Electronic Supplementary Material (ESI) for Chemical Science. This journal is © The Royal Society of Chemistry 2020

Supporting Information

for

A Modular and Divergent Approach to Spirocyclic Pyrrolidines

Benjamin D. A. Shennan, Peter W. Smith, Yusuke Ogura, and Darren J. Dixon*

Department of Chemistry, Chemistry Research Laboratory

University of Oxford, Mansfield Road, Oxford OX1 3TA (UK)

E-mail: darren.dixon@chem.ox.ac.uk

1.	General Information	2
2.	General Procedures for the Synthesis of 1-Azaspiro[4,4]non-8-en-9-ones	4
3.	Optimization of Cycloaddition and Phosphonate Condensation	8
4.	Nitrone Syntheses	10
5.	Synthesis of Phosphonates	20
6.	Synthesis and Characterisation of Cycloadducts	22
7.	Synthesis and Characterisation of Ketophosphonates	29
8.	Synthesis and Characterisation of Spirocycles	41
9.	Formal Synthesis of (±)-Cephalotaxine	54
10.	Challenging Substrates and Unsuccessful Intermediates	62
NMR Spectra for Novel Compounds		63
Refere	References1	

1. General Information

Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. All reagents were obtained from commercial suppliers and used without further purification. Where solvent dryness was important, CH₂Cl₂, Et₂O, THF or toluene were obtained from: dry solvent bottles with a septa (Aldrich or Acros) or an MBRAUN-SPS solvent purification system. All reactions were carried out under a nitrogen atmosphere.

Flash column chromatography was carried out using Merck Silicagel 60, particle size 40-63 µm. All reactions were followed by thin layer chromatography (TLC) when practical, using Merck aluminium-backed Silicagel 60 F254 fluorescent treated silica which was visualised under UV light (254 nm or 365 nm). In addition, TLC plates were stained with aq. basic potassium permanganate or ethanolic acidic vanillin.

¹**H**, ¹³**C**, ¹⁹**F** and ³¹**P NMR** spectra were recorded using Bruker AVIII HD 400 and Bruker AVII 500 spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm) relative to tetramethylsilane (δ =0) and are referenced to the solvent residual peak. Coupling constants

(J) are quoted in Hertz (Hz), rounded to the nearest 0.1 Hz. The ¹H NMR spectra are reported as follows: ppm (multiplicity, coupling constants, number of protons). NMR assignments, where present, use numbering independent from IUPAC, using two dimensional (COSY, HSQC, HMBC) NMR spectroscopy to assist the assignment. Where distinction between major and minor diastereomers/rotamers has been possible the notation maj/min has been employed after each resonance. **Infrared (IR) spectra** were recorded on a Bruker Tensor 27 FT-IR spectrometer. Absorption maxima (v_{max}) are reported in wavenumbers (cm⁻¹). Only selected absorption maxima are reported. **Low resolution mass spectra (LRMS)** were recorded on a Agilent single quadrupole with CTC-PAL mass spectrometer operating in positive ionisation mode. **High resolution mass spectra (HRMS)** were recorded on a Bruker Daltonics μTOF mass spectrometer. **Melting points (MP)** were recorded in degrees Celsius (°C), using a Leica Galen III hotstage microscope apparatus.

2. General Procedures for the Synthesis of 1-Azaspiro[4,4]non-8-en-9ones

Oxidation Procedure A



Following a modified literature procedure,¹ The secondary amine hydrochloride salt was dissolved in a minimum amount of H₂O, basified to > pH 10 with sat. aq. K₂CO₃ and then extracted with CH₂Cl₂. The combined organics were dried with Na₂SO₄, filtered and the solvent was removed under reduced pressure. To the resulting free amine was added H₂O (0.5 M), and the solution was cooled to 0 °C before adding Na₂WO₄ (5 mol%). H₂O₂ (30% aq., 2.2 eq.) was then added dropwise over 30 min and this was biphasic mixture was stirred under a N₂ atmosphere for 3 h, at which point it was cooled to 0 °C and excess H₂O₂ was quenched via addition of sat. aq. Na₂SO₃. The resulting aqueous mixture was extracted with CH₂Cl₂ and the combined organics were dried with Na₂SO₄, filtered and the solvent was removed under reduced pressure. The resulting crude oil was purified by FCC.

Oxidation Procedure B



Following a literature procedure,² to a suspension of secondary amine hydrochloride salt in MeCN (0.09 M) was added 35% ammonia solution (2.5 eq.). This was stirred under a N_2 atmosphere for 5 minutes before adding a solution of Davis' oxaziridine (2.5 eq.) in toluene (0.7 M) dropwise over 45 minutes. The reaction was stirred at r.t. until starting material was

consumed as determined by TLC, at which point brine was introduced. The aqueous phase was extracted with EtOAc and the organic layers were combined and washed with brine. The organic phase was dried with MgSO₄ then filtered before removing the solvent under reduced pressure. The crude product was purified as in Oxidation Procedure A.

Note: During the course of this work, different nitrone oxidation methodologies were investigated. The two detailed in this S.I. offer complementary approaches to this challenging transformation: Oxidation Procedure A is typically lower yielding but uses far cheaper reagents – all of which are commercially available – and is more amenable to scale-up, hence, it was used for less elaborate starting materials where chemical yield was less important; Oxidation Procedure B tended to give a higher yield however faces difficulties associated with using superstoichiometric Davis' Oxaziridine, it was therefore used on smaller scales where material was more precious. Additional oxidation procedures investigated included using methyl trioxorhenium/UHP, mCPBA, and Oxone however were inferior to the two detailed above for the substrates in question.³

Cycloadduct Preparation: General Procedure A



In an oven-dried sealable tube flushed with N_2 , nitrone **1a** (100 mg, 0.456 mmol) was mixed with the respective alkyne (1.369 mmol) in hexane (4 mL) and the tube was sealed and stirred at 70 °C for 20 h - or until the starting material was consumed as determined by TLC. The hexane was removed under a stream of N_2 and the crude oil that resulted was purified by FCC.

Ketophosphonate Preparation I: General Procedure B



A solution of cycloadduct starting material (~0.156 mmol) and dimethyl methylphosphonate (1.2 eq.) in dry degassed THF (0.2 M) was added dropwise to 1M LiHMDS in THF (3 eq.) at -78 °C under an argon atmosphere. The reaction mixture was stirred until the starting material was consumed as determined by TLC and then quenched by the addition of sat. aq. NH₄Cl (2 mL). After dilution with EtOAc (5 mL) and H₂O (5 mL), the aqueous phase was extracted with EtOAc (3 x 20 mL) and the organic layers were combined, dried with MgSO₄ and filtered. The solvent was removed under reduced pressure to yield a yellow oil that was purified by FCC (EtOAc) to yield the ketophosphonates as light yellow oils.

Ketophosphonate Preparation II: Modification to General Procedure B



A solution of cycloadduct **2d** starting material (0.156 mmol) and the respective phosphonate (2.1 eq.) in dry degassed THF (0.2 M) was stirred at -78 °C under an argon atmosphere. 1M LiHMDS in THF (467 μ L, 0.467 mmol) was added dropwise over 15 minutes and the reaction mixture was allowed to slowly warm to room temperature. After stirring at room temperature for 1 h, the solution was quenched with sat. aq. NH₄Cl (2 mL). The aqueous layer was diluted with H₂O (5 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried with MgSO₄ and filtered. The solvent was removed under reduced

pressure to yield yellow oils. Purification by FCC (2:1 EtOAc:pentane) yielded the substituted ketophosphonates as colourless oils.

Note: In some of the more challenging condensations, it was observed that holding the temperature at -78 °C for longer, e.g 4 hours, improved the yield.

Synthesis of N-Boc-Spiroamines: General Procedure C



To a fully purged round-bottomed flask under argon, a solution of ketophosphonate in dry THF (0.05 M) was added and cooled to -78 °C. 1M LiHMDS in THF (1 eq.) was added dropwise and then stirred for 20 min. 1M sodium naphthalenide (NaNap) in THF (~3 eq.) was added dropwise until complete consumption of starting material was observed by TLC (9:1 EtOAc:MeOH). H₂O (0.5 mL) was then added, followed by addition of sat. aq. K₂CO₃ (1 mL) and the biphasic mixture was stirred for 1 h before addition of a solution of Boc₂O (2 eq.) in THF (1 mL). After stirring at r.t. for 18 h, the aqueous phase was diluted (2 mL H₂O) and then extracted with EtOAc (3 x 20 mL) and the organic layers were combined, dried with MgSO₄ and filtered before removal of the solvent under reduced pressure. The resulting crude material was purified by FCC.

Note: In the early stages of the dropwise addition of the NaNap solution to the reaction mixture, the dark green colour of the NaNap was observed to rapidly disappear upon reaction with the starting material. As the addition continued, the colour was observed to linger and at

this point TLC analysis was carried out to confirm consumption of starting material was proceeding.

Note: Early experimentation with this method highlighted a detrimental effect in using a significant excess of NaNap. As such care must be taken in the later stage of the addition with more frequent TLC analyses.

Note: Upon completion the reaction mixture was typically a light brown solution. Overaddition of NaNap was evident from the solution remaining dark green or often an insoluble dark solid would form, presumably precipitated NaNap caused by the cryogenic temperatures. This solid would slowly dissolve/react upon warming to room temperature.

Preparation of 1M Sodium Naphthalenide (NaNap)

To a solution of naphthalene (1.28 g, 10 mmol) in dry THF (10 mL) was added sodium metal (0.345 g, 15 mmol) and the reaction was stirred under an atmosphere of N_2 for 16 h. The dark green solution that resulted was used in General Procedure C without further purification.

3. Optimization of Cycloaddition and Phosphonate Condensation



Table S1. Solvent screen for model cycloaddition. ^{a 1}H NMR yield using trimethoxybenzene as standard. ^bIsolated yield.



Table S2. Results from the phosphonate condensation optimisation. ^aCycloadduct in THF added to Liphosphonate solution. ^bTHF degassed, Liphosphonate formation stirred for 1 h, -78 °C maintained for an additional 2 h. ^cReaction stirred overnight. ^dTHF Solution of **2d** and phosphonate added dropwise to base.



Table S3. Results from the optimisation of the synthesis of α -substituted β -ketophosphonates. ^a-5 °C to 0 °C.⁴ ^bReverse addition (base added to cycloadduct-phosphonate solution), rigorously anhydrous conditions.

4. Nitrone Syntheses

Synthesis of Nitrone 1a



Scheme S1. Synthesis of Nitrone 1a

Cl

(S)-1-((benzyloxy)carbonyl)pyrrolidin-5-ium chloride (S1)

To a flask of N-Boc-proline (21.5 g, 100 mmol) dissolved CH₂Cl₂ (200 mL) was added DCC (22.7 g, 110 mmol), DMAP (1.2 g, 10 mmol) and benzyl alcohol (10.3 mL, 100 mmol). The reaction flask was stirred at r.t. for 16 h under a N₂ atmosphere before being cooled to -10 °C and filtered in *vacuo*.

The filtrate was concentrated under reduced pressure before being purified by FCC (3:1 pentane:EtOAc) to afford the benzyl ester of N-Boc-proline as a light yellow oil. The yield was assumed quantitative and the product was stirred in 4M HCl in dioxane (100 mL, 400 mmol) under a N₂ atmosphere for 4 h. Et₂O was added to the reaction mixture until a white solid was observed at which point the reaction was cooled to 0 °C. The mixture was filtered in *vacuo* to yield the title compound as a white solid (20.4 g, 85% *over 2 steps*). **MP** 148-149 °C (lit. 141-143 °C)⁵; ¹**H NMR** (400 MHz, CDCl₃) δ 10.60 (br s, 1H), 9.24 (br s, 1H), 7.35 – 7.27 (m, 5H), 5.25 – 5.07 (m, 2H), 4.48 (m, 1H), 3.59 – 3.37 (m, 2H), 2.41 – 2.28 (m, 1H), 2.20 – 1.90 (m, 3H); ¹³C **NMR** (101 MHz, CDCl₃) δ 168.7, 134.5, 128.7, 128.7, 128.5, 68.3, 59.3, 45.9, 28.7, 23.5; **LRMS** (ESI) mass calculated for [M+H]+ (C₁₂H₁₆NO₂) requires *m/z* 206.1, found *m/z* 206.2. Data are consistent with the literature.⁵

1-((Benzyloxy)carbonyl)-3,4-dihydro-2H-pyrrole 5-oxide (1a)



Using Oxidation Procedure A, the hydrochloride salt of proline benzyl ester **S1** (7.8 g, 32 mmol) was submitted to the reaction conditions. FCC purification (19:1 EtOAc:MeOH) afforded nitrone **1a** (2.57 g, 37%) as a colourless oil.

Using Oxidation Procedure B, hydrochloride salt **S1** (1.00 g, 4.15 mmol) was submitted to the reaction conditions. FCC purification (19:1 EtOAc:MeOH) afforded nitrone **1a** (463 mg, 51%) as a colourless oil.

IR (thin film) v_{max}/cm^{-1} 2953 (C-H), 1723 (C=O), 1696, 1553 (C=N), 1221 (N-O); ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.31 (m, 5H), 5.31 (app. d, *J* = 1.1 Hz, 2H), 4.27 – 4.15 (m, 2H), 3.13 – 3.02 (m, 2H), 2.25 – 2.14 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 159.3, 135.3, 133.8, 128.6, 128.4, 128.4, 66.8, 66.7, 29.7, 16.8; HRMS (ESI) mass calculated for [M+H]+ (C₁₂H₁₄O₃N) requires *m/z* 220.0968, found *m/z* 220.0971.

Synthesis of Nitrone 1b



Scheme S2. Synthesis of Nitrone 1b

Methyl (1S,3R)-3-((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carboxylate (S2)



Following adapted literature procedures,^{6,7,8} SOCl₂ (2.0 mL, 27 mmol) was added dropwise to a stirred and cooled (0 °C) solution of trans-4-hydroxy-L-proline (3.0 g, 23 mmol) in MeOH (38 mL). After 30 min, the

ice bath was removed and stirring was continued for 6 h. Evaporation of the solvent gave the ester hydrochloride as an off white solid (yield assumed quant.).

To a solution of the crude product and imidazole (9.4 g, 138 mmol) in CH₂Cl₂ (48 mL), was added TBSCl (4.1 g, 27 mmol) at 0 °C under N₂ atmosphere. After stirring for 6 h at r.t., the reaction was quenched with water (30 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by FCC (pentane:EtOAc 1:1) to give the title compound as a colourless oil (2.97 g, 50%). ¹H NMR (400 MHz, CDCl₃) δ 4.42 – 4.33 (m, 1H), 3.99 (t, *J* = 8.0 Hz, 1H), 3.72 (s, 3H), 3.10 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.84 (app. ddt, *J* = 11.4, 2.3, 1.1 Hz, 1H), 2.05 (m, 2H), 1.95 (ddd, *J* = 13.2, 8.0, 5.4 Hz, 1H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 175.5, 73.0, 58.7, 55.9, 52.1, 40.1, 25.8, 18.1, -4.8; LRMS (ESI) mass calculated for [M+H]+ (C₁₂H₂₅NO₃Si) requires *m*/z 260.2, found *m*/z 260.4. All data are consistent with the literature.⁸

(R)-3-((Tert-butyldimethylsilyl)oxy)-1-(methoxycarbonyl)-3,4-dihydro-2H-pyrrole 5oxide (1b)



63.6, 52.3, 40.8, 25.6, 17.9, -4.8, -4.9; **HRMS** (ESI) mass calculated for [M+H]+(C₁₂H₂₄O₄NSi) requires *m/z* 274.1469, found *m/z* 274.1465.

Synthesis of Nitrone 1c



Scheme S3. Synthesis of Nitrone 1c

Tert-butyl (S)-1-(quinolin-8-ylcarbamoyl)pyrrolidine-5-carboxylate (S3)

Following a literature procedure,⁹ HOBt hydrate (2.76 g, 15 mmol) was added to a solution of N-Boc-proline (3.23 g, 15 mmol) and 8-aminoquinoline (2.60 g, 18 mmol) in CH_2Cl_2 (60 mL) at r.t., and was stirred for 5 min. EDC.HCl (3.45 g, 18 mmol) was then added and the solution was stirred for 7 days. The reaction was diluted with CH_2Cl_2 (100 mL) and sat.

aq. NaHCO₃ (100 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL) and the combined organic extracts were dried with Na₂SO₄, filtered and the solvent was removed under reduced pressure. The resulting brown solid was purified by FCC (grading 9:1 to 4:1 pentane:EtOAc) to yield the title compound as an off-white solid (3.60 g, 70%). The product was characterised as a mixture of rotamers. **MP** 147-149 °C (lit. 136-139 °C)⁹; ¹**H NMR** (400 MHz, DMSO-d₆) δ 10.41 (br s, 0.4H), 10.26 (br s, 0.6H), 8.88 (s, 1H), 8.70 – 8.57 (m, 1H), 8.39 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.70 – 7.52 (m, 3H), 4.48 (dd, *J* = 8.5, 4.1 Hz,

1H), 3.53 - 3.37 (m, 2H), 2.31 - 2.11 (m, 1H), 2.02 (d, J = 22.5 Hz, 1H), 1.92 - 1.77 (m, 2H), 1.43 (s, 4H), 1.21 (s, 5H); ¹³C NMR (101 MHz, DMSO-d₆) δ 172.0, 171.3, 153.9, 149.4, 138.4, 137.1, 134.5, 128.3, 127.5, 122.7, 122.4, 116.5, 79.8, 79.5, 61.7, 47.2, 31.4, 30.2, 28.6, 28.3, 24.5, 23.9; LRMS (ESI) mass calculated for [M+Na]+ (C₁₉H₂₃N₃NaO₃) requires *m/z* 364.2, found *m/z* 364.2. The data were consistent with the literature.^{9*}

Tert-butyl (2S,3S)-2-phenyl-1-(quinolin-8-ylcarbamoyl)pyrrolidine-5-carboxylate (S4)



Following a literature procedure,⁹ a screw-cap tube was charged with tert-butyl (S)-2-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **S3** (1.00 g, 2.9 mmol), Ag₂CO₃ (810 mg, 2.9 mmol), pivalic acid (90 mg, 0.88 mmol), phenyl iodide (980 μ L, 8.8 mmol), Pd(OAc)₂ (66 mg, 0.29 mmol), and toluene (10 mL). The reaction vessel was flushed with

argon, sealed and placed in an oil bath (preheated to 110 °C) and stirred for 72 h. The reaction mixture was cooled to r.t. and EtOAc (50 mL) was added. The resulting solution was filtered through a pad of Celite[®], eluting with further EtOAc (2 x 50 mL). The solvent was removed under reduced pressure to yield a brown oil. Purification by FCC (grading 1% to 5% MeCN/ CH₂Cl₂) yielded the title compound as an off-white solid (642 mg, 53%). The product was characterised as a mixture of rotamers. **MP** 125-129 °C (lit 118-120 °C)⁹; ¹**H NMR** (400 MHz, DMSO-d₆) δ 9.72 (br s, 0.4H), 9.68 (br s, 0.5H), 8.83 (d, *J* = 5.1 Hz, 1H), 8.36 – 8.27 (m, 2H), 7.61 – 7.53 (m, 2H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 2H), 6.96 (t, *J* = 7.4 Hz, 1H), 4.86 (d, *J* = 8.5 Hz, 1H), 3.86 – 3.74 (m, 2H), 3.55 – 3.38 (m, 1H), 2.57 (app. q, *J* = 10.9 Hz, 1H), 2.11 (app. dd, *J* = 10.1, 4.4 Hz, 1H), 1.43 (s, 3H), 1.22 (s, 6H); ¹³C **NMR** (101 MHz, DMSO-d₆) δ 169.9, 153.7, 149.1, 138.2, 137.7, 136.9, 134.2, 128.5, 128.4, 128.0, 127.3, 127.2, 122.5, 122.1, 116.4, 79.4, 65.7, 47.9, 46.3,

^{*} Literature NMR data were taken at 373 K hence the lack of observable rotamers previously documented.

28.6, 28.3, 27.7; **LRMS** (ESI) mass calculated for $[M+H]+(C_{25}H_{28}N_3O_3)$ requires *m/z* 418.2, found *m/z* 418.7. All data were consistent with the literature.^{9*}

(1R, 2S)-1-(Methoxycarbonyl)-2-phenylpyrrolidin-5-ium chloride (S6)

 F_{0} F_{0

Following a modified literature procedure,¹⁰ a screw-cap tube was charged with **S4** (930 mg, 2.2 mmol), sodium hydroxide (890 mg, 22 mmol) and then dissolved in EtOH (12 mL). The tube was heated to 100 $^{\circ}$ C for 6 h before cooling to r.t.. The mixture was then diluted with EtOAc (12 mL) and 1M aq.

