutylammonium iodide (0.48 g, 2.6 mmol) in acetone (35 mL) and the mixture heated at 55 °C for 10 h. The solvent was removed in vacuo, water (30 mL) was added and the reaction mixture extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried with magnesium sulfate, and the solvent was removed in vacuo. The resulting oil was purified by flash chromatography using hexanes/ethyl acetate (4:1) as eluent to afford **16** (2.39 g, 93%) as a colourless solid; m.p. 47–48 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, J = 8.4 Hz, 2 H, ArH), 7.26–7.17 (m, 4 H, ArH), 6.94–6.91 (m, 2 H, ArH), 6.87–6.82 (m, 4 H, ArH), 5.01 (s, 2 H, OCH_2PhOCH_3), 4.96 (s, 2 H, OCH_2PhOCH_3), 3.80 (s, 3 H, OCH_2PhOCH_3), 3.79 (s, 3 H, OCH_2PhOCH_3), 3.68 (s, 2 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 159.5, 159.2, 156.7, 131.0, 129.9, 129.1, 128.7, 128.5, 128.2, 123.5, 120.7, 113.8, 111.8, 69.7, 66.2, 55.2, 36.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3007, 2834, 1733, 1512, 1239, 1152, 1029, 817 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{24}NaO_5$ $[M + Na]^+$ 415.1516; found 415.1512.

General Procedure for Dimethyl Methylphosphonate Addition: *n*-Butyllithium (1.6 M in hexanes, 3 equiv.) was added dropwise to a stirred solution of dimethyl methylphosphonate (3 equiv.) in tetrahydrofuran at –78 °C. The mixture was stirred at –78 °C for 30 min, followed by dropwise addition of a solution of ester (1 equiv.) in tetrahydrofuran. The reaction mixture was stirred at –78 °C for 2 h, after which it was quenched with saturated ammonium chloride and warmed to room temp. The resulting mixture was extracted with ethyl acetate, the combined organic extracts washed with brine, dried with magnesium sulfate and the solvent removed in vacuo before purification by flash chromatography using ethyl acetate as eluent.

Dimethyl {5-[(4-Methoxybenzyl)oxy]-2-oxopentyl}phosphonate (8): The general procedure was applied by using ester **14** (2.25 g, 6.5 mmol). The product was obtained as a yellow oil (1.89 g, 88%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 8.4 Hz, 2 H, OCH_2PhOCH_3) 6.86 (d, J = 8.4 Hz, 2 H, OCH_2PhOCH_3), 4.40 (s, 2 H, OCH_2PhOCH_3), 3.81 (s, 3 H, OCH_2PhOCH_3), 3.77 [d, J = 11.2 Hz, 6 H, $P(OCH_3)_2$], 3.45 (t, J = 6.0 Hz, 2 H, 5-H), 3.08 (d, J = 18.8 Hz, 2 H, 1-H), 2.71 (t, J = 6.8 Hz, 2 H, 3-H), 1.85–1.92 (m, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4, 158.9, 130.2, 129.0, 113.5, 72.3, 68.5, 55.0, 52.8, 41.7, 41.0, 23.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2956, 2854, 1713, 1513, 1244, 1022 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{24}O_6P$ $[M + H]^+$ 331.1305; found 331.1310.

Dimethyl [2-(2′-{[(4-Methoxybenzyl)oxy]methyl}phenyl)-2-oxoethyl]-phosphonate (9): The general procedure was applied by using ester **15** (2.50 g, 6.4 mmol). The product was obtained as a pale yellow oil (2.33 g, 97%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 7.6 Hz, 1 H, 6′-H), 7.75 (d, J = 8.0 Hz, 1 H, 3′-H), 7.54 (t, J = 7.6 Hz, 1 H, 5′-H), 7.39 (t, J = 8.0 Hz, 1 H, 4′-H), 7.31 (d, J =

8.8 Hz, 2 H, OCH_2PhOCH_3), 6.89 (d, J = 8.8 Hz, 2 H, OCH_2PhOCH_3), 4.84 (s, 2 H, CH_2OPMB), 4.55 (s, 2 H, OCH_2PhOCH_3), 3.78 (s, 3 H, OCH_2PhOCH_3), 3.74 [d, J = 11.6 Hz, 6 H, $P(OCH_3)_2$], 3.60 (d, J = 22.4 Hz, 2 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.4, 159.0, 140.0, 135.4, 132.3, 130.1, 129.4, 129.1, 127.7, 126.8, 113.5, 72.3, 69.8, 55.0, 52.8, 39.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2952, 2850, 1675, 1513, 1245, 1025 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{23}NaO_6P$ $[M + Na]^+$ 401.1124; found 401.1136.