NaOH (12 mL). The aqueous layer was collected and the organic layer was extracted with 1 M aq. NaOH (3 x 60 mL). All the aqueous layers were combined and washed with EtOAc (120 mL), then acidified to pH 2-3 with conc. HCl. This acidic layer was then extracted with EtOAc (4 x 240 mL). The combined organics were dried with Na₂SO₄, filtered and the solvent was removed under reduced pressure. The resulting brown oil was then triturated with Et₂O then pentane to yield a pale red solid which was used without purification. The crude carboxylic acid was dissolved in DMF (6 mL) and anhydrous K₂CO₃ (405 mg, 2.9 mmol) was added at 0 °C and the mixture was stirred for 10 min. MeI (180 µL, 2.9 mmol) was added and the reaction mixture was stirred for 18 h at r.t.. This was then filtered and the filtrate was dissolved in H₂O (20 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL) and the organics were combined and washed with brine (20 mL). The organics were then dried with Na₂SO₄, filtered and the solvent was removed under reduced pressure to yield the crude product as a dark brown oil. Purification by FCC (3:1 pentane: EtOAc) yielded the Boc-protected methyl ester S5. The resulting colourless oil was treated with 4 M HCl in dioxane (1.5 mL) under a N_2 atmosphere for 2 h. Et₂O was then introduced until precipitation of an off-white solid which was collected by filtration. Washing with pentane yielded the title

^{*} Literature NMR data were taken at 373 K hence the lack of observable rotamers in previous spectra.

compound as an off-white solid (305 mg, 58% over 3 steps). **MP** 168-172 °C; **IR** (thin film) v_{max}/cm^{-1} 3427 (N-H), 3031 (C-H), 1744 (C=O), 909; ¹**H NMR** (500 MHz, CDCl₃) δ 11.17 (br s, 1H), 9.58 (br s, 1H), 7.43 – 7.36 (m, 4H), 7.33 – 7.29 (m, 1H), 4.53 (d, *J* = 9.5 Hz, 1H), 3.86 – 3.79 (m, 1H), 3.74 (s, 3H), 3.65 (2H), 2.54 (dtd, *J* = 13.8, 7.0, 2.8 Hz, 1H), 2.37 (dtd, *J* = 13.2, 10.5, 7.9 Hz, 1H); ¹³**C NMR** (126 MHz, CDCl₃) δ 168.8, 138.1, 129.1, 127.9, 127.6, 64.5, 53.44, 48.6, 46.2, 34.0; **HRMS** (ESI) mass calculated for [M-Cl]+ (C₁₂H₁₆O₂N) requires *m/z* 206.1176, found *m/z* 206.1175

(S)-5-(Methoxycarbonyl)-4-phenyl-3,4-dihydro-2H-pyrrole 1-oxide (1c)



Oxidation Procedure B was followed using S6 (200 mg, 0.83 mmol). The reaction was determined to be complete by TLC after stirring at r.t. for 6 h. Purification by FCC (EtOAc) yielded the title compound as an off-white solid (87 mg, 48%). MP 116-118 °C; IR (thin film) v_{max}/cm^{-1} 3028 (C-H), 1722

(C=O), 1697, 1544 (C=N), 1222 (N-O); ¹**H** NMR (400 MHz, CDCl₃) δ 7.42 – 7.31 (m, 2H), 7.31 – 7.24 (m, 1H, 7.24 – 7.18 (m, 2H), 4.58 – 4.48 (m, 1H), 4.40 (dddd, *J* = 14.5, 9.1, 7.7, 2.1 Hz, 1H), 4.21 (dddd, *J* = 14.6, 9.8, 5.5, 1.2 Hz, 1H), 3.69 (s, 3H), 2.73 (app. dtd, *J* = 13.2, 9.6, 7.7 Hz, 1H), 2.10 (dddd, *J* = 13.3, 9.1, 5.5, 4.3 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 159.8, 141.4, 136.5, 129.0, 127.5, 126.8, 65.6, 52.1, 48.1, 27.5; **HRMS** (ESI) mass calculated for [M+H]+ (C₁₂H₁₄O₃N) requires *m/z* 220.0968, found *m/z* 220.0969.

Synthesis of Nitrone 1d



Scheme S4. Synthesis of Nitrone 1d

1-(Tert-butyl) 2-methyl (S)-5-oxopyrrolidine-1,2-dicarboxylate (S7)



Following a literature procedure,¹¹ to a stirred solution of L-pyroglutamic acid (2.0 g, 15 mmol) in MeOH (24 mL) at 0 °C was added $SOCl_2$ (2.26 mL, 31 mmol) dropwise over 5 min. The mixture was allowed to warm to r.t. and stirred for 2 h. The reaction mixture was concentrated under

reduced pressure and the resulting yellow oil was dissolved in CH_2Cl_2 (50 mL). The organic solution was washed with sat. aq. NaHCO₃ (25 mL) and brine (25 mL). The combined aqueous layers were further extracted with CH_2Cl_2 (5 x 25 mL). The combined organics were then dried over MgSO₄, filtered and concentrated under reduced pressure.

The resulting yellow oil was dissolved in MeCN (4 mL) and Boc₂O (3.93 g, 18 mmol) and DMAP (183 mg, 1.5 mmol) was added. After 3 h the reaction mixture was concentrated to a dark orange oil. Purification by FCC (4:1 CH₂Cl₂: EtOAc) followed by recrystallization (EtOAc/Et₂O) yielded the desired product as white crystals (3.39 g, 90%). ¹H NMR (400 MHz, CDCl₃) δ 4.60 (dd, J = 9.4, 3.0 Hz, 1H), 3.77 (s, 3H), 2.68 – 2.56 (m, 1H), 2.48 (ddd, J = 17.5, 9.4, 3.7 Hz, 1H), 2.31 (ddt, J = 13.4, 10.1, 9.4 Hz, 1H), 2.02 (dddd, J = 13.3, 9.6, 3.6, 3.0 Hz, 1H), 1.47 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 173.2, 171.8, 149.3, 83.6, 58.8,

52.5, 31.1, 27.9, 21.5; **LRMS (ESI)** mass calculated for $[M+Na]+ (C_{11}H_{17}NNaO_5)$ requires m/z 266.1, found m/z 266.0. All data are consistent with the literature.¹¹

1-(Tert-butyl) 2-methyl (2S,5R)-5-hydroxy-5-isopropylpyrrolidine-1,2-dicarboxylate (S8)



Following a literature procedure,¹² iPrMgBr (2 mL, 3 M in 2-MeTHF, 6.2 mmol) was added at -40 °C to a stirred solution of **S7** (1.0 g, 4.1 mmol) in

anhydrous THF (12 mL). After 2 h, the reaction was quenched with sat. aq. NH₄Cl (15 mL). The resulting aqueous layer was extracted with CH₂Cl₂ (3 x 60 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated under reduced pressure. Purification by FCC (4:1 to 1:1 pentane:EtOAc) yielded the title compound as a colourless oil (913 mg, 77%) with 10% existing as the open chain isomeric ketone. As such, the mixture was carried forward and not fully characterised. **LRMS** (ESI) mass calculated for [M+Na]+ (C₁₄H₂₅NO₅) requires m/z 310.2, found m/z 310.5.

1-(Tert-butyl) 2-methyl (2S,5R)-5-isopropylpyrrolidine-1,2-dicarboxylate (S9)



Following a literature procedure,¹² NaBH(OAc)₃ (816 mg, 3.9 mmol) was added at 0 °C to a stirred solution of **S8** (850 mg, 3.0 mmol) in EtOAc (12 mL). After 10 min, TFA (750 μ L, 9.8 mmol) was added dropwise over a period of 40 min. The mixture was stirred at 0 °C for 2 h and then

at r.t. for 16 h. Sat. aq. NaHCO₃ (35 mL) was added and most of the organic solvent was removed under reduced pressure. CH_2Cl_2 (35 mL) was added and the layers were separated. The organic layer was washed with sat. aq. NaHCO₃ (2 x 35 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were then

washed with brine (35 mL), dried with MgSO₄, filtered and the solvent removed under reduced pressure. The resulting yellow oil was purified by FCC (6:1 pentane:EtOAc) to yield the desired product as a colourless oil (627 mg, 77%). The product was characterised as a mixture of rotamers. ¹H NMR (400 MHz, CDCl₃) δ 4.28 (d, *J* = 8.8 Hz, 0.4H), 4.24 – 4.13 (m, 0.6H), 3.68 (dd, *J* = 3.3, 1.6 Hz, 3.6H), 3.59 (m, 0.4H), 2.27 – 2.10 (m, 1H), 2.00 (m, 0.4H), 1.91 – 1.83 (m, 1.4H), 1.78 (dq, *J* = 7.2, 3.4 Hz, 2H), 1.44 – 1.39 (m, 4H), 1.38 – 1.33 (m, 5H), 0.95 – 0.91 (m, 3H), 0.87 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 173.9, 155.1, 154.4, 79.8, 79.7, 64.3, 64.1, 60.4, 59.9, 51.9, 51.7, 31.4, 31.2, 29.1, 28.3, 28.2, 27.4, 26.4, 20.0, 19.8, 18.5, 18.1. LRMS (ESI) mass calculated for [M+Na]+ (C₁₄H₂₅NO₄Na) requires *m/z* 294.2, found *m/z* 294.2. All data are consistent with the literature.¹²

(2R,5S)-2-Isopropyl-5-(methoxycarbonyl)pyrrolidin-1-ium chloride (S10)



4M HCl in dioxane (2 mL, 7.38 mL) was added to **S9** (500 mg, 1.85 mmol) and stirred at r.t. for 2 h. Et_2O was added dropwise until a white solid was formed. The white solid was collected by filtration and washed

with pentane to yield the desired product as a white solid (376 mg, 98%). **MP** 155-156 °C; **IR** (thin film) v_{max}/cm^{-1} 3426 (N-H), 2962 (C-H), 1748 (C=O), 1236; ¹**H** NMR (400 MHz, CDCl₃) δ 11.88 (br s, 1H), 7.38 (br s, 1H), 4.50 (app. ddt, J = 9.9, 6.9, 3.8 Hz, 1H), 3.79 (s, 3H), 3.52 – 3.41 (m, 1H), 2.38 – 2.26 (m, 1H), 2.21 (ddt, J = 13.6, 7.3, 3.1 Hz, 1H), 2.09 (dddd, J = 13.4, 9.0, 5.9, 2.4 Hz, 2H), 1.65 (dtd, J = 13.2, 11.1, 7.4 Hz, 1H), 1.16 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H); ¹³**C** NMR (101 MHz, CDCl₃) δ 170.1, 67.5, 59.1, 53.8, 30.8, 28.7, 27.8, 20.7, 19.2; **HRMS (ESI)** mass calculated for [M-Cl]+ (C₉H₁₈O₂N) requires *m/z* 172.1332, found *m/z* 172.1332.

(R)-2-Isopropyl-5-(methoxycarbonyl)-3,4-dihydro-2H-pyrrole 1-oxide (1d)

Oxidation Procedure B was followed using **S10** (250 mg, 1.21 mmol). The reaction was determined to be complete by TLC after stirring at r.t. for 7 h. Purification by FCC (1:19 MeOH:EtOAc) yielded the title compound as a white solid (75 mg, 34%) **MP** 40-42 °C; **IR** (thin film) v_{max} /cm⁻¹ 2961 (C-H), 1726 (C=O), 1694, 1545 (C=N), 1223 (N-O), 1195; ¹H NMR (400 MHz, CDCl₃) δ 4.16 – 4.07 (m, 1H), 3.83 (s, 3H), 2.97 – 2.80 (m, 2H), 2.63 (app. ddp, J = 10.8, 6.9, 3.8 Hz, 1H), 2.11 (dtd, J = 13.4, 9.4, 5.9 Hz, 1H), 1.94 (ddt, J = 13.2, 9.3, 6.5 Hz, 1H), 0.96 (d, J = 7.1 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 160.4, 133.2, 81.7, 52.2, 28.6, 28.0, 18.7, 17.0, 14.7; HRMS (ESI) mass calculated for [M+H]+ (C₉H₁₆O₃N) requires m/z 186.1125, found m/z 186.1125.

5. Synthesis of Phosphonates

Dimethyl benzylphosphonate (S11)

Following an adapted literature procedure,¹³ to a solution of toluene was added benzyl bromide (0.595 mL, 5 mmol) and the mixture was heated to 110 °C for 20 h. The solvent and excess trimethyl phosphite were then removed under reduced pressure to yield the crude product as a colourless oil. This was purified by FCC (EtOAc) (95:5 EtOAc:MeOH) to yield the desired product with 11% impurity of trimethylphosphite. This was re-columned in the same conditions to afford the pure title compound as a colourless oil (498 mg, 50%). ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.17 (m, 5H), 3.62 (d, *J* = 10.8 Hz, 6H), 3.12 (d, *J* = 21.8 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 131.3 (d, *J* = 9.4 Hz), 129.7 (d, *J* = 6.4 Hz), 128.6 (d, *J* = 3.2 Hz), 127.0 (d, *J* = 3.4 Hz), 52.9 (d, *J* = 6.4 Hz), 32.9 (d, *J* = 138.3 Hz); ³¹P NMR (162 MHz, CDCl₃) δ 28.81; LRMS (ESI) mass calculated for [M+Na]+ (C₉H₁₃NaO₃P) requires m/z 223.1, found m/z 223.0. All data were consistent with the literature.¹⁴

Alkylation Procedure



in dry THF (10 mL) was cooled to -78 °C under a N₂ atmosphere before adding 2.5 M solution of *n*-BuLi in hexanes (2.4 mL, 6.0 mmol). This was stirred for 20 min before addition of the alkyl halide (1.3 eq.). The reaction was allowed to slowly warm to r.t. and then stirred for 20 h. Reaction completion was determined by TLC at which point it was quenched by brine (20 mL). The aqueous phase was extracted with Et₂O (3 x 50 mL). The combined organics were dried with MgSO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by FCC (2% MeOH in EtOAC as eluent) to yield the phosphonates as oils.

Dimethyl phenethylphosphonate (S12)



The general alkylation procedure was followed using benzyl bromide $^{\text{PL}}_{\text{OMe}}$ (770 µL, 6.5 mmol) to afford the title compound as a light yellow oil (687 mg, 64%). ¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.32 (m, 2H),

7.32 – 7.20 (m, 3H), 3.80 (app. dd, J = 10.8, 0.7 Hz, 6H), 3.05 – 2.92 (m, 2H), 2.22 – 2.08 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 140.8 (d, J = 17.4 Hz), 128.6, 128.0, 126.4, 52.3 (d, J = 7.0 Hz), 28.5 (d, J = 4.6 Hz), 26.6 (d, J = 139.1 Hz); ³¹P NMR (162 MHz, CDCl₃) δ 33.38; LRMS (ESI) mass calculated for [M+Na]+ (C₁₀H₁₅NaO₃P) requires *m/z* 237.0, found *m/z* 237.0. All data were consistent with the literature.¹⁶

Dimethyl but-3-en-1-ylphosphonate (S13)

The general alkylation procedure was followed using allyl bromide (560 μ L, 6.5 mmol) to afford the title compound as a colourless oil (470 mg, 57%). ¹**H NMR** (400 MHz, CDCl₃) δ 5.91 – 5.78 (m, 1H), 5.13 – 4.99 (m, 2H), 3.75 (app. dq, J = 10.8, 1.0 Hz, 6H), 2.40 - 2.30 (m, 2H), 1.92 - 1.78 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 137.0 (d, J = 17.3 Hz), 115.2, 52.3 (d, J = 6.4 Hz), 26.4 (d, J = 4.4 Hz), 24.0 (d, J = 4.4 Hz), 140.8 Hz); ³¹P NMR (162 MHz, CDCl₃) δ 34.07; LRMS (ESI) mass calculated for [M+Na]+ $(C_6H_{13}NaO_3P)$ requires m/z 187.0, found m/z 187.0. All data were consistent with the literature.¹⁷

6. Synthesis and Characterisation of Cycloadducts

Synthesis of 2a



General Procedure A was followed using *t*-Bu-acetylene (334 μ L, 2.74 mmol) and stirred for 74 h. The resulting oil was purified by FCC (4:1 pentane:EtOAc) to give the desired product as an amorphous white solid (92 mg, 67%). IR (thin film) v_{max}/cm^{-1} 2965 (C-H), 1735 (C=O), 1663 (C=C), 1235; ¹H NMR (400 MHz, CDCl₃) δ 7.4 - 7.3 (m, 5H, 18-22), 5.2 (d, J = 12.5 Hz, 1H, 23), 5.2 (d, J = 12.6 Hz, 1H, 23'), 4.4 (s, 1H, 8), 3.4 -3.2 (m, 2H, 2), 2.1 (ddd, J = 12.6, 8.3, 7.5 Hz, 1H, 5), 2.0 – 1.9 (m, 1H, 5'), 1.9 – 1.7 (m, 2H, 1), 1.1 (s, 9H, 11-13); ¹³C NMR (101 MHz, CDCl₃) δ 173.2 (14), 165.3 (7), 136.0 (17), 128.5 (19, 21), 128.1 (20), 127.8 (18, 22), 92.0 (8), 82.2 (4), 66.6 (23), 60.0 (2), 36.9 (5), 31.3 (9), 28.1 (11-13), 23.0 (1); **HRMS** (ESI) mass calculated for $[M+H]+(C_{18}H_{24}O_3N)$ requires m/z302.1751, found *m/z* 302.1747.

Synthesis of 2b



General Procedure A was followed, however 6 equivalents of alkyne were used. Thus 1-hexyne (310 μ L, 2.74 mmol) was added and the reaction mixture was stirred for 20 h. The crude oil that resulted was

purified by FCC (4:1 pentane:EtOAc) to give the title compound as a pale yellow oil (47 mg, 34%). **IR** (thin film) v_{max}/cm^{-1} 3033 (C-H), 1737 (C=O), 1250, 843; ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.28 (m, 5H), 5.20 (app. d, J = 1.0 Hz, 2H), 4.50 (t, J = 1.1 Hz, 1H), 3.36 – 3.29 (m, 2H), 2.19 – 2.09 (m, 3H), 2.00 (dddd, J = 12.5, 6.6, 4.8, 0.7 Hz, 1H), 1.90 – 1.76 (m, 2H), 1.52 – 1.43 (m, 2H), 1.38 – 1.27 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 173.2, 157.6, 136.0, 128.5, 128.1, 127.9, 94.4, 82.4, 66.7, 6.13, 36.9, 28.8, 25.5, 23.2, 22.2, 13.8; **HRMS** (ESI) mass calculated for [M+H]+ (C₁₈H₂₄O₃N) requires *m*/*z* 302.1751, found *m*/*z* 302.1750.

Synthesis of 2c



General Procedure A was followed using cyclohexylacetylene (360 μ L) and stirred for 22 h. The resulting oil was purified by FCC (4:1 pentane:EtOAc) to give the title compound as a colourless oil (71 mg, 52%). **IR** (thin film) ν_{max}/cm^{-1} 3034 (C-H), 1735 (C=O), 1172, 1016;

¹**H NMR** (400 MHz, CDCl₃) δ 7.37 – 7.28 (m, 5H), 5.24 – 5.15 (m, 2H), 4.45 (s, 1H), 3.30 (dd, J = 7.7, 5.8 Hz, 2H), 2.13 (m, 2H), 2.03 – 1.94 (m, 1H), 1.92 – 1.75 (m, 4H), 1.75 – 1.60 (m, 2H), 1.33 – 1.11 (m, 6H); ¹³**C NMR** (101 MHz, CDCl₃) δ 173.2, 161.9, 136.0, 128.5, 128.1, 127.8, 92.6, 82.2, 66.6, 60.1, 36.9, 35.3, 30.7, 30.5, 26.0, 25.7, 23.0; **HRMS** (ESI) mass calculated for [M+H]+ (C₂₀H₂₆O₃N) requires *m/z* 328.1907, found *m/z* 328.1903.

Synthesis of 2d



General Procedure A was followed using phenylacetylene (150 μ L) as the dipolarophile and the reaction was left for 21 h. The crude oil was purified by FCC (2:1 pentane:EtOAc) to give the desired product as a yellow oil (103 mg, 70%). **IR** (thin film) v_{max}/cm^{-1} 2980 (C-H),

1734 (C=O), 1382, 1154; ¹**H NMR** (400 MHz, CDCl₃) δ 7.56 – 7.46 (m, 2H), 7.39 – 7.28 (m, 8H), 5.23 (app. d, J = 0.8 Hz, 3H), 3.53 – 3.39 (m, 2H), 2.24 (ddd, J = 12.7, 8.7, 7.3 Hz, 1H), 2.15 (dddd, J = 12.8, 6.9, 4.8, 1.1 Hz, 1H), 1.98 – 1.81 (m, 2H); ¹³**C NMR** (101 MHz, CDCl₃) δ 172.8, 154.5, 135.8, 129.3, 128.6, 128.4, 128.2, 128.1, 128.0, 125.8, 94.8, 83.0, 67.0, 60.3, 37.2, 23.3; **HRMS** (ESI) mass calculated for [M+H]+ (C₂₀H₂₀O₃N) requires *m/z* 322.1438, found *m/z* 322.1436.