Dimethyl (3-{2′-[(4-Methoxybenzyl)oxy]phenyl}-2-oxopropyl)phosphonate (10): The general procedure was applied by using ester **16** (1.58 g, 4.0 mmol). The product was obtained as a pale yellow oil (0.69 g, 46%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, J = 8.8 Hz, 2 H, OCH_2PhOCH_3), 7.24 (dt, J = 7.6, 1.6 Hz, 1 H, 4′-H), 7.16 (d, J = 7.6 Hz, 1 H, 6′-H), 6.94–6.88 (m, 4 H, OCH_2PhOCH_3, 3′-H, 5′-H), 4.97 (s, 2 H, OCH_2PhOCH_3), 3.84 (s, 2 H, 3-H), 3.79 (s, 3 H, OCH_2PhOCH_3), 3.71 [d, J = 11.2 Hz, 6 H, $P(OCH_3)_2$], 3.05 (d, J = 22.0 Hz, 2 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 159.3, 156.3, 131.3, 129.0, 128.6, 128.6, 122.9, 120.8, 113.8, 111.6, 69.7, 55.1, 52.8, 45.6, 40.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2955, 1719, 1515, 1239, 1175, 1023, 821, 753 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{23}NaO_6P$ $[M + H]^+$ 401.1124; found 401.1119.

General Procedure for Horner–Wadsworth–Emmons Olefination: Phosphonate (1 equiv.) was taken up in tetrahydrofuran and added to a suspension of sodium hydride (60% in paraffin oil, 1 equiv.) in tetrahydrofuran at 0 °C, then warmed to room temperature for 0.5 h. A solution of aldehyde in tetrahydrofuran was then added and the reaction mixture stirred at room temp. or under reflux until the reaction was judged complete by TLC. Aqueous saturated ammonium chloride was added and the reaction mixture extracted with ethyl acetate. The combined organic extracts were dried with magnesium sulfate, and the solvent was removed in vacuo before purification by flash chromatography using hexanes/ethyl acetate (4:1) as eluent.

6-[(4-Methoxybenzyl)oxy]-1-{2-[(4-methoxybenzyl)oxy]phenyl}-hex-1-en-3-one (7): The general procedure was applied by using phosphonate **8** (0.10 g, 0.3 mmol) and aldehyde **11** (0.073 g, 0.3 mmol), stirring the reaction mixture at room temp. for 18 h. The product was obtained as a pale yellow oil (0.11 g, 76%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 16.4 Hz, 1 H, 1-H), 7.54 (dd, J = 8.0, 1.8 Hz, 1 H, 6′-H), 7.35 (d, J = 8.8 Hz, 2 H, OCH_2PhOCH_3), 7.31 (dd, J = 7.6, 1.5 Hz, 1 H, 3′-H), 7.25–7.23 (d, J = 8.8 Hz, 2 H, OCH_2PhOCH_3), 6.98–6.96 (m, 2 H, 4′-H and 5′-H), 6.91 (d, J = 8.8 Hz, 2 H, OCH_2PhOCH_3), 6.85 (d, J = 8.8 Hz, 2 H, OCH_2PhOCH_3), 6.79 (d, J = 16.4 Hz, 1 H, 2-H), 5.08 (s, 2 H, OCH_2PhOCH_3), 4.41 (s, 2 H, OCH_2PhOCH_3), 3.77 (s, 3 H, OCH_2PhOCH_3), 3.49 (t, J = 6.4 Hz, 2 H, 6-H), 2.73 (t, J = 7.2 Hz, 2 H, 4-H), 1.99–1.92 (m, 2 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.6, 159.5, 159.1, 157.6, 137.8, 131.6, 130.6, 129.2, 128.9, 128.7, 128.6, 127.0, 124.0, 121.1, 114.1, 113.8, 112.9, 72.5, 70.3, 69.2, 55.3, 55.2, 37.2, 24.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2934, 1681, 1584, 1514, 1232, 1026, 996 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{30}NaO_5$ $[M + Na]^+$ 469.1985; found 469.1998.

1-(2-{[(4-Methoxybenzyl)oxy]methyl}phenyl)-3-{2-[(4-methoxybenzyl)oxy]phenyl}prop-2-en-1-one (18): The general procedure was applied by using phosphonate **9** (0.94 g, 2.5 mmol) and aldehyde **11** (0.60 g, 2.5 mmol), stirring the reaction mixture at room temp. for 18 h. The product was obtained as a yellow oil (1.06 g, 86%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 16.4 Hz, 1 H, 3-H), 7.61 (d, J = 7.6 Hz, 1 H, ArH), 7.56 (d, J = 8.0 Hz, 1 H, ArH), 7.48–7.43 (m, 2 H, ArH), 7.35 (t, J = 7.6 Hz, 1 H, ArH), 7.30–7.26 (m, 4 H, 3 ArH and 2-H), 7.22 (d, J = 8.8 Hz, 2 H, OCH_2PhOCH_3), 7.00–6.97 (m, 2 H, ArH), 6.87 (d, J = 8.4 Hz, 2 H, OCH_2PhOCH_3), 6.79 (d, J = 8.4 Hz, 2 H, OCH_2PhOCH_3), 4.99, 4.70, 4.42 (s, 6 H, 2 CH_2PhOCH_3 and CH_2OPMB), 3.78 (s, 3 H, OCH_2PhOCH_3), 3.72 (s, 3 H, OCH_2PhOCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.0, 159.4, 159.1, 157.8, 141.6, 138.3, 138.2, 131.7, 130.5, 130.3, 129.6, 129.3, 128.9, 128.4, 128.3, 126.9, 124.0, 121.0, 114.0, 113.6, 112.6, 72.3, 70.2, 69.7, 55.3, 55.2 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2939, 2836, 1640, 1595, 1513, 1240 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{31}O_5$ $[M + H]^+$ 495.2166; found 495.2166.

1,4-Bis{2-[(4-methoxybenzyl)oxy]phenyl}but-3-en-2-one (19): The general procedure was applied by using phosphonate **10** (0.25 g, 0.7 mmol) and aldehyde **11** (0.16 g, 0.7 mmol), stirring the reaction mixture at room temp. for 18 h. The product was obtained as a pale yellow solid (0.29 g, 88%); m.p. 82–83 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 16.4 Hz, 1 H, 4-H), 7.43 (d, J = 8.0 Hz, 1 H, ArH), 7.31–7.25 (m, 5 H, ArH), 7.23–7.18 (m, 2 H, ArH), 6.95–6.87 (m, 6 H, ArH), 6.84 (d, J = 16.4 Hz, 1 H, 3-H), 6.78 (d, J = 8.4 Hz, 2 H, OCH_2PhOCH_3), 5.03 (s, 2 H, OCH_2PhOCH_3), 4.96 (s, 2 H, OCH_2PhOCH_3), 3.91 (s, 2 H, 1-H), 3.79 (s, 3 H, OCH_2PhOCH_3), 3.71 (s, 3 H, OCH_2PhOCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 159.3, 159.1, 157.5, 156.5, 137.9, 131.4, 131.3, 130.0, 128.8, 128.6, 128.5, 128.2, 126.3, 124.3, 124.0, 120.8, 114.0, 113.7, 112.8, 111.8, 70.1, 69.7, 55.2, 55.1, 42.7 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2955, 2836, 1684, 1588, 1514, 1453, 1236, 1174, 754 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{31}O_5$ $[M + H]^+$ 495.2166; found 495.2154.

(*E*)-6-(Benzyloxy)-1-[2-(benzyloxy)phenyl]hex-1-en-3-one (37): The general procedure was applied by using phosphonate **29** (0.71 g, 2.4 mmol) and aldehyde **30** (0.50 g, 2.4 mmol), stirring the reaction mixture at reflux for 2.5 h. The product was obtained as a colourless oil (0.72 g, 79%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, J = 16.5 Hz, 1 H, 1-H), 7.53 (d, J = 7.8 Hz, 1 H, 6′-H), 7.42–7.21 (m, 11 H, 2× C_6H_5 and 4′-H), 6.97–6.92 (m, 2 H, 3′-H and 5′-H), 6.81 (d, J = 16.5 Hz, 1 H, 2-H), 5.12 (s, 2 H, $ArOCH_2C_6H_5$), 4.47 (s, 2 H, $CH_2OCH_2C_6H_5$), 3.51 (t, J = 6.3 Hz, 2 H, 6-H), 2.74 (t, J = 7.2 Hz, 2 H, 4-H), 2.02–1.92 (m, 2 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.2, 157.3, 138.4, 137.4, 136.4, 131.4, 128.6, 128.5, 128.1, 127.9, 127.4, 127.1, 126.9, 123.7, 120.9, 112.6, 72.6, 70.2, 69.3, 37.0, 24.2 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2854, 1661, 1597, 1451, 1240, 1103, 743, 695 cm^{-1}. HRMS (EI): calcd. for $C_{26}H_{26}O_3$ $[M]^+$ 386.1882; found 386.1888.

(*E*)-6-(Benzyloxy)-1-[2-(benzyloxy)-3-methoxyphenyl]hex-1-en-3-one (38): The general procedure was applied by using phosphonate **29** (0.12 g, 0.4 mmol) and aldehyde **31** (0.10 g, 0.4 mmol), stirring the reaction mixture at reflux for 1 h and at room temp. for 1 h. The product was obtained as a pale yellow oil (0.14 g, 80%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, J = 16.5 Hz, 1 H, 1-H), 7.44–7.26 (m, 10 H, 2× $OCH_2C_6H_5$), 7.16 (dd, J = 8.0, 1.7 Hz, 1 H, 6′-H), 7.09 (t, J = 8.0 Hz, 1 H, 5′-H), 6.99 (dd, J = 8.0, 1.7 Hz, 1 H, 4′-H), 6.63 (d, J = 16.5 Hz, 1 H, 2-H), 5.06 (s, 2 H, $ArOCH_2C_6H_5$), 4.53 (s, 2 H, $CH_2OCH_2C_6H_5$), 3.91 (s, 3 H, OCH_3), 3.53 (t, J = 6.2 Hz, 2 H, 6-H), 2.68 (t, J = 7.2 Hz, 2 H, 4-H), 2.07–1.98 (m, 2 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.3, 153.1, 147.0, 138.4, 137.5, 137.0, 129.2, 128.6, 128.4, 128.3, 128.2, 127.6, 127.5, 127.4, 124.2, 118.7, 114.0, 75.6, 72.8, 69.4, 55.8, 36.3, 24.2 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3032, 2864, 1685, 1594, 1450, 1091, 733 cm^{-1}. HRMS (EI): calcd. for $C_{27}H_{28}NaO_4$ $[M + Na]^+$ 439.1880; found 439.1878.