Synthesis of 2e



General Procedure A was followed using 4-fluorophenylacetylene (160 mg) and stirred for 20 h. The resulting yellow oil was purified by FCC (2:1 pentane:EtOAc) to give the title compound as a yellow oil (134 mg, 87%). **MP** 54-56 °C; **IR** (thin film) v_{max}/cm^{-1} 2980 (C-H),

1735 (C=O), 1158; ¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.46 (m, 2H), 7.42 – 7.27 (m, 5H), 7.07 – 6.99 (m, 2H), 5.23 (d, 12.7 Hz, 1H), 5.22 (d, 12.7 Hz, 1H), 5.17 (s, 1H), 3.53 – 3.38 (m, 2H), 2.23 (ddd, J = 12.7, 8.5, 7.4 Hz, 1H), 2.17 – 2.09 (m, 1H), 1.97 – 1.83 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 172.7, 163.3 (d, J = 249.2 Hz), 153.6, 135.8, 128.6, 128.2, 128.0, 127.7 (d, J = 8.3 Hz), 124.4 (d, J = 3.1 Hz), 115.5 (d, J = 21.9 Hz), 94.5, 83.1, 67.0, 60.3, 37.1, 23.3; ¹⁹F NMR (376 MHz, CDCl₃) δ -111.11 (app. tt, J = 8.6, 5.3 Hz); HRMS (ESI) mass calculated for [M+H]+ (C₂₀H₁₉O₃NF) requires *m/z* 340.1344, found *m/z* 340.1341.

Synthesis of 2f



General Procedure A was followed using 4-methoxyphenylacetylene (180 μ L) and stirred for 24 h. The resulting crude oil was purified by FCC (3:1 pentane:EtOAc) to give the title compound as a white solid (103 mg, 65%). **MP** 71-72 °C; **IR** (thin film) v_{max}/cm^{-1} 2976 (C-H),

1725 (C=O), 1708 (C=C), 1258, 1068, 1030 (C-O); ¹H NMR (400 MHz, CDCl₃) δ 7.48 – 7.41 (m, 2H), 7.39 – 7.27 (m, 5H), 6.89 – 6.83 (m, 2H), 5.22 (d, 12.6 Hz, 1H), 5.22 (d, 12.6 Hz, 1H), 5.09 (s, 1H), 3.81 (s, 3H), 3.51 – 3.38 (m, 2H), 2.27 – 2.18 (m, 1H), 2.13 (dddd, J = 12.6, 6.9, 4.8, 1.0 Hz, 1H), 1.96 – 1.81 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 172.9, 160.4, 154.3, 135.9, 128.5, 128.2, 128.0, 127.3, 120.8, 113.8, 93.0, 83.0, 66.9, 60.3, 55.3, 37.1, 23.2; HRMS (ESI) mass calculated for [M+H]+ (C₂₁H₂₂O₄N) requires *m/z* 352.1543, found *m/z* 352.1540

Synthesis of 2g



General Procedure A was followed using cyclopropylacetylene (120 μ L) and stirred for 19 h. The resulting oil was purified by FCC (4:1 pentane:EtOAc) to give the title compound as a colourless oil (81 mg,

63%). **IR** (thin film) v_{max}/cm^{-1} 3012 (C-H), 1734 (C=O), 1175; ¹**H** NMR (400 MHz, CDCl₃) δ 7.38 – 7.27 (m, 5H), 5.19 (d, J = 1.6 Hz, 2H), 4.51 (s, 1H), 3.33 – 3.26 (m, 2H), 2.13 (ddd, J = 12.6, 8.5, 7.3 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.90 – 1.74 (m, 2H), 1.48 – 1.38 (m, 1H), 0.76 – 0.68 (m, 3H), 0.65 (dddd, J = 8.8, 5.2, 3.7, 1.6 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 173.1, 158.5, 136.0, 128.5, 128.1, 127.9, 92.9, 82.4, 66.7, 60.0, 36.9, 23.1, 7.0, 6.0, 5.7; **HRMS** (ESI) mass calculated for [M+H]+ (C₁₇H₂₀O₃N) requires m/z 286.1438, found m/z286.1436.

Synthesis of 2h



General Procedure A was followed using 2-methyl-3-butyn-2-ol (130 μ L) and stirred for 6 h. The resulting oil was purified by FCC (2:1 pentane:EtOAc) to give the title compound as a colourless oil (99 mg,

72%). **IR** (thin film) v_{max}/cm^{-1} 3399 (O-H), 2977 (C-H), 1733 (C=O), 1227 (C-O), 1172 (C-O); ¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.28 (m, 5H), 5.24 – 5.15 (m, 2H), 4.72 (s, 1H), 3.35 (dd, J = 7.1, 5.7 Hz, 2H), 2.22 – 2.11 (m, 1H), 2.02 (m, 2H), 1.90 – 1.77 (m, 2H), 1.40 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 172.8, 162.1, 135.8, 128.5, 128.2, 127.9, 93.5, 82.4, 68.2, 66.8, 60.1, 36.8, 28.2, 28.1, 23.1; **HRMS** (ESI) mass calculated for [M+H]+ (C₁₇H₂₂O₄N) requires *m/z* 304.1543, found *m/z* 304.1541.

Synthesis of 2i



General Procedure A was followed using nitrone **1a** (75 mg, 0.342 mmol) and mestranol (140 mg, 0.445 mmol) and stirred for 24 h. The resulting oil was purified by FCC (3:2

pentane:EtOAc) to give the both diastereomers of the title compound as white solids (127 mg, 70%, 1.2:1 dr).^{*} **Major: MP** 66-68 °C; **IR** (thin film) v_{max} /cm⁻¹ 3509 (O-H), 2934 (C-H), 2866 (C-H), 1733 (C=O), 1254; ¹H NMR (500 MHz, CDCl₃) δ 7.34 – 7.28 (m, 2H), 7.23 (dd, J = 8.4, 6.8 Hz, 2H), 7.17 – 7.11 (m, 2H), 6.71 (dd, J = 8.6, 2.8 Hz, 1H), 6.62 (d, J = 2.7 Hz, 1H), 5.22 – 5.13 (m, 2H), 4.68 (s, 1H), 3.78 (s, 3H), 3.44 – 3.33 (m, 2H), 2.89 – 2.73 (m, 2H), 2.28 (ddd, J = 12.7, 8.6, 7.1 Hz, 1H), 2.19 – 2.04 (m, 3H), 2.00 – 1.77 (m, 5H), 1.72 – 1.62 (m, 2H), 1.53 (td, J = 11.3, 7.3 Hz, 1H), 1.45 – 1.33 (m, 4H), 1.17 (app. qd, J = 11.9, 6.9 Hz, 1H), 0.88 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 172.9, 160.4, 157.4, 137.8, 135.6, 132.6, 128.5, 128.3, 128.2, 126.4, 113.7, 111.4, 97.4, 82.6, 82.4, 67.2, 60.2, 55.2, 48.8, 47.5,

^{*} Investigations into producing a single crystal of either diastereomer were unsuccesful.

43.4, 39.2, 36.3, 33.2, 29.8, 27.4, 26.3, 23.4, 23.0, 14.0; **HRMS** (ESI) mass calculated for $[M+H]+(C_{33}H_{40}O_5N)$ requires m/z 530.2901, found m/z 530.2901. **Minor: MP** 65-70 °C; **IR** (thin film) v_{max}/cm^{-1} 3491 (O-H), 2990 (C-H), 1731 (C=O), 1254, 1237; ¹H **NMR** (500 MHz, CDCl₃) δ 7.42 – 7.29 (m, 5H), 7.18 – 7.14 (m, 1H), 6.71 (dd, J = 8.6, 2.8 Hz, 1H), 6.62 (d, J = 2.8 Hz, 1H), 5.22 (app. d, J = 1.7 Hz, 2H), 4.78 (s, 1H), 3.78 (s, 3H), 3.45 (dddd, J = 12.3, 6.0, 4.6, 1.1 Hz, 1H), 3.35 (ddd, J = 12.6, 9.1, 5.8 Hz, 1H), 2.92 – 2.73 (m, 2H), 2.27 – 2.07 (m, 5H), 1.97 – 1.83 (m, 4H), 1.78 – 1.67 (m, 2H), 1.67 – 1.58 (m, 1H), 1.51 – 1.29 (m, 5H), 0.90 (s, 3H); ¹³C **NMR** (126 MHz, CDCl₃) δ 172.7, 161.0, 157.4, 138.0, 135.8, 132.7, 128.6, 128.3, 128.1, 126.3, 113.8, 111.4, 96.8, 82.6, 82.4, 67.0, 60.3, 55.2, 48.8, 47.5, 43.3, 39.4, 36.9, 36.8, 33.0, 29.9, 27.4, 26.3, 23.7, 23.5, 14.1; **HRMS** (ESI) mass calculated for [M+H]+ (C₃₃H₄₀O₅N) requires m/z 530.2901, found m/z 530.2896.

Synthesis of 2p



Nitrone **1d** (140 mg, 0.51 mmol) and *t*-Buacetylene (390 μ L, 3.1 mmol) were stirred in hexane (4 mL) for 2 days at 70 °C. The hexane was removed under a stream of N₂ and the resulting oil

was purified by FCC (9:1 pentane:Et₂O) to give the desired product as a colourless oil (134 mg, 74%, 1.7:1 dr). **Major: IR** (thin film) v_{max}/cm^{-1} 2956 (C-H), 1736 (C=O), 1252, 1118, 836, 776; ¹H NMR (500 MHz, CDCl₃) δ 4.50 – 4.35 (m, 2H), 3.75 (s, 3H), 3.39 – 3.21 (m, 2H), 2.25 – 2.19 (m, 2H), 1.11 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 173.4, 165.0, 92.8, 80.8, 70.1, 66.1, 52.6, 45.3, 31.3, 28.0, 25.7, 18.0, -4.9; **HRMS** (ESI) mass calculated for [M+H]+ (C₁₈H₃₄O₄NSi) requires *m/z* 356.2252, found *m/z* 356.2246. **Minor: IR** (thin film) v_{max}/cm^{-1} 2956 (C-H), 1735 (C=O), 1252, 1109, 836, 777; ¹H NMR (500 MHz, CDCl₃) δ 4.58 (s, 1H), 4.32 (qd, *J* = 6.6, 5.2 Hz, 1H), 3.73 (s, 3H),

3.65 - 3.60 (m, 1H), 3.07 (ddd, J = 10.6, 6.8, 0.8 Hz, 1H), 2.49 (ddd, J = 13.1, 6.6, 0.9 Hz, 1H), 2.05 (ddd, J = 13.1, 6.3, 0.9 Hz, 1H), 1.12 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H); 13 C NMR (126 MHz, CDCl₃) δ 173.8, 163.6, 93.7, 80.3, 69.2, 65.5, 52.6, 44.2, 31.0, 28.0, 25.8, 18.1, -4.8, -4.9; HRMS (ESI) mass calculated for [M+H]+ (C₁₈H₃₄O₄NSi) requires m/z 356.2252, found m/z 356.2245.

Synthesis of 2q



Nitrone **1c** (38 mg, 0.17 mmol) and *t*-Bu-acetylene (130 μ L, 1.0 mmol) were stirred in toluene (2 mL) for 4 days at 70 °C. The toluene was removed under a stream of N₂ and the resulting oil was purified by FCC (9:1 pentane:Et₂O) to give the title compound as a colourless

oil (22 mg, 42%, 12.5:1 dr). **Major: IR** (thin film) v_{max}/cm⁻¹ 2968 (C-H), 1739 (C=O), 1234, 1118; ¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.25 (m, 2H), 7.23 – 7.20 (m, 1H), 7.20 – 7.15 (m, 2H), 4.78 (s, 1H), 3.88 (dt, *J* = 10.3, 5.1 Hz, 1H), 3.48 (d, *J* = 8.1 Hz, 1H), 3.20 (m, 4H), 2.18 (td, *J* = 7.9, 4.9 Hz, 2H), 1.16 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 171.9 , 164.0, 139.2, 128.3, 127.9, 127.1, 92.9, 86.1, 58.4, 56.2, 51.5, 31.3, 28.6, 28.1; HRMS (ESI) mass calculated for [M+H]+ (C₁₈H₂₄O₃N) requires *m/z* 302.1751, found *m/z* 302.1748.^{*}

Synthesis of 2r



Nitrone **1b** (50 mg, 0.27 mmol) and *t*-Bu-acetylene (200 μ L, 1.6 mmol) were stirred in hexane (4 mL) for 2 days at 70 °C. The reaction was determined to be complete by TLC after 2 days and the hexane was

^{*} Minor diastereomer not isolated since only observed in trace quantities

removed under a stream of N₂. Purification by FCC (9:1 pentane:Et₂O) yielded the title compound as a colourless oil (46 mg, 64%, 18.4:1 dr). **Major**^{*}: **IR** (thin film) v_{max}/cm^{-1} 2958 (C-H), 1734 (C=O), 1661, 1244, 1128; ¹H NMR (400 MHz, CDCl₃) δ 4.54 (s, 1H), 3.71 (s, 3H), 2.84 (dt, *J* = 11.0, 6.1 Hz, 1H), 2.36 (ddd, *J* = 12.8, 7.9, 2.4 Hz, 1H), 2.00 – 1.83 (m, 2H), 1.74 (dddd, *J* = 12.6, 8.1, 5.9, 2.4 Hz, 1H), 1.53 (dtd, *J* = 12.6, 10.9, 7.9 Hz, 1H), 1.11 (s, 9H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 174.6, 163.7, 93.5, 80.7, 76.5, 52.4, 35.3, 31.1, 31.1, 28.1, 24.2, 20.5, 19.0; **HRMS** (ESI) mass calculated for [M+H]+ (C₁₅H₂₆O₃N) requires *m/z* 268.1907, found *m/z* 268.1907.[†]

7. Synthesis and Characterisation of Ketophosphonates

Synthesis of 3a



Synthesis of 3b

^{*} NOESY analysis was inconclusive, however stereochemistry was assigned based on the more decisive NOESY correlations of **3r**.

[†] Minor diastereomer not isolated since only observed in trace quantities.

General Procedure B was followed using cycloadduct **2b** (41 mg, 0.136 mmol). Purification by FCC yielded the title compound as a yellow oil (26 mg, 61%). **IR** (thin film) v_{max}/cm^{-1} 2957 (C-H), 1714 (C=O), 1249 (P=O), 1031 (P-O antisymmetric); ¹H NMR (400 MHz, CDCl₃) δ 4.32 (app. d, *J* = 1.1 Hz, 1H), 3.79 (d, *J* = 11.2 Hz, 3H), 3.77 (d, *J* = 11.2 Hz, 3H), 3.65 (dd, *J* = 21.4, 14.9 Hz, 1H), 3.28-3.26 (m, 3H), 2.31 – 2.21 (m, 1H), 2.17 – 2.08 (m, 2H), 1.94 – 1.79 (m, 2H), 1.78 – 1.69 (m, 1H), 1.54 – 1.43 (m, 2H), 1.41 – 1.28 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 202.4 (d, *J* = 6.8 Hz), 158.6, 94.5, 88.3 (d, *J* = 3.2 Hz), 59.9, 53.0 (d, *J* = 6.3 Hz), 52.8 (d, *J* = 6.2 Hz), 35.8 (d, *J* = 135.0 Hz), 33.8, 28.8, 25.5, 23.2, 22.2, 13.7; ³¹P NMR (162 MHz, CDCl₃) δ 24.14; HRMS (ESI) mass calculated for [M+H]+ (C₁₄H₂₅O₅NP) requires *m/z* 318.1465, found *m/z* 318.1468

Synthesis of 3c



General Procedure B was followed using cycloadduct 2c (50 mg, 0.153 mmol). Purification by FCC afforded the title compound as a yellow oil (35 mg, 67%). IR (thin film) v_{max}/cm⁻¹ 2929 (C-H), 1714 (C=O), 1258 (P=O), 1030 (P-O antisymmetric); ¹H NMR (400 MHz, CDCl₃) δ 4.27

(d, J = 1.0 Hz, 1H), 3.79 (d, J = 11.2 Hz, 3H), 3.77 (d, J = 11.2 Hz, 3H), 3.62 (dd, J = 21.4, 14.9 Hz, 1H), 3.32 – 3.18 (m, 3H), 2.31 – 2.21 (m, 1H), 2.16 – 2.07 (m, 1H), 1.91 – 1.78 (m, 4H), 1.73 (m, 3H), 1.65 (m, J = 11.2, 6.4, 2.5 Hz, 1H), 1.33 – 1.13 (m, 5H); ¹³C NMR (101 MHz, CDCl₃) δ 202.4 (d, J = 6.8 Hz), 163.0, 92.8, 88.1 (d, J = 3.2 Hz), 59.8, 53.0 (d, J = 6.3 Hz), 52.8 (d, J = 6.4 Hz), 35.6 (d, J = 134.9 Hz), 35.3, 33.6, 30.7, 30.6, 25.9, 25.7, 23.0; ³¹P NMR (162 MHz, CDCl₃) δ 24.19; HRMS (ESI) mass calculated for [M+H]+ (C₁₆H₂₇O₅NP) requires *m/z* 344.1621, found *m/z* 344.1624.

Synthesis of 3d



General Procedure B was followed using cycloadduct **2d** (50 mg, 0.16 mmol). FCC afforded the title compound as a yellow oil (37 mg, 70%). **IR** (thin film) v_{max} /cm⁻¹ 3058 (C-H), 1715 (C=O), 1260 (P=O), 1029 (P-O antisymmetric); ¹H NMR (400 MHz, CDCl₃) δ 7.51 (dddd, J = 6.7,

4.0, 2.6, 1.5 Hz, 2H), 7.38 – 7.33 (m, 3H), 5.06 (s, 1H), 3.78 (d, J = 11.2 Hz, 3H), 3.76 (d, J = 11.2 Hz, 3H), 3.71 (dd, J = 21.6, 14.7 Hz, 1H), 3.45 – 3.39 (m, 2H), 3.34 (dd, J = 21.2, 14.7 Hz, 1H), 2.36 (ddd, J = 12.9, 8.4, 7.0 Hz, 1H), 2.04 (dddd, J = 12.8, 7.0, 4.9, 0.9 Hz, 1H), 1.97 – 1.85 (m, 1H), 1.81 (app. ddq, J = 12.5, 7.1, 5.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 202.1 (d, J = 6.8 Hz), 155.3, 129.6, 128.5, 127.7, 125.8, 94.9, 88.9 (d, J = 3.2 Hz), 60.1, 52.9 (dd, J = 12.6, 6.4 Hz), 36.01 (d, J = 134.2 Hz), 34.0, 23.3; ³¹P NMR (162 MHz, CDCl₃) δ 23.79; **HRMS** (ESI) mass calculated for [M+H]+ (C₁₆H₂₁O₅NP) requires *m*/*z* 338.1152, found *m*/*z* 338.1148.

Synthesis of 3e



General Procedure B was followed using cycloadduct 2e (50 mg, 0.147 mmol). Purification by FCC afforded the title compound as a yellow oil (39 mg, 75%). IR (thin film) v_{max}/cm⁻¹ 2981 (C-H), 1734 (C=O), 1259
(P-O); ¹H NMR (400 MHz, CDCl₃) δ 7.51 – 7.45 (m, 2H), 7.07 – 6.99

(m, 2H), 5.00 (s, 1H), 3.77 (d, J = 11.2 Hz, 3H), 3.75 (d, J = 11.2 Hz, 3H), 3.70 (dd, J = 21.7, 14.7 Hz, 1H), 3.41 (dd, J = 7.7, 5.7 Hz, 2H), 3.32 (dd, J = 21.3, 14.7 Hz, 1H), 2.35 (ddd, J = 12.9, 8.5, 7.1 Hz, 1H), 2.08 – 1.97 (m, 1H), 1.96 – 1.73 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 202.0 (d, J = 6.5 Hz), 163.3 (d, J = 249.7 Hz), 154.3, 127.8 (d, J = 8.2 Hz), 124.0 (d, J = 3.2 Hz), 115.6 (d, J = 22.2 Hz), 94.7, 89.0 (d, J = 3.2 Hz), 60.1, 53.0 (d, J = 6.3 Hz), 52.9 (d, J = 6.3 Hz), 35.9 (d, J = 134.2 Hz), 34.0, 23.3; ¹⁹F NMR (377 MHz, CDCl₃) δ -

110.44 (app. tt, J = 8.5, 5.3 Hz); ³¹P NMR (162 MHz, CDCl₃) δ 23.69; HRMS (ESI) mass calculated for [M+H]+ (C₁₆H₂₀O₅NFP) requires *m/z* 356.1058, found *m/z* 356.1059.