(*E*)-6-(Benzyloxy)-1-[2-(benzyloxy)-4-methoxyphenyl]hex-1-en-3-one (39): The general procedure was applied by using phosphonate **29** (0.12 g, 0.4 mmol) and aldehyde **32** (0.10 g, 0.4 mmol), stirring the reaction mixture at room temp. for 23 h. The product was obtained as a colourless oil (0.16 g, 96%). ^1H NMR (300 MHz, $CDCl_3$): δ

= 7.91 (d, J = 16.2 Hz, 1 H, 1-H), 7.52–7.25 (m, 11 H, 2× $OCH_2C_6H_5$ and H6′), 6.76 (d, J = 16.2 Hz, 1 H, 2-H), 6.55–6.52 (m, 2 H, 3′-H and 5′-H), 5.14 (s, 2 H, $ArOCH_2C_6H_5$), 4.50 (s, 2 H, $CH_2OCH_2C_6H_5$), 3.81 (s, 3 H, OCH_3), 3.53 (t, J = 6.3 Hz, 2 H, 6-H), 2.74 (t, J = 7.2 Hz, 2 H, 4-H), 2.03–1.94 (m, 2 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.5, 162.7, 159.0, 138.5, 137.7, 136.4, 130.2, 128.7, 128.3, 128.1, 127.6, 127.5, 127.2, 124.8, 117.0, 105.9, 99.9, 72.8, 70.5, 69.6, 55.4, 37.1, 24.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3030, 2856, 1681, 1594, 1272, 1165, 1115, 696 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{28}NaO_4$ [M + Na]$^+$ 439.1880; found 439.1877.

(*E*)-6-(Benzyloxy)-1-[2,4-bis(benzyloxy)phenyl]hex-1-en-3-one (40): The general procedure was applied by using phosphonate **29** (0.71 g, 2.4 mmol) and aldehyde **33** (0.75 g, 2.4 mmol), stirring the reaction mixture at reflux for 2.5 h. The product was obtained as a yellow solid (0.91 g, 78%); m.p. 69–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 16.3 Hz, 1 H, 1-H), 7.48–7.46 (m, 1 H, 6′-H), 7.41–7.22 (m, 15 H, 3× $OCH_2C_6H_5$), 6.74 (d, J = 16.3 Hz, 1 H, 2-H), 6.59–6.57 (m, 2 H, 3′-H and 5′-H), 5.08 (s, 2 H, $ArOCH_2C_6H_5$), 5.03 (s, 2 H, $ArOCH_2C_6H_5$), 4.47 (s, 2 H, $CH_2OCH_2C_6H_5$), 3.50 (t, J = 6.2 Hz, 2 H, 6-H), 2.71 (t, J = 7.3 Hz, 2 H, 4-H), 1.99–1.93 (m, 2 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.4, 161.8, 158.9, 138.5, 137.6, 136.3, 130.1, 130.1, 128.6, 128.3, 128.1, 128.0, 127.5, 127.4, 127.1, 124.8, 117.1, 106.7, 100.6, 72.7, 70.4, 70.1, 69.5, 37.0, 24.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3031, 2855, 1679, 1591, 1562, 1181, 1127, 730 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{33}O_4$ [M + H]$^+$ 493.2373; found 493.2361.

(*E*)-6-(Benzyloxy)-1-[2,5-bis(benzyloxy)phenyl]hex-1-en-3-one (41): The general procedure was applied by using phosphonate **29** (0.19 g, 0.6 mmol) and aldehyde **34** (0.10 g, 0.3 mmol) (2.0 equiv. of **29** and NaH used relative to **34**), stirring the reaction mixture at room temp. for 17 h. The product was obtained as a pale yellow solid (0.57 g, 94%); m.p. 66–67 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, J = 16.5 Hz, 1 H, 1-H), 7.49–7.27 (m, 15 H, 3× $OCH_2C_6H_5$), 7.22 (d, J = 3.0 Hz, 1 H, 6′-H), 6.99 (dd, J = 9.0, 3.0 Hz, 1 H, 4′-H), 6.92 (d, J = 9.0 Hz, 1 H, 3′-H), 6.80 (d, J = 16.5 Hz, 1 H, 2-H), 5.12 (s, 2 H, $ArOCH_2C_6H_5$), 5.06 (s, 2 H, $ArOCH_2C_6H_5$), 4.54 (s, 2 H, $CH_2OCH_2C_6H_5$), 3.57 (t, J = 6.2 Hz, 2 H, 6-H), 2.80 (t, J = 7.4 Hz, 2 H, 4-H), 2.07–1.98 (m, 2 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.3, 152.9, 152.1, 138.4, 137.3, 136.8, 136.7, 128.5, 128.3, 127.9, 127.5, 127.42, 127.37, 127.2, 127.1, 124.7, 118.2, 114.4, 114.0, 72.7, 71.2, 70.6, 69.4, 37.0, 24.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3031, 2857, 1658, 1603, 1493, 1205, 733, 695 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{32}NaO_4$ [M + Na]$^+$ 515.2193; found 515.2174.