Synthesis of 3f



General Procedure B was followed using cycloadduct **2f** (50 mg, 0.141 mmol). Purification by FCC afforded the title compound as a yellow oil (37 mg, 72%). **IR** (thin film) v_{max}/cm^{-1} 2956 (C-H), 1713 (C=O), 1647, 1251 (P-O), 1030 (P=O antisymmetric); ¹H NMR (400

MHz, CDCl₃) δ 7.46 – 7.41 (m, 2H), 6.89 – 6.84 (m, 2H), 4.91 (s, 1H), 3.81 (s, 3H), 3.77 (d, J = 11.2 Hz, 3H), 3.76 (d, J = 11.2 Hz, 3H), 3.71 – 3.64 (dd, 1H), 3.40 (m, 2H), 3.33 (dd, J = 21.2, 14.7 Hz, 1H), 2.35 (ddd, J = 12.8, 8.4, 7.0 Hz, 1H), 2.02 (dddd, J = 12.7, 7.0, 5.0, 0.8 Hz, 1H), 1.96 – 1.72 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 202.2 (d, J = 6.4 Hz), 160.6, 155.1, 127.3, 120.3, 113.9, 93.1, 88.9 (d, J = 3.3 Hz), 60.0, 55.35, 53.0 (d, J = 6.3 Hz), 52.9 (d, J = 5.9 Hz), 35.9 (d, J = 134.3 Hz), 33.9, 23.2; ³¹P NMR (162 MHz, CDCl₃) δ 23.95; HRMS (ESI) mass calculated for [M+H]+ (C₁₇H₂₃O₆NP) requires *m/z* 368.1258, found *m/z* 368.1256.

Synthesis of 3g



General Procedure B was followed using cycloadduct 2g (35 mg, 0.123 mmol). Purification by FCC afforded the title compound as a yellow oil (27 mg, 74%). IR (thin film) ν_{max}/cm⁻¹ 2980 (C-H), 1713 (C=O), 1254 (P=O), 1030 (P-O antisymmetric); ¹H NMR (400 MHz, CDCl₃) δ 4.32

(s, 1H), 3.79 (d, J = 11.2 Hz, 3H), 3.77 (d, J = 11.2 Hz, 3H), 3.61 (dd, J = 21.4, 14.9 Hz, 1H), 3.34 – 3.17 (m, 3H), 2.30 – 2.19 (m, 1H), 1.93 – 1.78 (m, 2H), 1.78 – 1.67 (m, 1H), 1.49 – 1.39 (m, 1H), 0.80 – 0.63 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 202.2 (d, J = 6.3 Hz), 159.6, 92.9, 88.3 (d, J = 3.7 Hz), 59.7, 53.0 (d, J = 6.2 Hz), 52.8 (d, J = 6.1 Hz), 35.7 (d, J = 135.0 Hz), 33.6, 23.1, 7.0, 6.2, 5.9; ³¹P NMR (162 MHz, CDCl₃) δ 24.16; HRMS (ESI) mass calculated for [M+H]+ (C₁₃H₂₁O₅NP) requires *m/z* 302.1152, found *m/z* 302.1155.

Synthesis of 3h



² General Procedure B was followed using cycloadduct **2h** (50 mg, 0.166 mmol), and modified by the use of additional MePO(OMe)₂ (41 μ L, 0.38 mmol) and LiHMDS (680 μ L 1M in THF, 0.68 mmol). Purification by

FCC afforded the title compound as a colourless oil (36 mg, 68%). **IR** (thin film) v_{max}/cm^{-1} 3381 (O-H), 2977 (C-H), 1713 (C=O), 1243 (P=O), 1025 (P-O antisymmetric); ¹**H** NMR (400 MHz, CDCl₃) δ 4.54 (d, J = 0.8 Hz, 1H), 3.80 – 3.77 (m, 3H), 3.77 – 3.74 (m, 3H), 3.59 – 3.48 (m, 1H), 3.43 – 3.22 (m, 3H), 3.13 (s, 1H), 2.30 (dtd, J =11.6, 6.9, 6.3, 1.4 Hz, 1H), 1.97 – 1.79 (m, 2H), 1.79 – 1.65 (m, 1H), 1.41 (d, J = 1.8 Hz, 3H), 1.41 (d, J = 1.6 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 201.2 (d, J = 6.7 Hz), 163.6, 93.6, 88.0 (d, J = 2.9 Hz), 67.8, 59.6, 53.2 (d, J = 6.4 Hz), 52.9 (d, J = 6.4 Hz), 35.9 (d, J =132.7 Hz), 32.8, 28.3, 27.7, 22.9; ³¹P NMR (162 MHz, CDCl₃) δ 23.52; **HRMS** (ESI) mass calculated for [M+H]+ (C₁₃H₂₃O₆NP) requires *m/z* 320.1258, found *m/z* 320.1261.

Synthesis of 3i



General Procedure B was followed using cycloadduct (Major) **2i** (50 mg, 0.095 mmol), and modified by the use of additional MePO(OMe)₂ (24 μL, 0.219 mmol) and LiHMDS (390 μL, 1M in

THF, 0.390 mmol). Purification by FCC afforded the title compound as an amorphous white solid (33 mg, 64%). **IR** (thin film) v_{max}/cm^{-1} 3390 (O-H), 2932 (C-H), 1714 (C=O), 1254 (P=O), 1032 (P-O antisymmetric); ¹**H NMR** (400 MHz, CDCl₃) δ 7.21 – 7.16 (m, 1H), 6.70 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.62 (d, *J* = 2.8 Hz, 1H), 4.61 (s, 1H), 3.77 (s, 3H), 3.77 (d, *J* = 11.2

Hz, 3H), 3.73 (d, J = 11.2 Hz, 3H), 3.55 (dd, J = 21.0, 14.2 Hz, 1H), 3.49 – 3.39 (m, 1H), 3.38 – 3.30 (m, 2H), 3.13 (br s, 1H), 2.92 – 2.78 (m, 2H), 2.39 – 2.29 (m, 2H), 2.22 (ddd, J =14.2, 9.4, 5.9 Hz, 1H), 2.13 (td, J = 10.9, 4.2 Hz, 1H), 2.01 – 1.85 (m, 4H), 1.83 – 1.69 (m, 3H), 1.69 – 1.60 (m, 1H), 1.57 – 1.42 (m, 4H), 1.41 – 1.24 (m, 1H), 0.94 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 200.6 (d, J = 7.0 Hz), 162.7, 157.5, 138.0, 132.4, 126.2, 113.8, 111.5, 97.1, 88.2 (d, J = 2.4 Hz), 82.4, 60.0, 55.2, 53.3 (d, J = 6.4 Hz), 52.9 (d, J = 6.4 Hz), 49.1, 47.3, 43.9, 39.4, 36.4, 36.3 (d, J = 132.5 Hz), 33.7, 32.6, 29.8, 27.5, 26.4, 23.5, 23.4, 14.0; ³¹P NMR (162 MHz, CDCl₃) δ 23.38; HRMS (ESI) mass calculated for [M+H]+ (C₂₉H₄₁O₇NP) requires *m*/z 546.2615, found *m*/z 546.2612

Synthesis of 3j



The modification to General Procedure B was followed using cycloadduct **2d** (50 mg, 0.156 mmol) and phosphonate **S11** (65 mg, 0.327 mmol). Purification yielded the title compound as a white solid (45 mg, 69%). The product was isolated as a 1.3:1 mixture of diastereomers. **MP** 135-138 °C; **IR** (thin film) v_{max}/cm^{-1} 2957 (C-H), 1712 (C=O), 1255

(P=O), 1027 (P=O antisymmetric); ¹H NMR (500 MHz, CDCl₃) δ 7.55 – 7.47 (m, 2H_{maj}+2H_{min}), 7.44 – 7.40 (m, 2H_{maj}), 7.38 – 7.27 (m, 4H_{maj}+6H_{min}), 7.24 – 7.18 (m, 2H_{maj}+2H_{min}), 5.64 (d, *J* = 21.6 Hz, 1H_{maj}), 5.49 (d, *J* = 19.2 Hz, 1H_{min}), 5.18 (s, 1H_{min}), 4.62 (s, 1H_{maj}), 3.72 (d, *J* = 10.9 Hz, 3H_{maj}), 3.69 (d, *J* = 11.0 Hz, 3H_{maj}), 3.67 (d, *J* = 10.8 Hz, 3H_{min}), 3.62 (d, *J* = 11.0 Hz, 3H_{min}), 3.47 (dd, *J* = 7.3, 5.5 Hz, 2H_{maj}), 3.29 (dt, *J* = 11.9, 5.8 Hz, 1H_{min}), 2.89 (ddd, *J* = 12.4, 8.6, 5.6 Hz, 1H_{min}), 2.53 – 2.44 (m, 1H_{maj}), 2.07 - 1.71 (m, 3H_{maj}+3H_{min}), 1.46 – 1.38 (m, 1H_{min}); ¹³C NMR (126 MHz, CDCl₃) δ 203.5 (d, *J* = 5.1 Hz)_{min}, 202.6 (d, *J* = 4.8 Hz)_{maj}, 155.3_{maj}, 154.9_{min}, 131.6 (d, *J* = 9.4 Hz)_{maj}, 128.6_{min}, 128.5_{maj},

128.3_{min}, 127.9_{min}, 127.8 (d, J = 3.3 Hz)_{min}, 127.7_{maj}, 127.6 (d, J = 3.1 Hz)_{maj}, 125.8_{maj+min}, 95.4_{maj}, 95.3_{min}, 89.5 (d, J = 4.8 Hz)_{min}, 89.2 (d, J = 4.3 Hz)_{maj}, 60.1_{maj}, 59.9_{min}, 53.8 (d, J = 6.4 Hz)_{min}, 53.7 (d, J = 6.6 Hz)_{min}, 53.4 (d, J = 7.0 Hz)_{maj}, 53.4 (d, J = 7.0 Hz)_{maj}, 52.30 (d, J = 134.7 Hz)_{min}, 52.30 (d, J = 134.7 Hz)_{maj}, 36.0_{min}, 33.9_{maj}, 23.4_{maj}, 23.1_{min}; ³¹**P NMR** (162 MHz, CDCl₃) δ 22.46_{min}, 22.21_{maj}; **HRMS** (ESI) mass calculated for [M+H]+ (C₂₂H₂₅O₅NP) requires *m/z* 414.1465, found *m/z* 414.1458.

Synthesis of 3k



The modification to General Procedure B was followed using cycloadduct **2d** (50 mg, 0.156 mmol) and phosphonate **S12** (70 mg, 0.327 mmol). Purification yielded the title compound as a yellow oil (41 mg, 61%). The product was isolated as a 2.3:1 mixture of diastereomers. **IR** (thin film)

 $v_{\rm max}/{\rm cm}^{-1}$ 2956 (C-H), 1708 (C=O), 1251 (P=O), 1028 (P-O antisymmetric); ¹H NMR (500 MHz, CDCl₃) δ 7.48 – 7.44 (m, 2H_{min}), 7.35 – 7.27 (m, $3H_{mai}+3H_{min}$), 7.25 – 7.14 (m, $2H_{mai}$), 7.06 – 7.00 (m, $2H_{mai}+2H_{min}$), 6.94 – 6.88 (m, $3H_{mai}+3H_{min}$), 5.08 (s, $1H_{min}$), 4.73 (ddd, J = 23.6, 12.0, 3.4 Hz, $1H_{mai}$), 4.67 (ddd, J = 21.6, 9.0, 6.5 Hz, $1H_{min}$), 4.01 (s, $1H_{maj}$), 3.84 (d, J = 11.0 Hz, $6H_{maj}$), 3.69 (d, J = 11.0 Hz, $3H_{min}$), $3.68 (d, J = 11.0 Hz, 3H_{min}), 3.46 - 3.34 (m, 2H_{maj}), 3.30 - 3.20 (m, 1H_{maj} + 1H_{min}), 3.10 (ddd, J = 11.0 Hz, 3H_{min}), 3.46 - 3.34 (m, 2H_{maj}), 3.30 - 3.20 (m, 1H_{maj} + 1H_{min}), 3.10 (ddd, J = 11.0 Hz, 3H_{min}), 3.46 - 3.34 (m, 2H_{maj}), 3.30 - 3.20 (m, 1H_{maj} + 1H_{min}), 3.10 (ddd, J = 11.0 Hz, 3H_{min}), 3.46 - 3.34 (m, 2H_{maj}), 3.30 - 3.20 (m, 1H_{maj} + 1H_{min}), 3.10 (ddd, J = 11.0 Hz, 3H_{min}), 3.46 - 3.34 (m, 2H_{maj}), 3.30 - 3.20 (m, 1H_{maj} + 1H_{min}), 3.10 (ddd, J = 11.0 Hz, 3H_{min}), 3.46 - 3.34 (m, 2H_{maj}), 3.30 - 3.20 (m, 1H_{maj} + 1H_{min}), 3.10 (ddd, J = 11.0 Hz, 3H_{min}), 3.10 (ddd, J = 11.0 Hz), 3H_{min}), 3H_{mi$ J = 13.3, 9.1, 3.4 Hz, 1H_{mai}), 2.69 (ddd, J = 12.7, 9.4, 5.2 Hz, 1H_{min}), 2.30 - 2.23 (m, $1H_{mai}+1H_{min}$), 1.99 (dddd, J = 12.7, 6.3, 5.0, 1.0 Hz, $1H_{mai}$), 1.85 - 1.72 (m, $2H_{mai}$), 1.70 -1.54 (m, 2H_{min}), 1.29 – 1.18 (m, 2H_{min}); ¹³C NMR (126 MHz, CDCl₃) δ 206.6 (d, J = 6.1Hz)_{min}, 204.3 (d, J = 5.1 Hz)_{maj}, 154.7_{maj}, 154.1_{min}, 138.9 (d, J = 16.7 Hz)_{min}, 138.6 (d, J = 16.7 Hz)_m 16.8 Hz)_{mai}, 129.3_{mai}, 129.3_{min}, 128.9_{mai+min}, 128.5 - 128.4 (app. m)_{min}, 128.2_{mai}, 128.0_{mai}, 126.7_{\min} , 126.3_{\max} , 125.9_{\max} , 125.6_{\min} , 95.7_{\min} , 93.6_{\max} , 89.9 - 89.7 (m)_{mai}, 89.1 (d, J = 2.1 Hz_{min} , 60.1_{min}, 59.7_{mai}, 53.5 (d, $J = 6.6 Hz_{mai}$, 53.1 (d, J = 6.8, 2.1 Hz_{min}, 48.5 (d, J = 124.1

Hz)_{maj}, 47.97 (d, J = 127.1 Hz)_{min}, 34.8_{maj}, 34.6_{min}, 34.0 (d, J = 4.7 Hz)_{min}, 33.6 (d, J = 4.9 Hz)_{maj}, 23.3_{maj}, 22.8_{min}; ³¹**P** NMR (162 MHz, CDCl₃) δ 24.56_{maj}, 24.24_{min}; **HRMS** (ESI) mass calculated for [M+H]+ (C₂₃H₂₇O₅NP) requires *m/z* 428.1621, found *m/z* 428.1617.

Synthesis of 31



The modification to General Procedure B was followed using cycloadduct **2d** (50 mg, 0.156 mmol) and diethyl allylphosphonate (44 mg, 0.296 mmol). Purification yielded the title compound as a light yellow oil (30 mg, 49%). The product was isolated as a 2:1 mixture of diastereomers. **IR**

(thin film) v_{max}/cm^{-1} 2980, 1642, 1611, 1563, 1243 (P=O), 1020 (P-O antisymmetric); ¹**H NMR** (400 MHz, CDCl₃) δ 7.56 – 7.50 (m, 2H_{min}+2H_{min}), 7.50 – 7.44 (m, 2H_{maj}), 7.34 (qd, J= 4.0, 2.0 Hz, 3H_{maj}+3H_{min}), 5.97 (app. dtdd, J = 16.8, 9.7, 6.4, 3.5 Hz, 1H_{maj}+1H_{min}), 5.38 – 5.25 (m, 2H_{min}), 5.21 (s, 1H_{min}), 5.20 – 5.11 (m, 2H_{maj}), 4.93 (s, 1H_{maj}), 4.86 (dd, J = 20.8, 9.1 Hz, 1H_{min}), 4.23 – 4.10 (m, 4H_{maj}+2H_{min}), 4.10 – 4.03 (m, 2H_{min}), 3.54 – 3.41 (m, 2H_{maj}+1H_{min}), 3.29 (ddd, J = 12.5, 8.7, 5.6 Hz, 1H_{min}), 2.38 (ddd, J = 12.8, 9.0, 7.0 Hz, 1H_{maj}), 2.31 (ddd, J = 12.9, 8.7, 7.0 Hz, 1H_{min}), 2.10 (dddd, J = 12.6, 6.8, 4.4, 1.0 Hz, 1H_{maj}), 2.01 (dddd, J = 14.2, 7.0, 4.1, 1.9 Hz), 1.96 – 1.80 (m, 2H_{maj}+1H_{min}), 1.76 (ddq, J = 12.3, 7.0, 5.0 Hz, 1H_{min}), 1.32 (q, J = 7.0 Hz, 6H_{maj}), 1.24 (dt, J = 13.0, 7.1 Hz, 6H_{min}). ¹³C NMR (126 MHz, CDCl₃) δ 203.8 (d, J = 5.8 Hz)_{maj}, 202.7 (d, J = 6.4 Hz)_{min}, 155.2_{maj}, 155.0_{min}, 129.8 (d, J = 11.9 Hz)_{maj}, 129.5_{maj}, 129.5_{min}, 129.3 (d, J = 11.7 Hz)_{min}, 128.5_{maj+min}, 60.2_{min}, 89.4 (d, J = 2.3 Hz)_{maj}, 89.1 (d, J = 2.8 Hz)_{min}, 62.93 (app dt, J = 29.7, 6.5 Hz)_{maj+min}, 60.2_{min}, 60.0_{maj}, 52.1 (d, J = 132.1 Hz)_{min}, 52.0 (d, J = 128.8 Hz)_{maj}, 34.8_{maj}, 34.7_{min}, 23.4_{maj}, 23.4_{min}, 16.5 – 16.3 (m)_{maj+min}.³¹P NMR (162 MHz, CDCl₃) δ 19.52_{min}, 19.36_{maj}.

Synthesis of 3m


The modification to General Procedure B was followed using cycloadduct **2d** (40 mg, 0.125 mmol) and phosphonate **S13** (43 mg, 0.262 mmol). Purification yielded the title compound as a yellow oil (25 mg, 53%). The product was isolated as a 2:1 mixture of diastereomers. **IR** (thin film)

 v_{max} /cm⁻¹ 2953 (C-H), 1708 (C=O), 1250 (P=O), 1026 (P=O antisymmetric) ¹H NMR (500 MHz, CDCl₃) δ 7.54 – 7.51 (m, 2H_{min}), 7.49 – 7.46 (m, 2H_{mai}), 7.35 (dp, J = 4.6, 1.5 Hz, $3H_{mai}+3H_{min}$), 5.79 – 5.70 (m, 1H_{min}), 5.55 (dddd, J = 16.4, 10.1, 7.6, 6.1 Hz, 1H_{mai}), 5.19 (s, $1H_{min}$), 5.06 (dd, J = 17.0, 1.5 Hz, $1H_{min}$), 5.00 (dd, J = 17.0, 1.0 Hz, $1H_{mai}+1H_{min}$), 4.90-4.86 (m, $2H_{maj}$), 4.52 (ddd, J = 23.4, 10.9, 3.9 Hz, $1H_{maj}$), 4.31 (ddd, J = 20.8, 10.3, 4.4 Hz, $1H_{min}$), 3.80 (d, J = 11.0 Hz, $3H_{mai}$), 3.80 (d, J = 10.9 Hz, $3H_{mai}$), 3.70 (d, J = 11.2 Hz, $3H_{min}$), 3.67 (d, J = 11.0 Hz, $3H_{min}$), 3.56 - 3.42 (m, $2H_{mai}+1H_{min}$), 3.24 (ddd, J = 12.6, 9.1, 5.6 Hz, $1H_{min}$), 2.79 - 2.60 (m, $1H_{mai} + 2H_{min}$), 2.58 - 2.48 (m, $1H_{mai}$), 2.33 (ddd, J = 12.8, 8.9, 7.2 Hz, $1H_{mai}$), 2.22 (ddd, $J = 12.9, 9.1, 6.9 Hz, 1H_{min}$), 2.15 (dddd, $J = 12.8, 6.8, 4.6, 1.1 Hz, 1H_{mai}$), 2.00 (dddd, J = 12.8, 7.0, 4.3, 1.3 Hz, 1H_{min}), 1.95 - 1.79 (m, 2H_{maj}+1H_{min}), 1.79 - 1.70 (m, 1H_{min}); ¹³C NMR (126 MHz, CDCl₃) δ 205.6 (d, J = 4.9 Hz)_{maj}, 205.4 (d, J = 5.7 Hz)_{min}, 155.0_{maj} , 154.7_{min} , 135.2 (d, J = 15.3 Hz)_{min}, 134.9 (d, J = 15.9 Hz)_{maj}, 129.5_{maj} , 129.4_{min} , 128.5_{maj+min}, 128.0_{min}, 127.8_{maj}, 125.8_{maj}, 125.7_{min}, 117.2_{min}, 117.0_{maj}, 95.8_{min}, 94.9_{maj}, 89.6_{maj}, 89.1 (d, J = 1.9 Hz)_{min}, 60.3_{min}, 59.9_{maj}, 53.4 (d, J = 6.3 Hz)_{maj+min}, 53.1 (d, J = 6.6 Hz)_{maj+min}, 45.9 (d, $J = 126.0 \text{ Hz})_{\text{mai}+\text{min}}$, 35.1_{mai}, 34.5_{min}, 32.7 (d, $J = 4.9 \text{ Hz})_{\text{min}}$, 31.9 (d, $J = 5.1 \text{ Hz})_{\text{mai}}$, 23.4_{min}, 23.3_{mai}; ³¹**P NMR** (162 MHz, CDCl₃) δ 24.91_{mai}, 24.90_{min}; **HRMS** (ESI) mass calculated for $[M+H]+(C_{19}H_{25}O_5NP)$ requires m/z 378.1465, found m/z 378.1463.