(*E*)-6-(Benzyloxy)-1-[2-(benzyloxy)-6-methoxyphenyl]hex-1-en-3-one (42): The general procedure was applied by using phosphonate **29** (0.12 g, 0.4 mmol) and aldehyde **35** (0.10 g, 0.4 mmol), stirring the reaction mixture at room temp. for 23 h. The product was obtained as a pale yellow oil (0.16 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, J = 16.8 Hz, 1 H, 1-H), 7.46–7.23 (m, 12 H, 2 $CH_2C_6H_5$ and 4′-H and 2-H), 6.63–6.57 (m, 2 H, 3′-H and 5′-H), 5.17 (s, 2 H, $ArOCH_2C_6H_5$), 4.51 (s, 2 H, $CH_2OCH_2C_6H_5$), 3.89 (s, 3 H, OCH_3), 3.54 (t, J = 6.2 Hz, 2 H, 6-H), 2.74 (d, J = 7.2 Hz, 2 H, 4-H), 2.02–1.96 (m, 2 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6, 160.2, 159.1, 138.5, 136.5, 133.5, 131.2, 129.3, 128.6, 128.3, 128.0, 127.5, 127.4, 127.1, 112.7, 105.2, 103.9, 72.7, 70.7, 69.6, 55.7, 37.2, 24.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3032, 2861, 1682, 1593, 1474, 1103, 730 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{28}NaO_4$ [M + Na]$^+$ 439.1880; found 439.1875.

(*E*)-6-(Benzyloxy)-1-[2,6-bis(benzyloxy)phenyl]hex-1-en-3-one (43): The general procedure was applied by using phosphonate **29** (0.18 g, 0.6 mmol) and aldehyde **36** (0.18 g, 0.6 mmol), stirring the reaction mixture at room temp. for 17.5 h. The product was obtained as a pale yellow solid (0.27 g, 96%); m.p. 62–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, J = 16.4 Hz, 1 H, 1-H), 7.49–7.19 (m, 17 H, 3 OBn, 2-H and 4′-H), 6.62 (d, J = 8.4 Hz, 2 H, 3′-H and 5′-H), 5.17 (s, 4 H, 2 $ArOCH_2C_6H_5$), 4.50 (s, 2 H, $CH_2OCH_2C_6H_5$), 3.50 (t, J = 6.4 Hz, 2 H, 6-H), 2.67 (t, J = 7.4 Hz, 2 H, 4-H), 1.98–1.91 (m, 2 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.5, 159.2, 138.6, 136.5, 133.3, 131.1, 129.4, 128.6, 128.3, 128.0, 127.6, 127.4, 127.2, 126.9, 113.2, 105.5, 72.8, 70.7, 69.6, 37.6, 24.2 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3032, 2864, 1685, 1593, 1452, 1252, 1091, 733 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{32}NaO_4$ [M + Na]$^+$ 515.2193; found 515.2176.

General Procedure for the Reduction of Enones 7, 18 and 19: Enone (0.08 mmol) in dichloromethane (3 mL) was added to a stirred suspension of titanocene dichloride (0.008 mmol), zinc dust (0.2 mmol) and triethylamine hydrochloride (0.4 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at room temp. for 1 h. Saturated ammonium chloride was added and the reaction mixture filtered through Celite and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried with magnesium sulfate, and the solvent was removed in vacuo before purification by flash chromatography using hexanes/ethyl acetate (4:1) as eluent.

6-[(4-Methoxybenzyl)oxy]-1-{2-[(4-methoxybenzyl)oxy]phenyl}-hexan-3-one (20): The general procedure was applied by using enone **7** (36 mg, 0.08 mmol). The product was obtained as pale yellow oil (28 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, J = 8.6 Hz, 2 H, $OCH_2PhOCH3$), 7.22 (d, J = 8.6 Hz, 2 H, OCH_2-$PhOCH_3$), 7.18–7.11 (m, 2 H, ArH), 6.92–6.83 (m, 6 H, ArH), 4.99 (s, 2 H, OCH_2PhOCH_3), 4.36 (s, 2 H, OCH_2PhOCH_3), 3.79 (s, 3 H, OCH_2PhOCH_3), 3.77 (s, 3 H, OCH_2PhOCH_3), 3.39 (t, J = 8.4 Hz, 2 H, 6-H), 2.90 (t, J = 10.2 Hz, 2 H, 2-H), 2.69 (t, J = 10.2 Hz, 2 H, 1-H), 2.43 (t, J = 9.6 Hz, 2 H, 4-H), 1.86–1.77 (m, 2 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.3, 159.3, 159.1, 156.6, 130.5, 130.1, 129.8, 129.3, 129.2, 128.7, 127.3, 120.7, 113.9, 113.7, 111.7, 72.4, 69.6, 69.0, 55.2, 42.7, 39.3, 25.1, 23.8 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2933, 1710, 1612, 1513, 1239, 1173, 1032 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{32}NaO_5$ [M + Na]$^+$ 471.2142; found 471.2133.