Synthesis of 3n



The modification to General Procedure B was followed using cycloadduct **2d** (68 mg, 0.212 mmol) and diethyl methylthiomethylphosphonate (78

μL, 0.445 mmol). Purification yielded the title compound as a light yellow oil (47 mg, 54%). The product was isolated as a 1:1 mixture of diastereomers. **IR** (thin film) v_{max}/cm^{-1} 2981 (C-H), 1706 (C=O), 1252 (P=O), 1023 (P-O antisymmetric) ¹H NMR (500 MHz, CDCl₃) δ 7.45-7.41 (m, 2H_{maj}+2H_{min}), 7.30-7.27 (m, 3H_{maj}+3H_{min}), 5.12 (s, 1H_{maj}), 5.11 (s, 1H_{min}), 4.86 (d, *J* = 18.9 Hz, 1H_{min}), 4.66 (d, *J* = 15.2 Hz, 1H_{maj}), 4.29 – 4.08 (m, 4H_{maj}+4H_{min}), 3.52 – 3.41 (m, 2H_{maj}+2H_{min}), 2.38 (ddd, *J* = 12.9, 8.9, 7.0 Hz, 1H_{min}), 2.30 (m, 4H_{maj}), 2.21 – 2.09 (m, 1H_{maj}+2H_{min}), 1.97 – 1.80 (m, 2H_{maj}+2H_{min}), 1.38 – 1.32 (m, 6H_{min}), 1.26 (app. dt, *J* = 15.4, 7.1 Hz, 6H_{maj}); ¹³C NMR (126 MHz, CDCl₃) δ 202.5_{min}, 199.9_{maj}, 155.1_{min}, 154.9_{maj}, 129.6_{min}, 129.5_{maj}, 128.5_{min}, 128.5_{maj}, 127.8_{maj}, 63.6 (d, *J* = 5.9 Hz)_{min}, 63.5 (d, *J* = 6.7 Hz)_{min}, 63.3 (d, *J* = 6.5 Hz)_{maj}, 63.2 (d, *J* = 6.9 Hz)_{maj}, 60.2_{maj}, 60.1_{min}, 44.9 (d, *J* = 140.2 Hz)_{min}, 43.1 (d, *J* = 148.6 Hz)_{maj}, 36.4_{maj}, 35.0_{min}, 23.6_{maj}, 23.4_{min}, 16.5 – 16.3 (m)_{maj+min}, 16.1 (d, *J* = 4.7 Hz)_{min}, 15.2 (d, *J* = 1.9 Hz)_{maj}; ³¹P NMR (202 MHz, CDCl₃) δ 19.05_{maj}, 18.36_{min}; HRMS (ESI) mass calculated for [M+H]+ (C₁₉H₂₇O₅NPS) requires *m*/z 412.1342, found *m*/z 412.1334.

Synthesis of 30



The modification to General Procedure B was followed using cycloadduct **2d** (50 mg, 0.156 mmol) and diethyl ethylphosphonate (53 μ L, 0.327 mmol). Purification yielded the title compound as a light brown oil (35 mg, 60%). The product was isolated as a 2.0:1 mixture of diastereomers.

IR (thin film) v_{max}/cm⁻¹ 2979 (C-H), 1710 (C=O), 1243 (P=O), 1022 (P-O)

antisymmetric); ¹**H** NMR (500 MHz, CDCl₃) δ 7.56 – 7.51 (m, 2H_{min}), 7.51 – 7.46 (m, 2H_{maj}), 7.35 (m, 3H_{maj}+3H_{min}), 5.24 (s, 1H_{min}), 5.00 (s, 1H_{maj}), 4.40 (dq, *J* = 22.2, 7.2 Hz, 1H_{maj}), 4.21–3.99 (m, 4H_{maj}+5H_{min}), 3.55 – 3.42 (m, 2H_{maj}+1H_{min}), 3.28 (ddd, *J* = 12.3, 8.4,

5.5 Hz, 1H_{min}), 2.44 – 2.37 (m, 1H_{min}), 2.32 (ddd, J = 12.9, 9.3, 7.1 Hz), 2.13 (dddd, J = 12.7, 6.7, 4.1, 1.1 Hz, 1H_{maj}), 1.98 – 1.82 (m, 2H_{maj}+3H_{min}), 1.43 (dd, J = 18.4, 7.1 Hz, 3H_{min}), 1.33 (app d, J = 8.7 Hz, 9H_{maj}), 1.28 – 1.18 (m, 6H_{min}); ¹³C NMR (126 MHz, CDCl₃) δ 207.8 (d, J = 5.0 Hz)_{maj}, 205.6 (d, J = 5.5 Hz)_{min}, 155.1_{min}, 154.9_{maj}, 129.5_{maj}, 129.5_{min}, 128.5_{maj+min}, 127.9_{min}, 127.8_{maj}, 125.8_{min}, 125.8_{maj}, 95.7_{min}, 95.1_{maj}, 89.5 (d, J = 2.2 Hz)_{maj}, 89.1 (d, J = 2.5 Hz)_{min}, 62.7 – 62.6 (m)_{maj}, 62.5 – 62.3 (m)_{maj}, 60.3_{min}, 60.2_{maj}, 40.9 (d, J = 133.0 Hz)_{min}, 40.4 (d, J = 129.9 Hz)_{maj}, 35.2_{maj}, 33.8_{min}, 23.5_{min}, 23.4_{maj}, 16.6 – 16.3 (m)_{maj}+_{min}, 13.6 (d, J = 7.0 Hz)_{min}, 13.3 (d, J = 7.0 Hz)_{maj}; ³¹P NMR (162 MHz, CDCl₃) δ 24.24_{min}, 23.98_{maj}; HRMS (ESI) mass calculated for [M+H]+ (C₁₉H₂₇O₅NP) requires *m*/*z* 380.1621, found *m*/*z* 380.1616.

Synthesis of 3p



General Procedure B was followed using cycloadduct **2p** (60 mg, 0.169 mmol). Purification by FCC (1:1 pentane:EtOAc) afforded the title compound as a colourless oil (51 mg, 68%). **IR** (thin film) v_{max}/cm^{-1} 2956 (C-H), 1717 (C=O), 1254 (P=O),

1031 (P-O antisymmetric); ¹**H NMR** (400 MHz, CDCl₃) δ 4.42 – 4.34 (m, 2H), 3.78 (d, *J* = 11.1 Hz, 3H), 3.76 (d, *J* = 11.2 Hz, 3H), 3.47 (d, *J* = 20.2 Hz, 2H), 3.35 (ddd, *J* = 12.0, 4.8, 1.1 Hz, 1H), 3.18 (ddd, *J* = 12.0, 4.9, 1.2 Hz, 1H), 2.31 (ddd, *J* = 13.2, 4.9, 1.1 Hz, 1H), 2.12 (ddd, *J* = 13.2, 5.5, 1.2 Hz, 1H), 1.11 (s, 9H), 0.84 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 202.6 (d, *J* = 7.0 Hz), 165.5, 92.9, 86.3 (d, *J* = 4.7 Hz), 70.2, 66.2, 53.0 (d, *J* = 6.3 Hz), 52.7 (d, *J* = 6.4 Hz), 43.1, 34.9 (d, *J* = 137.5 Hz), 31.4, 28.0, 25.7, 18.0, -5.0; ³¹P NMR (162 MHz, CDCl₃) δ 24.61; **HRMS** (ESI) mass calculated for [M+H]+ (C₂₀H₃₉O₆NPSi) requires *m/z* 448.2279, found *m/z* 448.2275.

Synthesis of 3q



General Procedure B was followed using cycloadduct 2q (22 mg, 0.073 mmol), 2 equivalents of MePO(OMe)₂ and the period at -78 °C was increased to 7 h. Purification by FCC (1:1 pentane:EtOAc) afforded the title compound as a yellow oil (15 mg, 52%). **IR** (thin

film) v_{max}/cm^{-1} 2959 (C-H), 1714 (C=O), 1259 (P=O), 1032 (P-O antisymmetric); ¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.23 (m, 2H), 7.22 – 7.16 (m, 1H), 7.13 – 7.06 (m, 2H), 4.62 (s, 1H), 3.88 – 3.78 (m, 1H), 3.63 (m, 7H), 3.33 – 3.24 (m, 1H), 3.12 (dd, J = 20.5, 15.7 Hz, 1H), 2.97 (dd, J = 20.7, 15.7 Hz, 1H), 2.32 (app. dq, J = 12.6, 7.4 Hz, 1H), 2.00 – 1.89 (m, 1H), 1.16 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 201.2 (d, J = 7.4 Hz), 166.1, 139.8, 128.7, 128.0, 127.0, 93.2, 91.5 (d, J = 4.7 Hz), 58.5, 54.0, 52.8 (d, J = 30.9 Hz), 52.8 (d, J = 30.8 Hz), 37.3 (d, J = 136.6 Hz), 31.4, 30.5, 28.0; ³¹P NMR (162 MHz, CDCl₃) δ 23.53; HRMS (ESI) mass calculated for [M+H]+ (C₂₀H₂₉O₅NP) requires m/z 394.1778, found m/z 394.1767.

Synthesis of 3r



² General Procedure B was followed using cycloadduct 2r (42 mg, 0.157 mmol). FCC (1:1 pentane:EtOAc) afforded the title compound as a colourless oil (38 mg, 67%). IR (thin film) v_{max}/cm⁻¹ 2960 (C-H), 1715 (C=O), 1258 (P=O), 1032 (P-O antisymmetric);

¹**H NMR** (400 MHz, CDCl₃) δ 4.37 (s, 1H), 3.77 (d, J = 11.2 Hz, 3H), 3.76 (d, J = 11.2 Hz, 3H), 3.54 (dd, J = 20.6, 15.5 Hz, 1H), 3.23 (dd, J = 20.5, 15.5 Hz, 1H), 2.86 (dt, J = 11.3, 6.2 Hz, 1H), 2.57 – 2.49 (m, 1H), 1.87 – 1.67 (m, 3H), 1.35 (dtd, J = 12.6, 10.9, 7.9 Hz, 1H), 1.11 (s, 9H), 1.01 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H); ¹³**C NMR** (101 MHz, CDCl₃) δ 202.4 (d, J = 7.0 Hz), 164.9, 93.5, 86.3 (d, J = 4.0 Hz), 76.0, 52.8 (d, J = 6.0 Hz), 52.7 (d, J = 6.1 Hz), 34.8 (d, J = 136.9 Hz), 31.6, 31.3, 31.2, 28.0, 24.3, 20.2, 19.0; ³¹**P NMR** (162

MHz, CDCl₃) δ 24.84; **HRMS** (ESI) mass calculated for [M+H]+ (C₁₇H₃₁O₅NP) requires *m/z* 360.1934, found *m/z* 360.1930.

8. Synthesis and Characterisation^{*} of Spirocycles

Synthesis of 4a

General Procedure C was followed using ketophosphonate **3a** (47 mg, 0.15 mmol). FCC purification (2:1 pentane:EtOAc) afforded the title compound as a colourless oil (38 mg, 87%). **IR** (thin film) v_{max}/cm^{-1} 2968 (C-H), 1714 (C=O), 1695 (C=O), 1603 (C=C), 1390; ¹H NMR (400 MHz, CDCl₃) δ 5.97 (dd, J = 2.1, 1.2 Hz, 1H_{min}, 8_{min}), 5.93 (dd, J = 2.1, 1.3 Hz, 1H_{maj}, 8_{maj}), 3.63 – 3.43 (m, 2H_{maj}+2H_{min}, 2_{maj}, 2_{min}), 3.07 (dd, J = 17.0, 2.1 Hz, 1H_{min}, 6_{min}), 2.91 (dd, J = 17.5, 2.0 Hz, 1H_{maj}, 6_{maj}), 2.57 (dd, J = 17.5, 1.4 Hz, 1H_{maj}, 6'maj), 2.51 (dd, J = 17.1, 1.2 Hz, 1H_{min}, 6'min), 2.09 – 1.92 (m, 2H_{maj}, 3_{maj}, 4_{maj}), 1.90 – 1.78 (m, 1H_{maj}, 3'maj), 1.77 – 1.64 (m, 1H_{maj}, 4'maj), 1.41 (s, 9H_{min}, 17_{min}-19_{min}), 1.31 (s, 9H_{maj}, 17_{maj}-19_{maj}), 1.17 (s, 9H_{maj}+9H_{min}, 12_{maj}-14_{maj}, 12_{min}-14_{min}); ¹³C NMR (101 MHz, CDCl₃) δ 208.4 (9_{maj}), 208.2 (9_{min}), 185.6 (7_{min}), 185.4 (7_{maj}), 153.2 (20_{min}), 153.1 (20_{maj}), 124.8 (8_{maj}), 124.7 (8_{min}), 80.3 (5_{maj}), 79.6 (5_{min}), 69.4 (16_{min}), 68.9 (16_{maj}), 48.2 (2_{min}), 48.0 (2_{maj}), 42.6 (6_{maj}), 41.4 (6_{min}), 40.2 (4_{maj}), 39.3 (4_{min}), 35.1 (11_{min}), 35.0 (11_{maj}), 28.5 – 28.2 (m, 12_{maj}-14_{maj}, 17_{maj}-19_{maj}, 12_{min}-14_{min}, 17_{min}-19_{min}), 23.9 (3_{min}), 23.3 (3_{maj}); **HRMS** (ESI) mass calculated for [M+Na]+ (C₁₇H₂₇O₃NNa) requires *m/z* 316.1883, found *m/z* 316.1882.

Synthesis of 4b

^{*} NMR spectra of N-Boc-protected spirocycles were recorded as a mixture of rotamers in all cases (labelled maj/min where distinction possible)



The modification to General Procedure C was followed using ketophosphonate **3b** (20 mg, 0.063 mmol). FCC purification (1:1 pentane:EtOAc) afforded the title compound as a yellow oil (7.7 mg,

42%). IR (thin film) v_{max}/cm⁻¹ 2970 (C-H), 1715 (C=O), 1695 (C=O),

1615, 1392, 1161; ¹**H** NMR (500 MHz, CDCl₃) δ 6.00 (t, J = 1.5 Hz, 1H_{min}), 5.94 (t, J = 1.7 Hz, 1H_{maj}), 3.62 – 3.49 (m, 2H_{maj}+2H_{min}), 3.11 – 3.05 (m, 1H_{min}), 2.95 – 2.88 (m, 1H_{maj}), 2.45 (dd, J = 22.9, 17.4 Hz, 1H_{maj}+1H_{min}), 2.46 – 2.29 (m, 2H_{maj}+2H_{min}), 2.06 (ddd, J = 14.9, 10.8, 5.0 Hz, 1H_{maj}+1H_{min}), 1.99 (dddd, J = 12.1, 9.0, 6.2, 2.9 Hz, 1H_{maj}+1H_{min}), 1.90 – 1.78 (m, 1H_{maj}+1H_{min}), 1.74 (tdd, J = 14.9, 6.3, 3.1 Hz, 1H_{maj}+1H_{min}), 1.61 – 1.51 (m, 2H_{maj}+2H_{min}), 1.42 (s, 9H_{min}), 1.41 – 1.34 (m, 2H_{maj}+2H_{min}), 1.32 (s, 9H_{maj}), 0.94 (app. dt, J = 10.1, 7.3 Hz, 3H_{maj}+3H_{min}); ¹³C NMR (126 MHz, CDCl₃) δ 208.0_{maj+min}, 178.3_{min}, 177.9_{maj}, 153.3_{min}, 153.1_{maj}, 127.1_{maj+min}, 80.2_{maj}, 79.7_{min}, 68.9_{min}, 68.6_{maj}, 48.1_{min}, 48.0_{maj}, 46.3_{maj}, 45.1_{min}, 40.1_{maj}, 39.1_{min}, 33.4_{min}, 33.3_{maj}, 29.0_{maj}, 28.7_{min}, 28.5_{min}, 28.3_{maj}, 23.9_{min}, 23.3_{maj}, 22.5_{maj}, 22.5_{min}, 13.8_{min}, 13.8_{maj}; **HRMS** (ESI) mass calculated for [M+Na]+ (C₁₇H₂₇O₃NNa) requires *m*/z 316.1885, found *m*/z 316.1885.

Synthesis of 4c



General Procedure C was followed using ketophosphonate **3c** (24 mg, 0.07 mmol). FCC purification (2:1 pentane:EtOAc) afforded the title compound as a colourless oil (15 mg, 67%). **IR** (thin film) v_{max}/cm^{-1} 2973 (C-H), 2928 (C-H), 1716 (C=O), 1697, 1391, 1161; ¹H NMR (400 MHz,

CDCl₃) δ 5.96 (dt, J = 2.6, 1.3 Hz, 1H_{min}), 5.91 (dt, J = 2.0, 1.3 Hz, 1H_{maj}), 3.63 – 3.46 (m, 2H_{maj}+2H_{min}), 3.10 – 3.02 (m, 1H_{min}), 2.92 (dd, J = 17.7, 2.0 Hz, 1H_{maj}), 2.53 – 2.43 (m, 1H_{maj}+1H_{min}), 2.25 (m, 1H_{maj}+1H_{min}), 2.04 (m, 1H_{maj}+1H_{min}), 1.97 (m, 1H_{maj}+1H_{min}), 1.93 – 1.77 (m, 5H_{maj}+5H_{min}), 1.77 – 1.62 (m, 2H_{maj}+2H_{min}), 1.41 (s, 9H_{min}), 1.31 (s, 9H_{maj}), 1.38 –

1.15 (m, $4H_{maj}+4H_{min}$); ¹³C NMR (101 MHz, CDCl₃) δ 208.1_{maj}, 208.0_{min}, 182.1_{maj}, 181.9_{min}, 153.3_{min}, 153.1_{maj}, 125.5_{maj+min}, 80.2_{maj}, 79.6_{min}, 68.8_{min}, 68.4_{maj}, 48.2_{min}, 48.0_{maj}, 44.5_{maj}, 43.2_{min}, 42.0_{maj}, 41.8_{min}, 40.2_{maj}, 39.3_{min}, 31.1_{maj}, 30.9_{maj}, 30.8_{min}, 30.7_{min}, 28.5_{maj+min}, 26.08 – 25.87 (m)_{maj+min}, 23.9_{min}, 23.3_{maj}; **HRMS** (ESI) mass calculated for [M+Na]+ (C₁₉H₂₉O₃NNa) requires *m/z* 342.2040, found *m/z* 342.2034.