1-(2-{[(4-Methoxybenzyl)oxy]methyl}phenyl)-3-{2-[(4-methoxybenzyl)oxy]phenyl}propan-1-one (21): The general procedure was applied by using enone **18** (40 mg, 0.08 mmol). The product was obtained as a colourless solid (33 mg, 83%); m.p. 81–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 7.7 Hz, 1 H, ArH), 7.54 (d, J = 7.7 Hz, 1 H, ArH), 7.43 (t, J = 7.6 Hz, 1 H, ArH), 7.34–7.27 (m, 4 H, ArH), 7.22–7.13 (m, 3 H, ArH), 6.93–6.85 (m, 6 H, ArH), 5.00, 4.78, 4.48 (s, 6 H, 2 CH_2PhOCH_3 and CH_2OPMB), 3.78 (s, 3 H, OCH_2PhOCH_3), 3.77 (s, 3 H, OCH_2PhOCH_3), 3.18 (t, J = 10.4 Hz, 2 H, 2-H), 3.02 (t, J = 10.4 Hz, 2 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.8, 159.3, 159.1, 156.7, 139.2, 136.7, 131.3, 130.4, 130.2, 129.7, 129.3, 129.2, 129.0, 128.5, 127.9, 127.4, 126.8, 120.7, 114.0, 113.7, 111.7, 72.5, 70.1, 69.7, 55.2, 41.3, 26.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2934, 2838, 1682, 1512, 1252, 1235, 746 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{32}NaO_5$ [M + Na]$^+$ 519.2142; found 519.2140.

1,4-Bis{2-[(4-methoxybenzyl)oxy]phenyl}butan-2-one (22): The general procedure was applied by using enone **19** (40 mg, 0.08 mmol). The product was obtained as a colourless solid (36 mg, 89%); m.p. 70–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.18 (m, 5 H, ArH), 7.13 (t, J = 7.8 Hz, 1 H, ArH), 7.07–7.04 (m, 2 H, ArH), 6.90–6.81 (m, 8 H, ArH), 4.93 (s, 2 H, OCH_2PhOCH_3), 4.90 (s, 2 H, OCH_2PhOCH_3), 3.78 (s, 3 H, OCH_2PhOCH_3), 3.75 (s, 3 H,

OCH_2PhOCH_3), 3.61 (s, 2 H, 1-H), 2.86 (t, J = 8.0 Hz, 2 H, 3-H), 2.70 (t, J = 8.0 Hz, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.4, 159.3, 159.2, 156.5, 156.4, 131.2, 130.1, 129.8, 129.3, 128.9, 128.9, 128.6, 128.3, 127.2, 124.1, 120.7, 120.6, 113.9, 111.7, 111.6, 69.7, 69.5, 55.2, 44.8, 42.0, 25.0 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2961, 2933, 1716, 1514, 1237, 1006 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{32}NaO_5$ $[M + Na]^+$ 519.2142; found 519.2135.

General Procedure for the Cyclisation. Method A: A mixture of dihydroxy ketone (1 equiv.) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (3 equiv.) in dichloromethane/water (10:1) was stirred at room temp. for 7–24 h. Aqueous saturated sodium hydrogen carbonate was added, and the solvent was removed in vacuo. The resulting mixture was extracted with ethyl acetate, the combined organic extracts were washed with aqueous saturated sodium hydrogen carbonate and brine, and the solvent was removed in vacuo. The resulting oil was purified by preparative thin layer chromatography using hexanes/ethyl acetate (4:1) as eluent. **Method B:** Anhydrous hydrochloric acid (4 M in dioxane) was added to a stirred solution of dihydroxy ketone in THF and the resultant mixture stirred at room temp. for 48 h. The reaction mixture was neutralised with aqueous sodium hydroxide and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried with magnesium sulfate, and the solvent was removed in vacuo before purification by preparative thin layer chromatography using hexanes/ethyl acetate (4:1) as eluent.

4′,5′-Dihydro-3′*H*-spiro[chroman-2,2′-furan] (4): Method A: Dihydroxy ketone **20** (50 mg, 0.1 mmol); the product was obtained as a colourless oil (8.0 mg, 40%). Method B: Dihydroxy ketone **20** (33 mg, 0.07 mmol); the product was obtained as colourless oil (8.4 mg, 60%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.05 (m, 2 H, 5-H and 6-H), 6.91–6.75 (m, 2 H, 7-H and 8-H), 4.13–3.93 (m, 2 H, 5′-H), 3.11–2.99 (m, 1 H, 4-H), 2.74 (dt, J = 4.9, 16.3 Hz, 1 H, 4-H), 2.32–1.82 (m, 6 H, 3 CH_2) ppm. The ^1H NMR spectroscopic data obtained was in agreement with that reported in the literature.[1c]

3′*H*-Spiro[chroman-2,1′-isobenzofuran] (5): Method B: Dihydroxy ketone **21** (50 mg, 0.1 mmol); the product was obtained as a pale yellow solid (14 mg, 58%); m.p. 70–71 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.38 (m, 3 H, ArH), 7.34–7.32 (d, J = 7.2 Hz, 1 H, ArH), 7.16–7.07 (m, 3 H, ArH), 6.91 (t, J = 6.4 Hz, 1 H, ArH), 6.81–6.78 (m, 2 H, ArH), 5.30 (d, J = 12.8 Hz, 1 H, 3′-H), 5.07 (d, J = 12.8 Hz, 1 H, 3′-H), 3.36–3.24 (m, 1 H, 4-H), 2.89 (ddd, J = 16.3, 5.8, 2.0 Hz, 1 H, 4-H), 2.45 (dt, J = 13.2, 5.8 Hz, 1 H, 3-H), 2.20 (ddd, J = 13.2, 5.7, 2.1 Hz, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 140.0, 129.4, 129.1, 127.9, 127.4, 122.0, 121.7, 121.3, 120.8, 117.1, 108.2, 71.7, 30.2, 21.7 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3044, 2942, 1583, 1488, 1231, 1002, 745 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{15}O_2$ $[M + H]^+$ 239.1067; found 239.1062.

3*H*-Spiro[benzofuran-2,2′-chroman] (6): Method A: Dihydroxy ketone **22** (77 mg, 0.2 mmol); the product was obtained as a colourless solid (0.013 g, 35%); m.p. 71–72 °C (ref.[13] oil). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 8.0 Hz, 1 H, ArH), 7.17–7.09 (m, 3 H, ArH), 6.94–6.90 (m, 2 H, ArH), 6.80–6.78 (m, 2 H, ArH), 3.45 (d, J = 16.4 Hz, 1 H, 3′-H), 3.31–3.21 (m, 2 H, 3′-H, 4-H), 2.83 (ddd, J = 16.4, 6.0, 2.7 Hz, 1 H, 4-H), 2.33 (ddd, J = 13.2, 6.0, 2.7 Hz, 1 H, 3-H), 2.20 (ddd, J = 13.2, 13.2, 6.0 Hz, 1 H, 3-H) ppm. The ^1H and ^{13}C NMR spectroscopic data obtained was in agreement with that reported in the literature.[13]

General Procedure for the Hydrogenation/Cyclisation of Enones 37–43. Method A: The appropriate enone was taken up in tetrahydrofuran, and catalytic palladium (10% on carbon) or palladium hydroxide (20% on carbon) was added and the resulting reaction mixture stirred under hydrogen until the reaction was judged complete by TLC. The solvent was removed in vacuo, and the reaction mixture was purified by flash or preparative thin layer chromatography. **Method B:** A solution (0.1 g/50 mL) of the appropriate enone in ethyl acetate/methanol (1:1) was hydrogenated by means of an H-Cube® HC-2 continuous hydrogenation apparatus (THALES Nanotechnology Inc.) using a 20% palladium hydroxide cartridge with a flow rate of 1 mL/min and a column block temperature of 20 °C and a pressure of 20 bar in full H_2 mode. The solvent was removed in vacuo and the resulting crude product purified by flash or preparative thin layer chromatography.

4′,5′-Dihydro-3′*H*-spiro[chroman-2,2′-furan] (4): Method A: Enone **37** (0.20 g, 0.5 mmol) was reduced in the presence of Pd/C or $Pd(OH)_2$ catalyst with a reaction time of 72 h; purification was carried out by flash chromatography using hexanes/ethyl acetate (4:1) to afford a colourless oil (87 mg, 88%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.05 (m, 2 H, 5-H and 6-H), 6.91–6.75 (m, 2 H, 7-H and 8-H), 4.13–3.93 (m, 2 H, 5′-H), 3.11–2.99 (m, 1 H, 4-H), 2.74 (dt, J = 16.3, 4.9 Hz, 1 H, 4-H), 2.32–1.82 (m, 6 H, 3 CH_2) ppm. The ^1H NMR spectroscopic data obtained was in agreement with that reported in the literature.[1c]

8-Methoxy-4′,5′-dihydro-3′*H*-spiro[chroman-2,2′-furan] (23): Method B: Enone **38** (90 mg, 0.2 mmol); purification was carried out by flash chromatography using hexanes/ethyl acetate (4:1) to afford a colouress oil (33 mg, 68%). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.81–6.77 (m, 1 H, 6-H), 6.72–6.69 (m, 2 H, 5-H and 7-H), 4.11 (dt, J = 8.0, 6.0 Hz, 1 H, 5-H), 3.97 (dt, J = 8.0, 6.0 Hz, 1 H, 5-H), 3.82 (s, 3 H, OCH_3), 3.11–3.02 (m, 1 H, 4-H), 2.78–2.72 (m, 1 H, 4-H), 2.40–2.24 (m, 2 H, CH_2), 2.12–1.87 (m, 4 H, 2 CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 142.7, 122.7, 121.2, 119.8, 109.9, 106.6, 66.2, 56.1, 37.0, 29.9, 24.2, 22.8 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2940, 2899, 1585, 1481, 1262, 1190, 1074 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{17}O_3$ $[M + H]^+$ 221.1172; found 221.1165.

7-Methoxy-4′,5′-dihydro-3′*H*-spiro[chroman-2,2′-furan] (24): Method A: Enone **39** (0.10 g, 0.2 mmol) was reduced in the presence of Pd/C catalyst, with a reaction time of 21 h; purification was carried out by preparative thin layer chromatography using hexanes/ethyl acetate (4:1) to afford a colourless oil (28 mg, 53%). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.96 (d, J = 8.3 Hz, 1 H, 5-H), 6.46 (dd, J = 8.3, 2.6 Hz, 1 H, 6-H), 6.36 (d, J = 2.4 Hz, 1 H, 8-H), 4.14–3.94 (m, 2 H, 5′-H), 3.75 (s, 3 H, OCH_3), 3.03–2.92 (m, 1 H, 4-H), 2.69 (dt, J = 15.9, 5.0 Hz, 1 H, 4-H), 2.30–2.18 (m, 2 H, CH_2), 2.07–1.83 (m, 4 H, 2 CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 153.8, 129.5, 113.9, 107.3, 106.8, 102.0, 68.1, 55.3, 36.9, 30.1, 24.1, 22.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2936, 1620, 1583, 1505, 1442, 1155, 1132, 982, 849 cm^{-1} HRMS (ESI): calcd. for $C_{13}H_{17}O_3$ $[M + H]^+$ 221.1172; found 221.1168.