Synthesis of 4d



General Procedure C was followed using ketophosphonate **3d** (40 mg, 0.12 mmol). FCC purification (1:1 pentane:EtOAc) afforded the title compound as a white solid (19 mg, 52%). **MP** 128-129 °C; **IR** (thin film) v_{max}/cm^{-1} 2974 (C-H), 1707 (C=O), 1692 (C=O), 1600 (C=C),

1392, 1161; ¹H NMR (400 MHz, CDCl₃) δ 7.67 – 7.59 (m, 2H_{maj}+2H_{min}), 7.52 – 7.38 (m, 3H_{maj}+3H_{min}), 6.64 (dd, J = 2.1, 1.3 Hz, 1H_{min}), 6.56 (t, J = 1.7 Hz, 1H_{maj}), 3.69 – 3.54 (m, 2H_{maj}+2H_{min}), 3.51 (dd, J = 17.0, 2.1 Hz, 1H_{min}), 3.32 (dd, J = 17.4, 2.0 Hz, 1H_{maj}), 2.97 (app. td, J = 17.1, 1.5 Hz, 1H_{maj}+1H_{min}), 2.21 – 1.99 (m, 2H_{maj}+2H_{min}), 1.99 – 1.78 (m, 2H_{maj}+2H_{min}), 1.42 (s, 9H_{min}), 1.28 (s, 9H_{maj}); ¹³C NMR (101 MHz, CDCl₃) δ 207.6_{maj}, 207.5_{min}, 168.9_{maj}, 168.8_{min}, 153.4_{min}, 153.1_{maj}, 134.0_{min}, 133.9_{maj}, 131.4_{maj}, 131.2_{min}, 129.0_{maj}, 128.7_{min}, 127.0_{min}, 126.7_{maj}, 125.1_{min}, 125.0_{maj}, 80.3_{maj}, 79.8_{min}, 69.0_{min}, 68.6_{maj}, 48.2_{min}, 48.0_{maj}, 43.7_{maj}, 42.3_{min}, 40.2_{maj}, 39.3_{min}, 28.5_{min}, 28.2_{maj}, 24.0_{min}, 23.3_{maj}; HRMS (ESI) mass calculated for [M+Na]+ (C₁₉H₂₃O₃NNa) requires *m/z* 336.1570, found *m/z* 336.1567.

Synthesis of 4e



General Procedure C was followed using ketophosphonate **3e** (44 mg, 0.124 mmol). FCC purification (3:1 pentane:EtOAc) afforded the title compound as a white solid (24 mg, 59%). **MP** 162-164 °C; **IR** (thin

film) v_{max}/cm^{-1} 2975 (C-H), 1707 (C=O), 1689 (C=O), 1602 (C=C),1392, 1161; ¹H NMR (400 MHz, CDCl₃) δ 7.67 – 7.58 (m, 2H_{maj}+2H_{min}), 7.20 – 7.08 (m, 2H_{maj}+2H_{min}), 6.57 (t, J =1.7 Hz, 1H_{min}), 6.50 (t, J = 1.7 Hz, 1H_{maj}), 3.68 – 3.52 (m, 2H_{maj}+2H_{min}), 3.49 (dd, J = 17.0, 2.1 Hz, 1H_{min}), 3.29 (dd, J = 17.4, 1.9 Hz, 1H_{maj}), 2.93 (app ddd, J = 18.3, 17.2, 1.4 Hz, 1H_{maj}+1H_{min}), 2.21 – 2.00 (m, 2H_{maj}+2H_{min}), 1.98 – 1.79 (m, 2H_{maj}+2H_{min}), 1.42 (s, 9H_{min}), 1.27 (s, 9H_{maj}); ¹³C NMR (101 MHz, CDCl₃) δ 207.4_{maj}, 207.3_{min}, 167.5_{maj}, 167.5_{min}, 164.8 (d, J = 253.5 Hz)_{maj}, 164.7 (d, J = 253.2 Hz)_{min}, 153.5_{min}, 153.0_{maj}, 130.4 (d, J = 2.9 Hz)_{min}, 130.2 (d, J = 3.2 Hz)_{maj}, 129.1 (d, J = 8.7 Hz)_{min}, 128.8 (d, J = 8.7 Hz)_{maj}, 124.9_{min}, 124.8_{maj}, 116.3 (d, J = 22.1 Hz)_{maj}, 115.9 (d, J = 22.0 Hz)_{min}, 80.4_{maj}, 79.9_{min}, 69.1_{min}, 68.6_{maj}, 48.2_{min}, 48.0_{maj}, 43.7_{maj}, 42.4_{min}, 40.2_{maj}, 39.3_{min}, 28.5_{min}, 28.2_{maj}, 24.0_{min}, 23.3_{maj}; ¹⁹F NMR (377 MHz, CDCl₃) δ -107.66 (app tt, J = 8.4, 5.3 Hz)_{maj}, -108.09 (app tt, J = 8.4, 5.3 Hz)_{min}; HRMS (ESI) mass calculated for [M+Na]+ (C₁₉H₂₂O₃NFNa) requires *m/z* 354.1476, found *m/z* 354.1476.

Synthesis of 4f



General Procedure C was followed using ketophosphonate **3f** (60 mg, 0.163 mmol). FCC purification (2:1 pentane:EtOAc) afforded the title compound as an amorphous white solid (33 mg, 59%). **IR** (thin film) v_{max}/cm^{-1} 2984 (C-H), , 1709 (C=O), 1606 (C=C),

1112, 1059; ¹**H** NMR (400 MHz, CDCl₃) δ 7.64 – 7.55 (m, 2H_{maj}+2H_{min}), 6.99 – 6.95 (m, 2H_{maj}), 6.95 – 6.88 (m, 2H_{min}), 6.52 (t, J = 1.6 Hz, 1H_{min}), 6.45 (t, J = 1.6 Hz, 1H_{maj}), 3.87 (s, 3H_{maj}), 3.85 (s, 3H_{min}), 3.69 – 3.53 (m, 2H_{maj}+2H_{min}), 3.52 – 3.42 (m, 1H_{min}), 3.27 (dd, J = 17.3, 1.9 Hz, 1H_{maj}), 2.94 (app td, J = 17.2, 1.5 Hz, 1H_{maj}+1H_{min}), 2.21 – 1.98 (m, 2H_{maj}+2H_{min}), 1.97 – 1.77 (m, 2H_{maj}+2H_{min}), 1.42 (s, 9H_{min}), 1.27 (s, 9H_{maj}); ¹³C NMR (101 MHz, CDCl₃) δ 207.4_{maj}, 207.3_{min}, 168.5_{maj+min}, 162.3_{maj}, 162.1_{min}, 153.4_{min}, 153.2_{maj},

128.8_{min}, 128.5_{maj}, 126.8_{min}, 126.5_{maj}, 123.1_{min}, 123.0_{maj}, 114.4_{maj}, 114.1_{min}, 80.2_{maj}, 79.7_{min}, 69.0_{min}, 68.6_{maj}, 55.5_{maj}, 55.4_{min}, 48.2_{min}, 48.0_{maj}, 43.6_{maj}, 42.3_{min}, 40.2_{maj}, 39.3_{min}, 28.5_{min}, 28.2_{maj}, 24.0_{min}, 23.3_{maj}; **HRMS** (ESI) mass calculated for $[M+Na]+(C_{20}H_{25}O_4NNa)$ requires *m/z* 366.1676, found *m/z* 366.1675.

Synthesis of 4g

General Procedure C was followed using ketophosphonate **3g** (47 mg, 0.15 mmol). FCC purification (1:1 pentane:EtOAc) afforded the title compound as a yellow oil (10 mg, 23%). **IR** (thin film) v_{max}/cm^{-1} 2974 (C-H), 1694 (C=O), 1602 (C=C), 1392, 1161; ¹**H NMR** (400 MHz, CDCl₃) δ 5.99 (t, *J* = 1.6 Hz, 1H_{min}), 5.91 (t, *J* = 1.7 Hz, 1H_{maj}), 3.60 – 3.46 (m, 2H_{maj}+2H_{min}), 2.94 (dd, *J* = 17.2, 1.9 Hz, 1H_{min}), 2.75 (dd, *J* = 17.5, 1.8 Hz, 1H_{maj}), 2.33 (dd, *J* = 17.5, 1.5 Hz, 1H_{maj}), 2.25 (dd, *J* = 17.2, 1.4 Hz, 1H_{min}), 2.11 – 1.91 (m, 2H_{maj}+2H_{min}), 1.87 – 1.78 (m, 2H_{maj}+2H_{min}), 1.78 – 1.64 (m, 1H_{maj}+1H_{min}), 1.42 (s, 9H_{min}), 1.33 (s, 9H_{maj}), 1.11 – 0.99 (m, 2H_{maj}+2H_{min}), 0.95 – 0.78 (m, 2H_{maj}+2H_{min}); ¹³C NMR (101 MHz, CDCl₃) δ 207.1_{maj}, 206.9_{min}, 180.3_{min}, 180.0_{maj}, 125.1_{min}, 124.8_{maj}, 80.2_{maj}, 79.7_{min}, 68.7_{min}, 68.2_{maj}, 48.2_{min}, 47.9_{maj}, 43.2_{maj}, 41.8_{min}, 9.2_{min}; **HRMS** (ESI) mass calculated for [M+Na]+ (C₁₆H₂₃O₃NNa) requires *m/z* 300.1570, found *m/z* 300.1570.

Synthesis of 4h

General Procedure C was followed using ketophosphonate **3h** (32 mg, 0.100 mmol) however an additional equivalent of base was used. FCC purification (EtOAc) afforded the title compound as an off-white solid (18 mg, 61%). **MP** 109-111 °C; **IR** (thin film) v_{max}/cm^{-1} 3437 (O-H), 2976 (C-H), 1698 (C=O), 1611 (C=C), 1394, 1161; ¹H NMR (400 MHz, CDCl₃) δ 6.11 (dd, J = 2.1, 1.4 Hz, 1H_{min}), 6.10 (dd, J = 2.1, 1.4 Hz, 1H_{maj}), 3.64 – 3.45 (m, 2H_{maj}+2H_{min}), 3.13 (dd, J = 17.6, 2.1 Hz, 1H_{min}), 2.95 (dd, J = 17.7, 2.1 Hz, 1H_{maj}), 2.61 (td, J = 17.6, 1.4 Hz, 1H_{maj}+1H_{min}), 2.50 – 2.42 (m, 1H_{min}), 2.14 – 2.10 (m, 1H_{maj}), 2.09 – 1.93 (m, 2H_{maj}+2H_{min}), 1.91 – 1.80 (m, 1H_{maj}+1H_{min}), 1.80 – 1.67 (m, 1H_{maj}+1H_{min}), 1.46 (s, 3H_{maj}+3H_{min}), 1.45 (s, 3H_{maj}+3H_{min}), 1.40 (s, 9H_{min}), 1.32 (s, 9H_{maj}); ¹³C NMR (101 MHz, CDCl₃) δ 207.9_{maj}, 182.2_{min}, 181.9_{maj}, 153.4_{min}, 153.1_{maj}, 125.0_{min}, 124.9_{maj}, 80.4_{maj}, 79.8_{min}, 71.5_{maj}, 71.2_{min}, 69.3_{min}, 69.1_{maj}, 48.2_{min}, 48.0_{maj}, 42.4_{maj}, 41.2_{min}, 40.2_{maj}, 39.1_{min}, 28.8_{min}, 28.7_{min}, 28.4_{min}, 23.9_{min}, 23.3_{maj}; **HRMS** (ESI) mass calculated for [M+Na]+ (C₁₆H₂₅O₄NNa) requires *m/z* 318.1676, found *m/z* 318.1676.

Synthesis of 4i



General Procedure C was followed using ketophosphonate **3i** (30 mg, 0.055 mmol) however an additional equivalent of base was used. FCC purification (2:1 pentane:EtOAc) afforded the title compound as a white solid (8.4 mg, 29%). **MP** 105-111 °C; **IR** (thin

film) v_{max}/cm^{-1} 3474 (O-H), 2929 (C-H), 1696 (C=O), 1608, 1394, 1162; ¹H NMR (500 MHz, CDCl₃) δ 7.14 (t, J = 9.0 Hz, +1H_{min}), 6.70 (ddd, J = 11.9, 8.5, 2.8 Hz, 1H_{maj}+1H_{min}), 6.63 (dd, J = 5.7, 2.7 Hz, 1H_{maj}+1H_{min}), 6.06 (app d, J = 1.7 Hz, 1H_{min}), 6.02 (dd, J = 1.1 Hz, 1H_{maj}), 3.77 (s, 3H_{min}), 3.77 (s, 3H_{maj}), 3.65 – 3.58 (m, 1H_{maj}), 3.58 – 3.45 (m, 1H_{maj}+2H_{min}), 3.06 – 2.99 (m, 1H_{min}), 2.95 (dd, J = 14.2, 1.7 Hz, 1H_{maj}), 2.91 – 2.81 (m, 3H_{maj}+3H_{min}), 2.32 – 2.16 (m, 3H_{maj}+2H_{min}), 2.13 (app q, J = 10.5, 8.7 Hz, 1H_{min}), 2.08 – 1.95 (m, 3H_{maj}+3H_{min}), 1.95 – 1.83 (m, 3H_{maj}+3H_{min}), 1.83 – 1.70 (m, 2H_{maj}+2H_{min}), 1.70 – 1.31 (m, 8H_{maj}+8H_{min}), 1.40 (s, 9H_{min}), 1.36 (s, 9H_{maj}), 1.02 (s, 3H_{maj}), 0.99 (s, 3H_{min}); ¹³C NMR (126 MHz, CDCl₃) δ 207.9_{min}, 207.0_{maj}, 181.7_{min}, 181.3_{maj}, 157.6_{maj}, 157.4_{min}, 153.2_{maj}, 153.1_{min}, 138.0_{min},

137.8_{maj}, 132.7_{min}, 132.1_{maj}, 129.2_{maj}, 129.1_{min}, 126.2_{maj}, 126.1_{min}, 113.9_{maj}, 113.7_{min}, 111.5_{maj},
111.4_{min}, 85.7_{min}, 85.6_{maj}, 80.7_{maj}, 79.6_{min}, 69.1_{maj}, 68.2_{min}, 55.2_{min}, 55.2_{maj}, 49.0_{maj}, 48.6_{maj},
48.6_{min}, 48.1_{min}, 48.1_{min}, 47.7_{maj}, 44.6_{min}, 44.5_{maj}, 43.0_{maj}, 42.9_{min}, 41.0_{maj}, 39.7_{maj}, 39.5_{maj},
39.4_{min}, 39.1_{min}, 38.9_{min}, 33.1_{maj}, 32.7_{min}, 29.8_{min}, 29.7_{maj}, 28.6_{maj}, 28.4_{min}, 27.6_{maj}, 27.2_{min},
26.6_{min}, 26.2_{min}, 24.1_{maj}, 23.7_{min}, 23.6_{maj}, 23.1_{min}, 14.4_{maj}, 14.4_{min}; **HRMS** (ESI) mass
calculated for [M+Na]+ (C₃₂H₄₃O₅NNa) requires *m/z* 544.3033, found *m/z* 544.3022.

Synthesis of 4j



General Procedure C was followed using ketophosphonate **3j** (45 mg, 0.110 mmol). FCC purification (2:1 pentane:EtOAc) afforded the title compound as a yellow amorphous solid (15 mg, 35%). **IR** (thin film) v_{max}/cm^{-1} 2974 (C-H), 1688 (C=O), 1695 (C=O), 1619 (C=C), 1390; ¹H

NMR (500 MHz, CDCl₃) δ 7.38 – 7.27 (m, 8H_{maj}+8H_{min}), 7.27 – 7.22 (m, 2H_{maj}+2H_{min}), 3.71 – 3.56 (m, 2H_{maj}+3H_{min}), 3.43 (d, J = 17.5 Hz, 1H_{maj}), 2.93 (d, J = 17.5 Hz, 1H_{maj}), 2.85 (d, J = 16.8 Hz, 1H_{min}), 2.28 – 2.15 (m, 1H_{maj}+1H_{min}), 2.07 (app. ddt, J = 11.7, 6.6, 3.2 Hz, 1H_{maj}+1H_{min}), 1.99 – 1.89 (m, 2H_{maj}+2H_{min}), 1.44 (s, 9H_{min}), 1.33 (s, 9H_{maj}); ¹³C NMR (126 MHz, CDCl₃) δ 205.8_{maj}, 205.9_{min}, 163.3_{maj}, 162.8_{min}, 153.4_{min}, 153.1_{maj}, 137.5_{min}, 137.1_{maj}, 135.7_{min}, 135.6_{maj}, 132.4_{min}, 132.0_{maj}, 129.9_{maj}, 129.8_{min}, 129.7_{min}, 129.5_{maj}, 128.5_{maj}, 128.5_{min}, 128.4_{maj}, 128.3_{min}, 128.1_{maj}, 128.0_{maj}, 39.6_{min}, 28.5_{maj}, 23.9_{min}, 23.4_{maj}; **HRMS** (ESI) mass calculated for [M+Na]+ (C₂₅H₂₇O₃NNa) requires *m/z* 412.1883, found *m/z* 412.1895

Synthesis of 4k



General Procedure C was followed using ketophosphonate 3k (40 mg, 0.09 mmol). FCC purification (2:1 pentane:EtOAc) afforded the title compound as an off-white amorphous solid (12 mg, 32%). IR (thin film) v_{max}/cm^{-1} 2973 (C-H), 1693 (C=O), 1620 (C=C), 1391; ¹H NMR (400 MHz, CDCl₃) δ 7.48 – 7.38 (m, 5H_{maj}), 7.38 – 7.34 (m, 5H_{min}), 7.28 – 7.23 (m, $2H_{mai}+2H_{min}$), 7.22 – 7.13 (m, $3H_{mai}+3H_{min}$), 3.97 – 3.85 (m, $1H_{mai}$), 3.74 (d, J =15.5 Hz, $1H_{min}$), 3.69 - 3.55 (m, $3H_{maj}+3H_{min}$), 3.46 (m, $1H_{maj}+1H_{min}$), 2.81 (m,

 $1H_{mai}+1H_{min}$), 2.21 - 2.00 (m, $2H_{mai}+2H_{min}$), 1.97 - 1.80 (m, $2H_{mai}+2H_{min}$), 1.45 (s, $9H_{min}$), 1.26 (s, 9H_{mai}); ¹³C NMR (101 MHz, CDCl₃) δ 208.0_{min}, 207.4_{mai}, 164.1_{mai}, 153.2_{mai}, 139.1_{maj}, 136.8_{maj}, 135.8_{maj}, 129.9_{maj}, 129.7_{min}, 128.8_{maj}, 128.6_{maj}, 128.5_{min}, 128.2_{maj}, 128.1_{min}, 127.8_{min}, 127.4_{maj}, 126.2_{maj}, 125.9_{min}, 80.11_{maj}, 79.7_{min}, 68.3_{min}, 67.7_{maj}, 48.3_{min}, 48.1_{maj}, 45.1_{maj}, 43.5_{min}, 40.3_{maj}, 39.3_{min}, 30.1_{min}, 30.0_{maj}, 28.5_{min}, 28.3_{maj}, 23.9_{min}, 23.3_{maj}; **HRMS** (ESI) mass calculated for [M+Na]+ (C₂₆H₂₉O₃NNa) requires m/z 426.2040, found m/z426.2038.

Synthesis of 41

General Procedure C was followed using ketophosphonate 31 (22 mg, 0.057 mmol). FCC purification (2:1 pentane:EtOAc) afforded the title compound as a yellow oil (13 mg, 67%). IR (thin film) ν_{max}/cm^{-1} 2974 (C-H), 1710 (C=O), 1696 (C=O), 1391, 1171; ¹H NMR (400 MHz, CDCl₃) δ 7.56 - 7.36 (m, 5H_{mai}+5H_{min}), 6.58 - 6.27 (m, 2H_{mai}+2H_{min}), 5.49 - 5.39 (m, $1H_{mai}+1H_{min}$), 3.67 – 3.54 (m, $2H_{mai}+3H_{min}$), 3.29 (d, J = 18.1 Hz, $1H_{mai}$), 2.87 – 2.79 (m, $1H_{mai}$), 2.72 (d, J = 17.3 Hz, $1H_{min}$), 2.24 – 2.10 (m, $1H_{mai}+1H_{min}$), 2.05 (tdd, J = 11.0, 5.5, 1002.4 Hz, $1H_{maj}+1H_{min}$), 1.94 - 1.76 (m, $2H_{maj}+2H_{min}$), 1.44 (s, $9H_{min}$), 1.29 (s, $9H_{maj}$); ¹³C **NMR** (101 MHz, CDCl₃) δ 206.2_{maj}, 163.7_{maj}, 153.1_{maj}, 135.9_{maj}, 132.7_{maj}, 129.9_{maj}, 129.7_{min}, 128.7_{maj}, 128.4_{min}, 128.4_{min}, 127.9_{maj}, 126.8_{min}, 126.7_{maj}, 121.0_{maj}, 120.9_{min}, 80.2_{maj}, 79.7_{min}, 68.0_{maj}, 48.3_{min}, 48.0_{maj}, 44.8_{maj}, 43.1_{min}, 40.3_{maj}, 39.5_{min}, 28.5_{min}, 28.3_{maj}, 23.9_{min}, 23.5_{maj}; **HRMS** (ESI) mass calculated for [M+Na]+ ($C_{21}H_{25}O_3NNa$) requires *m/z* 362.1727, found *m/z* 362.1730.

Synthesis of 4m

General Procedure C was followed using ketophosphonate **3m** (27 mg, 0.07 mmol). FCC purification (2:1 pentane:EtOAc) afforded the title compound as a yellow oil (18 mg, 70%). **IR** (thin film) v_{max}/cm^{-1} 2968 (C-H), 1705 (C=O), 1693 (C=O), 1621 (C=C), 1390; ¹H NMR (400 MHz, CDCl₃) δ 7.55 – 7.38 (m, 5H_{maj}+5H_{min}), 5.97 (ddt, *J* = 17.1, 10.3, 5.8 Hz), 5.13 – 5.00 (m, 2H_{maj}+2H_{min}), 3.69 – 3.53 (m, 2H_{maj}+3H_{min}), 3.45 – 3.36 (m, 1H_{maj}), 3.34 – 3.19 (m, 1H_{maj}+1H_{min}), 3.16 – 3.05 (m, 1H_{maj}+1H_{min}), 2.77 (dd, *J* = 18.4, 17.2 Hz, 1H_{maj}+1H_{min}), 2.19 – 1.98 (m, 2H_{maj}+2H_{min}), 1.95 – 1.78 (m, 2H_{maj}+2H_{min}), 1.44 (s, 9H_{min}), 1.29 (s, 9H_{maj}); ¹³C NMR (126 MHz, CDCl₃) δ 207.0_{maj}, 206.9_{min}, 163.4_{maj}, 163.3_{min}, 153.3_{min}, 153.2_{maj}, 135.9_{min}, 135.8_{min}, 135.7_{maj}, 134.9_{min}, 134.7_{maj}, 129.9_{maj}, 129.7_{min}, 128.8_{maj}, 128.5_{min}, 127.8_{min}, 127.5_{maj}, 115.8_{maj}, 115.5_{min}, 80.1_{maj}, 79.6_{min}, 68.2_{min}, 67.6_{maj}, 48.3_{min}, 48.0_{maj}, 44.8_{maj}, 43.4_{min}, 40.2_{maj}, 39.4_{min}, 28.7_{maj}, 28.6_{min}, 28.5_{min}, 28.3_{maj}, 23.9_{min}, 23.4_{maj}; HRMS (ESI) mass calculated for [M+Na]+ (C₂₂H₂₇O₃NNa) requires *m/z* 376.1883, found *m/z* 376.1877.

Synthesis of 4n



General Procedure C was followed using ketophosphonate **3n** (22 mg, 0.054 mmol). FCC purification (2:1 pentane:EtOAc) afforded the title compound as a yellow oil (14 mg, 74%). **IR** (thin film) v_{max}/cm^{-1} 2980 (C-H), 1713 (C=O), 1693 (C=O), 1390, 1167, 767; ¹H NMR (400 MHz,

 $CDCl_{3}) \ \delta \ 7.79 - 7.74 \ (m, \ 2H_{min}), \ 7.74 - 7.67 \ (m, \ 2H_{maj}), \ 7.52 - 7.39 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.39 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.52 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.59 \ (m, \ 3H_{maj} + 3H_{min}), \ 3.70 - 7.59 \ (m, \ 3H_{maj} + 3H_{maj} + 3H_{maj}), \ 3.70 - 7.59 \ (m, \ 3H_{maj} + 3H_{maj} + 3H_{maj} + 3H_{maj}), \ 3.70 - 7.59 \ (m, \ 3H_{maj} + 3H_{m$

 $3.51 \text{ (m, } 2H_{\text{maj}}+3H_{\text{min}}\text{)}, 3.34 \text{ (d, } J = 17.4 \text{ Hz}, 1H_{\text{maj}}\text{)}, 2.94 \text{ (d, } J = 17.4 \text{ Hz}, 1H_{\text{maj}}\text{)}, 2.85 \text{ (d, } J = 17.4 \text{ Hz}, 1H$ 16.8 Hz, 1H_{min}), 2.46 (s, 3H_{mai}), 2.44 (s, 3H_{min}), 2.21 - 1.97 (m, 2H_{mai}+2H_{min}), 1.97 - 1.78 (m, 2H_{mai}+2H_{min}), 1.43 (s, 9H_{min}), 1.32 (s, 9H_{mai}); ¹³C NMR (101 MHz, CDCl₃) δ 204.7_{mai}, 163.6_{min}, 163.2_{maj}, 153.1 – 152.9 (m)_{maj+min}, 135.2_{maj}, 132.4_{maj}, 130.3_{maj}, 130.2_{min}, 128.5_{maj}, 128.2_{\min} , $128.0_{\max i+\min}$, 81.2_{\min} , $80.4_{\max i}$, 68.0_{\min} , $67.5_{\max i}$, $48.0_{\max i}$, $45.2_{\max i}$, 43.8_{\min} , $40.3_{\max i}$, 40.3 28.5_{min} , 28.3_{mai} , 23.3_{mai} , 15.3_{min} , 14.9_{mai} ; **HRMS** (ESI) mass calculated for [M+Na]+ (C₂₀H₂₅O₃NNaS) requires *m/z* 382.1447, found *m/z* 382.1449.

Synthesis of 40



General Procedure C was followed using ketophosphonate **30** (30 mg, 0.079 mmol). FCC purification (2:1 pentane:EtOAc) afforded the title compound as a colourless oil (17 mg, 66%). **IR** (thin film) v_{max}/cm^{-1} 2974 (C-H), 1698 (C=O), 1392, 1172; $^1\!H$ NMR (400 MHz, CDCl₃) δ 7.58 – 7.38 (m, $5H_{maj}+5H_{min}$), 3.69 – 3.54 (m, $2H_{maj}+2H_{min}$), 3.49 (dd, J = 16.6, 2.6 Hz, $1H_{min}$), 3.32 -3.23 (m, 1H_{mai}), 2.81 (dd, J = 17.1, 1.8 Hz, 1H_{mai}), 2.73 (dd, J = 16.6, 1.8 Hz, 1H_{min}), 2.18 - $1.99 (m, 2H_{maj}+2H_{min}), 2.04 (m, 3H_{min}), 2.02 - 1.99 (m, 3H_{maj}), 1.96 - 1.75 (m, 2H_{maj}+2H_{min}), 1.96 - 1.75 (m, 2H_{maj}+2H_{maj}$ 1.43 (s, 9H_{min}), 1.28 (s, 9H_{mai}); ¹³C NMR (101 MHz, CDCl₃) δ 207.9_{mai}, 161.8_{mai}, 153.3_{mai}, 136.0_{maj}, 134.1_{maj}, 129.6_{maj}, 129.4_{min}, 128.7_{maj}, 128.4_{min}, 128.0_{min}, 127.6_{maj}, 80.0_{maj}, 67.4_{maj}, 48.2_{min}, 47.9_{maj}, 44.8_{maj}, 43.2_{min}, 40.2_{maj}, 39.5_{min}, 28.5_{min}, 28.3_{maj}, 24.0_{min}, 23.5_{maj}, 10.5_{min}, 10.3_{mai}; **HRMS** (ESI) mass calculated for $[M+Na]+(C_{20}H_{25}O_3NNa)$ requires m/z 350.1727, found *m/z* 350.1725

Synthesis of **4p**



General Procedure C was followed using ketophosphonate **3p** (46 mg, 0.103 mmol). FCC purification (10:1 pentane:EtOAc) afforded the title compound as a white solid (28 mg, 64%). **MP** 143-144 °C; **IR** (thin film) v_{max}/cm^{-1} 2959 (C-H), 1716 (C=O), 1699 (C=O), 1603, 1392, 1125, 1110, 838; ¹H NMR (400 MHz, CDCl₃) δ 5.99 (dd, J = 2.1, 1.2 Hz, 1H_{min}), 5.94 (dd, J = 2.0, 1.3 Hz, 1H_{maj}), 4.42 – 4.29 (m, 1H_{maj}+1H_{min}), 3.77 (m, 1H_{maj}), 3.67 (ddd, J = 10.0, 7.2, 1.1 Hz, 1H_{min}), 3.24 (m, 1H_{maj}+1H_{min}), 3.04 – 2.96 (m, 1H_{min}), 2.93 – 2.84 (m, 1H_{maj}), 2.56 (dd, J = 17.5, 1.4 Hz, 1H_{maj}), 2.49 (dd, J = 17.0, 1.2 Hz, 1H_{min}), 2.08 (ddd, J = 11.6, 10.5, 0.9 Hz, 1H_{maj}), 2.00 (ddd, J = 11.6, 10.5, 0.9 Hz, 1H_{min}), 0.86 (s, 9H_{min}), 1.30 (s, 9H_{maj}), 1.17 (s, 9H_{maj}), 1.17 (s, 9H_{min}), 0.86 (s, 9H_{min}), 0.85 (s, 9H_{maj}), 0.06 (s, 3H_{min}), 0.05 (s, 3H_{maj}+3H_{min}), 0.04 (s, 3H_{maj}), 125.0_{maj+min}, 80.6_{maj}, 79.9_{min}, 68.9_{min}, 68.3_{maj}, 67.8_{min}, 67.3_{maj}, 54.0_{min}, 53.6_{maj}, 47.8_{maj}, 47.1_{min}, 42.9_{maj}, 41.8_{min}, 35.0_{min}, 35.0_{maj}, 28.4_{min}, 28.3_{maj}, 28.2_{min}, 25.7_{maj+min}, 17.9_{maj+min}, -4.8_{maj}, -4.8_{min}, -4.9_{maj}; **HRMS** (ESI) mass calculated for [M+H]+ (C₂₃H₄₂O₄NSi) requires *m/z* 424.2878, found *m/z* 424.2873

Synthesis of 4q



General Procedure C was followed using ketophosphonate **3q** (26 mg, 0.066 mmol). FCC purification (3:1 pentane:EtOAc) afforded the title compound as a yellow oil (17 mg, 69%). **IR** (thin film) v_{max}/cm^{-1} 2969 (C-H), 1705 (C=O), 1694 (C=O), 1604, 1389, 1176, 1129; ¹H NMR (400 MHz, CDCl₃) δ 7.20 (app. tt, *J* = 3.8, 1.6 Hz, 3H_{mai}+3H_{min}), 7.14 (app. dt, *J*

= 6.1, 3.4 Hz, $2H_{maj}+2H_{min}$), 5.45 (t, J = 1.6 Hz, $1H_{min}$), 5.41 – 5.35 (m, $1H_{maj}$), 4.09 (dd, J = 10.6, 8.3 Hz, $1H_{maj}$), 3.94 (dd, J = 10.5, 8.5 Hz, $1H_{min}$), 3.57 – 3.38 (m, $1H_{maj}+2H_{min}$), 3.36 – 3.21 (m, $2H_{maj}+1H_{min}$), 2.79 – 2.58 (m, $2H_{maj}$, $3_{maj}+2H_{min}$), 1.91 (dtd, J = 12.0, 5.7, 2.7 Hz, $1H_{maj}+1H_{min}$), 1.45 (s, $9H_{min}$), 1.32 (s, $9H_{maj}$), 0.96 (s, $9H_{maj}+9H_{min}$); ¹³C NMR (101 MHz,

CDCl₃) δ 208.0_{min}, 207.7_{maj}, 185.9_{min}, 185.2_{maj}, 153.9_{maj}, 153.8_{min}, 136.3_{min}, 136.3_{maj}, 128.4_{min}, 128.4_{maj}, 128.2_{maj+min}, 127.7_{maj}, 127.6_{min}, 125.3_{min}, 125.2_{maj}, 80.4_{maj}, 79.7_{min}, 72.8_{min}, 72.5_{maj}, 57.4_{maj}, 56.3_{min}, 47.2_{min}, 47.0_{maj}, 41.2_{maj}, 39.4_{min}, 34.9_{min}, 34.8_{maj}, 28.5_{min}, 28.4_{maj}, 28.4_{maj}, 28.4_{min}, 28.0_{min}, 27.6_{maj}; **HRMS** (ESI) mass calculated for [M+Na]+ (C₂₃H₃₁O₃NNa) requires *m/z* 392.2196, found *m/z* 392.2198.

Synthesis of 4r



General Procedure C was followed using ketophosphonate **3r** (36 mg, 0.100 mmol). FCC purification (2:1 pentane:EtOAc) afforded the title compound as a yellow oil (16 mg, 47%). **IR** (thin film) v_{max}/cm^{-1} 2964

(C-H), 1717 (C=O), 1693 (C=O), 1603 (C=C), 1378, 1366, 1114; ¹H **NMR** (400 MHz, CDCl₃) δ 5.97 (t, J = 1.6 Hz, 1H_{min}), 5.93 (t, J = 1.6 Hz, 1H_{maj}), 3.80 (ddd, J = 7.5, 5.1, 1.7 Hz, 1H_{maj}), 3.65 (dd, J = 7.8, 5.7 Hz, 1H_{min}), 3.02 – 2.96 (m, 1H_{min}), 2.81 (dt, J = 17.4, 1.4 Hz, 1H_{maj}), 2.54 (dd, J = 17.4, 1.4 Hz, 1H_{maj}), 2.44 (dd, J = 16.8, 1.2 Hz, 1H_{min}), 2.30 (m, 1H_{maj}+1H_{min}), 2.17 – 1.97 (m, 1H_{maj}+1H_{min}), 1.95 – 1.75 (m, 2H_{maj}+2H_{min}), 1.53 – 1.44 (m, 1H_{maj}+1H_{min}), 1.41 (s, 9H_{min}), 1.31 (s, 9H_{maj}), 1.16 (s, 9H_{maj}), 1.16 (s, 9H_{min}), 0.98 (d, J = 6.9 Hz, 3H_{maj}+3H_{min}), 0.93 (d, J = 7.0 Hz, 3H_{maj}+3H_{min}). ¹³C NMR (101 MHz, CDCl₃) δ 210.6_{min}, 207.8_{maj}, 184.8_{min}, 184.1_{maj}, 153.4_{min}, 153.3_{maj}, 125.2_{maj}, 125.0_{min}, 80.2_{maj}, 79.6_{min}, 70.4_{min}, 69.8_{maj}, 64.2_{maj}, 64.0_{min}, 42.6_{maj}, 40.8_{min}, 39.1_{maj}, 38.1_{min}, 35.0_{min}, 34.9_{maj}, 31.5_{min}, 30.5_{maj}, 28.4_{maj+min}, 28.3_{maj}, 28.2_{min}, 25.8_{min}, 24.6_{maj}, 20.5_{min}, 20.2_{maj}, 17.7_{min}, 17.3_{maj}. **HRMS** (ESI) mass calculated for [M+Na]+ (C₂₀H₃₃O₃NNa) requires *m/z* 358.2353, found *m/z* 358.2346.

Synthesis of 4a'



LiHMDS in THF (114 µL, 0.114 mmol). The reaction was stirred for 10 min before adding 1M sodium naphthalenide in THF (568 µL, 0.568 mmol) dropwise until complete consumption of starting material was observed by TLC. H₂O (0.5 mL) was then added, followed by addition of sat. aq. K₂CO₃ (1 mL). The reaction mixture was then stirred for 30 min. The aqueous phase was then extracted with EtOAc (3 x 20 mL) and the organic layers were combined, dried with MgSO₄ and filtered before removal of the solvent under reduced pressure. The resulting crystalline crude material was purified by FCC (9:1 EtOAc:MeOH) to yield the title compound as a yellow oil (14 mg, 63%). **IR** (thin film) v_{max}/cm^{-1} 2965 (C-H), 1704 (C=O), 1599 (C=C), 1249, 867; ¹**H NMR** (400 MHz, CDCl₃) δ 5.93 (t, *J* = 1.7 Hz, 1H), 3.30 – 3.20 (m, 1H), 3.02 – 2.93 (m, 1H), 2.64 (d, *J* = 1.7 Hz, 2H), 2.28 – 2.13 (m, 1H), 2.01 – 1.77 (m, 3H,), 1.72 – 1.60 (m, 1H), 1.17 (s, 9H); ¹³C **NMR** (101 MHz, CDCl₃) δ 211.6, 188.8, 124.4, 70.6, 47.9, 45.2, 38.6, 35.2, 28.4, 26.5. **HRMS** (ESI) mass calculated for [M+H]+ (C₁₂H₂₀ON) requires *m*/*z* 194.15394, found *m*/*z* 194.15402.

9. Formal Synthesis of (±)-Cephalotaxine



Scheme S5. Formal synthesis of (\pm) -cephalotaxine.

Synthesis of 2s



General Procedure A was followed using nitrone **1a** (100 mg, 0.456 mmol), trimethylsilane acetylene (190 μ L) and stirred for 22 h. The resulting oil was purified by FCC (4:1 pentane:EtOAc) to give the

title compound as a colourless oil (97 mg, 67%). **IR** (thin film) v_{max}/cm^{-1} 2960 (C-H), 1732 (C=O), 1249, 1109, 836 (C-Si); ¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.28 (m, 5H), 5.22 (d, J = 12.5 Hz, 1H), 5.17 (d, J = 12.5 Hz, 1H), 4.87 (s, 1H), 3.39 – 3.24 (m, 2H), 2.16 (ddd, J = 12.7, 9.2, 6.9 Hz, 1H), 2.00 (dddd, J = 12.4, 6.9, 4.1, 1.1 Hz, 1H), 1.84 – 1.68 (m, 2H), 0.17 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 172.9, 160.0, 136.0, 128.5, 128.1, 127.8, 108.7, 82.0, 66.7, 60.4, 36.9, 23.1, -2.2; **HRMS** (ESI) mass calculated for [M+H]+ (C₁₇H₂₄O₃NSi) requires m/z 318.1520, found m/z 318.1520. As a large-scale modification to General Procedure A, nitrone **1a** (3.59 g, 16.4 mmol) was stirred in hexane at 70 °C in a round-

bottomed flask with a reflux condenser attached. To this was added TMS-acetylene (6.8 mL, 49.2 mmol) and the heterogeneous mixture stirred vigorously under an N_2 atmosphere for 20 h. The solvent was then removed under reduced pressure to yield an orange oil as the crude product. FCC purification (4:1 pentane: EtOAc) yielded the title compound as a colourless oil (4.30 g, 83%).

Synthesis of 3s

General Procedure B was followed using cycloadduct **2s** (50 mg, 0.158 mmol). FCC afforded the title compound as a yellow oil (34 mg, 65%). **IR** (thin film) v_{max}/cm^{-1} 3032 (C-H), 1713 (C=O), 1250 (P=O), 1031 (P-O antisymmetric); ¹H NMR (400 MHz, CDCl₃) δ 4.69 (s, 1H), 3.79 (d, J = 6.9 Hz, 3H), 3.76 (d, J = 6.9 Hz, 3H), 3.62 (dd, J = 21.3, 14.9 Hz, 1H), 3.30 – 3.22 (m, 2H), 3.21 (dd, J = 21.0, 14.9 Hz, 1H), 2.26 (m, J = 12.8, 8.0 Hz, 1H), 1.92 – 1.85 (m, 1H), 1.76 – 1.68 (m, 2H), 0.17 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 204.3 (d, J = 6.4 Hz), 163.1, 111.1, 90.3 (d, J = 3.6 Hz), 62.4, 55.2 (d, J = 6.3 Hz), 55.1 (d, J = 6.3 Hz), 37.8 (d, J = 134.9 Hz), 36.1, 25.5, -0.0; ³¹P NMR (162 MHz, CDCl₃) δ 24.17; HRMS (ESI) mass calculated for [M+H]+ (C₁₃H₂₅O₅NPSi) requires *m/z* 334.1234, found *m/z* 334.1232. On a larger scale, General Procedure B was followed using cycloadduct **2s** (4.3 g, 13.6 mmol) to yield the title compound as a yellow oil (3.20 g, 71%).

Synthesis of 4s

General Procedure C was followed using ketophosphonate **3s** (33 mg, 0.099 mmol). FCC purification (4:1 pentane:EtOAc) afforded the title compound as a colourless oil (15 mg, 49%). **IR** (thin film) v_{max}/cm^{-1} 2971 (C-H), 1717 (C=O), 1697 (C=O), 1391, 1210, 842; ¹H NMR (400 MHz, CDCl₃) δ 6.41 (dd, J = 2.5, 1.5 Hz, 1H_{min}), 6.36 (dd, J = 2.4, 1.8 Hz, 1H_{mai}), 3.63 – 3.45 (m, 2H_{mai}+2H_{min}),

3.13 (dd, J = 17.5, 2.5 Hz, 1H_{min}), 2.98 (dd, J = 18.1, 2.4 Hz, 1H_{maj}), 2.62 (ddd, J = 24.5, 17.8, 1.7 Hz, 1H_{maj}+1H_{min}), 2.07 – 1.93 (m, 2H_{maj}+2H_{min}), 1.92 – 1.77 (m, 1H_{maj}+1H_{min}), 1.77 – 1.59 (m, 1H_{maj}+1H_{min}), 1.41 (s, 9H_{min}), 1.30 (s, 9H_{maj}), 0.20 (s, 9H_{maj}), 0.19 (s, 9H_{min}); ¹³C **NMR** (101 MHz, CDCl₃) δ 208.6_{maj}, 179.3_{maj}, 153.0_{maj}, 139.1_{min}, 139.1_{maj}, 80.2_{maj}, 79.6_{min}, 68.6_{min}, 67.9_{maj}, 48.1_{min}, 47.9_{maj}, 46.5_{maj}, 45.2_{min}, 40.3_{maj}, 39.5_{min}, 28.5_{min}, 28.3_{maj}, 24.0_{min}, 23.4_{maj}, -2.6_{maj+min}; **HRMS** (ESI) mass calculated for [M+Na]+ (C₁₆H₂₇O₃NNaSi) requires *m/z* 332.1652, found *m/z* 332.1651.