4′,5′-Dihydro-3′*H*-spiro[chroman-2,2′-furan]-7-ol (25): Method A: Enone **40** (0.10 g, 0.2 mmol) was reduced in the presence of $Pd(OH)_2$ catalyst, with a reaction time of 72 h; purification was carried out by preparative thin layer chromatography using hexanes/ethyl acetate (4:1) to afford a colourless solid (32 mg, 76%); m.p. 85–86 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.85 (d, J = 8.4 Hz, 1 H, 5-H), 6.33 (dd, J = 8.4, 2.4 Hz, 1 H, 6-H), 6.27 (d, J = 2.4 Hz, 1 H, 8-H), 5.72 (br. s, 1 H, OH), 4.17–3.93 (m, 2 H, 5′-H), 2.97–2.86 (m, 1 H, 4-H), 2.64 (dt, J = 15.9, 5.1 Hz, 1 H, 4-H), 2.24–2.16 (m, 2 H, CH_2), 2.05–1.80 (m, 4 H, 2 CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.0, 153.5, 129.6, 113.6, 108.2, 106.9, 103.8, 68.1, 36.7, 30.0, 23.8, 22.0 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3359, 2934, 1711, 1622, 1151, 990, 844 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{15}O_3$ $[M + H]^+$ 207.1016; found 207.1009.

4′,5′-Dihydro-3′*H*-spiro[chroman-2,2′-furan]-6-ol (26): Method B: Enone **41** (0.20 g, 0.4 mmol); after hydrogenation, the solvent stream was run through a 2 × 4 cm loosely packed column of Amberlyst 15® acidic resin (Sigma–Aldrich) before the solvent was removed in vacuo; purification was carried out by flash chromatography using hexanes/ethyl acetate (4:1) to afford a colourless solid (67 mg, 80%); m.p. 125–126.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.63 (d, J = 8.8 Hz, 1 H, 8-H), 6.55 (dd, J = 8.8, 2.8 Hz, 1 H, 7-H), 6.50 (d, J = 2.8 Hz, 1 H, 5-H), 5.12 (br. s, 1 H, OH), 4.09–3.94 (m, 2 H, 5′-H), 3.02–2.93 (m, 1 H, 4-H), 2.65 (dt, J = 16.8, 4.8 Hz, 1 H, 4-H), 2.26–2.18 (m, 2 H, CH_2), 2.07–1.84 (m, 4 H, 2 CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2, 146.8, 122.5, 117.6, 115.3, 114.3, 106.5, 68.0, 36.9, 29.8, 24.0, 22.8 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3264, 2257, 1646, 1496, 1194, 1074, 914 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{15}O_3$ $[M + H]^+$ 207.1016; found 207.1007.

5-Methoxy-4′,5′-dihydro-3′*H*-spiro[chroman-2,2′-furan] (27): Method A: Enone **42** (0.10 g, 0.2 mmol) was reduced in the presence of Pd/C catalyst, with a reaction time of 70 h; purification was carried out by preparative thin layer chromatography using hexanes/ethyl acetate (4:1) to afford a yellow oil (33 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (t, J = 8.3 Hz, 1 H, 7-H), 6.46–6.42 (m, 2 H, 6-H, 8-H), 4.12–3.94 (m, 2 H, 5′-H), 3.81 (s, 3 H, OCH_3), 2.81–2.77 (m, 2 H, 4-H), 2.31–2.19 (m, 2 H, CH_2), 2.08–1.80 (m, 4 H, 2 CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) 157.6, 153.8, 127.0, 110.8, 109.9, 106.4, 102.2, 68.1, 55.4, 36.7, 29.4, 24.0, 17.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2960, 2895, 1591, 1469, 1249, 1077 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{17}O_3$ $[M + H]^+$ 221.1172; found 221.1165.

4′,5′-Dihydro-3′*H*-spiro[chroman-2,2′-furan]-5-ol (28): Method A: Enone **43** (0.20 g, 0.4 mmol) was reduced in the presence of $Pd(OH)_2$ catalyst, with a reaction time of 65 h, purification was carried out by flash chromatography using pentane/diethyl ether (3:2) to afford a colourless solid (52 mg, 64%); m.p. 98–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (t, J = 8.4 Hz, 1 H, 7-H), 6.40 (dd, J = 8.4, 0.8 Hz, 1 H, 8-H), 6.34 (dd, J = 8.4, 0.8 Hz, 1 H, 6-H), 4.76 (br.s, 1 H, OH), 4.10–3.95 (m, 2 H, 5′-H), 2.86–2.71 (m, 2 H, 4-H), 2.29–2.18 (m, 2 H, CH_2), 2.11–1.83 (m, 4 H, 2 CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 154.1, 154.0, 127.1, 109.4, 106.9, 106.4, 68.2, 36.8, 34.1, 29.3, 24.0, 17.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3360, 2928, 1616, 1591, 1463, 1007, 773 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{15}O_3$ $[M + H]^+$ 207.1016; found 207.1016.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for selected compounds.

Acknowledgments

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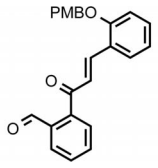

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