2-(3,4-Dimethoxyphenyl)acetyl chloride (S14)

Oxalyl chloride (8.04 mL, 95 mmol) was added to a solution of homoveratric acid (3.92 g, 20.0 mmol) and DMF (1.54 mL) in pentane (800 mL) at r.t.. After 1 h the solid was observed to have been completely consumed and the mixture was filtered and the residue concentrated to afford a yellow oil. The yield was assumed to be quantitative and this crude product was used directly in preparing spiroenone **5** without purification or characterisation.

Synthesis of 5



General Procedure C was followed using ketophosphonate 3s (100 mg, 0.30 mmol) however, rather than quenching with a THF solution of Boc₂O, a THF solution of acid chloride **S14** (2 eq.) was used. The resulting biphasic mixture was stirred for 6 hours before being worked up in the

usual manner. The crude crystalline material was purified by FCC (EtOAc)

to yield the title compound as a colourless oil (76 mg, 65%) **IR** (thin film) v_{max}/cm^{-1} 2954 (C-H), 1711 (C=O), 1638 (C=O), 1590 (C=C), 1515, 1409, 1249, 1020, 841; ¹H NMR (400 MHz, CDCl₃) δ 6.84 – 6.73 (m, 3H), 6.42 (dd, J = 2.4, 1.6 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.63 – 3.48 (m, 4H), 3.15 (dd, J = 17.5, 2.4 Hz, 1H), 2.54 (dd, J = 17.6, 1.6 Hz, 1H), 2.09 –

1.98 (m, 1H), 1.99 – 1.86 (m, 2H), 1.68 – 1.59 (m, 1H), 0.17 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 207.2, 178.2, 168.7, 149.2, 147.8, 139.2, 127.0, 121.0, 111.8, 111.3, 69.4, 55.9 (app. d, *J*= 1.8 Hz), 48.6, 44.9, 41.7, 38.5, 24.7, -2.6; **HRMS** (ESI) mass calculated for [M+H]+ (C₂₁H₃₀O₄NSi) requires *m*/*z* 388.1932, found *m*/*z* 388.1928. This procedure was repeated on a larger scale (2.30 g, 6.9 mmol) to yield the title compound as a yellow oil (1.49 g, 56%).

Synthesis of S15



Following a modified literature procedure,¹⁸ to a stirred solution of spiroenone **5** (800 mg, 2.1 mmol) in propan-2-ol (21 mL, 0.1 M) was added Al(O*i*-Pr)₃ (16 g, 79 mmol). The mixture was heated at 80 °C and the temperature was increased to 130 °C over the course of 30 min with concurrent distillation of the solvent. The reaction was then stirred for 2 h at 130 °C. The molten mixture was poured into 1 M HCl (400 mL) at -10 °C. The solid residue left in the flask was dissolved in cold 1M HCl using sonication and this was added to the rest of the reaction mixture. The resulting aqueous suspension was extracted with CHCl₃ (3 x 250 mL). The organics were combined, dried with Na₂SO₄ and filtered before removal of the solvent under reduced pressure. The resulting crude yellow oil was purified by FCC (1:1 pentane:EtOAc to 100% EtOAc, eluent cooled to 0 °C) to yield the title compound as a colourless oil (423 mg, 52%). **IR** (thin film) v_{max}/cm^{-1} 3386 (O-H), 2953, 1619, 1514, 1248; ¹**H NMR** (400 MHz, CDCl₃) δ 6.79 – 6.68 (m, 3H), 5.82 (p, *J* = 1.3 Hz, 1H), 5.71 (app. q, *J*

= 1.9 Hz, 1H), 3.81 (app. d, J = 2.1 Hz, 6H), 3.52 (d, J = 2.9 Hz, 2H), 3.49 – 3.36 (m, 2H), 3.25 (dt, J = 15.2, 2.4 Hz, 1H), 2.38 (ddd, J = 12.6, 9.0, 6.5 Hz, 1H), 2.07 (dt, J = 15.3, 1.5 Hz, 1H), 1.83 (tdd, J = 11.8, 6.6, 5.2 Hz, 1H), 1.70 (ddtd, J = 12.2, 8.9, 7.6, 6.3 Hz, 1H), 1.41 (dt, J = 12.1, 5.9 Hz, 1H), -0.00 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 171.9, 151.3, 150.1, 148.5, 144.1, 129.7, 123.3, 114.2, 113.5, 81.5, 78.2, 58.1 (app. d, J = 6.8 Hz), 51.4, 47.3, 45.5, 35.8, 25.8, -0.0; **HRMS** (ESI) mass calculated for [M+H]+ (C₂₁H₃₂O₄NSi) requires *m/z* 390.2095, found *m/z* 390.2098.

Major side products for this reaction included a base-mediated condensation product and the elimination of the secondary alcohol:





condensation side product

elimination side product

Synthesis of 6



Following a modified literature procedure,¹⁸ to a suspension of $LiAlH_4$ (141 mg, 3.7 mmol) in dry THF (9 mL), was slowly added a THF solution (9 mL) of allylic alcohol **S15** (400 mg,

1.0 mmol). The resulting mixture was heated at 66 °C for 80 minutes. The reaction was cooled to r.t., diluted with Et₂O (20 mL) before slow addition of H₂O in THF (2 mL in 38 mL) followed by addition of 2M NaOH solution (2 mL). This suspension was filtered and the solvents were removed under reduced pressure. The resulting crude yellow oil was purified by FCC (95:5:1 CHCl₃:MeOH:NH₃(aq)) to yield the title compound as a colourless oil (257 mg, 68%)

IR (thin film) v_{max} /cm⁻¹ 3362 (O-H), 2951, 1591, 1515, 1261; ¹H NMR (400 MHz, CDCl₃) δ 6.78 (d, J = 8.7 Hz, 1H), 6.75 – 6.68 (m, 2H), 5.91 (q, J = 1.9 Hz, 1H), 4.65 (q, J = 1.6 Hz, 1H), 3.85 (app. d, J = 4.6 Hz, 6H), 3.12 (td, J = 8.7, 5.8 Hz, 1H), 2.78 – 2.63 (m, 4H), 2.52 – 2.36 (m, 2H), 2.30 – 2.19 (m, 1H), 2.15 (dt, J = 16.4, 1.6 Hz, 1H), 1.91 – 1.76 (m, 2H), 1.53 (ddd, J = 12.4, 8.3, 5.8 Hz, 1H), 0.05 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 151.0, 149.6, 149.2, 143.6, 135.5, 122.7, 114.3, 113.4, 81.4, 78.7, 58.1 (app. d, J = 2.8 Hz) 53.9 (app d, J =12.5 Hz), 41.5, 37.8, 34.3, 23.1, -0.0; HRMS (ESI) mass calculated for [M+H]+ (C₂₁H₃₄O₃NSi) requires m/z 376.2302, found m/z 376.2304.

Investigation of Intramolecular Friedel-Crafts

HO N TMS acid, conditions N N N N N HO OMe MeO OMe Mori's intermediate, 7								
entry	acid	solvent	NMR yield	observations				
1 ^a	PPA	neat	37%	-				
2 ^b	Eaton's reagent	neat	64%	-				
3 ^c	Eaton's reagent	neat	58%	-				
4 ^d	H ₂ SO ₄	AcOH	60%	-				
5 ^d	TsOH	HFIP	-	m/z 358 dominant				
6 ^c	н	PhMe	-	m/z 288 dominant				
7 ^e	TsOH then HI	HFIP then PhMe	-	m/z 288 dominant				
8 ^c	TfOH	neat	-	m/z 272 dominant				

Table S4. Screen of different acids to bring about key Friedel-Crafts reaction. ^a 65 °C for 43 h. ^br.t. for 4 h. ^c 55 °C for 4-6 h. ^d 55 °C for 3 d. ^e 55 °C for 5 h then solvent swap and r.t. for 2 d.

Synthesis of Mori's intermediate 7



To **6** (120 mg, 0.32 mmol) was added Eaton's Reagent (7.7 wt % P_2O_5 in MsOH, 3.2 mL) and the mixture stirred at r.t. for 5 h. Sat. aq.

NaHCO₃ was slowly introduced before the mixture was basified to

pH 10 with 2M aq. NaOH. The aqueous phase was extracted with CH₂Cl₂ (4 x 50 mL) and the combined organics were dried with Na₂SO₄, filtered and the solvent was removed under reduced pressure. Purification by FCC (95:5:1 EtOAc:MeOH:NH₃ (35% aq)) yielded the title compound as a colourless oil (67 mg, 73%). **IR** (thin film) v_{max} /cm⁻¹ 2926 (C-H), 1684, 1515, 1220, 1126; ¹H NMR (400 MHz, CDCl₃) δ 6.68 (s, 1H), 6.62 (s, 1H), 5.79 (dq, *J* = 5.2, 2.5 Hz, 1H), 5.54 (dq, *J* = 6.0, 2.3 Hz, 1H), 3.89 (dq, *J* = 5.2, 2.4 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.20 (ddd, *J* = 14.0, 12.3, 7.4 Hz, 1H), 3.08 (td, *J* = 9.0, 4.6 Hz, 1H), 2.94 (td, *J* = 11.9, 6.8 Hz, 1H), 2.76 (dq, *J* = 17.8, 2.6 Hz, 1H), 2.57 (dd, *J* = 11.4, 7.4 Hz, 1H), 2.47 – 2.31 (m,

2H), 2.05 - 1.93 (m, 3H), 1.74 (tddd, J = 12.6, 10.8, 8.6, 4.6 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 147.6, 147.2, 132.5, 131.1, 130.9, 128.5, 114.1, 113.1, 68.1, 62.3, 56.1, 56.0, 53.7, 49.1, 43.4, 34.7, 30.4, 19.9. **HRMS** (ESI) mass calculated for [M+H]+ (C₁₈H₂₄NO₂) requires m/z 286.1802, found m/z 286.1801. Data were consistent with the literature.¹⁹

10. Challenging Substrates and Unsuccessful Intermediates

Despite the numerous successful applications of this method and the significant broadening of synthetic access to this chemical space, a number of additional substrates failed at various points along the sequence. Scheme S5 details the additional substrates investigated and at which stage along the three-step sequence issues were encountered.



Scheme S6. Challenging substrates

NMR Spectra for Novel Compounds

¹H NMR Spectra for Compound 1a



¹³C NMR Spectra for Compound 1a



¹H NMR Spectra for Compound 1b



¹³C NMR Spectra for Compound 1b



¹H NMR Spectra for Compound S6



¹³C NMR Spectra for Compound S6



¹H NMR Spectra for Compound 1c



¹³C NMR Spectra for Compound 1c



¹H NMR Spectra for Compound S10



¹³C NMR Spectra for Compound S10



¹H NMR Spectra for Compound 1d



¹³C NMR Spectra for Compound 1d



¹H NMR Spectra for Compound 2a



¹³C NMR Spectra for Compound 2a



¹H NMR Spectra for Compound 2b



¹³C NMR Spectra for Compound 2b



¹H NMR Spectra for Compound 2c



¹³C NMR Spectra for Compound 2c

173.20	161.92	136.02 128.47 128.06 127.83	92.58	82.18	66.63	36.94 35.28 30.72 30.52 25.74 23.01
		$ \lor$				11 Y Y Z


¹H NMR Spectra for Compound 2d



¹³C NMR Spectra for Compound 2d



¹H NMR Spectra for Compound 2e



¹³C NMR Spectra for Compound 2e



¹⁹F NMR Spectra for Compound 2e



¹H NMR Spectra for Compound 2f



¹³C NMR Spectra for Compound 2f



¹H NMR Spectra for Compound 2g





¹³C NMR Spectra for Compound 2g



¹H NMR Spectra for Compound 2h



¹³C NMR Spectra for Compound 2h



¹H NMR Spectra for Compound 2i major





¹³C NMR Spectra for Compound 2i major



¹³C NMR Spectra for Compound 2i minor



¹H NMR Spectra for Compound 2p Major



¹³C NMR Spectra for Compound 2p Major



¹H NMR Spectra for Compound 2p Minor



¹³C NMR Spectra for Compound 2p Minor



¹H NMR Spectra for Compound 2q



¹³C NMR Spectra for Compound 2q



¹H NMR Spectra for Compound 2r



¹³C NMR Spectra for Compound 2r



¹H NMR Spectra for Compound 3a



¹³C NMR Spectra for Compound 3a



³¹P NMR Spectra for Compound 3a



¹H NMR Spectra for Compound 3b



¹³C NMR Spectra for Compound 3b



³¹P NMR Spectra for Compound 3b



¹H NMR Spectra for Compound 3c



¹³C NMR Spectra for Compound 3c



³¹P NMR Spectra for Compound 3c



¹H NMR Spectra for Compound 3d



¹³C NMR Spectra for Compound 3d



³¹P NMR Spectra for Compound 3d



¹H NMR Spectra for Compound 3e



¹³C NMR Spectra for Compound 3e



¹⁹F NMR Spectra for Compound 3e



³¹P NMR Spectra for Compound 3e



¹H NMR Spectra for Compound 3f



¹³C NMR Spectra for Compound 3f



³¹P NMR Spectra for Compound 3f



¹H NMR Spectra for Compound 3g



¹³C NMR Spectra for Compound 3g



³¹P NMR Spectra for Compound 3g



¹H NMR Spectra for Compound 3h



¹³C NMR Spectra for Compound 3h



³¹P NMR Spectra for Compound 3h



¹H NMR Spectra for Compound 3i



¹³C NMR Spectra for Compound 3i



³¹P NMR Spectra for Compound 3i



¹H NMR Spectra for Compound mixture 3j







¹³C NMR Spectra for Compound mixture 3j

³¹P NMR Spectra for Compound mixture 3j



¹H NMR Spectra for Compound mixture 3k



¹³C NMR Spectra for Compound mixture 3k



³¹P NMR Spectra for Compound mixture 3k



¹H NMR Spectra for Compound mixture 31







³¹P NMR Spectra for Compound mixture 31



¹H NMR Spectra for Compound mixture 3m



¹³C NMR Spectra for Compound mixture 3m



³¹P NMR Spectra for Compound mixture 3m



¹H NMR Spectra for Compound mixture 3n



¹³C NMR Spectra for Compound mixture 3n



³¹P NMR Spectra for Compound mixture 3n



¹H NMR Spectra for Compound mixture 30



¹³C NMR Spectra for Compound mixture 30



³¹P NMR Spectra for Compound mixture 30



¹H NMR Spectra for Compound 3p



¹³C NMR Spectra for Compound 3p



³¹P NMR Spectra for Compound 3p


¹H NMR Spectra for Compound 3q



¹³C NMR Spectra for Compound 3q



³¹P NMR Spectra for Compound 3q



¹H NMR Spectra for Compound 3r



¹³C NMR Spectra for Compound 3r



³¹P NMR Spectra for Compound 3r



¹H NMR Spectra for Compound 4a



¹³C NMR Spectra for Compound 4a



¹H NMR Spectra for Compound 4b



¹³C NMR Spectra for Compound 4b



¹H NMR Spectra for Compound 4c



¹³C NMR Spectra for Compound 4c



¹H NMR Spectra for Compound 4d



¹³C NMR Spectra for Compound 4d



¹H NMR Spectra for Compound 4e



¹³C NMR Spectra for Compound 4e



¹⁹F NMR Spectra for Compound 4e



¹H NMR Spectra for Compound 4f



¹³C NMR Spectra for Compound 4f



¹H NMR Spectra for Compound 4g



¹³C NMR Spectra for Compound 4g



¹H NMR Spectra for Compound 4h



¹³C NMR Spectra for Compound 4h



¹H NMR Spectra for Compound 4i



¹³C NMR Spectra for Compound 4i



¹H NMR Spectra for Compound 4j



¹³C NMR Spectra for Compound 4j



¹H NMR Spectra for Compound 4k



¹³C NMR Spectra for Compound 4k



¹H NMR Spectra for Compound 4l



¹³C NMR Spectra for Compound 41



¹H NMR Spectra for Compound 4m



¹³C NMR Spectra for Compound 4m



¹³C NMR Spectra for Compound 4n



¹H NMR Spectra for Compound 40



¹³C NMR Spectra for Compound 40



¹H NMR Spectra for Compound 4p



¹³C NMR Spectra for Compound 4p



¹H NMR Spectra for Compound 4q



¹³C NMR Spectra for Compound 4q



¹H NMR Spectra for Compound 4r



¹³C NMR Spectra for Compound 4r



¹H NMR Spectra for Compound 4a'



¹³C NMR Spectra for Compound 4a'



¹H NMR Spectra for Compound 2s



¹³C NMR Spectra for Compound 2s



¹H NMR Spectra for Compound 3s



¹³C NMR Spectra for Compound 3s



³¹P NMR Spectra for Compound 3s



¹H NMR Spectra for Compound 4s



¹³C NMR Spectra for Compound 4s



¹H NMR Spectra for Compound 5



¹³C NMR Spectra for Compound 5



¹H NMR Spectra for Compound S15



¹³C NMR Spectra for Compound S15



¹H NMR Spectra for Compound 6



¹³C NMR Spectra for Compound 6



¹H NMR Spectra for Compound 7



¹³C NMR Spectra for Compound 7



References

- (1) S. I. Murahashi, H. Mitsui, T. Shiota, T. Tsuda and S. Watanabe, J. Org. Chem., 1990, 55, 1736–1744.
- (2) W. W. Zajac, T. R. Walters and M. G. Darcy, J. Org. Chem., 1988, 53, 5856–5860.
- (3) S. I. Murahashi and Y. Imada, *Chem. Rev.*, 2019, **119**, 4684–4716.
- (4) K. M. Maloney and J. Y. L. Chung, J. Org. Chem., 2009, 74, 7574–7576.
- (5) R. Madsen, C. Roberts and B. Fraser-Reid, J. Org. Chem., 1995, 60, 7920–7926.
- (6) T. Imaoka, O. Iwamoto, K. I. Noguchi and K. Nagasawa, Angew. Chemie Int. Ed., 2009, 48, 3799–3801.
- (7) J. Peng and D. L. J. Clive, *Org. Lett.*, 2007, **9**, 2939–2941.
- (8) D. V. Gribkov, S. J. Pastine, M. Schnürch and D. Sames, J. Am. Chem. Soc., 2007, **129**, 11750–11755.
- (9) D. P. Affron and J. A. Bull, *European J. Org. Chem.*, 2016, 139–149.
- (10) D. Antermite, D. P. Affron and J. A. Bull, Org. Lett., 2018, 20, 3948–3952.
- (11) V. K. Aggarwal, C. J. Astle, H. Iding, B. Wirz and M. Rogers-Evans, *Tetrahedron Lett.*, 2005, 46, 945–947.
- (12) F. Prause, J. Kaldun, B. Arensmeyer, B. Wennemann, B. Fröhlich, D. Scharnagel and M. Breuning, Synth., 2015, 47, 575–586.
- (13) S. D. Taylor, C. C. Kotoris, A. N. Dinaut and M. J. Chen, *Tetrahedron*, 1998, 54, 1691–1714.
- (14) S. Ganapathy, B. B. V. Soma Sekhar, S. M. Cairns, K. Akutagawa and W. G. Bentrude, J. Am. Chem. Soc., 1999, 121, 2085–2096.
- (15) D. W. G. Wone, J. A. Rowley, A. W. Garofalo and C. E. Berkman, *Bioorganic Med. Chem.*, 2006, 14, 67–76.
- (16) S. Chen, Y. Ruan, J. D. Brown, C. M. Hadad and J. D. Badjić, J. Am. Chem. Soc., 2014, 136, 17337–17342.
- (17) H. Wang, L. Huang, X. Cao, D. Liang and A. Y. Peng, Org. Biomol. Chem., 2017, 15, 7396–7403.
- (18) Z. Zhao and P. S. Mariano, *Tetrahedron*, 2006, **62**, 7266–7273.
- (19) a) N. Isono and M. Mori, J. Org. Chem, 1995, 60, 115–119; b) N. Y. Kuznetsov, G. D. Kolomnikova, V. N. Khrustalev, D. G. Golovanov and Y. N. Bubnov, European J. Org. Chem., 2008, 5647–5655.